Drug GMP Warning Letters CY2017

Data Governance and Data Integrity

INTRODUCTION:

This article represents the third year that we have published an evaluation of warning letters associated with data governance and data integrity deficiencies. Articles for 2015 and 2016 may be found HERE and HERE respectively. Failures in data integrity and data governance is an enforcement area that began almost twenty years ago and continues to increase in visibility and number of warning letter enforcement actions. FDA is not the only health authority that identifies these issues in inspections and enforcement actions, but FDA's transparency ensures these data are readily available. In this summary we:

- Briefly review the history that serves as background to where we are now,
- Identify CY2017 warning letters that cite data integrity deficiencies,
- Identify the number of warning letters citing this topic in the past 10 years and the country location of these sites,
- Identify the regulations cited most frequently in CY2017 Drug GMP warning letters citing data integrity failures

BACKGROUND:

Let's begin with a review of where and when this topic originated. The "generics scandal" of the 1980's identified falsified data submitted to FDA in support of ANDA drug approvals. In response, FDA brought a new focus to pre-approval inspections (PAI) to evaluate raw laboratory data included in the marketing application and evaluate whether the site was capable of manufacture as described in the application.

In parallel, FDA recognized the pharmaceutical industry's increased reliance on computerized systems. In response, FDA developed and published 21 CFR11, the final rule on *Electronic Records and Electronic Signatures* in 1997 and its preamble. While the requirements for electronic signatures were understood, confusion remained on both sides regarding the interpretation and enforcement of requirements for electronic records. Following enforcement actions against Able Laboratories in 2005, and against Ranbaxy in 2006 and 2008, FDA announced a pilot program in 2010 to evaluate data integrity as part of routine GMP inspections. FDA planned to use the information gained from these inspections to determine whether revisions to Part 11 or additional guidance on the topic were necessary. FDA Investigator Robert Tollefsen describes the program in a slide deck presented at a variety of industry conferences in 2010. In the slide deck, FDA stresses that they will *"continue to enforce all predicate rule requirements, including requirements for records and recordkeeping*." In fact, deficiencies in Part 11 are rarely, if ever, cited in warning letters because almost all failures are those where firms fail to comply with the predicate rules. Further, enforcement directed at data governance and data integrity is not limited to the GMP area but now includes GCP. Some data integrity failures address clinical investigators and IRBs that fail to collect data or fail to retain data. The most dramatic cases, however, include those where problems occur at sites that perform bioavailability and bioequivalence studies including GVK and Semler Research.

Fundamentally, all data integrity deficiencies identified in forms-483 and warning letters are failures to follow CGMPs as specified in the predicate rules. The FDA has not implemented novel interpretations or requirements governing data governance. The use of computer systems and other electronic systems require different approaches to ensure compliant practices, but these are all based on the existing regulations in 21CFR211.

CY2017 Data Integrity Drug GMP Warning Letters and Trends from the Past Ten Years

Table 1 lists the warning letters that include data integrity deficiencies, the date of issuance and the country location of the facility. The country column is color-coded, and I consolidate all European countries into a single group in subsequent tables and figures. FDA issued eighty-two warning letters, excluding those issued to compounding pharmacies and outsourcing facilities in CY2017. Fifty-six warning letters included a data integrity component, a total of 68% of the warning letters.

TABLE 1: CY2017 Drug Warning Letters with Data Integrity Deficiencies

DATE	COMPANY	COUNTRY
1/6/2017	Sato Yakuhin Kogyo Co., Ltd.	Japan
1/6/2017	Suzhou Pharmaceutical Technology Co., Ltd	China
1/6/2017	Ningbo Zhixin Bird Clean-Care Product Company, Ltd.	China
1/13/2017	FACTA Farmaceutici S.p.A.	Italy (Europe)
1/18/2017	CTX Life Sciences Pvt., Ltd.	India
1/26/2017	Zhejiang Bangli Medical Products Co., Ltd.	China
1/26/2017	Humco Holding Group, Inc.	USA
2/14/2017	Chongqing Pharma Research Institute Co., Ltd.	China
2/17/2017	Morton Grove Pharmaceuticals, Inc. (owned by Wockhardt)	USA
2/24/2017	Jinan Jinda Pharmaceutical Chemistry Co., Ltd.	China
2/24/2017	Megafine Pharma (P) Ltd.	India
3/2/2017	Badrivishal Chemicals & Pharmaceuticals	India
3/2/2017	Lumis Global Pharmaceuticals Co., Ltd.	China
3/10/2017	USV Private Limited	India
3/16/2017	Opto-Pharm Pte Ltd.	Singapore
4/3/2017	Mylan Laboratories Limited	India
4/13/2017	Divi's Laboratories Ltd. (Unit III)	India
4/20/2017	Sal Pharma	India

4/20/2017	Huron Pharmaceuticals, Inc.	USA
4/24/2017	Qinhuangdao Zizhu Pharmaceutical Co., Ltd.	China
4/28/2017	Vikshara Trading & Investments Ltd.	India
5/8/2017	Howard Phillips, LLC.	USA
5/11/2017	Changzhou Jintan Qianyao Pharmaceutical Raw Material Factory	China
5/17/2017	Med-Pharmex, Inc.	USA
5/25/2017	Yusef Manufacturing Laboratories, LLC	USA
6/22/2017	Shandong Analysis and Test Center	China
6/29/2017	ChemRite CoPac, Inc.	USA
7/6/2017	Center for Reproductive Health / Joliet IVF LLC	USA
8/1/2017	Foshan Flying Medical Products Co., Ltd.	China
8/2/2017	Cellex-C International Inc.	Canada
8/11/2017	Bicooya Cosmetics Limited	China
8/24/2017	US Stem Cell Clinic, LLC	USA
9/1/2017	Nova Homeopathic Therapeutics, Inc.	USA
9/7/2017	HomeoCare Laboratories, Inc.	USA
9/7/2017	Wuxi Medical Instrument Factory	China
9/12/2017	Shandong Vianor Biotech Co., Ltd.	China
10/10/2017	Vital Laboratories PVT Limited	India
10/13/2018	Ridge Properties LLC dba Pain Relief Naturally	USA
10/16/2017	Kim Chemicals Private Ltd.	India
10/30/2017	Guangdong Zhanjiang Jimin Pharmaceutical Co., Ltd.	China
11/1/2017	Baiyunshan Hejigong Pharmaceutical Factory	China
11/6/2017	Hubei Danjiangkou Danao Pharmaceutical Co., Ltd.	China
11/6/2017	Lupin Limited	India
11/8/2017	RTI Surgical, Inc.	USA
11/14/2017	Bayer Pharma AG	Germany
11/17/2017	Hangzhou Facecare Cosmetics Co. Ltd.	China
11/20/2017	Dae Young Foods Company, Ltd.	South Korea

12/4/2017	Fresenius Kabi Oncology Ltd.	India
12/5/2017	Shanwei Honghui Daily Appliance Co., Ltd.	China
12/13/2017	Amaros Co., Ltd.	South Korea
12/18/2017	Prosana Distribuciones S.A. de C.V.	Mexico
12/18/2017	Deserving Health International Corp	Canada
12/19/2017	C.O. Truxton, Inc.	USA
12/18/2017	Wuhan Chinese Moxibustion Technology Dev. Co., Ltd	China
12/20/2017	Scrofner Cosmetics Gmbh	Austria (Europe)
12/21/2017	Continental Manufacturing Chemist Inc.	USA

As mentioned in the background section, FDA began enforcement in this area nearly twenty years ago. Table 2 and Figure 2 present data over the last ten years, CY2008 through CY2017. During this time, the number of warning letters including this topic ranged from four to six from 2008 through 2013, doubled in CY2014 to ten. The number of warning letters was followed by a marked increase between CY2015 through the current year, increasing from fifteen in 2015 to forty-one in 2016 and fifty-six in 2017. The number of countries associated with these warning letters also increased similarly, and in 2017 nine countries were associated with the sites that were subject to the warning letters.

Table 2: Number of Data Integrity Associated Warning Letters by Country CY2008 - 2017

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	TOTAL
China	1	1	3	1			2	2	14	19	43
USA	1	2	1	1	1			0	7	15	28
India	1	1		2		6	7	10	9	12	48
Europe		1					1	2	6	3	13
Brazil								0	3		3
Japan	1							0	2	1	4
Thailand								1			1
Canada			1		1					2	4
Mexico					2					1	3
UAE					1						1
Jamaica					1						1
South Korea										2	2
Singapore										1	1
TOTAL	**4**	**5**	**5**	**4**	**6**	**6**	**10**	**15**	**41**	**56**	**152**

Figure 2: Data Integrity Associated Warning Letters, CY2008 – CY2017

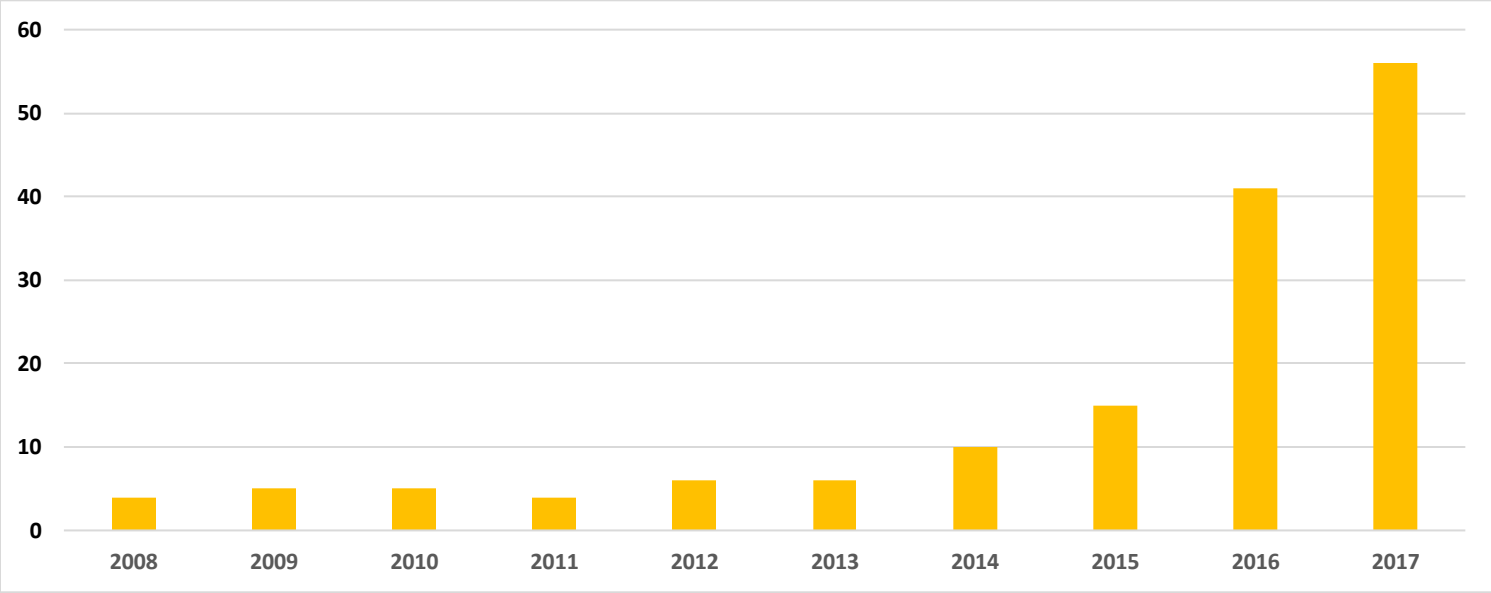

Table 4 compares the number and percentage of warning letters citing data governance and data integrity in both the past ten years and the most recent three years. In the past ten years, sites in India have been the subject in the most warning letters of this type, whereas in the past three years, China rose to the head of the list. Overall the US has received approximately 20% of the warning letters, European countries have received approximately 10% and the rest of the world claim approximately 12%.

Table 4: Geographic Totals and Percentage, 2015 - 2017 and 2008- 2017

COUNTRY	TOTAL NUMBER 2015-2017	% of TOTAL 2015 - 2017	TOTAL NUMBER 2008-2017	% of Total 2008-2017
China	35	31%	43	28%
India	31	28%	48	32%
United States	22	20%	28	18%
Europe	11	10%	13	9%
Rest of World	13	12%	20	13%

Table 5: Regulations Cited in 2017 Data Integrity Associated Drug Warning Letters

21 CFR Reference	Number of Times Cited	Title of CFR Section
211.188	9	Batch Production and Control Records
211.194	9	Laboratory Records, Review of All Data
211.22	8	Responsibilities of the Quality Control Unit
211.192	5	Production Record Review, Deviations, and Investigations
211.68	3	Automatic, Mechanical, and Electronic Equipment

CONCLUSION:

Data integrity and data governance remain an initiative of global health authorities. The U.K.'s Medicines and Healthcare Products Regulatory Agency (MHRA) was the earliest to enter the area in 2015 with their guidance and a published draft revision in 2016. European Medicines Agency (EMA), World Health Organization (WHO), Pharmaceutical Inspection Co-operation Scheme (PIC/S), Australia, Canada, and China followed in 2016. Further, this is not limited to the GMP area but now includes GCP, with the most impactful cases at sites that perform bioavailability and bioequivalence studies. For these firms, the data for hundreds of products are now questionable. Sponsors must frequently repeat the studies at a different site. Most recently this has included failures identified at GVK and Semler Research. Consequences at Semler included a 3-page form 483, untitled letter, WHO notice of concern and EMA recommendation of suspension.

GMP enforcement citing data governance and data integrity has not diminished, expanding both the number of warning letters and their geographic distribution. Although the number of warning letters has increased markedly over the past three years, the percentage has decreased slightly. In CY2017 an increasing number of countries were home to sites that were the subject of these

warning letters. Deficiencies in the area of data governance and data integrity have remained markedly consistent over the ten years addressed in this report, with a few new areas identified each year. This year saw the addition of three new focus areas including:

- Firms that repackage APIs were transferring analytical results onto a Certificate of Analysis on their letterhead making it appear that they generated the results. Inadequate labeling obscures the supply chain from the company that purchases and uses the material in the manufacture of drug products.
- FDA cited firms for an apparently excessive number of aborted analytical runs and
- FD cited firms for manipulation of “integration suppression” within chromatography data systems intending to obscure or minimize impurity peaks.

These three areas merit our attention as we progress through 2018. I watch for this type of problem to expand in scope to more OTC manufacturers because actions in this area is a clear trend that began in 2017. I also watch for this topic to be cited more frequently in enforcement actions taken against compounding pharmacies and outsourcing facilities. Previously most of the problems in this area addressed failures in aseptic processing including facilities and equipment issues. I look for data integrity to be cited more frequently in both forms 483 and warning letters issued to these firms.

Data Governance and Data Integrity Warning Letters, 2017

DATE	COUNTRY	COMPANY	TEXT of WARNING LETTER
1/6/2017	Japan	*Sato Yakuhin Kogyo Co Ltd*	**1. Your firm failed to ensure that laboratory records include complete data derived from all tests necessary to assure compliance with established specifications and standards (21 CFR 211.194(a)(4)).** *Reliance on incomplete data* Our investigator reviewed the audit trails generated by your high performance liquid chromatography (HPLC) system for impurities testing that you conducted on **(b)(4)** (lots **(b)(4)**, **(b)(4)**, **(b)(4)**). The audit trail showed that you performed this testing in duplicate. The audit trail indicated that you conducted a chromatography sequence analyzing impurities on samples of these lots beginning at **(b)(4)** on April14, 2014. The audit trail showed that a new sequence was started approximately 24 hours later, at **(b)(4)** on April 15, 2014, for impurities testing that again included samples for lots **(b)(4)**, **(b)(4)**, and **(b)(4)**. None of the 19 chromatograms generated in the first sequence were maintained and available for review. Only the second set of chromatograms was maintained and relied upon in releasing lots **(b)(4)**, **(b)(4)**, and **(b)(4)** for use in the manufacture of products for the U.S. market. You could not provide any rationale for not maintaining the original data, and you failed to document a scientific justification for repeating the analysis. *Failure to appropriately maintain data* You do not maintain electronic data on your ultraviolet-visible spectrophotometer UV SP-502 which you use for content uniformity and identity testing of **(b)(4)** capsules, and it does not have an audit trail. In your response, you acknowledged that your data integrity controls were deficient. You stated that the chromatography software version was upgraded and that you are retaining all electronic data as of June 1, 2016. You also committed to upgrade UV SP-502 and to appropriately control access to data for this instrument. In addition, you provided the revised procedure, *Procedure on Testing Records* (QC Standard 3-C-017), which stipulates, “All the data generated from any analytical devices should be kept as records.” However, your response is inadequate. You have not conducted a retrospective review to determine how your failure to maintain complete records affected the quality of your drugs. Moreover, you have not shown how your revised laboratory procedures prevent the deletion, manipulation, or exclusion of data from the records relied upon for batch release and other quality review decisions.

1/6/2017	Japan	*Sato Yakuhin Kogyo Co Ltd*	**2. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).** Your analysts told our investigator that, until June 1, 2016, they were permitted to perform repeat testing without scientific justification or documentation. They also told our investigator that they were not required to maintain the data from the original results when performing investigations of system suitability failures, suspected errors, or out-of-trend results. Our investigator reviewed records of your investigations for a two-year period and found that you recorded only two minor deviations in the production area and no out-of-specification investigations. In your response you stated, "The analysts will not make the decision to perform re-analysis at their discretion and the investigation shall be conducted on the initial failure and the testing results shall be verified." In addition, you stated that you will revise your procedure (*Procedure on Unexpected Testing Results (OOT),* QC Standard 3-C-006) to require that records be retained. However, you failed to describe the role of the quality unit in this procedure. Include this procedure as a part of your response to this letter. For more information about handling failing, out-of-specification, out-of-trend, or other unexpected results and documentation of your investigations, please see two FDA guidance for industry documents:
1/6/2017	Japan	*Sato Yakuhin Kogyo 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.
1/6/2017	China	*Suzhou Pharmaceutical Technology Co Ltd*	**1. Failure to transfer all quality or regulatory information received from the API manufacturer to your customers.** You omitted the name and address of the original API manufacturer on the certificates of analysis (CoA) you issued to your customers, and did not include copies of the original batch certificate. For multiple API, you generated CoA by copying and pasting analytical results from the original API manufacturer, replacing the manufacturer's information with your letterhead, then issuing these CoA to your customers. You omitted critical information including the original manufacturers' names and addresses and the names, addresses, and telephone numbers of laboratories that performed the testing.

			Customers and regulators rely on CoA for information about the quality and sourcing of drugs and their components. Omitting information from CoA compromises supply-chain accountability and traceability, and may put consumers at risk.
1/6/2017	China	*Ningbo Zhixin Bird Clean-Care Product Company Ltd*	**1. Your firm's quality control unit failed to review and approve all drug product production and control records, including those for packaging and labeling, to determine compliance with all established, approved written procedures before a batch is released or distributed (21 CFR 211.192).** Your firm's Quality Control Unit (QCU) failed to review and approve drug product production and control records. For example, your QCU did not identify discrepancies between your batch production records and your product labeling for the type and concentration of active ingredient in your **(b)(4)** gel and lotion products.
1/6/2017	China	*Ningbo Zhixin Bird Clean-Care Product Company Ltd*	**3. Your firm failed to establish and follow an adequate written testing program designed to assess the stability characteristics of drug products and to use results of such stability testing to determine appropriate storage conditions and expiration dates (21 CFR 211.166(a)).** You did not retain any samples to test and evaluate product stability and had no data to support the **(b)(4)** shelf life claim of your products.
1/13/2017	Italy	*FACTA Farnaceutici S.p.A.*	**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)).** For multiple sterile drug product lots, your original data showed failing results, but data you reported showed passing results. This discrepancy was not adequately explained. You stored original data in an "unofficial" and uncontrolled electronic spreadsheet on a shared computer network drive. Your analyst stated that original data was first recorded in this "unofficial" spreadsheet and transcribed later to an "official" form. This spreadsheet showed failing results above the limits you established in your procedure, PCH 035 *Visible Particle Determination* in use prior to September 1, 2014. For example, the spreadsheet showed glass, metal, fibers, and other particles that were out-of-specification (OOS) in **(b)(4)** finished code **(b)(4)**, lot **(b)(4)**. The spreadsheet showed five glass particulates (100-200 microns) in the **(b)(4)** sample. However, your reported data stated zero glass particulates.

			According to your analyst, a second reviewer may have determined that the number and type of particles originally recorded for glass, metal, fibers, and other particles were incorrect. However, no documentation showed that a second reviewer evaluated the results. According to your response, the procedure PCH 035 "was for internal information purposes only" and the analyst did not follow this procedure. All results were "preliminary" until a second chemist "with much more experience" reviewed them. When "an experienced analyst" tested the retained samples, passing results were obtained and recorded. Your response is inadequate because you did not include details to support your assertion that the original analyst lacked the necessary experience, nor did you provide supporting documentation for the secondary review. In response to this letter: • Evaluate training in your quality control laboratory, specifically for your procedure PCH 035. • Specify how you assign tasks so that qualified and experienced personnel review and document critical test results. • Comprehensively evaluate test samplesperformed by other analysts from January to September, 2014, when the unofficial spreadsheet was in use. • Evaluate the extent of uncontrolled spreadsheets at your facility. • Indicate which visual inspection procedure was utilized for release of drug products to the U.S. prior to implementation of procedure PCH 047 on September 1, 2014
1/13/2017	Italy	*FACTA Farnaceutici S.p.A.*	**2. 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 materials, labeling, and drug products (21 CFR 211.22(a)).** Our investigator observed many copies of uncontrolled blank and partially-completed CGMP forms (e.g., environmental monitoring recordings, OOS forms, water testing sheets, and clean room entry and exit logs) without any accountability or oversight of your quality unit. For example, a supervisor said he photocopied a blank OOS form and transcribed the information because he had made mistakes in the original document. Although your procedures required correcting mistakes on the original form, he made a new copy of a blank OOS form and rewrote the data. Our investigator documented that your employees used paper shredders to destroy critical laboratory and production records without the appropriate controls and procedures. Shredded documents

			included High Performance Liquid Chromatography (HPLC) chromatograms and a partially-completed OOS form. Your quality unit is responsible for reviewing and approving these critical production records to ensure that, if an error occurred, a comprehensive investigation is conducted. Uncontrolled destruction of CGMP records also raises concerns, because retention of CGMP records must follow established procedures approved by your quality unit. These findings raise questions about the effectiveness of your quality unit and the integrity and accuracy of your CGMP records. In your response, you stated that you "do not consider this OOS form to be an official document until it is initiated into the QA system" and that "OOS forms…are not intended to collect raw data… [but] are used to create the narrative which contains transcriptions of the details in order to described the event." Your response is inadequate. For more information about proper handling of OOS results and documenting your investigations, refer to the FDA guidance for industry *Investigating Out-of Specification (OOS) Test Results for Pharmaceutical Production* at www.fda.gov/downloads/Drugs/.../.../ucm070287.pdf. In response to this letter: • Evaluate all OOS test reports from January 2014 to January 2016 associated with the release of your products. Document the associated HPLC and gas chromatography data. Include your detailed action plan and schedule to fully investigate the extent of your deficient handling of OOS test results
1/13/2017	Italy	*FACTA Farnaceutici S.p.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 manufacturing and laboratory 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.

1/18/2017	India	*CTX Lifesciences Private Ltd.*	**2. Failure of your quality unit to exercise its responsibility to ensure the API manufactured at your facility are in compliance with CGMP, and meet established specifications for quality and purity.** Our investigator found that on June 30, 2014, batches **(b)(4)** and **(b)(4)** of **(b)(4)** United States Pharmacopeia (USP) API were released without testing by ultraviolet (UV) spectrometry for identity or **(b)(4)** content, because the UV was out of order. Your change control form stated, "Batches shall be released on conditional basis and as soon as UV maintenance issue rectified analysis shall be performed for identification and **(b)(4)** content." Your June 30, 2014 certificate of analysis states "UV & **(b)(4)** result shall be updated." However, our inspection found that identity and **(b)(4)** testing was never performed. It is unacceptable to distribute batches without conducting the required quality control tests to assure your API meets its quality attributes. In your response, you state that your UV spectrophotometer broke down. Your quality department felt the quality of the released batches was adequate because other required release tests were passed, high performance liquid chromatography (HPLC) testing was done, and trend data for **(b)(4)** was satisfactory. Your response is inadequate. In response to this letter, provide: • A detailed summary of all batches released without all required testing. Identify the tests you did not perform, and how you plan to ensure that released products meet specifications. • A list of the improvements you have made to your batch release process to ensure that you do not release future batches before all required tests are completed. • Improvements made to your existing system to ensure required equipment is available to conduct testing for batch release. • A summary of your method validation study to support the use of HPLC in lieu of the compendial method for determining identity.
1/26/2017	China	*Zhejiang Bangli Medical Products Co., Ltd*	**5. Your firm delayed, denied, or limited an inspection, or refused to permit the FDA inspection.** You limited FDA's inspection because you refused to provide FDA with records related to suppliers of components and products that you repackage at your facility.

			Although you provided the names of two of your suppliers, you refused to provide documentation to show the identities of components or products you obtained from these suppliers, or whether these suppliers performed appropriate release testing on the materials before you received them. Refusing to provide records requested by the FDA investigator that FDA has authority to inspect is considered limiting an inspection. When an owner, operator, or agent delays, denies, limits, or refuses an inspection, the drugs may be deemed adulterated under section 501(j) of the FD&C Act. See FDA's guidance, *Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection*, available online at www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM360484.pdf
1/26/2017	USA	*Humco Holding Group Inc*	**1. Your firm failed to establish 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)).** **Failure to Validate Drug Manufacturing Processes** **You have not validated the manufacturing processes for (b)(4) drug products you manufacture,** including, but not limited to, Lugol's Solution, Shohl's Solution, Potassium Chloride, and **(b)(4). You were previously cited for failing to validate manufacturing processes at the conclusion of our 2012 inspection of your facility.** **Your July 21, 2015 response states that you have traditionally validated your processes through** "historical review" and **(b)(4) product reviews.** You have not shown how these "historical reviews" support the validity of your manufacturing processes, nor have you pr**ovided documented retrospective or continuous verification activities for approximately (b)(4) of your drug manufacturing processes.** **In response to this letter provide details, including timeframes, on how you will validate manufacturing processes for all of your drugs.** FDA's guidance document on **Process Validation: General Principles and Practices may help you understand our current thinking on approaches to process validation. The guidance is available at UCM070336.pdfhttp://www.fda.gov/downloads/Drugs/Guidances/.** **Failure to Validate Purified Water System**

			You have not validated the purified water system that you have been using for at least three years to manufacture products that are ingested, inhaled, or applied topically. Some of these products are indicated to treat irritated tissues or wounds that may be more vulnerable to infection. Although you partially documented the results of validation activities you conducted in 2013 following relocation of your water system in a report dated April 28, 2014, your report does not include the results of microbiological tests, (b)(4) tests, or (b)(4) tests that you performed during your validation activities. The same report states the microbial load of your purified water system steadily increased following the (b)(4)-day validation period in May, 2013, and that additional maintenance activity was required to address the increased microbiological load. You failed to validate the purified water system after completing the required maintenance activities. **Additionally, on multiple occasions, components of the water system failed. At least one of these incidents resulted in the water system operating without (b)(4). For example, on February 26, 2015, the (b)(4) of the (b)(4) failed and the system was(b)(4) until the (b)(4) was rebuilt on March 4, 2015. You did not conduct an investigation to evaluate the effects of this or other failures on the quality of the products you manufactured and released for distribution during this time.** **Your August 31, 2015, response states you have contracted with a third party company to conduct a full validation of your water system. In response to this letter, provide the validation protocol and the final validation report**
2/14/2017	China	Chongqing Pharma Research Institute Co., Ltd	**Failure to maintain complete data derived from all laboratory tests conducted to ensure compliance with established specifications and standards.** **Our investigators reviewed audit trails from various stand-alone pieces of laboratory equipment you used to perform high performance liquid chromatography (HPLC) and gas chromatography (GC) analyses. Our investigators found that you had deleted entire chromatographic sequences and individual injections from your stand-alone computers.** **For example, your written system suitability procedure for (b)(4) requires only six injections. However, your records showed that on January 5, 2016, you injected seven system suitability standards when performing system suitability for batch #(b)(4). The audit trail showed that the final standard injection was permanently deleted** from the instrument's computer. Your analyst **told our investigator that it is laboratory practice to perform more injections than are required by**

			the procedure, and then delete any undesirable result to ensure passing system suitability results. Without providing scientific justification, you repeated analyses until you obtained acceptable results. You failed to investigate original out-of-specification or otherwise undesirable test results, and you only documented passing test results in logbooks and preparation notebooks. You relied on these manipulated test results and incomplete records to support batch release decisions.
2/14/2017	China	Chongqing Pharma Research Institute 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.**
2/17/2017	USA	Morton Grove PHarmaceuticals (Wockhardt)	**2. 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 records showed that multiple in-process and finished batches of fluticasone propionate nasal spray USP failed assay for (b)(4). For example, in-process batches (b)(4) and (b)(4) initially failed release criteria for (b)(4), as did their respective finished product batches (b)(4) and (b)(4).** **When our investigator reviewed your investigation into these initial (b)(4) failures, we found that your investigation protocol (b)(4) assigned the cause of the failures to analyst error if repeat tests delivered passing results. The original results were invalidated without scientific justification under the protocol and only re-test results were reported as part of batch release decisions. The original results were not reported or considered in evaluating the quality of your drugs for release.**

2/17/2017	USA	Morton Grove PHarmaceuticals (Wockhardt)	**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)).** **Our investigators observed that information technology (IT) staff at your facility share usernames and passwords to access your electronic storage system for (b)(4) data. Your IT staff can delete or change directories and files without identifying individuals making changes. After a previous inspection in which FDA observed similar deficiencies, you committed to eliminate these and other data integrity vulnerabilities.** **In response to this letter:** • **Provide your detailed plan to ensure that each current and future employee will have a unique username and password to allow traceability of changes to electronic data back to specific authorized personnel.** • **Describe the specific changes made to your software and electronic systems to ensure the effectiveness of your corrective actions.** • **Include a detailed description of the role of your quality unit to ensure that the corrections are appropriately implemented and sustainable.**
2/17/2017	USA	Morton Grove PHarmaceuticals (Wockhardt)	**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 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.**
2/24/2017	China	Jinan Jinda Pharmaceutical Chemistry Co. Ltd.	**1. Failure of your quality unit to exercise its responsibility to ensure the API manufactured at your facility are in compliance with CGMP, and meet established specifications for quality and purity.**

			Your quality control laboratory disregarded multiple out-of-specification (OOS) impurity results without justification. For example, on September 22, 2015, you encountered an OOS unknown impurity peak during high performance liquid chromatography (HPLC) testing of (b)(4) 36-month stability batch (b)(4). You terminated the analysis. Testing of a new sample also showed the OOS impurity peak. The chromatogram was then manually rescaled, which hid the presence of this peak. Your laboratory set the integration parameters to omit this peak from integration. Because the peak was omitted, the quality unit was not provided with full information to evaluate whether the stability batch, and potentially other marketed batches, continued to meet quality standards. In addition, your audit trail showed that from July 1 to 2, 2015, you performed seven sample injections of (b)(4) 60-month stability batch (b)(4) to test for impurities using HPLC. You permanently deleted the first five sample injections. You then renamed the last two injections and reported that they met specifications. Your quality unit failed to identify and address these serious data manipulations. We acknowledge your commitment to hire a third-party consultant to rebuild your quality system by July 2018. However, your response is inadequate. You lack a detailed interim plan to mitigate risk while you work to resolve deficiencies and implement a robust quality system by mid-2018
2/24/2017	China	Jinan Jinda Pharmaceutical Chemistry Co. Ltd.	2. Failure to adequately investigate out-of-specification results. Your firm did not initiate investigations into failing results as required by your standard operating procedure (SOP) ZL/SOP/ZK/00405. On October 5, 2015, when you encountered an OOS value for an unknown impurity peak through HPLC testing of (b)(4) API 12-month stability batch (b)(4), you prepared and tested new aliquots. You did not investigate the failing result. We acknowledge your commitment to hire a third-party consultant to identify and evaluate all batches compromised by data integrity lapses. However, you failed to perform a comprehensive retrospective evaluation to determine whether appropriate corrective actions and preventive actions were identified and implemented for each OOS result obtained. Also, your retrospective review does not appear to address whether data integrity breaches occurred when using laboratory methods and systems that do not generate electronic data. For more information about handling OOS results and documentation of your investigations, please refer to the FDA guidance for industry publication Investigating Out-of-Specification

			(OOS) Test Results for Pharmaceutical Production available online at http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070287.pdf.
2/24/2017	China	Jinan Jinda Pharmaceutical Chemistry Co. Ltd.	**3. 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 your staff from altering or deleting electronic data. Analysts manipulated and deleted audit trails. You lacked adequate controls for all HPLC, gas chromatography, and ultra-violet systems.** **For example, an analyst deleted audit trails in your gas chromatography equipment #YQ-07-10 from September 15, 2015, through April 24, 2016, and permanently deleted audit trails from November 6 to 13, 2015. In addition, our investigator observed that your quality control manager and quality control deputy manager had full administrative rights on all of your computerized systems, which allows them to manipulate data and turn off audit trails.** **We acknowledge that you commit 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 software features are insufficient to achieve CGMP compliance. These steps will be effective only if you implement 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.** **Your response states that your SOP for electronic data management specifies that only information technology staff will have full administrator rights. However, you did not specify which information technology personnel will have these administrator rights. In addition, this SOP became effective on May 9, 2016, prior to the FDA inspection. However, your quality control management still had full administrative rights to all computerized systems during our inspection from May 30 to June 1, 2016.**
2/24/2017	China	Jinan Jinda Pharmaceutical Chemistry 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 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 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 imp**rovements) designed to ensure the integrity of your company's data. • **A status report for any of the above activities already underway or completed.**

2/24/2017	India	Megafine Pharma (P) Limited	**3. Failure to ensure all specifications and test procedures are scientifically sound and appropriate to ensure that your drugs conform to established standards of quality and/or purity.** **Your test methods were not capable of demonstrating the purity of your drugs. Specifically, (b)(4) batches (b)(4)and (b)(4) displayed an unidentified peak, or shoulder, overlapping the principal peak. You neither integrated nor investigated this potential impurity. In addition, analysts reprocessed data up to 12 times, and only included the final result in the report for review by Quality Assurance. Your Deputy Manager, Quality Control stated that it is** common practice to "play with parameters" to get the proper integration. **Your firm reviewed (b)(4) batches and determined they all had a similar shoulder, which you concluded was a distortion of the principal peak. However, you did not provide sufficient data to support this determination.** **In response to this letter, identify the unknown peak(s), with data to support your identification including mass spectrometry results and a risk assessment for the impact on drugs in the U.S. market.**
2/24/2017	India	Megafine Pharma (P) Limited	**4. Failure to control the issuance, revision, superseding, and withdrawal of all documents by maintaining revision histories.** **Your quality assurance unit provides analysts with blank controlled document forms that have already been approved and signed. Investigators observed torn, partially complete QA-signed calibration records in the trash and observed QA staff shredding documents without recording the identity or the reason for shredding the documents.** **In your response, you acknowledged the importance of maintaining complete reconciliation details for document control and revised your document control procedures. However, your response is inadequate as you did not provide a risk assessment for the impact on drugs in the U.S. market.**
2/24/2017	India	Megafine Pharma (P) 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.**

			In response to this letter, provide the following. **A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting.** **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.** **Reference Megafine Nashik Warning Letter 320-16-13 for additional details to provide on data integrity remediation**
3/2/2017	India	Badrivishal Chemicals & Pharmaceuticals	**2. Failure of your quality unit to prepare, review, and approve documents related to the manufacturing of API.** **On August 16, 2016, our investigators found a large number of trash bags behind a building on your property. The trash bags contained torn original laboratory and production records, such as analytical test reports, (b)(4) water testing reports, and sample notebooks. The information on these discarded, torn documents did not match the official records. Your quality unit did not investigate these discrepancies. On August 18, 2016, when our investigators revisited the area where the trash bags had been, they found that the documents had been removed from the site. These findings indicate that your quality unit is not exercising its responsibilities.** In your response, you admitted that a "gap exist[ed] in the Quality Assurance department" **concerning document control. You stated that you implemented enhanced document controls and trained employees to complete records contemporaneously.** **However, your response is inadequate because you did not provide any details of your corrective and preventive actions. You also did not address any changes made to ensure that discrepancies are properly investigated. Furthermore, removal of the trash bags containing additional torn documents prevented our investigators from examining these documents. It also prevented your firm from performing a global reconciliation of all torn documents with their official versions.** **In response to this letter, provide:** • **details and a summary of the system that you established for reviewing CGMP documents to ensure documents are tracked and disposed of properly** • **your procedure for handling discrepancies and ensuring ongoing quality unit oversigh**

3/2/2017	India	Badrivishal Chemicals & Pharmaceuticals	**3. Failure to verify the suitability of analytical methods.** **You failed to ensure that the methods used by your contract testing laboratory, (b)(4), have been verified as suitable for their intended use. It is your responsibility to use a qualified contract testing laboratory that produces accurate and reliable results.** **Your firm contracts with (b)(4) for release testing. Your quality assurance agreement with (b)(4) does not specify method validation responsibilities. During the inspection, our investigators requested the method verifications for the residual solvent, impurity, and microbiological tests performed by (b)(4). You stated that the requested documents were located at (b)(4) and that you would retrieve them within 15 days.** **In your response, you did not provide the requested documents from (b)(4), but instead provided draft protocols for the residual solvent, impurity, and microbiological testing. You stated that these protocols would be verified by December 15, 2016, but it is unclear which company would perform the verification experiments.** **Your response is inadequate. In response to this letter, clarify which company performed the verification. Also, provide the results of an internal review of all the other test methods for your drugs to determine the need for method verification or method validation, as appropriate. If verification or validation is needed, provide a timeline for completion and the company that will perform the verification or validation**
3/2/2017	India	Badrivishal Chemicals & Pharmaceuticals	**4. Failure to adequately investigate critical deviations.** **(b)(4) sent you impurity testing chromatograms that contained unexplained discrepancies in run times as well as aborted runs and reprocessing of data for at least six batches over at least three months. You did not document or investigate these discrepancies.** **In your response, you stated that** your firm "did not have **expertise to interpret, review the outcome of the HPLC chromatograms as to the standards of regulatory agencies**." You **proposed having (b)(4)** retest the six batches in the presence of an "expert representative" from Badrivishal to ensure "good chromatographic practices." Moreover, your quality assurance **agreement with (b)(4) does not specify communication of out-of-specification results or discrepancies.**

			Your response is inadequate because it lacks details. In response to this letter, describe the corrective and preventive actions you have taken, such as on-site audits and method validations or verifications, that show (b)(4) is now qualified to test your drugs. Also, provide proof that your "expert representative" has sufficient education, training, and experience to perform the **indicated function. In addition**, provide details about your proposed "outside laboratory data review unit" and laboratory review training content to show they can achieve their **intended quality control unit oversight purpose.** **For further reference regarding OOS test results, see the FDA guidance for industry, Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production at http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070287.pdf.**
3/2/2017	India	Badrivishal Chemicals & Pharmaceuticals	**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. 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. Des**cribe 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 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.**
3/2/2017	China	Lumis Global Pharmaceuticals Co., Ltds.	**1. Failure to transfer all quality or regulatory information received from the API manufacturer to your customers.** **You omitted the name and address of the original API manufacturers on the certificates of analysis (COA) you issued to your customers, and did not include copies of the original batch certificate.** **For multiple API, you generated COA by copying and pasting analytical results from the original** API manufacturers, replacing the manufacturers' information with your letterhead, then issuing **these COA to your customers. You omitted critical information, including the original** manufacturers' names and addresses and the names, addresses, and telephone numbers of **laboratories that performed the testing.** **Customers and regulators rely on COA for information about the quality and sourcing of drugs and their components. Omitting information from COA compromises supply-chain accountability and traceability, and may put consumers at risk.**

3/2/2017	China	Lumis Global Pharmaceuticals Co., Ltds.	**3. Failure of your quality unit to exercise its responsibility to ensure the API relabeled at your facility are in compliance with CGMP.** **Your relabeling operation was not documented adequately. You did not document the time and date of relabeling operations, nor the employee who conducted relabeling operations for API you distributed. You did not sign and date records at the same time the activites were performed.**
3/10/2017	India	USV Limited	**3. 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, during inspection of the sterile manufacturing and QC microbiology areas, our investigators observed:** **A. Deletion of at least six (b)(4) and (b)(4) tests in the audit trails for two instruments used to test sterile (b)(4). Your systems allowed operators to delete files. You had no procedure to control this practice or to ensure a backup file was maintained. When you reviewed the audit trail data further, you identified a total of 25 deleted (b)(4) test results. In your response, you** state that the production staff now only have "view and print" privileges. However, your response **is inadequate because it lacks details of how appropriate oversight will be exercised over data backup to ensure it is appropriately retained.** **B. No restricted access to the microbial identification instrument. Further, you lacked restricted access to the external hard drive used for backup of this instrument. All users could delete or modify files. In your response, you commit to limit access to the system and external hard drive. However, your response is inadequate because you did not provide a retrospective risk assessment of the impact and scope of inadequate system controls at your firm**
3/10/2017	India	USV Limited	**4. Your firm failed to ensure that laboratory records included complete data derived from all tests necessary to assure compliance with established specifications and standards (21 CFR 211.194(a)).** **(b)(4) failed identity testing. You accepted a passing retest result without any investigation of the failed result.**

			In your response, you state that you attempted to conduct a retrospective investigation of the analysis which occurred more than a year earlier, and tentatively concluded that the out-of-specification (OOS) result might have been caused by analyst error. Also, your investigation recommends replacement of the polarimeter on which the OOS result was obtained. Your response did not include a commitment to revisit the adequacy of your OOS procedures. When an OOS result is obtained, initiation of a prompt laboratory investigation is critical. In addition, you must provide all data obtained during testing to the quality unit for batch record review. If the laboratory invalidates an OOS result, it is essential that the batch record include the relevant investigation. Only a scientifically sound and conclusive investigation can justify the exclusion of an OOS result from the final certificate of analysis. For more information about the proper handling of OOS results and documentation of your investigations, see FDA's guidance document, Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production, at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070287.pdf
3/10/2017	India	USV 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 retrospective investigation into the extent of the inaccuracies in data records and reporting. B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analysis 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.

			Reference USV Private Limited, Mumbai, Warning Letter 320-14-03 for additional details to provide on data integrity remediation.
3/16/2017	Singapore	Opto-Pharm Pvt Ltd	**3. Your firm failed to ensure that your drug products bore an expiration date that was supported by appropriate stability testing (21 CFR 211.137(a)).** **Your firm failed to conduct stability studies for Buffered Saline and (b)(4) ophthalmic solutions produced in 2014 and 2015. Furthermore, at the time of the inspection, you could not provide raw data to support test results from stability studies you conducted for other products.** **Your failure to conduct stability studies and lack of data supporting expiration dates compromises your ability to detect quality problems with marketed ophthalmic products. Without stability data, you cannot assure the quality of your products throughout their labeled shelf lives. In addition, you have received multiple customer complaints of leaking ophthalmic containers, which also calls into question your ability to maintain sterility of your ophthalmic products throughout their labeled expiration dates.** **In your response, you commit to conducting stability studies on your Buffered Saline and (b)(4) products. However, you did not provide the raw stability data for other ophthalmic products.** **In response to this letter, provide the following:** • **raw stability data for all of your ophthalmic products manufactured for the U.S. market within expiry** • **antimicrobial effectiveness testing that evaluates whether your products contain a suitable preservative system** • an evaluation of whether your products' preservative systems remain effective at their **expiration dates**
4/3/2017	India	Mylan Laboratories Limited	**1. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).** **From January 1 to June 30, 2016, your firm invalidated 101 out of 139 (about 72 percent) initial out-of-specification (OOS) assay results without sufficient investigation to determine the root cause of the initial failure.**

			For example, you opened laboratory investigation report PR 908027 for an initial OOS six-month stability assay result of (b)(4) percent (specification (b)(4)–(b)(4) percent) for (b)(4) mg tablets, lot (b)(4). You invalidated the initial failing result without adequate investigation, performed re-testing, and then reported the (b)(4) results of these replicate re-tests ((b)(4) percent). Your investigation did not reach an assignable cause, nor did you take appropriate corrective actions and preventive actions to ensure that the significant "analytical bias" to which you ultimately attributed the initial failure would not affect other analytical work in your laboratory. In your response, you state that laboratory decisions are to be made on the basis of scientific evaluation, and that they are to determine whether OOS laboratory results are the result of the laboratory process or the manufacturing process. However, in the example above, your investigation assumed "analytical bias" in your laboratory process but failed to determine how this apparently significant error in your analyses could be eliminated or mitigated in the future. Your response is inadequate because you failed to implement a corrective action and preventive action (CAPA) plan to mitigate errors that you attribute to laboratory process. Further, you did not include these improperly invalidated OOS results in your analysis of laboratory investigation trends. According to your Laboratory Investigation Report procedure MLLNSK-SOP-QA-GMP-0138, version 6, only "confirmed" root causes are to be identified and trended in laboratory investigation reports. Because your laboratory investigations frequently invalidate initial failures without cause, your laboratory trending excludes a large proportion of data that would otherwise alert you to problems in your laboratory system. Failure to identify trends in OOS investigations is a repeat observation from the previous FDA inspection, March 19 to 26, 2015. In response to this letter, conduct and provide the results of a trend analysis of all your OOS results that includes both "confirmed" root causes and the initial OOS results that you have previously excluded as invalid without assignable root causes. For each invalidated result, indicate the product tested, date of analysis, type of analysis, purpose of the test, original result, retest results, and your unconfirmed assignable root cause. Revise and provide your updated Laboratory Investigation Report procedure. Specify how your revised procedure ensures that all OOS investigations are included in your trending.
4/3/2017	India	Mylan Laboratories Limited	2. Your firm failed to establish an adequate quality control unit with the authority 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 unit failed to monitor and investigate error signals generated by the computerized systems that you use for high performance liquid chromatography and gas chromatography.

			These signals indicated the loss or deletion of original CGMP analytical data. However, your quality unit did not comprehensively address the error signals or determine the scope or impact of lost or deleted data until after these problems were reviewed during our inspection. For example, our investigator reviewed audit trails from August 2016 assay testing on (b)(4) batch (b)(4) and dissolution testing for (b)(4) tablets batch (b)(4). The audit trail for these tests included the message, "deleted result set," but neither of these two incidents were recorded in the analytical packages for these batches of drug products, nor were they reviewed or investigated by the quality unit. In addition, during the inspection, our investigator observed that your Empower 3 system audit trail displayed many instances of a "Project Integrity Failed" message, which indicates that injections were missing from the results of analytical testing. For example, in (b)(4) analysis for (b)(4) tablets batch (b)(4) conducted on June 20, 2016, no chromatogram was rendered for the initial run of testing. The data package for this testing clearly shows that the initial run is missing, but your quality unit did not investigate the incident. Although you showed our investigator isolated examples of interrupted, missing, deleted, and lost data for which you had opened investigations, you reached similar conclusions in many of these investigations regarding the root cause of your loss of data integrity but failed to take appropriate corrective action and preventive action in response. Our investigator observed that you attributed numerous incidents to power interruptions, connectivity problems (disconnection of the Ethernet or power cord), and instrument malfunctions. You could not explain why these events occurred with frequency in your laboratory, nor had you undertaken a comprehensive investigation into the problem or sought to correct it and prevent its recurrence. In your written response dated February 17, 2017, you identified seven samples from a single week of testing for which original results were lost following data acquisition interruptions at the time of initial analysis. Instead of uniformly initiating an investigation into the root cause of each interruption when it occurred or even documenting it for later review and investigation by the quality unit, you explained in your response that you retested the samples immediately after the interruptions. Your response is inadequate because you have not identified and investigated each instance in which data acquisition was interrupted. While you assessed a limited number of error codes from a seven day period, you did not evaluate the effects of other error codes identified in your simulation exercise report on the reliability, accuracy, or completeness of the data you use to

			evaluate the quality of your drugs. Although you have submitted multiple responses, you have not yet: • shown exactly how widespread these problems are; • evaluated their full effects on the quality of your drugs; • explained why these events occurred with frequency in your laboratory; • or demonstrated how you will ensure that your quality unit reviews, investigates, and acts upon codes that affect the reliability of your CGMP data. In response to this letter, provide your validation of laboratory instrument error codes. Identify the specific codes that may impact product quality and the reliability of CGMP data, and provide your procedures to demonstrate how your quality unit will review, investigate, and respond to these specific codes.
4/3/2017	India	Mylan Laboratories 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: 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 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 the testing data integrity deficiencies. 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:

			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.
4/13/2017	India	Divi's Laboratories Ltd (Unit III)	1. Failure to ensure that test procedures are scientifically sound and appropriate to ensure that your API conform to established standards of quality and/or purity. Our investigators observed that the software you use to conduct high performance liquid chromatography (HPLC) analyses of API for unknown impurities is configured to permit extensive use of the "inhibit integration" function without scientific justification. For example, our investigator reviewed the integration parameters you used for HPLC identification of impurities in release testing for (b)(4). These parameters demonstrated that your software was set to inhibit peak integration at four different time periods throughout the analysis. Similarly, in the impurities release testing you performed for (b)(4), your HPLC parameters were set to inhibit integration at four different time periods throughout the analysis. Inhibiting integration at various points during release testing for commercial batches is not scientifically justified. It can mask identification and quantitation of impurities in your API, which may result in releasing API that do not conform to specifications. In your response, you stated that you have made several corrective actions, including updating your procedure Peak Integration Techniques for Chromatography to include controls on the use of inhibit integration events. However, your response is inadequate in that it did not provide specific corrective action or supportive documentation for each drug's chromatographic processing parameters, including API not cited on Form FDA 483. You have not shown how you will ensure that your test methods are appropriate to determine whether your API conform to established standards and specifications. Consequently, the summary data you provided does not demonstrate that previously released lots do not contain excessive levels of unknown impurities. In response to this letter, provide updated analyses of all lots within expiry that take into account any changes to specific test methods and chromatographic parameters.

4/13/2017	India	Divi's Laboratories Ltd (Unit III)	**2. Failure to prevent unauthorized access or changes to data and failure to provide adequate controls to prevent manipulation and omission of data.** **During the inspection, our investigators discovered a lack of basic laboratory controls to prevent changes to and deletions from your firm's electronically-stored data in laboratories where you conduct CGMP activities. Specifically, audit trail functionality for some systems you used to conduct CGMP operations was enabled only the day before the inspection, and there were no quality unit procedures in place to review and evaluate the audit trail data. For example, you used standalone HPLC (2-RD HP/SM/32) to conduct analyses for Drug Master File (DMF) submissions and investigations, such as characterization of a starting material for your (b)(4) DMF. You also used uncontrolled systems to conduct out-of-specification (OOS) investigations for in-process materials used to manufacture (b)(4) API.** **We acknowledge the corrective actions described in your response, including enabling audit trail functionality for all chromatographic systems in your laboratories, as well as procedural updates that require review and evaluation of the data generated by these systems. However, your response did 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 controls are documented, implemented, and followed.**
4/13/2017	India	Divi's Laboratories Ltd (Unit III)	**3. Limiting access to or copying of records** **Your firm limited access to or copying of records that our investigators were entitled to inspect. For example, our investigators requested records of your audit trail data from all chromatographic systems used to test drugs for the U.S. market at your facility. The files you ultimately provided (in the form of Excel spreadsheets rather than direct exports from your chromatographic software) were not the original records or true copies, and showed signs of manipulation. The records you did provide contained highlighting, used inconsistent date formats, and lacked timestamp data; these features are inconsistent with original data directly exported from chromatographic testing software.** **Our investigators and their supervisor explained at least twice that the data you provided was not representative of actual audit trail data from the chromatographic systems, and requested that you provide the original, unmodified records. Your firm stated, without reasonable explanation, that you could not provide the requested audit trail records. When our investigators explained that your failure to provide the requested records would be documented as a refusal, you acknowledged the refusal.**

			Our investigators documented other instances in which your firm limited the inspection by providing some, but not all, of the records requested by the FDA investigator that FDA had authority to inspect. At multiple times during the inspection, FDA requested records of CGMP activities performed in your R&D laboratories at the behest of your quality unit. However, you limited the inspection by providing only a subset of the requested records, and our investigators also found at least one of the requested records shredded in the trash. Finally, our investigators requested chromatograms to substantiate your claim that you had identified and quantitated the impurities in (b)(4), but you never provided the records that our investigators asked for to support your claim. When an owner, operator, or agent delays, denies, limits, or refuses an inspection, the drugs may be deemed adulterated under section 501(j) of the FD&C Act. See FDA's guidance document, Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection, at https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM360484.pdf.
4/13/2017	India	Divi's Laboratories Ltd (Unit III)	**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 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 i**mprovements) designed to ensure the integrity of your company's data. • **A status report for any of the above activities already underway or completed.**
4/20/2017	India	Sal Pharma	**1. Failure to transfer all quality or regulatory information received from the API manufacturer to your customers.** **You omitted the names and addresses of the original manufacturers of your API on certificates of analysis (COA) you issued to your customers. You generated your COA by replacing the** original manufacturers' information with your letterhead**.**

			During our inspection, we found that two of your suppliers were not registered with the FDA as drug manufacturers at the time of inspection. However, you shipped API from these firms to the United States, and declared on importation documents and the COA that you provided to your customers that you were the manufacturer. Your failure to declare the original manufacturers on your importation documents and COA provided to your customers enabled the entry of unregistered firms' products into the United States. **Customers and regulators rely on COA for information about the quality and source of drugs and their components. Omitting information from COA compromises supply-chain accountability and traceability, and may put consumers at risk.**
4/20/2017	USA	Huron Pharmaceuticals, Inc	**1. Failure to transfer all quality or regulatory information received from the API manufacturer to your customers.** **You repeatedly omitted the name and address of the original API manufacturer on the certificates of analysis (COA) you issued to your customers and did not include a copy of the original batch certificate. Additionally, your firm did not conduct a secondary review of COA you generated to ensure the information presented to your customers was accurate.** **Regulators and customers rely on the COA to provide accurate information about the quality and sourcing of drugs and their components. Omitting information on a COA compromises supply chain accountability and traceability, and may put consumers at risk.**
4/20/2017	USA	Huron Pharmaceuticals, Inc	**2. Failure to establish, document, and implement an effective system for managing quality.** **Your firm had no written procedures for supplier qualification, relabeling and repackaging operations, sampling, product release, stability, and document retention. You failed to maintain master production batch records for any of the API you repackaged and distributed. Additionally, you released API for distribution before you received and reviewed records from your drug testing lab.**
4/24/2017	China	Qinhuangdao Zizhu Pharmaceutical Co., Ltd	**1. Failure to prevent unauthorized access or changes to data, and failure to provide adequate controls to prevent omission of data.** **Our inspection found your laboratory systems lacked controls to prevent deletion of and alterations to electronic raw data.**

			a. Our review of audit trail data revealed that your analysts manipulated the date/time settings on your high performance liquid chromatography (HPLC) systems. During the inspection your analysts admitted to setting the clock back and repeating analyses for undocumented reasons. Initial sample results were overwritten or deleted, and unavailable for our investigators' review. Your firm reported only the passing results from repeat analyses. When test results are overwritten, the quality unit is presented with incomplete and inaccurate information about the quality of the drugs produced by your firm. b. Your quality control analysts used a shared login account to access HPLC systems. This shared account allowed analysts, without traceability, to change the date/time settings of the computer, to modify file names, and to delete original HPLC data. c. Seven out of (b)(4) of your firm's HPLC systems used for API testing had the audit trail feature disabled, although all (b)(4) had audit trail functionality. In your response, you acknowledged that you lacked effective measures to control data within your computerized systems. You committed to revising procedures for computerized systems, locking date/time settings, and enabling audit trail functions. However, you noted that you do not expect audit trail functions for all quality control instruments to be completely activated until September 30, 2017. In the interim, you committed to control measures, including updated software and logbooks. Your response is insufficient because it did not specify who holds administrative privileges on your computers, or address the significant pattern of data manipulation (e.g., deletions, date/time alterations) we observed at your facility. In response to this letter: • Clarify the specific user roles and detail the associated privileges for each laboratory system. • Provide an assessment of the effectiveness of your interim system controls. • Provide a commitment to conduct a similar future assessment of the effectiveness of all system controls expected to be in place by September 2017. • Explain the oversight role of the quality unit in implementing these improvements and ensuring they remain effective.

4/24/2017	China	Qinhuangdao Zizhu Pharmaceutical Co., Ltd	**2. Failure to maintain complete data derived from all laboratory tests conducted to ensure compliance with established specifications and standards.** **Our investigators found that you failed to maintain complete data for all laboratory analyses, and you relied on incomplete information to determine whether your drugs met established specifications.** **a.** HPLC chromatograms were deleted and not available for our investigators' review. In your response, you acknowledged that in January 2016, "some data was deleted" while the network edition of the chromatographic operating system software was installed. **b. Our investigators found a recurring practice of re-testing samples until acceptable results were obtained. For example, our investigators found repeat HPLC testing for related substances of crude (b)(4), batch (b)(4). The initial test displayed an unknown peak in the chromatogram. A different analyst retested the batch five days later: this analysis did not display the unknown peak. Only the results of the second analysis were used for batch disposition, without documented justification or investigation.** **Your response is inadequate because you did not include an assessment of the deleted data. Your response also lacked commitments to investigate the unknown peak in the chromatogram for crude (b)(4) batch (b)(4), and to discontinue repeating tests without justification and investigation.**
4/24/2017	China	Qinhuangdao Zizhu Pharmaceutical Co., Ltd	**3. Failure of your quality unit to exercise its responsibility to ensure the API manufactured at your facility are in compliance with CGMP, and meet established specifications for quality and purity.** **Our investigators found batch production records that contained blank or partially completed manufacturing data and lacked dates and signatures for verification. For example, in your (b)(4) plant, our investigators found a batch record for (b)(4) starting material, batch (b)(4), with sticky notes from the quality assurance department directing operators to enter manufacturing data, such as missing weight and volume entries. Also, your quality unit did not approve this batch record before the material was used in further manufacturing.** **All data in CGMP records must be complete and reliable so it can be evaluated by the quality unit during its batch review, as well as maintained for additional CGMP purposes.**

			Other documents—including cleaning records and equipment use logs—were also found to be partially completed, without dates and signatures for verification, or with pages or spaces intentionally left blank for documentation at a later time. **Your quality unit was aware of these unacceptable production department practices but did not ensure they were corrected.** **Your response is inadequate because the investigation you documented under Deviation No.: PC-002216-02 did not determine the impact of this missing manufacturing data on drug quality.** **In response to this letter:** • **Provide an update on your retrospective review of batch records for data integrity.** • **Explain how your firm conducted this assessment, including your method(s) to determine if documentation was contemporaneous.** • **Perform a comprehensive assessment of the sufficiency of the quality unit function at your facility.** • **Provide a comprehensive assessment of your deviation and investigation systems, and a CAPA that remediates this significantly deficient part of your operation. Include specific measures you are taking to ensure all deviations and atypical events are immediately documented and fully investigated.** **Our significant inspection findings indicate that your quality unit is not fully exercising its authority and/or responsibilities. You must provide your quality unit with appropriate authority and resources to carry out its responsibilities and consistently ensure drug quality**
4/24/2017	China	Qinhuangdao Zizhu Pharmaceutical 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 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 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. This includes a complete and comprehensive audit of all data from testing (including stability tests) used to support pending or approved applications.** • **A comprehensive retrospective evaluation of the nature of the testing and manufacturing data integrity deficiencies. We recommend 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.**

4/28/2017	India	Vikshara Trading & Investments Ltd.	**1. Your firm delayed FDA's attempts to schedule a pre-announced inspection.** **On April 25, 2016, FDA contacted your firm to facilitate the inspection process and ensure appropriate records and personnel would be available. On June 18, 2016, you notified FDA that** "factory workers and staff have gone on strike." On June 20, 2016, you **informed FDA that workers had blocked off the entrance of the facility as part of their protest. As a result of these communications FDA cancelled our pre-announced June 27, 2016, inspection.** **On July 15, 2016, you informed FDA that your employees remained on strike. On August 8, 2016, you provided purported evidence of the strike, including copies of employee resignation letters and a photograph of striking employees blocking the entrance to your facility.** **Despite your assertions that your employees were on strike, FDA obtained evidence that your firm actively manufactured numerous products, including at least (b)(4) batches of drugs, between July 11, 2016 and August 9, 2016.** **Your false statements to FDA regarding the purported strike at your fa**cility delayed FDA's **scheduling and conducting of a pre-announced inspection.**
4/28/2017	India	Vikshara Trading & Investments Ltd.	**2. Your firm limited FDA's inspection.** FDA entered your facility on October 18, 2016. Your firm's actions during this inspection **significantly hindered FDA from fully assessing your compliance with CGMP. For example, doors to the (b)(4) vessel room and packaging and labeling storage areas were locked, impeding reasonable access for the investigator to these areas, and limiting this inspection.**
4/28/2017	India	Vikshara Trading & Investments Ltd.	**3. Failure to provide records required to be readily available for authorized inspection (21 CFR 211.180(c)).** During the inspection on October 18, 2016, your firm did not provide batch records to our investigator. At the conclusion of the inspection, you stated that you would provide these records electronically within a matter of days. To date, FDA has not received any batch records.
5/8/2017	USA	Howard Phillips LLC	**6. 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).**

			Your firm lacked complete batch records for all drug products you manufacture. For example, you were unable to locate the batch record for a distributed batch of Tetracycline-ABC, lot 511110. Batch records that you were able to locate were incomplete, as they lacked critical information regarding bulk processing, filling, and packaging operations that establish whether the manufacturing process was followed and is reproducible. During our August 2016 inspection, we also noted your failure to adequately prepare and maintain batch records for drug products you manufacture
5/11/2017	China	Changzhou Jintan Qianyao Pharmaceutical Raw Materials	**2. Failure to have adequate written procedures for the receipt, identification, quarantine, storage, sampling, testing, handling, and approval or rejection of raw materials.** For example, when our investigator asked for a list of your critical raw materials and your sampling requirements, you told our investigator that you had no written procedures for testing and sampling incoming materials. Instead, you explained, your warehouse employees accounted for incoming raw material handling, sampling, and testing "in their heads."
5/11/2017	China	Changzhou Jintan Qianyao Pharmaceutical Raw Materials	**3. Failure to have laboratory control records that include complete data derived from all laboratory tests conducted to ensure compliance with established specifications and standards.** **For example, our investigator reviewed the audit trail from your assay testing for (b)(4) lot (b)(4), and found that you tested the same sample set three times over several days without documentation or investigation. You reported only the result of the third and final test for purposes of completing your certificate of analysis and releasing this batch of API.**
5/11/2017	China	Changzhou Jintan Qianyao Pharmaceutical Raw Materials	**4. Failure to prepare adequate batch production records and record the activities at the time they are performed.** **For example, our investigator found that your operator used process parameter values from previous batches of (b)(4) to complete new batch records when she was too tired to immediately record the data and had forgotten the values.**
5/17/2017	USA	Med-Pharmex, Inc.	**2. Your firm does not exercise appropriate controls over computer related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel [21 C.F.R. 211.68(b)]. For example:**

			A. Your "Processed By" dates and times listed on printed chromatograms do not always **show** the same "Processed By" dates and times listed on the system chromatograms. **B. Your data in the audit trails does not always show the same data listed on your printed chromatograms.** **Your response states you have not observed any test result data discrepancies between your printed versions of the test results. However, this does not address adequate electronic data controls to prevent inconsistencies between the printed and electronic data. Your responses for 2A and 2B above are not adequate in that your firm did not provide any corrective action addressing the assessment of all relevant data in the audit trails.** **C. Your firm enters data into (b)(4) files to complete plate assay calculations but they are not locked from editing once the file has been reviewed.** **Your response fails to include any corrective action to ensure that there is no further access or ability to save over test results in (b)(4) spreadsheets once reviewed and approved.** **D. Your firm did not give unique sample set names to different sequences of samples run on different instruments on the same day.** **Your response is not adequate. Your firm did not address the concern of the possibility of sample sets with the same name overwriting each other during the data backup process.**
5/17/2017	USA	Med-Pharmex, Inc.	**6. Your firm does not have laboratory records that include complete data derived from all tests necessary to assure compliance with established specifications and standards, including examinations and assays. [21 C.F.R. 211.194(a)].** **Specifically, on January 26, 2017, our investigator observed your microbiologist read (b)(4), (b)(4) for Tri-Otic Ointment, lots H6510 and H6514, using the antibiotic zone reader (instrument Asset (b)(4)). Our investigator verified your microbiologist recording the correct value as read from the plate reader; with a range of (b)(4) to (b)(4). Then our investigator copied the handwritten zone diameter test results taken at the time of testing for the (b)(4) and (b)(4)** zones of the standard series from the microbiologist's issued worksheet.

			Your procedure is to then enter the raw data into document number MIC-0066-13-01 titled "(b)(4)", Attachment 1. On the completed form, the (b)(4) test results for the (b)(4) zones were not the same as observed by our Investigator; the range was 11.4 to 15.1. Your firm used an Excel spreadsheet to calculate the potencies of Tri-Otic Ointment lots H610 and H6514 as (b)(4) and (b)(4), respectively. **Your response does not provide documentation of the January 26, 2017 handwritten zone diameter results for Tri-Otic Ointment (Lots H6510 and H6514), which you allege differ from our investigators' direct observation. We note your response acknowledges that you should have provided our Investigator a copy of the handwritten zone diameter results. You have not subsequently verified complete raw data was maintained**
5/25/2017	USA	Yusef Manufacturing Laboratories, LLC	**Discrepancies in documents** **Your response included SOP 05-105.00 Master Formulation File Change Control. According to this procedure, your Research & Development Department is responsible for approving changes to drug product formulations. You also provided SOP 00-100.5 Quality Unit which specifies your plant manager, president, and QA manager as members of the quality unit. It is important that your quality unit maintains appropriate independence, is adequately resourced, and is fully empowered to fulfill its accountabilities and responsibilities under CGMP.**
6/22/2017	China	Shandong Analysis and Test Center	**1. Failure to ensure that test procedures are scientifically sound and appropriate to ensure that your API conform to established standards of quality and/or purity.** **Your site is a contract testing lab that analyzes samples of heparin and heparin-related drugs for the presence of over-sulfated chondroitin sulfate (OSCS) using Nuclear Magnetic Resonance (NMR) spectroscopy.** **You failed to routinely establish system suitability when testing samples for OSCS.** **Furthermore, on December 26, 2014, you conducted a system suitability test that failed. You did not investigate why your equipment failed system suitability for detection of OSCS, or determine the reliability of other OSCS tests conducted prior to the date of the system suitability failure.** **In your response, you acknowledge that your laboratory performed system suitability** infrequently, noting that "the heparin standards (USP) and OSCS were detected at least **(b)(4)**."

			You committed to routinely establish system suitability before analyzing batch samples in the future. Your response is inadequate because you did not investigate the validity of all test results for OSCS in heparin or heparin-related drugs during the period in which you failed to conduct system suitability in coordination with sample analyses. System suitability testing determines whether requirements for precision are satisfied and ensures the NMR spectrometer is fit for the intended testing before analyzing samples. It is critical that your system be demonstrated as suitable for detecting OSCS contamination in heparin to avoid the possibility of samples erroneously passing when an instrument is not working properly. For further reference regarding heparin, see the guidance for industry Heparin for Drug and Medical Device Use: Monitoring Crude Heparin for Quality at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291390.pdf.
6/22/2017	China	Shandong Analysis and Test Center	2. 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. During our inspection, we requested that you display original electronic data for analysis of heparin and heparin-related drug samples. Your analyst was unable to retrieve requested data, and explained that he deletes older data to make space for newly acquired data. In your response, you committed to revise procedures regarding analyst computer permission levels, but did not address the data that was deleted
6/22/2017	China	Shandong Analysis and Test Center	Access to information during inspection During the inspection, you provided a document listing the names of (b)(4) customers for which you performed testing. However, you only provided additional requested information, such as sample information and test results, regarding (b)(4) of these customers. You stated that you would not provide data related to testing performed for other customers until you obtained their prior consent.

			For example, you failed to provide information pertaining to samples analyzed for (b)(4), a firm that produces heparin and heparin-related drugs for the U.S. supply chain. **When an owner, operator, or agent delays, denies, limits, or refuses an inspection, the drugs manufactured, processed, packed, or held in the facility may be deemed adulterated under section 501(j) of the FD&C Act.** See FDA's guidance document, **Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection, at https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm360484.pdf .**
6/29/2017	USA	ChemRite CoPac Inc.	**2. Your firm does not have, for each batch of drug product, appropriate laboratory testing, as necessary, of each batch of drug product required to be free of objectionable organisms (21 CFR 211.165(b)).** **You released at least 24 batches of your OTC drug product (b)(4) between 2013 and 2015 without performing analyses to assess whether they met all microbiological finished product specifications. Your batch records for this drug report results for analysis of the objectionable organism Pseudomonas aeruginosa of less than 1 colony forming unit/ml. However, the test results provided to you by your contract test laboratory did not report the results of any P. aeruginosa analysis. We also reviewed the raw data for the microbiological tests performed by your contract testing laboratory. We found that there was no raw data to indicate that the contract testing laboratory had performed P. aeruginosa analysis. Despite these discrepancies, you released multiple batches of this drug.** In your response, you stated, "A process deviation **report was initiated on 8-1-2016. The report cites the favorable microbial results obtained from the customer. The results will demonstrate** that the target or observed pathogen was effectively absent from the bulk material upon receipt." **Your response is inadequate. The effective absence of P. aeruginosa from materials tested by your customer does not satisfy the requirement that you perform appropriate laboratory testing on your drugs to ensure that the drugs meet their microbiological specifications before you release them for distribution. You failed to conduct retrospective testing on your retain samples for lots of this drug that you released without complete testing for all required specifications. Moreover, you failed to explain why your batch records report the absence of P. aeruginosa when the test results you received from your contract testing laboratory do not contain information about this type of testing.** **In response to this letter, provide your investigation into your failure to perform the required testing for objectionable organisms. Include your root cause analysis, a timeline for completing**

			retain testing, and a summary of your retrospective review of all released lots of (b)(4). Also evaluate and provide a report on all other lots of drugs you have distributed, within expiry, to determine whether you released any of them without complete or adequate microbiological testing.
7/6/2017	USA	Center for Reproductive Health / Joliet IVF LLC	3. Failure to retain records that are accurate, indelible, and legible [21 CFR 1271.55(d)(2)]. The records for the following oocyte donors contained multiple dates and/or altered dates on the Donor Physical Assessment Form and/or Medical History Interview Form. For example: a. The Donor Physical Assessment Form and Medical History Interview Form for anonymous donor (b)(4)are documented with two dates: October 16, 2015 and January 27, 2016. Your Establishment was unable to identify which date accurately reflected when the donor screening and physical examination were performed. b. The Donor Physical Assessment Form and Medical History Interview Form for anonymous donor (b)(4)have been altered with white-out and are documented with two dates: February 2, 2015 and March 11, 2015. Your establishment was unable to identify which date accurately reflected when the donor screening and physical examination were performed. c. The Donor Physical Assessment Form and Medical History Interview Form for anonymous donor (b)(4) are documented with two dates: October 20, 2014 and December 29, 2014. Your Establishment was unable to identify which date accurately reflected when the donor screening and physical examination were performed. d. The Donor Physical Assessment Form and Medical History Interview Form for anonymous donor (b)(4)have been altered with white-out and are documented with two dates: December 18, 2015 and January 27,2016. Your establishment was unable to identify which date accurately reflects when the donor screening and physical examination were performed
8/1/2017	China	Foshan Flying Medical Products 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, and to maintain such records for at least one year after the expiration of the batch (21 CFR 211.188 and 211.180(a)). During the inspection, our investigator asked to review batch records for your products. Your employee was only able to provide a single recent batch record for (b)(4) your (b)(4) products. When our investigator asked to see your other batch records, your staff stated that there were

			no other records. Your firm's senior management stated that batch records **are only retained for approximately six months after production.** You are required to maintain records associated with a batch of drug product for at least one year after the expiration date of the batch. **Your batch record also lacked sufficient information** necessary to determine whether your products were manufactured properly. For instance, your batch records lacked: • batch numbers for raw materials used in the manufacturing process; and • information on equipment and methods used to (b)(4) active ingredients (e.g., (b)(4); (b)(4)). In response to this letter, provide your: • revised master records for each of your drug products that fully document the manufacturing operation, including one executed batch production and control record for each product; and • remediated record retention policy setting forth acceptable retention periods.
8/1/2017	China	Foshan Flying Medical Products Co., Ltd.	**6. Your firm failed to ensure that each person engaged in the manufacture, processing, packing, or holding of a drug product has the education, training, and experience, or any combination thereof, to enable that person to perform his or her assigned functions (21 CFR 211.25(a)).** **Your firm was unable to provide any CGMP-related training documentation.** Your firm's senior management further stated that no CGMP-related training has ever been provided to employees. In response to this letter, provide details of your proposed training program to ensure that each person is equipped to effectively perform his or her assigned functions. Include provisions for an ongoing training program for all staff who conduct or supervise CGMP functions. Also include individual training records demonstrating that employees are qualified to perform their functions.
8/2/2017	Canada	Cellex-C International Inc.	**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).** **Your batch production records were incomplete. They lacked information regarding critical steps in your filling and packaging operations.** According to your response, you have revised your manufacturing formulation worksheet. Your response is inadequate. The worksheets you provided still omitted information about your manufacturing processes, such as identification of all critical equipment used during

			manufacturing, descriptions of the final drug product containers and closures, and details about in-process and finished product sampling.
8/11/2017	China	Bicooya Cosmetics Limited	**4. 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).** **Our investigator requested batch records for OTC drug product lots distributed to the United States, including (b)(4) Ointment and (b)(4). You were unable to provide batch records.** **In addition, analytical testing records were missing data, dates, and signatures. Our investigator observed your staff altering information in analytical test reports during the inspection. For example, you significantly altered the analytical testing report for (b)(4) Ointment lot (b)(4), although this lot had already been distributed to the U.S. market.**
8/11/2017	China	Bicooya Cosmetics 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.** **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 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.
8/24/2017	USA	US Stem Cell Clinic LLC	6. Failure to have a written record of major equipment cleaning, maintenance and use [21 CFR 211.182]. Specifically, your firm lacks records reflecting that cleaning, sanitizing, and inspections of equipment have been performed prior to, during, or after the manufacture of each batch of SVF product.
8/24/2017	USA	US Stem Cell Clinic LLC	12. Failure to prepare batch production and control records for each batch of drug product produced with complete information relating to the production and control of each batch. These records shall include documentation that each significant step in the manufacture, processing, packing, or holding of the batch was accomplished [21 CFR 211.188(b)].

			For example, you did not document each significant step in the manufacture, processing, packing, or holding of each batch of your SVF product, including the identify of each batch of component or in-process material used and all persons performing each significant step
9/1/2017	USA	Nova Homeopathic Therapeutics Inc	**2. Your firm failed to conduct at least one test to verify the identity of each component of a drug product. Your firm also failed to test each component for conformity with all appropriate written specifications for purity, strength, and quality (21 CFR 211.84(d)(1) & (2)).** **You did not test any of the components you use to manufacture your drugs to verify their identities before using them. For example, you performed no identity tests on components such as belladonna mother tincture and ethyl alcohol.** **Furthermore, you failed to determine whether each component conformed with all appropriate written specifications for purity, strength, and quality before using them. You asserted in your signed affidavit that all of your products are (b)(4) over-the-counter products and each of your products contains (b)(4). Although the Certificate of Analysis for the (b)(4) you use in all of your** drugs explicitly states, "Disclaimer: For Industrial/Lab use only. **Not intended as a Drug** Substance…" **you could not provide any scientific evidence that this component was compliant with USP specifications for use in human drugs, and did not perform any testing to determine whether this component conformed with specifications.** **In your response, you committed to draft procedures for handling drug product containers, closures, and packaging. However, you failed to address your critical failure to test all components for identity prior to use. Your response was also inadequate because you failed to provide evidence that your components met appropriate written specifications of identity, strength, quality, and purity. You did not address potential risks to patients. Finally, you did not address how failure to conduct required testing on components to verify identity and determine conformance with specifications for purity, strength, and quality may have compromised the quality of the products you have previously manufactured.** **In response to this letter, provide a risk assessment for any drug products manufactured using components which were not adequately tested and controlled. Include all products within expiry and distributed within the United States. Describe any specific additional risks posed to infants and children, for whom many of your products are intended.**
9/7/2017	China	Wuxi Medical	**1. Your firm failed to establish written procedures for production and process controls 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)).**

		Instrument Factory	**You failed to adequately validate the process used to manufacture your sterile (b)(4). During the inspection, you could not provide process qualification batch records and quality control test documentation. You provided only a protocol and a summary report with insufficient data. Batch records for your commercial product also failed to document all significant process parameters (e.g., (b)(4) times), order of ingredient addition, sampling frequency, and sample size. You lacked assurance that in-process materials and finished drug products met predetermined manufacturing and quality requirements.** **The purpose of validation is to determine whether your processes can operate within established parameters to assure consistent batch uniformity, integrity, and drug quality. Reliable and well-documented batch operations are essential to ensuring process control and drug quality.** See FDA's guidance document, **Process Validation: General Principles and Practices, at https://www.fda.gov/downloads/drugs/guidances/ucm070336.pdf.** **In response to this letter, provide:** • **A data-driven and scientifically sound program that identifies and controls all known sources of variability, such that your production and packaging processes will consistently meet appropriate parameters. This includes, but is not limited to, evaluating suitability of equipment for its intended use, assuring quality of input materials, and determining the capability and reliability of each manufacturing process step and control.** • **Revised procedures that establish an ongoing program for monitoring process control and detecting variation throughout the product lifecycle.** • **An updated master batch record for manufacturing sterile (b)(4) that requires specific processing details in order to fully document each significant manufacturing step.**
9/7/2017	China	Wuxi Medical Instrument Factory	**4. Your firm failed to maintain adequate written records of major equipment maintenance (21 CFR 211.182).** **During the inspection, you provided our investigator with records documenting (b)(4) sanitization of your (b)(4) loop. The records, covering January to March, 2017, were signed by two employees, and indicated that sanitization had been completed and verified contemporaneously throughout this period. However, our investigator found that these operations were not documented at the time of their actual performance, but were instead created and completed on March 7, 2017, the second day of the inspection.**

			Your response acknowledges this data integrity issue and indicates that you have taken some remediation steps. In response to this letter, provide: **A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. 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, and provide an evaluation of the nature of the data integrity deficiencies.** **B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs.** **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 comprehensive description of the root causes of your data integrity lapses, the interim measures you have taken or will take to protect patients and to ensure the quality of your drugs while remediation is ongoing, and the long-term measures you will take to** ensure the integrity of your company's data. Include a **status report for any of the above activities already underway or completed.**
9/12/2017	China	Shandong Vianor Biotech Co., Ltd.	**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 management acknowledged falsifying analytical test results that were used to support your release of (b)(4) (lot (b)(4)) to the United States.**
9/12/2017	China	Shandong Vianor Biotech Co., Ltd.	**2. 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 materials, labeling, and drug products (21 CFR 211.22(a)).** Your laboratory analysis revealed that **(b)(4)** lot **(b)(4)** was subpotent. However, the certificate of analysis (CoA) provided showed that it was within specification. When questioned about why the CoA reported passing results even though the batch actually failed, your quality unit manager stated, "I made a mistake."
9/12/2017	China	Shandong Vianor	**Access to information during inspection** During the inspection, you initially barred our investigator from accessing a room identified as a laboratory. You eventually allowed the investigator to inspect the laboratory, but he found that it

		Biotech Co., Ltd.	contained no equipment. You then stated that the laboratory was offsite at a **(b)(4)** residence and that you could not give our investigator access as it was not a convenient time. When an owner, operator, or agent delays, denies, limits, or refuses an inspection, the drugs manufactured, processed, packed, or held in the facility may be deemed adulterated under section 501(j) of the FD&C Act. See FDA's guidance document, *Circumstances that Constitute Delaying, Denying, Limiting or Refusing a Drug Inspection*, at https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm360484.pdf.
10/10/2017	India	Vital Laboratoreis PVT LTd Plant II	**2. Failure to adequately document the completion of each significant step in the batch production records with signatures of the persons performing and directly supervising or checking each critical step in the operation.** **Your batch production records omitted signature fields to document who performed, directly supervised, and checked each critical step in your manufacturing process. For example, the batch production record for (b)(4)batch (b)(4), Section E, Packing Details, indicates a gross weight of (b)(4), a tare weight of (b)(4), and a calculated net weight of (b)(4)** for "Drum No. 4." **The correct calculated net weight should be (b)(4). There are no signatures to identify who performed the weighing operation and who subsequently verified it. We also observed that the** "done by" and "checked by" fields in many of your other batch production records were **completed by the same person. During the inspection, you stated that it was general practice for supervisors to initial or sign for operators.** **In your response, you stated that you revised your (b)(4) batch records to include space for operators and verifiers to sign. You explained that supervisors were signing for operators** because the operators' "hands were dirty" and y**our corrective action and preventive action (CAPA) was to provide operators with gloves. Additionally, you noted that your batch records were in English but many of your operators only understand Hindi. Thus, you proposed bilingual English and Hindi batch records to improve operator understanding and compliance.** **Your response is inadequate. Your revision of the batch record for (b)(4) was insufficient because you did not review all batch records for all of your drugs to identify any additional critical steps (besides weighing) that may have been inadequately performed, documented, and reviewed or checked. Your CAPA of providing gloves to operators and proposal to generate bilingual batch records did not directly address the observed deficiency of supervisors signing records on behalf of operators who performed critical steps.**-

			In your response to this letter, provide the results of a retrospective investigation of batch records for all of your API distributed to the U.S. that are within expiry. Your review should identify any instances in which your batch records indicate inadequate performance, documentation, or review of critical steps in the operation, and should include a risk assessment to determine the impact on the quality of your API for any such identified instances. Also provide the specific actions you have taken to ensure that current and future batch records for all products are adequate and signed correctly, such as establishing a documented system of regular, periodic quality unit audits of your batch records.
10/10/2017	India	Vital Laboratoreis PVT LTd Plant II	**3. Failure to adequately investigate and document out-of-specification results and implement appropriate corrective actions.** **Your firm ignored aberrant analytical test results rather than investigating them, determining the root cause, and implementing appropriate corrective actions. You relied on these out-of-specification (OOS) results** to assign "expiration dates" to your API. For example, our **investigator reviewed your 48-month stability gas chromatography (GC) test results for (b)(4) content in (b)(4) validation batches (b)(4), (b)(4), and (b)(4).** **Our investigator observed that all three chromatograms for these batches displayed an unknown peak at an earlier retention time than the internal standard peak. The unknown peak did not appear in the internal standard blank run. Prior to our inspection, you did not initiate an investigation into this OOS result, nor did your firm determine the root cause or assess the effects of the unknown peak on the quality of your drugs. Instead, you reviewed, approved, and** used the stability data for these batches to determine the "expiration date" **for your commercial (b)(4) API batches.** **In your response, you stated that you performed a retrospective investigation, and determined** that the unknown peak was due to "injector contamination" of **(b)(4) precipitation in the needle of the GC injector. You concluded that the unknown peaks were isolated, and did not reflect systemic product quality deviations or affect the reported values of (b)(4) or labeled expiration dates. You revised your procedures to require chemists to document and investigate OOS results, and stated that you would purchase new GC equipment.** **Your response is inadequate. You did not expand the scope of your investigation to determine if** other drugs tested on the same GC equipment were affected by similar "injector contamination" **events. You also failed to explain why you neglected to investigate these aberrant test results in** the first instance, or relied on OOS results to assign "expiration dates" to your API.

			In your response to this letter, provide your investigation report and risk analysis for all drugs tested on the affected GC equipment since 2015. Indicate the steps you will take for any analytical test results you identify as having been affected by needle contamination or carryover. Also provide your revised stability program to indicate how you will ensure that your "expiration dates" are based only on analytical data that meets scientifically valid and appropriate **specifications.**
10/10/2017	India	Vital Laboratoreis PVT LTd Plant II	**4. Failure of your quality unit to adequately perform annual product reviews.** **We reviewed your annual product reviews (APR) for multiple products and observed a variety of deficiencies. For example, the stability data from your 2016 (b)(4) APR was identical to the data included in your 2015 APR for the same API. Your 2016 (b)(4) APR also included stability data that could not have been generated at the time points provided in the APR. Your 2016 APR for (b)(4) also included multiple errors. For example, the mean values for product quality attributes such as water content, impurities, and optical rotation exceed the maximum values. Product quality tables of numerical minimum** values also reported maximum values as "not detected." In another instance, mean values **were reported for a single batch.** **Such reporting errors are repeat deviati**ons from FDA's 2013 inspection of this site. In your response, you attributed these APR errors to personnel using the previous year's APR as a template. You revised your procedures to include a blank template. You also stated that "all **the error was tra**nscription error and review error by all managers of concerned departments." **You indicated that you would avoid such errors in the future by using enterprise resource planning to compile QMS data online.** **Your response is inadequate. You did not explain how your use of an enterprise resource planning system will prevent APR errors in the future. Further, you did not perform a retrospective review of all APR to ensure that there were no errors that may have compromised or obscured indicia of drug quality.** **In your response to this letter, conduct a retrospective review of all APR for the past three years, and provide a tabular summary of your review. Also provide annotated copies of your revised 2015 and 2016 (b)(4) and (b)(4)APR, referencing the underlying data along with copies of the records containing the underlying data.**

10/13/2018	USA	Ridge Properties LLC	**4. 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).** **Your firm lacked batch records for all drug products you manufactured from May 2015 to February 2017. You did not document significant production details, including but not limited to the personnel, dates, equipment, raw material identity, and labeling, for each batch. We acknowledge that you created a batch record template during the inspection for your Lidocaine Carbomer Free Gel drug product. However, this batch record template lacked provisions for data on processing, filling, and packaging operations. Such data is necessary to establish that the manufacturing process was followed and is reproducible.**
10/16/2017	India	Kim Chemicals Private Ltd.	**1. Your firm failed to 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)).** **For example, multiple batches of Vaporizing Chest Rub and (b)(4) failed to meet finished product specifications, including active ingredient content. Despite these failing test results, you shipped these drugs to the United States.** **Additionally, your staff informed our investigator that batches are not routinely tested. Instead, your firm re-uses test results from a past batch produced several years ago, and enters those results on certificates of analysis for new batches.** **Your brief response indicated that your firm is performing batch testing, but included no raw data or test results.**
10/16/2017	India	Kim Chemicals Private 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)).** **You had no records to support the analytical testing results reported on your certificate of analyses. Your firm indicated to our investigator that you document finished product analysis on a pad of paper, transcribe the test results onto a certificate of analysis, and then destroy the piece of paper. There is no assurance that the testing was conducted in the first place, and there is no record that any associated calculations were performed.**

10/16/2017	India	Kim Chemicals Private 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 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.
10/30/2017	China	Guangdong Zhanjiang Jimin Pharmaceutical CO., Ltd	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 materials, labeling, and drug products (21 CFR 211.22(a)). You manufacture a topical OTC drug product labeled as containing the active ingredient hydrocortisone. During our inspection, our investigators reviewed records showing that the active pharmaceutical ingredient (API) actually used in this product was dexamethasone acetate—a different API. When our investigator inquired about the incorrect API, your firm stated that there was a translation mistake, and the two API were believed to be the same ingredient. Your quality unit approved multiple lots of this drug product for distribution to the United States containing the incorrect active ingredient. You recalled all lots of this drug distributed to the U.S. on August 30, 2017. However, you have not provided details of an investigation of the failure of your quality unit and your action plan to prevent recurrence. You also have not provided details of an evaluation to ensure all the drug products you released for distribution to the U.S. were manufactured with appropriate components.
11/6/2017	China	Hubei Danao Pharmaceutical Co. Ltd.	3. Failure to ensure that all test procedures are scientifically sound and appropriate to ensure that your API conform to established standards of quality and purity. You failed to establish adequate test procedures. For example, your analyst manually integrated a high performance liquid chromatography test for (b)(4) API despite the fact that the chromatogram lacked peak resolution. When a chromatogram lacks peak resolution, detailed methods and appropriate oversight are essential to ensure test results, considered by the quality

			unit in batch release decisions, are scientifically valid. You lacked an approved protocol for manual integration or quality oversight of the practice.
11/6/2017	India	Lupin Limited	1. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192). Your firm frequently invalidated initial out-of-specification (OOS) laboratory results without an adequate investigation that addressed potential manufacturing causes. A. Assay Failure While conducting component release testing on (b)(4) active pharmaceutical ingredient (API) batch (b)(4), your firm obtained a failing assay result of (b)(4)% (specification (b)(4)% to (b)(4)%). Data from the investigation demonstrated that multiple retest results were comparable to the initial OOS result. Initial retests yielded four results ranging from (b)(4)% to (b)(4)%. These results included a freshly prepared sample, which tested at (b)(4)%. A second analyst tested a new set of samples and obtained results including (b)(4)%, (b)(4)%, and (b)(4)%. You then performed the test again. Only the last samples yielded significantly different assay results ((b)(4)–(b)(4)%). Despite the findings of multiple values close to the original OOS value, your firm invalidated the initial failing result, stating that the initial result "shall be considered an outlier and retest results shall be reported as final results." Although the investigation failed to identify a conclusive laboratory root cause, you did not conduct an evaluation of your supplier, and reported an average result for batch release. It is not appropriate to use an "outlier test" to invalidate your API assay result. Such statistical treatments do not identify the cause of an extreme observation, and are only of informational use in an investigation of chemical testing. Further, in this case, your investigation included multiple retests that were the same or very similar to the original OOS result. Our inspection also revealed additional inappropriate uses of outlier testing. Your firm released other raw materials and drug product batches by retesting and concluding that the original OOS result was an "outlier."

			We acknowledge your firm's change control on January 18, 2017, to remove the outlier test in **your Handling of Out of Specification Test Results standard operating procedure (SOP). You also reversed your original decision to release (b)(4) batch (b)(4), and have now rejected it. However, your response did not address API quality issues that may have caused the low assay, and lacked an adequate reassessment of the other batches released with the outlier test.**
11/6/2017	India	Lupin Limited	**2. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).** **Your firm invalidated initial OOS laboratory results without adequate investigations. From January 1, 2015, to December 31, 2016, you invalidated nearly all (134 out of 139) initial OOS results and attributed them to laboratory error. Although some investigations failed to clearly establish that laboratory error occurred, you did not conduct a full-scale investigation to thoroughly review potential manufacturing causes and assess commercial history to identify similar instances of high variation or OOS results.** **For example, you opened laboratory investigation OOS/C/16/IN2/FP/011 after obtaining an OOS finished product assay result of (b)(4)% (release testing specification: (b)(4)–(b)(4)%) for (b)(4) tablets USP (b)(4) mg, batch (b)(4). You discarded the original vial that yielded the OOS result, which violates your OOS procedure. Testing of stock solutions, including (b)(4) and re-dilution, yielded slightly higher passing results ((b)(4)%, (b)(4)%, (b)(4)%). Based on a triplicate retest, you invalidated the initial failing result without investigating the potential manufacturing root causes.** **You had also obtained a low assay result for batch (b)(4), and again reported passing retest results without an investigation of potential manufacturing causes of the OOS assay result.** **Your CAPA have often been limited to retraining your analysts. Improvements in analytical methods and equipment were not generally implemented to enhance robustness and prevent errors.** **In your response, you committed to track and trend OOS results to identify specific tests and analysts who may be sources of the root cause. Additionally, you stated that your process for invalidating an OOS result and accepting retest results will be more rigorous.**

11/8/2017	USA	RTI Surgical, Inc	**9. 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]. Specifically, master production records have not been prepared to assure uniformity from batch to batch of the (b)(4) with complete information documenting each significant step that was accomplished in the manufacture, processing, packing, or holding of the batch**
11/14/2017	Germany	Bayer AG	**3. 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 materials, labeling, and drug products, and that approves or rejects all procedures or specifications impacting on the identity, strength, quality, and purity of the drug product (21 CFR 211.22(a) and (c)).** **Your quality control unit did not sufficiently oversee adequacy of procedures at your facility to assure drug product quality.** **A. Discarded training records** **Our investigators observed discarded original personnel training records. Your procedure 3-040-127, Use of the Schulungsdatenbank (Learning Management System) in the Supply Center Leverkusen requires these records to be maintained. In your response, you committed to retain original training records. However, you did not reassess your program to ensure that personnel were trained and capable of performing their assigned functions.** **B. Discarded automated visual inspection machine parameters** **In a (b)(4) department office waste bin, our investigators observed discarded forms used to document and set inspection parameters for your automated tablet visual inspection machinery. These parameters are used to accept or reject tablets. In your response, you noted that you documented and approved final set-**up parameters, "**but historically the calculations generated in** support of those parameters have not been preserved." **You indicate that programming the visual inspection machine to detect defects may not be a CGMP activity. We note that the parameters of this machinery are used to discriminate between acceptable and unacceptable tablets. Accordingly, entering reliable settings into machine programming is part of CGMP.** **In response to this letter:** • **Reassess any systems or activities associated with drug manufacturing or testing equipment** that you consider "non-GMP." Provide your reassessment and describe improvements in **your procedures for document handling, retention, and destruction.**

			• **Rev**iew your training program's effectiveness, including but not limited to evaluating the **reason(s) that some individuals failed to follow standard operating procedures. Summarize your CAPA.**
11/14/2017	Germany	Bayer AG	**4. Your firm failed to ensure that laboratory records included complete data derived from all tests necessary to assure compliance with established specifications and standards (21 CFR 211.194(a)).** **When reviewing audit trails, our investigator observed unreported data from in-process tablet weight checks. You programmed your in-process weight checker not to report values that varied more than (b)(4)% from the tablet target weight.** **In your response, you committed to suspend this procedure, investigate any such values, and perform a retrospective assessment of tablet weight checker data. However, your retrospective tablet weight assessment was limited to all rejected measurements from February 1 to March 15, 2017, and about 8,000 rejected measurements representing an unspecified percentage of the total number of rejected measurements from August 1, 2016, to February 1, 2017. There was no commitment to revisit equipment qualification(s) and process validation(s) to ensure they included complete data.** **In response to this letter, as part of your retrospective tablet weight assessment, explain whether your findings impact data supporting tablet manufacturing equipment qualification and manufacturing process validation studies. Provide a summary listing of equipment qualification and process validation documents that you reviewed.**
11/17/2017	China	Hangzhou Facecare Cosmetics Co., Ltd.	**1. Your firm failed to 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)).** **You released over-the-counter (OTC) drug products without adequate acceptance testing for conformance to specifications, including identity and strength. During the inspection, you could not provide analytical data to support the release of your OTC drug products.** **Your response stated that you or a contract testing laboratory currently test active ingredient content prior to release of OTC drug products. You also provided results for two finished drug** product lots tested by a contract testing laboratory after FDA's inspection of your facility.

11/17/2017	China	Hangzhou Facecare Cosmetics Co., Ltd.	**3. 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)).** **During the inspection, our investigator found that you shipped OTC drug products to the United States without expiration dates, and you did not have stability data to demonstrate these products meet their specifications (e.g., active ingredient content) throughout their shelf lives.** **Your response stated** "As we understand, our customers conduct testing to confirm stability and expiration dating." You also indicated that you were in the process of contacting your customers **to confirm responsibilities and OTC drug product expiration dating.**
11/20/2017	South Korea	Dae Young Foods Co., Ltd.	**3. Your firm failed to establish an adequate quality control unit and procedures applicable to the quality control unit with the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging materials, labeling, and drug products (21 CFR 211.22(a) and (d)).** **Your firm lacks an adequate quality control unit.** **You failed to establish written procedures for numerous functions. For example, there were no procedures addressing the quality control unit, complaints, deviations, investigations, and various other basic drug manufacturing operations.** **Further, your quality unit lacked documentation to demonstrate acceptability of batch manufacturing and quality. For instance, you lacked records relating to:** • **change control;** • **annual product reviews;** • **batch record review to assure that any errors were discovered and fully investigated; and** • **approval or rejection of your drug products.** **During our inspection one of your employees confirmed that that your quality unit does not review the complete batch records for your finished drug products prior to release. In response to this letter, provide your corrective actions to ensure that:** • **you establish an adequate quality control unit with the appropriate authority and sufficient resources to carry out its responsibilities and consistently ensure drug quality;**

			• you establish adequate procedures in accord with CGMP covering all aspects of your facility and operations that may compromise the identity, strength, quality, and purity of your drug products; and • you create and maintain full documentation to demonstrate acceptability of all operations.
12/4/2017	India	Fresenius Kabi Oncology Ltd.	**1. Failure to adequately investigate and document out-of-specification results according to a procedure.** **Our review of your out-of-specification (OOS) investigations found that you did not use adequate OOS procedures, and lacked scientific justification to invalidate initial OOS results. For example:** **a. Investigation report OOS/2015/098 was initiated for an initial OOS result in your related substances test, where (b)(4)% and (b)(4)% (specification: not more than (b)(4)%) was obtained for Impurity (b)(4) in (b)(4) API batches (b)(4) and (b)(4), respectively. Your investigation concluded that over-sonication might have increased the temperature of the water bath and caused degradation of the sample solution.** **However, your investigation lacked evidence to support this possible root cause. Instead, your investigation found that the analyst only briefly sonicated the solution (for about (b)(4)) at (b)(4) temperature. In addition, degradation studies conducted as part of high performance liquid chromatography (HPLC) validation showed that heat degradation was minimal even after (b)(4) at extremely high ((b)(4)°C) temperatures.** **Although your investigation was inconclusive, you did not proceed to Phase 2 and investigate potential causes of the OOS result relating to deficient manufacturing and product quality.** **b. Investigation report OOS 50989 was initiated f**ollowing initial OOS results for "related **substances**–unspecified impurities" for **(b)(4) API stability batches (b)(4) and (b)(4). You concluded that the most probable cause of the OOS result was contamination, although the source of the contamination was not identified or confirmed through your hypothesis study. You invalidated the OOS results (as well as an additional failing retest from a fresh sample preparation by a second analyst for batch (b)(4)) and reported the average of six retests. You failed to expand the investigation to review potential causes of the OOS result relating to deficient manufacturing and product quality.**

			c. Your OOS investigation procedure 036/—/QS/QA permits an analyst to abort a chromatographic run if an apparent OOS is observed prior to completing analysis of all samples scheduled to be injected in the sequence. Your quality control (QC) manager confirmed that analysts abort HPLC analyses if they "expect to invalidate" them later for an assignable cause. **For example, you aborted the HPLC sequence of (b)(4) API batch (b)(4) while observing the** chromatographic run on the screen ("online monitoring") in which an individual unknown impurity **tested at (b)(4)% (specification: NMT (b)(4)%). There was no machine malfunction (e.g., unstable system) that would justify aborting the automated analysis.** **Our investigators documented approximately 248 instances of aborted sequences.** **Your SOP was inadequate. When performing a sample preparation, it may be possible to identify an obvious manual error at the time of the mistake. In such a limited instance, it can be appropriate to discontinue the sample preparation, immediately document the deviation, and justify a new sample preparation. However, it is not appropriate to stop an in-progress automated analysis because of an assumption that an earlier error may be causing an OOS** result. Obtaining an unexpected result does not constitute an "assignable cause" and the **assumption of such a cause is not a valid basis for interrupting an analysis. The automated analytical sequence should be allowed to proceed to completion, irrespective of the appearance of undesirable analytical results on the computer screen.** **We acknowledge your commitment to correct this deficient SOP. Your response was inadequate because your corrections did not ensure that lab investigations will be started immediately after obtaining an OOS result. You acknowledged that in about nine of the examples referenced by the investigator, the original samples were not re-injected due to sample solution stability. Notably, your method validation data show that some of these sample solutions are stable for up to (b)(4) at room temperature. Prompt re-testing of the actual stock, working, and HPLC vial solutions is essential to determine if mechanical error or preparation error may have occurred. Timely investigations of potential original laboratory sample preparations are essential to provide clear evidence and credibility for laboratory error hypotheses.** **Your response was also inadequate because your OOS procedure failed to ensure that you proceed to Phase 2 whenever you lack conclusive evidence of laboratory error. A possible laboratory error is insufficient to close an investigation at Phase 1. In addition, your procedure indicated that you can close an investigation when a second analyst confirms the initial OOS without moving to a Phase 2 investigation. It remains unclear whether all failing results would be**

			investigated for their manufacturing root causes prior to closing an investigation. Further, even if an OOS result is not confirmed by a second analyst, it should not be assumed that the initial OOS test result was attributable to analytical error. Whenever an investigation lacks conclusive evidence of laboratory error, a thorough investigation of potential manufacturing causes must be performed. **In response to this letter,** • **Provide a retrospective review of all invalidated OOS (in-process and finished testing) results obtained for products on the U.S. market. Assess whether the scientific justification and evidence was conclusive. For investigations that conclusively established laboratory root cause, determine adequacy of the corrective action and preventive action (CAPA), and ensure that other laboratory methods vulnerable to the same root cause are identified for remediation. For any OOS with an inconclusive or no root cause identified in the laboratory, include a thorough review of production (e.g., batch manufacturing records, adequacy of manufacturing steps, raw materials, process capability, deviation history, batch failure history). Provide a CAPA plan that identifies the potential manufacturing root causes for each such investigation, and includes process improvements where appropriate.** • **Provide an assessment of your overall system for investigating OOS results. Provide a CAPA to improve quality of OOS investigations in all Fresenius Kabi facilities. Elements of your CAPA should include, but not be limited to, enhanced quality assurance participation in individual laboratory investigations, identified adverse laboratory control trends, and proper initiation of the Phase 2 manufacturing quality investigation stage. It should also include improved laboratory supervision of analysts.** • **Evaluate all instances in which a chromatographic run was interrupted or aborted. Determine the potential effect on the quality of API released for distribution. Provide your assessment once completed, and a fully remediated SOP.** • **Provide your updated laboratory investigation procedure. Describe how your revised procedure ensures that all OOS investigations expand to a review of manufacturing history and potential root causes whenever a cause is not conclusively found in the laboratory. Also describe how investigation of laboratory deviations will be improved.** **For more information about handling failing, out-of-specification, out-of-trend, or other** unexpected results and documentation of your investigations, see FDA's guidance document, **Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production, at https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070287.pdf.**

12/5/2017	China	Shanwei Honghui Daily Appliance Co., Ltd.	**3. Your firm failed to perform, 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, and conduct appropriate laboratory testing for each batch of drug product required to be free of objectionable microorganisms (21 CFR 211.165(a) and (b)).** **Your firm had no test records to support the release of drug products for the U.S. market. Your engineer and quality assurance supervisor stated that no microbiology tests were performed, there was no record of pH testing, and that the concentration of active ingredients such as (b)(4) and (b)(4) were not determined. You stated that some tests were sent to a contract testing laboratory. However, you did not provide any test reports during the inspection.**
12/5/2017	China	Shanwei Honghui Daily Appliance 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).** **Your firm failed to provide batch records for (b)(4) of (b)(4) batches manufactured for the U.S. market. You stated to our investigator that there was not a batch record for each batch.**
12/13/2017	South Korea	Amaros Co., Ltd.	**2. Your firm failed to have written procedures describing the receipt, identification, storage, handling, sampling, examination, and/or testing of labeling and packaging materials, which shall be representatively sampled, examined or tested upon receipt and before use in packaging or labeling of a drug product (21 CFR 211.122(a)).** **You released packaging and labeling materials for use in drug product manufacturing without written procedures. You also stated to our investigator that you examine only (b)(4) units of packaging material, regardless of the batch size. You had no data to demonstrate that (b)(4) units were a representative sample.** **In response to this letter, provide an adequate procedure for releasing packaging and labeling materials for use in manufacturing**
12/18/2017	Mexico	Prosana Distribuciones SA de CV	**1. Your firm failed to 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)).**

			You distributed two batches of Bicaruvas before receiving certificates of analysis (COA) containing the finished product test results from your third-party testing laboratory, (b)(4). **Your management could not locate the COA for Bicaruvas batches EBU02 and EBU03. During the inspection, you retrieved the COA from your third-party testing laboratory. You had already distributed batches EBU02 and EBU03 to the United States.** **Drugs must be manufactured in conformance with CGMP. FDA is aware that many drug manufacturers use independent contractors, such as production facilities, testing laboratories, packagers, and labelers. FDA regards contractors as extensions of the manufacturer.** **You are responsible for the quality of drugs you produce, regardless of agreements in place with your contract testing laboratory. You are required to ensure that drugs are made in accordance with section 501(a)(2)(B) of the FD&C Act to ensure safety, identity, strength, quality, and purity.** See FDA's guidance document, **Contract Manufacturing Arrangements for Drugs: Quality Agreements, at https://www.fda.gov/downloads/drugs/guidances/ucm353925.pdf**
12/18/2017	Mexico	Prosana Distribuciones SA de CV	**3. Your firm failed to prepare batch production and control records for each batch of drug product that include complete documentation of the accomplishment of each significant step in the manufacture, processing, packing, or holding of the batch, including a statement of the actual yield, and a statement of a percentage of theoretical yield at appropriate phases of processing. (21 CFR 211.188(b)(7)).** **During the inspection,** your firm's management stated that operators "made up" yield results in **your batch records for processing steps such as weighing, (b)(4), and filling, as well as for label reconciliation. Management informed our investigator that operators falsified batch records because there were no established calculations for determining yields.**
12/18/2017	Mexico	Prosana Distribuciones SA de CV	**4. 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)).** **You have not validated the processes used to manufacture your drug products. You did not perform process performance qualification studies, and lacked an ongoing program for monitoring process control to ensure stable manufacturing operations and consistent drug quality.**

			You also lacked adequate master production and control records for Bicaruvas with established process controls. For example, you did not have a master batch record for each batch size that you manufacture. Our investigator noted that you manufactured Bicaruvas batches EBU01, EBU02, and EBU03 with five times the amount of calcium carbonate specified on the product label. Firm management stated that personnel performed a calculation on the spot for customer orders of more than (b)(4), and that they used a wrong formula for these three batches. See FDA's guidance document, **Process Validation: General Principles and Practices, for general principles and elements of process validation at https://www.fda.gov/downloads/drugs/guidances/ucm070336.pdf**
12/18/2017	Canada	Deserving Health International Corp	**2. Your firm failed to establish an adequate quality control unit and procedures applicable to the quality control unit with the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging materials, labeling, and drug products (21 CFR 211.22(a) and (d)).** **You lacked quality oversight for finished drug products manufactured in your facility, including a sterile homeopathic drug product, Symbio Muc Eye Drops 5X.** **You failed to establish written procedures for numerous functions. For example, there were no procedures addressing the quality control unit, deviations, investigations, stability studies, quality review of incoming materials, finished product batch release, and various other basic drug manufacturing operations.** **Further, your quality control unit lacked documentation to demonstrate acceptability of batch manufacturing and quality. For instance, you lacked records relating to:** • **annual product reviews;** • **full batch record review to evaluate if instructions were followed, and to assure that any errors or anomalies were fully investigated; and** • **approval or rejection of your drug products.** **During the inspection, our investigator determined that your production manager conducts the final batch review and releases the finished drug product, which is a quality control unit responsibility.**

12/19/2017	USA	C.O. Truxton Inc	**2. Your firm failed to establish and follow written procedures to assure that correct labels and packaging materials are used for drug products (21 CFR 211.130).** **Your firm performs repackaging and labeling operations but did not have written procedures governing the application of packaging and labeling materials to your drug products. You incorrectly labeled a container filled with Phenobarbital tablets 30 mg as Phenobarbital tablets, USP 15 mg (schedule IV) lot 70952A. In the affidavit collected during the inspection, you stated,** "I have no records to show the repackaging operation." **You did not address this observation in your response. In your response to this letter, provide your plan, including written procedures, to ensure compliance with CGMP for all drug repackaging activities in which you engage.**
12/19/2017	USA	C.O. Truxton Inc	**4. Your firm failed to establish a written distribution procedure to include a system by which each lot of drug product can be readily determined to facilitate its recall if necessary (21 CFR 211.150(b)).** **Your firm lacked any procedures describing your drug distribution system. Your distribution system was deficient in that it could not differentiate between the lot number your firm assigns and the lot number assigned by the manufacturer, and therefore there is no product traceability if a recall is required. Our investigator observed that neither your receiving or shipping records included the lot numbers of products you received and shipped.** **In your response, you stated that, moving forward, only Phendimetrazine manufactured and packaged by (b)(4) will bear the Truxton label. Your response was inadequate because you did** not address your firm's lack of traceability for your repackaged drug **products.** **In your response to this letter, provide your drug distribution and tracking procedures for your repackaged drug products.**

12/19/2017	USA	C.O. Truxton Inc	**5. Your firm failed to establish and follow a written testing program designed to assess the stability characteristics of drug products and to use results of such stability testing to determine appropriate storage conditions and expiration dates (21 CFR 211.166(a)).** **You had no data to support the expiration date of Phenobarbital tablets, USP 15 mg (schedule IV) lot 70952A repackaged from original container-closure system (500-count bottle size) to a new container- closure system (1000-count bottle size). You had not performed stability testing of the drug product in the new container-closure system and you did not have any supporting stability data to support the use of the new container-closure system. In addition, you were unable to provide documentation to show that the container-closure system used to repackage drug products was identical or equivalent to their original container-closure systems.** **You did not address this observation in your response. In your response to this letter, provide your evaluation of any other drug products that may have been repackaged into a different container-closure system, and the procedures and controls you have in place to assess stability of the drug products in their new container-closure systems. Include your corrective action plan if you find drug products that are unstable in the new container-closure system.**
12/18/2017	China	Wuhan Chine Moxibustion Technology Dev. Co., Ltd	**2. Your firm failed to prepare master production and control records designed to assure uniformity from batch to batch (21 CFR 211.186(b)).** **Your firm lacked product-specific master production and control records that included, for example, (b)(4) speed, (b)(4) time, and the order of component addition for your (b)(4)((b)(4) Patch). Your production records also lacked usage instructions for the (b)(4) and (b)(4) that you used to apply active pharmaceutical ingredient (API) (b)(4)solution on (b)(4) Patch (b)(4).** **In response to this letter, provide your established master production and control records for the (b)(4) Patch that fully document each significant and validated manufacturing step, and provide one executed batch record for the (b)(4) Patch.**
12/18/2017	China	Wuhan Chine Moxibustion Technology Dev. Co., Ltd	**3. 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)).**

			Your (b)(4) Patches claim (b)(4)% (b)(4) as the active ingredient, but you indicated that your (b)(4) testing for finished patches relies on qualitative methods that cannot measure and quantify the (b)(4) content in the product. Moreover, our review of (b)(4) Patch batch production records showed no test results for (b)(4) API in released batches (b)(4), (b)(4), and (b)(4). In response to this letter, provide your corrective action plan to ensure that all drug product batches meet pre-established specifications before you release them. Provide procedures and validated testing method(s) for each release test, including quantitative methods for (b)(4) API content.
12/20/2017	Austria	Scrofner Cosmetics Gmbh	2. Your firm failed to establish and 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)). Your firm did not prepare any master production records or batch production records for your drug product, (b)(4). Without master batch records, you cannot assure the uniformity of your drug products from batch to batch.
12/21/2017	USA	Continental Manufacturing Chemist Inc.	4. Your firm failed to ensure that laboratory records included complete data derived from all tests necessary to assure compliance with established specifications and standards (21 CFR 211.194(a)). Your firm did not keep laboratory records of sample preparations and analyses. Our investigator observed that during your laboratory analysis of Veterinary Liniment, lot 155476, your analysts did not record the method used, analytical steps performed, reagents used, the sample used, or which analyst prepared the sample. Our investigator requested laboratory records of sample preparation and analyses for other drug products. Your Vice President of Operations stated in an affidavit that your firm could not provide these records because they do not exist. He stated that your lab analysts currently do not document their process of sample preparation for HPLC and GC testing. In your response, you stated that you will train your employees on record keeping practices by May 26, 2017. You also stated that you will develop an interim procedure for proper record keeping practices and will issue laboratory notebooks and preparation worksheets by May 26, 2017.

			Your response was inadequate. You did not assess the risks to patients and product quality posed by your failure to maintain complete laboratory records. **In response to this letter, summarize your efforts to ensure that your laboratory records include complete data for all laboratory tests. Include your risk assessment, revised procedures, and any other supporting documentation for your corrective actions.**