DATE	COUNTRY	COMPANY	TEXT of WARNING LETTER
1/2/2018	China	Yicheng Chemical Corp	**2. Failure of your quality unit to review batch production records prior to distribution of an API batch.** Your firm failed to have repackaging batch records. Furthermore, your quality unit lacked written procedures for API repackaging batch review, approval, and release prior to distribution. In response to this letter, provide your repackaging batch review and release procedure which ensures that API repackaged at your facility are in compliance with CGMP
			3. Failure to maintain complete traceability of API in commercial distribution. Your firm lacked documentation or procedures to ensure that each batch can be traced from your API suppliers, through your repackaging operations, and into commercial distribution. In response to this letter, provide your procedure to ensure the integrity, traceability, and transparency of your API supply chain.
1/9/2018	China	Hunan Norchem Pharmaceeutical Co. Ltd.	**1. Failure to prepare and use production and control records for each intermediate and API batch.** Your Quality Unit failed to retain and locate 20 of **(b)(4)** of your **(b)(4)** base batch records, including but not limited to records for batches **(b)(4)** and **(b)(4)**. In your response, you stated the batch records "are not missing" and are "archived properly." Your response is inadequate because you did not provide evidence, such as copies of the executed batch records. Additionally, your Quality Assurance department approved batch record 0220151203 and batch record 0220151204 despite the inaccuracy of the weight of raw materials added. In your response, you stated the operator "did not follow the procedure" and did not recognize this as a deviation. You also stated personnel had "inadequate awareness of deviations." It is your responsibility to ensure the accuracy and completeness of your batch records in order to establish that your manufacturing process was followed and is reproducible.
			2. Failure to maintain complete data derived from all laboratory tests conducted to ensure your API and intermediates comply with established specifications and standards.

			Your firm failed to retain and locate the analytical raw data for batches **(b)(4)** and **(b)(4)** of **(b)(4)** base which you shipped to the United States in 2014. In your response, you stated the "analytical data was not backed up." You also said that you transferred the instrument that generated the data to your **(b)(4)** branch in 2015 and that the staff there deleted the data. It is essential to retain raw data to ensure the ability to reconstruct CGMP activities and review raw data, as necessary, for deviations and investigations. Our findings demonstrate that you lack understanding of the basic elements of a compliant manufacturing operation, such as adequate documentation, trained personnel, and written procedures
1/18/2018	Japan	Daito Kasei Kogyo Co., LTD	**1. Failure to ensure that, for each batch of API, appropriate laboratory tests are conducted to determine conformance to specifications.** You released numerous drugs without completing all required testing. You claimed that the drugs were tested for identity and assay, and met required specifications for these attributes. However, these tests were never conducted, so you had no assurance that the drugs conformed to specification. Your actions may have put consumers at risk in at least two ways: first, through use of potentially ineffective **(b)(4)**, and second, through possible exposure to toxic impurities such as **(b)(4)** and **(b)(4)**. In your response, you said that the former quality control manager decided that identification tests would not be required if "…identification tests of raw materials were confirmed with COA provided by the raw material manufacturers" and that "The QC manager at the time approved the product without testing…" Your revised SOP for issuing COA requires confirmation of raw data. Your response was inadequate because you have not shown how you intend to confirm such data, who is responsible for conducting tests, and how you intend to ensure the integrity of this data. You also failed to conduct a risk assessment on the effects of the lack of release testing on the quality of drugs you distributed. In response to this letter, provide: • A detailed description of how you plan to test each component for conformity with all appropriate written specifications for identity, purity, strength and quality. • A detailed description of how you plan to test bulk API to determine conformance to specifications. • A detailed explanation of who will conduct raw material and finished API testing and how you plan to assure the suitability of test methods and the reliability of test results.

			• A risk assessment for any API within the re-test date and distributed within the United States that were released with inaccurate COA.
			2. Failure to completely report test results on certificates of analysis. During the inspection, we reviewed certificates of analysis (COA) for batches of **(b)(4)** API that you manufactured and released between June 2011 and February 2016. Your quality control unit signed these COA, which indicated that all required tests had been conducted on these batches. However, you told our investigator during the inspection that you signed these COA without having conducted all the tests for which you reported results on these COA. For example, your COA reported the results of identity and impurities tests that you never conducted. You falsified the COA you issued to your customers. Regulators and customers rely on COA for accurate information about the quality and sourcing of drugs and their components. Falsifying information about the quality of your drugs on COA compromises supply chain accountability and traceability, and may put consumers at risk. We acknowledge that, due to our inspection, your firm conducted a voluntary recall of all lots of **(b)(4)** API that you produced between June 2011 and February 2016. In your response to the inspection, you said you had no standard operating procedure (SOP) that required you to check the raw data before issuing COA, and that the quality control manager decided identity tests could be assessed by COA of raw materials. In addition, you said the quality control manager deleted columns for the results of these tests from your Product Analysis Data Sheet, and that although "…subsequent personnel involved in quality control had recognized this deviation, it continued without being corrected." Your response was inadequate. You did not identify the extent of falsification at your facility, or provide details of your plans to correct the conditions that led to falsification of your COA.
2/2/2018	South Korea	Cosmecca Korea 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 211.192(a)).** You released over-the-counter (OTC) **(b)(4)** drug products without data to support their conformance to specifications (e.g., strength). During our investigator's review of batch records for five of your OTC products, you could not provide analytical data to support the

			release of these products. One of your lab personnel also stated that you did not test every lot of finished products prior to release.
			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)). Our investigator documented multiple examples of falsifying laboratory records. Your quality control laboratory employee stated that he fabricated laboratory data for untested finished drug products by manipulating electronic laboratory records. For example, he changed the file names for test results of previously tested drugs so that the file names appeared to reflect the results of other lots of product. Your firm used this falsified laboratory data to determine the strength of your OTC **(b)(4)** drug products. Your response stated that your quality assurance manager instructed laboratory analysts to manipulate, falsify, or fabricate data
			3. Your firm's quality control unit failed to review and approve all drug product production and control records to determine compliance with all established, approved written procedures before a batch is released or distributed (21 CFR 211.192). Your OTC sunscreen drug product, **(b)(4)**, contains **(b)(4)** active ingredients: **(b)(4)**. Your batch records for lot **(b)(4)**of this product included concentration values for these active ingredients that did not match the data found in your instruments. You used the inaccurate data reported in your batch records to calculate potency results that were within specification, and you relied on these inaccurate results to release your product. However, when we used the instrument data instead of the results in your batch records to perform the same calculations, we found that the lot was out-of-specification (OOS) (superpotent) for **(b)(4)** active ingredients. Your quality unit did not identify this discrepancy prior to releasing this lot.
			4. Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records (21 CFR 211.68(b)). Laboratory equipment used to generate analytical data for release purposes lacked restricted access. For example, analysts shared usernames and passwords, and all users had administrator rights that permitted them to delete or modify files in high-performance liquid chromatography and *gas chromatography* equipment. You had no mechanism to facilitate traceability of the individuals who changed, adjusted, or modified data generated by computerized systems.

2/7/2018	China	Shanghai Weierya Daily Cheemicals Factory	**1. 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)).** Your firm released your finished over-the-counter (OTC) drug product, **(b)(4)** CT, without adequate testing for total count and objectionable microorganisms. You did not test each batch prior to release and distribution (e.g., batch **(b)(4)**). Your procedures permitted you to test one lot every six months. Without testing each batch, you do not have scientific evidence that all drug product batches conformed to specifications prior to release
			2. Your firm failed to ensure the identity of components, including your active ingredients and excipients from various suppliers (21 CFR 211.84(d)(1)). Your firm failed to adequately test incoming components, including excipients, you use in manufacturing your OTC drug product to determine their identity prior to use in manufacturing. You stated in your response that you only tested a subset of lots of incoming active pharmaceutical ingredients. You must test all lots of incoming components for identity prior to release by the quality unit.
2/18/2018	India	Alchymars ICM SM Private LImited	**1. Failure to have laboratory control records that include complete data derived from all laboratory tests conducted to ensure your API complies with established specifications and standards.** Our investigator found that your firm was falsifying laboratory data. For example, the number of colony-forming units (CFU) found on **(b)(4)** plates for **(b)(4)** water point-of-use tests differed substantially from the number recorded on your **(b)(4)** water report. For multiple points of use, your analyst reported far fewer CFU than observed on the plate by our investigator. In addition, while you reported absence of growth on a selective media plate used to detect objectionable microorganisms, our investigator observed growth on this plate. This is concerning because you use **(b)(4)** water to manufacture products, such as **(b)(4)** API, that are intended for use in sterile injectable dosage forms. We acknowledge your decision to suspend production of **(b)(4)** and **(b)(4)** API based on your risk assessment, and your commitment to a third party data integrity assessment. We also acknowledge your commitment to conduct a risk analysis and data review for distributed products, and to sanitize and validate the **(b)(4)** water system. We request that you notify FDA before resuming production of **(b)(4)** and **(b)(4)** API for U.S. supply.

			In response to this letter, provide your data integrity remediation efforts as requested in the Data Integrity Remediation section of this letter below. In addition, provide the following: • An independent assessment of your water system design, control, and maintenance; • A comprehensive corrective action and preventive action (CAPA) plan for improving design, control, and maintenance of your water system; • Your **(b)(4)** water system validation report; • A summary of improvements made to your water system design, as well as to your program for ongoing control and maintenance; • The total count and endotoxin limits that you currently use for this system.
			2. Failure to properly maintain equipment and to keep complete records of major equipment maintenance. Our investigator found damaged product-contact surfaces on your multi-product equipment. For example, the manhole gasket of **(b)(4)**111 was deteriorating and wrapped in peeling tape. A gasket on the **(b)(4)**102 was also cracked in one area and wrapped in peeling tape. Your SOP/ENG/39-1, *Gasket Management for Equipments and Pipelines which are in Direct Contact with the Product*, section 4.18, requires you to replace gaskets in critical areas, including gaskets for **(b)(4)**111 and **(b)(4)**102, **(b)(4)**. Your firm was unable to provide gasket replacement records for this equipment during the inspection. Furthermore, the most recent records of your firm checking the condition of the gaskets for **(b)(4)**102 were from January 2017, more than **(b)(4)** before our inspection. This is a repeat observation from our February 2015 inspection. We also note that you have found deteriorating gaskets to be the root cause for finished API particle complaints. Your response is inadequate. You stated that the “involved gasket was immediately substituted” but did not evaluate all other gaskets on your manufacturing equipment. You indicated that you will update your procedure to require a supervisor walk-through to assess product contact surfaces, but did not include sufficient detail (e.g., frequency of equipment inspection). You also failed to address the lack of gasket maintenance records. In response to this letter provide a comprehensive assessment and corrective action and preventive action (CAPA) plan to address the adequacy of your maintenance program for all equipment. This systemic assessment and CAPA should also remediate your maintenance

			record deficiencies. In addition, provide procedures that specify the frequency of gasket assessment and your preventive maintenance replacement requirements.
2/23/2018	China	Zhejiang Ludao Technology 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 firm lacks basic laboratory controls to prevent changes to paper and electronic records for your over-the-counter (OTC) drug products. You were not able to provide analytical test data for three batches of **(b)(4)** spray and one batch of **(b)(4)**. We found that you created certificates of analysis (COA) for these four batches before they were manufactured and tested. When questioned, your firm acknowledged falsifying the analytical test results on the COA you used to support release and distribution of **(b)(4)** spray and **(b)(4)** drug products to the United States. In addition, we found three electronic data files in the electronic recycle bin of the stand-alone HPLC system you used to test finished drug product **(b)(4)** spray. Because this instrument lacks back-up and audit trail capabilities, we could not determine how frequently test data obtained prior to "official" batch testing was discarded. You were unable to explain why these electronic files were deleted. CGMP-related data must be retained by a laboratory to enable appropriate assessments and decisions by the quality unit regarding batch disposition and to demonstrate ongoing control. In your response, you provided a revised procedure that requires retention of all test-related records and implements routine data review. Your response also committed to upgrading your analytical instrumentation to comply with CGMP requirements. However, your response was insufficient. You did not perform a retrospective evaluation of the scope of poor data retention practices in other electronic data systems and assess the potential impact on your drug products. Your response also failed to provide details about the audit trail capability or adequately describe validation of the new HPLC system. See the Data Integrity Remediation section of this letter below.

2/23/2018	Hong Kong China	Nan San (HK) Pharmaceutical Factory Limited	**1. 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 for each batch of drug product required to be free of objectionable microorganisms, appropriate laboratory testing, as necessary (21 CFR 211.165(a) and (b)).** Your firm failed to test all batches of over-the-counter (OTC) topical liquid analgesics for conformance to their specifications before releasing each batch. For example, you did not perform microbial limit tests for each batch of your Easy-Flex analgesic lotion released between 2013 and 2016. Instead, you performed microbial limit testing on one batch in 2013, and reported the same results to release subsequently-manufactured batches to the United States. You also used a contract laboratory to conduct finished product testing. Although your finished drug products contain **(b)(4)** active ingredients, your contract laboratory only tested for the strength and identity of one of those ingredients in the finished product testing on which you relied to release your drug products.
			4. 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)). Your firm labeled your drug products with a **(b)(4)**-year expiration date without adequately assessing the stability characteristics of these drug products. Your firm does not have adequate stability data to support the assigned expiration date
3/9/2018	Dominican Republic	Labocont Industrial SRL	**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 firm does not ensure that complete data from assay testing of your finished drug products and active pharmaceutical ingredients (API) are maintained and reviewed by your quality unit. For example, our investigator observed that an analyst failed to document absorbance data generated during assay analysis, and only reported calculated results. Because you do not document and maintain complete data from your analyses, it is not possible to evaluate whether the method was followed and data is valid, or to substantively investigate sources of deviations and variation in your laboratory. It is essential that all data generated during analysis is maintained and reviewed to determine whether laboratory

			procedures are followed, and raw materials and drug products conform to established specifications. In response to this letter: • Provide a comprehensive investigation into the inadequacies in data records and reporting for all products manufactured for the U.S. market and within expiry. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. In addition, describe all parts of your facility's operations in which CGMP information is not recorded and maintained. Include a corrective action and preventive action (CAPA) plan to remediate data recording and retention practices throughout your operation. • Provide a risk assessment summarizing the affect of incomplete data on assessing laboratory control and product quality. • Provide a detailed corrective action plan that describes how you intend to ensure the reliability and completeness of all the data you generate, including analytical and manufacturing data. This should include procedures that detail your documentation, data evaluation, review, retention, and quality oversight practices. Outline how you will assess your corrective actions for effectiveness.
3/15/2018	India	Keshava Organics Pvt. Ltd.	**1. Failure to adequately investigate out-of-specification results and implement appropriate corrective actions.** Your investigations of out-of-specification (OOS) results were inadequate. For example, in multiple instances, you disregarded the original failing result based on a retest, but you lacked a Phase 1 laboratory investigation to support invalidation of the result. You also often lacked Phase 2 investigations to evaluate your manufacturing operation for potential root causes. Your response includes a retrospective review of OOS results. Your review shows a pattern of recurring, similar OOS results for which investigations were insufficient, including a lack of corrective actions and preventive actions (CAPA). Notably, your response adds that it was impossible to make reliable retrospective root cause determinations for the failing results and provide scientific rationales for decisions because considerable time had elapsed since the original OOS occurrences. Timely investigations are essential for providing credible information and scientific evidence for laboratory error hypotheses.

			We also found that you investigated numerous OOS results between February 2015 and April 2017 as “incidents” and not as OOS results. Your “incident” procedure did not require a substantive investigation of OOS results. Your response acknowledges that this procedure was inadequate and that consequently your decisions regarding OOS results were not supported by sufficient inquiry and scientific rationale. You also commit to not invalidate OOS results without appropriate scientific justification and to use your OOS procedure in the future. 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/guidances/ucm070287.pdf. In response to this letter, provide the following. • 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 establish laboratory root cause, determine adequacy of the CAPA, and ensure that other laboratory methods vulnerable to the same root cause are identified for remediation. For any OOS with inconclusive or no root cause identified in the laboratory, include a thorough review of production (e.g., batch manufacturing records, adequacy of the 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. • An independent assessment of your system for investigating OOS results. Include a CAPA to remediate OOS investigations at your facility. Elements of your CAPA should include, but not be limited to, immediate laboratory investigation of OOS results, enhanced quality assurance participation in investigations, identification of adverse laboratory control trends, and proper initiation of the Phase 2 manufacturing quality investigation stage. • An independent assessment and CAPA of your overall investigation systems, including: investigating deviations, atypical events, OOS results, complaints, and failures. The CAPA should include but not be limited to, enhanced investigation competencies, improved procedures, and substantial improvements in quality unit oversight of investigations.
			2. Failure to maintain complete laboratory control records for test methods.

			In several instances, you failed to maintain complete data for API tested and distributed to the U.S. For example, we found test data sheets with missing sample weights for identity testing, batch/lot numbers for reference standards and reagents, equipment identification, and complete thin layer chromatography data for related compounds. In response to this letter: • Provide a comprehensive investigation into the inadequacies in data, records, and reporting. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. In addition, describe all parts of your facility's operations in which CGMP information is not recorded and maintained. Include a CAPA to remediate data recording and record retention practices throughout your operation. • Provide a risk assessment summarizing the effect of incomplete data on assessing laboratory control and product quality. • Provide a comprehensive corrective action plan, with a target date, to ensure that laboratory records are complete.
3/29/2018	South Korea	Hanbul Co., Ltd dba Hanbul Cosmetics 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 firm could not provide raw data to verify that you performed microbiological finished product testing for your over-the-counter (OTC) drug products.
			3. 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 records do not include significant production details, including but not limited to weights and measurements of raw materials used in the manufacturing process, start and stop times of **(b)(4)** processes, signatures verifying each significant step in the manufacturing process, and copies of finished product labeling.
4/18/2018	Mexico	Degasa S.A. De C.V.	**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 firm was unable to provide complete raw data related to the qualification of your "**(b)(4)**" water system. You lacked basic information (including missing sanitization data) to assess water system performance. According to your employee, half the data you generated over a year was lost. Your laboratory also lacked data such as weight of samples, test methods, records of calculations performed, standards used for release of final products, and water monitoring data. Our inspection also indicated that your water system is not suitable for its intended use. Specifically, our findings indicate that your water system was not appropriately designed, controlled, and maintained to consistently produce high-purity water. Water is a major ingredient in your drug products. It is essential that you employ a water system that is robustly designed, and that you effectively control, maintain, and monitor the system to ensure it consistently produces water suitable for pharmaceutical use that conforms to the USP monograph for purified water and appropriate microbial standards. We acknowledge your commitment to update your procedure for laboratory records. However, you did not address how you will assure that procedures are appropriate, properly implemented, and followed. You also did not adequately address the impact of your insufficient data on decisions made by your firm regarding manufacturing and product quality. In your response to this letter, provide the following: • A comprehensive independent evaluation of the water system design, including a thorough corrective action and preventive action plan (CAPA) to install and validate a suitable water system. • An effective program for ongoing control, maintenance, and routine monitoring that ensures the remediated system consistently produces water that meets USP Purified Water monograph specifications and appropriate microbial limits. Regarding the latter, your topical products necessitate significantly tighter total count action limits than those currently used by your firm. • Investigation of the missing water system data, including root causes, and your CAPA plan. Include a risk assessment of the impact on product quality of using water from this system in the manufacture of your drug products. • A retrospective review of both in-process and finished product test results to determine where product quality may have been compromised due to your practice of not maintaining complete analytical data.

			• A comprehensive assessment of the documentation systems used throughout your manufacturing and laboratory operations to determine where else you lack complete records. Include a detailed CAPA plan with systemic remediations to assure your facility maintains complete records. The CAPA should include, but not be limited to, revised procedures, training, and systemic actions implemented to assure integrity of all CGMP records.
4/19/2018	China	Lijiang Yinghua Biochemical and Pharmaceutical Co. Ltd.	**1. Failure to exercise sufficient controls over computerized systems to prevent unauthorized access or changes to data.** Laboratory equipment used to generate analytical data for batch release purposes by your quality unit lacked restricted access. For example, the high-performance chromatography (HPLC) and gas chromatography systems each had a single username with administrator rights. All users could delete or modify files, and there was no mechanism to trace individuals who may have created, modified, or deleted data generated by computerized systems. In your response to a previous FDA inspection conducted March 30 to April 3, 2015, you committed to: • enabling the audit trail function on laboratory electronic instruments; • assigning unique user names and passwords for each staff member; and • authorizing **(b)(4)** levels of accessibility to prevent electronic data from being deleted, removed, transferred, renamed or altered. In the October 2017 inspection, our investigator observed that you had not implemented any of these promised corrective actions.
			2. Failure to maintain complete data derived from all laboratory tests conducted to ensure your API and intermediates comply with established specifications and standards. Your firm performed HPLC assay testing for **(b)(4)** API release to the United States, along with stability and intermediate testing, on your Waters HPLC system between September 25, 2011, and May 5, 2017. Official quality control data packages presented to the quality unit for batch disposition decisions reported the results of testing performed during this timeframe on this equipment. During our inspection, when we sought to reconcile assay results reported in the quality control data package for a released batch with the underlying electronic data, you responded that you could not provide the electronic data from laboratory analyses on this equipment for the above period of several years. You explained that the electronic data in question had been deleted by accident and was no longer available.

			In your response, you stated that the electronic data had been downloaded to a "mobile hard disk for backup" and that you would be able to recover the data after you have upgraded your HPLC software. However, you did not include evidence to support recovery of deleted electronic data or demonstrate how you will prevent such deletions from recurring in the future.
			3. Failure to document, explain, and investigate any deviation from established procedures. During the inspection, our investigator reviewed the electronic HPLC injection history for **(b)(4)** intermediate stability sample, batch **(b)(4)**. The history indicated that the same vial was injected twice on June 14, 2017. The first injection was not included in the final data packet provided to the quality unit for batch review, and the intermediate batch was ultimately cleared for and used in manufacturing a finished lot of **(b)(4)** API, batch **(b)(4)**. According to your quality control analyst, the first injection appeared abnormal because it did not show a peak at the expected retention time. The second injection, within specification, was used to release the batch. There was no documentation, explanation, or investigation of the abnormal result of the first injection. Our investigator also observed similar instances in which abnormal injections were disregarded without investigation. In your response, you stated that you conducted a deviation investigation of batch **(b)(4)** on October 21, 2017, and you started retesting retention samples of related batches at that time. Your response is inadequate because it lacks details of this deviation investigation. It also lacks a comprehensive assessment and remediation of your overall system for investigations of deviations, atypical events, complaints, out-of-specification results, and failures.
			4. Failure of your quality unit to review and approve all appropriate quality-related documents. Your quality unit approved the certificate of analysis (COA) for release of an API batch to your customer before testing was complete and available for review. During the inspection, our investigator reviewed the COA for **(b)(4)** API batch **(b)(4)**. Your quality unit reviewed and approved this COA on May 29, 2015. However, the test for related substances on this batch was not performed until May 30, 2015. During the inspection, your

			quality control manager explained that this specific COA had been released early to the quality unit because it was urgent and needed to be provided to your customer. In your response, you summarized your standard operating procedures for testing, reviewing, and approving COA. Your response did not explain the reasons for this failure or indicate how your proposed revision to the reporting structure and approval procedures will prevent recurrence.
5/9/2018	India	Reine Lifescience	**1. Failure to validate and verify the suitability of analytical methods.** You lacked documentation of method validation or verification of your analytical methods. Our investigator also observed analytical data in a folder named "PD Trial." While the folder was normally intended for product development, the folder contained batch data for API, and results appeared to differ significantly from recorded test results. In your response, you committed to completing method validation and performing an "impact assessment" for commercially distributed batches by February 2018. Your response is inadequate because you did not provide updated procedures that will implement use of only validated (or verified, if compendium is used) methods for testing future batches of API intended for the U.S. supply chain. Also, you have not provided any updates on your method verification/validation or impact assessment. In response to this letter, provide: • a summary of method validation and verification studies for all analytical methods used for product release; • a summary of the impact assessment for released batches; • improved procedures regarding validation/verification requirements and updated analytical methods; • a comprehensive, independent review of your laboratory practices, methods, equipment, and analyst competencies. Based on this review, provide a detailed corrective action and preventive action (CAPA) plan to fully remediate your laboratory system. • a global CAPA plan as requested below under "Data Integrity Remediation."
			2. Failure to exercise sufficient controls over computerized systems to prevent unauthorized access or changes to data, and failure to have adequate controls to prevent omission of data.

			Our investigator observed that the audit trail feature was disabled on instruments you use for quality control testing of your API, including your high performance liquid chromatography system. Your analytical systems also lacked controls to prevent users from deleting or altering electronic data. For example, your quality assurance executive, who also performed your analytical tests, had administrator access to each system. In your response, you committed to validating all computerized systems with incorporation of audit trails, restrictions on data, and user-access controls by March 31, 2018. Your response is insufficient because it does not include interim control measures and procedural changes for the control and review of analytical data. You also do not specify who will have administrator privileges on your analytical instrument systems used for CGMP quality control testing. In response to this letter: • provide a summary of your interim controls to prevent deletion and modification of data; • define the roles and responsibilities of personnel who have access to analytical instruments and data; • provide a standard operating procedure (SOP) that ensures that all quality control tests are performed by an analyst and receive second-tier review (e.g., by a manager) from a separate individual; • detail the associated user privileges for each analytical system; • provide a detailed summary of your procedural updates and associated training for user role assignment and controls; and • provide detailed procedures for your review of audit trail data.
5/9/2018	US	Cerno Pharmaceutical	**3. Your firm failed to maintain adequate written records of major equipment maintenance and use (21 CFR 211.182).** You do not have equipment use logs for the blender and filler you use for manufacturing liquid products. Your firm uses combined “Room/Equipment Cleaning and Use Logs” to document equipment cleaning and use, but the logs do not contain adequate information to document who performed what operations and when. For example, our investigator asked you whether the log entries “**(b)(4)**” on May 26, 2017, and “**(b)(4)**” on July 31, 2017, indicated

			cleaning of the mixer, filler, or room. You did not know. Furthermore, multiple fields in the logs were blank. In your response, you provided the same combined room and equipment cleaning and use logs for Suites **(b)(4)**, **(b)(4)**, and **(b)(4)** that our investigator collected at the inspection. These combined logs are unacceptable because they do not show, for each piece of equipment, the date, time, product, and lot number of each batch processed, with signatures. In your response, provide copies of your revised equipment logs demonstrating how your will account for all the information for each piece of equipment. Also, provide the controls you are putting into place to ensure your operators use the logs correctly and maintain them properly.
5/9/2018	China	Nox Bellcow Cosmetics Lo. Ltd.	**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)).** You failed to maintain data generated for numerous tests performed on your drug product. For example, during the inspection, you were not able to provide complete data for microbial, pH, weight, and dimension tests performed on your drug product. In addition, you were not able to provide complete data to support testing of your API, in-process testing for **(b)(4)**, and microbial testing of **(b)(4)**. You only reported final calculated results on your CoA and in analytical laboratory records for each of the tests performed. In response to this letter, include the following: • Describe how you will ensure that test methods and equipment are adequately validated, verified, or calibrated at appropriate intervals and fit for purpose. • Provide a comprehensive, independent review of your laboratory practices, methods, equipment, and analyst competencies. Based on this review, provide a detailed CAPA plan to fully remediate your laboratory system. Your plan should also include your process for evaluating the effectiveness of the implemented CAPA.
			5. 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, you could not provide stability data to support the **(b)(4)** expiration date for your drug product. In addition, you indicated that you did not perform any ongoing monitoring of stability for your product. In response to this letter, provide your plan, with timelines, to develop and implement a complete drug stability program. This plan should also include an assessment of the stability of drug product currently on the U.S. market.
5/14/2018	China	Jilin Shulan Synthetic Pharmaceutical Co Ltd	**1. Failure to document known deviations and out-of-specification results and conduct a thorough investigation.** *Undocumented manufacturing deviation* You failed to ensure that manufacturing process deviations are documented, and any critical process deviations are investigated, and resolved. Specifically, the **(b)(4)**. Our investigator found a note in your batch record stating that the **(b)(4)**(which violated the process) and the operator was to be fined 50 yuan. There was no formal deviation report documented. You failed to investigate the effects of this deviation on product quality, nor did you evaluate the criticality of this process parameter. In your response, you said the operator violated your procedure for **(b)(4)**. Your response was inadequate because you did not explain why the operator did not follow the procedure. Also, you did not explain how you will ensure all deviations are documented and critical deviations are investigated as required. *Dual sets of laboratory records and uninvestigated OOS results* Our investigator also found that you failed to document, investigate, and resolve out-of-specification (OOS) results in your laboratory. The investigator identified two sets of laboratory testing records for four **(b)(4)** batches and five **(b)(4)** batches: one set of records included OOS results; the second set included results within specifications. You could not provide evidence to support the passing results. You also failed to conduct investigations for the OOS results. Your quality department acknowledged this practice during the inspection. In your response, you stated that the failure to investigate these deviations was due to the staff's lack of CGMP knowledge. You provided retest results and your updated "*Out-Of-Trend (OOT) Manage Procedure*." Your response was inadequate because you addressed OOT results instead of OOS results; you did not provide your investigations into the original OOT/OOS results. You also failed to identify the root causes of the OOS results.

			For more information about handling failing, OOS, OOT, 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/guidances/ucm070287.pdf.
			2. Failure to exercise sufficient controls over computerized systems to prevent unauthorized access or changes to data, and failure to have adequate controls to prevent omission of data. Our investigator found that audit trails in your standalone instruments (**(b)(4)** high-performance liquid chromatography systems, **(b)(4)** gas chromatography systems, and **(b)(4)** infrared radiation system) were not enabled. You also did not have other mechanisms for recording and monitoring any changes to data generated on these instruments. Your firm backed up electronic data from these instruments to a portable drive **(b)(4)**. However, the drive was not password-protected, and it was stored in an unlocked drawer in an unlocked office. Our investigator also found that operators had full system permissions, including the ability to modify and delete files. For example, our investigator found files related to system suitability tests for **(b)(4)** in the recycle bin folder on the computer connected to high performance liquid chromatography system. In your response, you committed to upgrading your chromatography computer systems to a software version with audit trails. Your response was inadequate because you did not provide appropriate procedures or details on your updated computer systems to demonstrate how you will restrict access or changes to your data.
			3. Failure to record activities at the time they are performed. Our investigator found numerous examples of your failure to record manufacturing operations contemporaneously with their performance. For example, our investigator discovered blank batch production records that were pre-signed by your operator, partially-completed batch records, and batch records with data changes in pencil without any justification. Our investigator also identified two process batch records for the same operation for **(b)(4)** batch **(b)(4)**; one record was partially filled out by one operator and the second record was completed by a different operator.

			In your response, you indicated that these deficiencies were due to the lack of oversight by your quality assurance department. Your response was inadequate because you did not explain why your quality unit did not ensure contemporaneous documentation or exercise adequate oversight.
5/18/2018	South Korea	Kolmar Korea Co Ltd	**2. Your firm failed to follow written procedures applicable to the quality control unit (21 CFR 211.22(d)).** Your firm failed to ensure that your employees followed your written procedure, *Document Control SOP KO-3 Rev. 9*, requiring quality unit approval prior to discarding documents and records. Our investigator observed documents and records, including batch production records, certificates of analysis, and laboratory worksheets, that were torn and discarded without documented quality unit approval. In your response, you acknowledged that your personnel were inadequately trained in CGMP-compliant document control practices and procedures. Your firm's response identified plans to address the issues mentioned above by discontinuing poor CGMP practices, revising procedures, and providing employee training. Your response is inadequate because you did not address the effectiveness of your training program, and specific measures you will take to ensure that your employees follow written procedures. In response to this letter, provide: • A detailed plan for evaluating the effectiveness of your training program. • A complete assessment of documentation systems used throughout your manufacturing and laboratory operations to determine where documentation practices are insufficient. Include a detailed CAPA plan that comprehensively remediates documentation practices, and ensures you retain complete and accurate records.
5/23/2018	Australia	ITD Australia Ltd	**1. You firm failed to establish and follow adequate required laboratory control mechanisms, including any changes made to them which were drafted by the appropriate organizational unit and reviewed and approved by the quality control unit (21 CFR 211.160(b)).** Your firm reported multiple microbial test results for the **(b)(4)** system used to **(b)(4)** as ">80 CFU" when the actual number of CFU was too numerous to count. Days after you obtained these results, you resampled and diluted the new sample until colonies could be counted. If the diluted sample was within acceptable limits, you disregarded the original result. Your **(b)(4)** sample collection and test methods could have masked failing microbial results and your **(b)(4)** system may not have been suitable to **(b)(4)**.

			Your response stated that you will modify the sample size to ensure a proper count at each sampling event. Your response is inadequate. You failed to evaluate how your practice of disregarding original results may have affected the reliability of data about your **(b)(4)**system. In your response to this letter, provide the scientific rationale for your modified **(b)(4)** sample collection and test methods. In addition, assess the product quality and safety risks of using potentially contaminated **(b)(4)**.
			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)). Our review of your laboratory records revealed that you failed to report non-conforming test results on multiple occasions in multiple parts of your operations. *Analytical Testing* During testing of **(b)(4)** exhibit batch **(b)(4)** in March 2016, three consecutive identity test failures occurred. The fourth test passed and you reported this conforming result. You did not include the three failures in the data package submitted to the quality unit for review or your application submission for this product. You did not conduct an investigation into the non-conforming results. At the time of the inspection, you were unaware that your analysts had not reported the failing results to your quality unit for review. Your response stated that you will revise your procedures and train your analysts to assure that all data is reported. Your response is inadequate. You failed to investigate the nonconforming identity test results. You also failed to evaluate other **(b)(4)** test records to identify other unreported nonconformances. You also failed to determine whether there were unreported nonconformances for commercial products that you released for distribution. *Microbial Testing* During microbial testing of your cleaning water, results for samples collected on November 23, November 24, and December 1, 2017, were not reported before the **(b)(4)** plates were destroyed. Your firm stated that the plates were destroyed because the incubator had failing temperature mapping results. Your investigation into the failing temperature mapping results stated the plate results were passing but no individual plate counts were recorded. In your response, you stated that you have reviewed all 2017 results and found them to be complete. Your response is inadequate. You did not explain your rationale for limiting your review to a single year, nor did you include sufficient details to support your conclusion that

			2017 records were complete. You also have not evaluated the effects of your incomplete microbial test records on the quality and safety of your products.
			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 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 review high performance liquid chromatography (HPLC) assay data for release and stability of your **(b)(4)** product. During review of your HPLC's electronic data, we discovered at least 100 "test" injections. Your analytical procedures and methods do not discuss "test" injections. Your laboratory supervisors did not review these injections prior to submitting the data packages for approval. You informed our investigator that, per procedure, your laboratory supervisors and quality unit only review the chromatograms printed and submitted to them by the analysts. Because your analysts did not print the chromatographic results of "test" injections, neither laboratory supervisors nor your quality unit reviewed these injections. Your procedure did not require review of the underlying electronic records or data by either laboratory supervisors or the quality unit to ensure their accuracy or completeness. Accordingly, your quality unit relied on incomplete data for batch disposition decisions. Your quality unit failed to ensure the adequacy of procedures for assessing the quality of your drug products. We observed other examples of your quality unit's failure provide adequate data management and review procedures, including the following: • Your analysts performed manual integration of chromatograms without instructions that describe when manual integration is permitted and how it is to be done. • You did not have procedures for reviewing audit trails or electronic data for the Fourier-transform infrared spectroscopy or ultraviolet systems.
5/31/2018	Taiwan	Taiwan Biotech Company Ltd	**1. Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas (21 CFR 211.42(c)(10)(iv)).** During the inspection, our investigator found the following issues related to your sterile over-the-counter **(b)(4)**: **(b)(4)** and **(b)(4)**. *Environmental and Personnel Monitoring Alert Investigations*

			Our investigator identified several environmental monitoring plates from the ISO 5 (Class A) and the surrounding ISO 8 (Class C) clean areas which exceeded action limits and for which investigations were not initiated. On September 6, 2017, our investigator found containers storing environmental and personnel monitoring microbiological samples, dated August 30 and 31, 2017. Numerous samples lacked basic documentation, including missing colony-forming unit (CFU) counts and the identity of the person who collected the sample. At the request of our investigator, your firm enumerated CFU for these plates. While several plates exhibited counts outside of action limits, your firm had not initiated investigations. As an example, a sample taken for **(b)(4)** lot **(b)(4)** yielded an extremely high count of 140 CFUs in your ISO 5 area. The action limit for this critical area is < **(b)(4)** CFU. Due to our investigator's findings, you initiated investigations during the inspection regarding the undocumented microbial growth. On September 7, 2017, you provided a copy of these initial investigations. Notably, when asked by the investigator to provide all deviations from environmental monitoring limits, your firm had reported no results outside limits for over a year prior to the inspection date. This reported level of environmental control is dubious, in that during the current FDA inspection, several environmental monitoring samples were found to have significant growth, and these results had not been enumerated and recorded. Your failure to accurately account for numerous environmental monitoring plates, enumerate the results, and fully investigate the systemic flaws that led to the unreported data raises questions regarding the integrity of data generated by your firm. *Insufficient surface monitoring* On September 6, 2017, our investigator determined that your microbiology technician had not collected required surface samples since September 1, 2017. Further, our inspection revealed that your firm lacked environmental sampling during your **(b)(4)** and **(b)(4)**. Your management acknowledged that deficient environmental monitoring on these production **(b)(4)** had been occurring for approximately 1–2 years. In your response, you stated that you created a standard operating procedure (SOP) to track your environmental monitoring samples, and committed to hiring more personnel to supervise activities. However, your response was inadequate. You did not provide the SOP or indicate plans to fully remediate your environmental monitoring program. You also did not

			indicate whether all unaccounted samples identified by our investigator were enumerated, and if investigations and risk assessments were initiated in response to any results outside established limits. In addition, you did not indicate whether a comprehensive review of all laboratory practices and controls was conducted to ensure reliable laboratory operations, including but not limited to accurate reporting of all laboratory data. In response to this letter, provide the following. • Further details on additional microbiological plates that were not initially enumerated and the results that your firm ultimately obtained for these plates. Also, summarize all lots made without sufficient environmental monitoring on the **(b)(4)** and **(b)(4)**. Provide risk assessments for any potentially affected products marketed to the United States. • Your investigations of multiple deviations from action limits for ISO 5 and other clean areas. • A thorough, independent assessment with corrective actions and preventive actions (CAPA) for your environmental monitoring and personnel monitoring programs. For instance, your remediation should include adequate sampling procedures, media suitability, sample accountability (e.g., identification, storage, logging, analysis dates/times), appropriate locations and frequencies, proper responses to alert and action limits, routine identification of microbes isolated from cleanroom and personnel samples, and various other elements of an effective program. • A comprehensive, independent review of your laboratory practices, methods, equipment, and analyst competencies. Based on this review, provide a detailed CAPA plan to fully remediate your laboratory system. Your plan should also include the process you will use to evaluate the effectiveness of the implemented CAPA. • A comprehensive identification of all contamination hazards in your aseptic processes, equipment, and facilities. Provide an independent risk assessment that covers, among other things, all human interactions with the ISO 5 area, equipment placement and ergonomics, air quality in the ISO 5 area and surrounding room, facility layout, personnel flow, and material flow.
			3. Your firm failed to maintain written records so that data therein could be used for evaluating, at least annually, the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures (21 CFR 211.180(e)). Your annual product reviews (APR) only included batches shipped to the United States and the associated deviation investigations. The APR did not include batches shipped to countries other than the United States, but manufactured under the same conditions.

			For example, your 2016 APR of **(b)(4)** mL included only **(b)(4)** batches and two deviation investigations. However, in 2016, you manufactured **(b)(4)** batches of this product for all markets at your facility and conducted 16 investigations of which 15 were related to product yield failures. Because all the batches were manufactured using the same manufacturing operation, each of these batches should be included in your APR to allow meaningful trends to be detected. Your firm did not provide a sufficient response to this violation. For example, there was no indication that you are remediating your APR program or retrospectively reviewing trends by incorporating batches not shipped to the United States into annual reviews. In response to this letter, provide an assessment of manufacturing and quality data associated with each drug marketed to the United States. Include remediated procedures and retrospective trending to identify any adverse findings and determine the need for changes to manufacturing, control, or specifications.
6/21/2018	China	Henan Lihua Pharmaceutical Co. Ltd.	**1. Failure of your quality unit to review and approve all appropriate quality-related documents.** Our investigator observed numerous blank batch manufacturing records in an open cabinet in your manufacturing workshop office. Among these were multiple blank, product release forms marked with a red quality assurance release stamp as “Permitted to Leave [the] Factory.” Our investigator also observed two record issuance stamps for batch and page number in the open cabinet. These blank records and stamps were uncontrolled, although your standard operating procedure states that your quality unit is responsible for release of blank CGMP records. Your quality unit failed to control these records to assure that information entered on these forms is accurate and reliable. The use of uncontrolled records without quality unit review and approval poses a risk to data integrity and adequate assurance of product quality. FDA recommends that, if used, blank forms be controlled by the quality unit or by another document control method. In your response, you said the product release form was “stamped in advance for convenience of release and warehousing of products” from your facility. You also said the quality unit record controller “did not realize the risk of the damaged lock” on the cabinet containing the records and stamps.

			We note you revised your standard operating procedures and re-trained your quality personnel. Your response is inadequate because it does not provide assurance that your employees are adequately qualified and trained to perform their duties.
			2. Failure to maintain complete data derived from all laboratory tests conducted to ensure your API complies with established specifications and standards. You used a **(b)(4)** instrument (FK03011) for stability testing for multiple API, including **(b)(4)** and **(b)(4)**. You subsequently used the same instrument and software to perform in-process analytical testing. Our investigator reviewed the audit trail on this instrument and observed that the software was configured to permit continuous use of the "preview run" function and routine overwriting of previous runs. Only the final "preview run" **(b)(4)** in each project folder was retained. Our review of the audit trail demonstrated that multiple distinct **(b)(4)** were performed and that the length of each **(b)(4)** was consistent with the time required to perform blank, sample, and standard **(b)(4)**. It is essential to retain raw data to ensure the ability to reconstruct CGMP activities and to review raw data, as necessary, for CGMP control testing. In your response, you stated the software did not allow retrieval of "non-data acquisition **(b)(4)**," and you did not realize that you needed to retain the preview run data. We acknowledge that you intend to replace the affected **(b)(4)** instruments. However, procuring new instruments, installing new and upgraded data acquisition software, and enabling various features on software are not sufficient alone. These steps will be effective only if you implement appropriate procedures and systems to ensure that you retain data as required so that your quality unit can review production and control data and associated audit trails as part of evaluating whether your API complies with all established criteria for in-process and stability testing.
6/22/2018	China	Sichuan Friendly Pharmaceutical Co., Ltd	**3. Failure to design a documented, on-going stability testing program to monitor the stability characteristics of API and to use the results to confirm appropriate storage conditions and retest or expiry dates.** During the inspection, you were unable to provide data to support your **(b)(4)** API's **(b)(4)** shelf-life labelled to meet the United States Pharmacopeia. In your response, you indicated that you tested retain samples using a different pharmacopeia, and stated that data indicates your drug is stable. However, you also observed that your methods may differ from the USP and "maybe that the test results are not the same." You committed to test the retention samples of **(b)(4)** batches according to the

			USP monograph to confirm that the API meet specifications after storage for more than **(b)(4)**. Your response is inadequate because you did not commit to develop a complete stability program for your API or to demonstrate that your methods meet the USP label claim, and did not demonstrate that your test methods are stability-indicating. In response to this letter, provide the following: • An updated stability program, including stability-indicating methods, and methods that detect changes in the physical appearance of the API which could indicate degradation. • Retention sample test data for all batches of **(b)(4)** distributed to the U. S. market within expiry using stability-indicating methods.
			4. Failure to exercise sufficient controls over computerized systems to prevent unauthorized access or changes to data, and to have adequate controls to prevent omission of data. You used a non-validated Excel spreadsheet to calculate assay results for **(b)(4)** USP for product release and stability testing. Our investigator found that this spreadsheet lacked password protection and contained unlocked calculation formulas which were incorrect. During the inspection, your QC manager acknowledged that the formula in the spreadsheet used to calculate assay results was incorrect. Because of these incorrect formulas, multiple certificates of analysis (COA) contained inaccurate data. In your response, you identified multiple batches with incorrectly calculated release assay results, including instances of stability results that your spreadsheet calculated as in specification, but were in fact out-of-specification (OOS). Your response is inadequate because you did not adequately address these OOS results, and you failed to address the deficient data review process by your Quality Unit. Although you committed to validate your Excel spreadsheets, you failed to specify which spreadsheet controls will prevent unauthorized access, modifications, or deletion of data. Your response also lacked a comprehensive assessment and retrospective review of all data generated from all computerized laboratory systems used in CGMP operations. In response to this letter, provide the following: • A comprehensive assessment of your data review system used throughout your manufacturing and laboratory operations to determine where else it is deficient. Include a

			detailed corrective action and preventive action (CAPA) plan with systemic remediation to address deficient data review, including quality unit oversight. The CAPA should include, but not be limited to, revised procedures, training, and systemic actions implemented to assure the integrity of all CGMP records. • An assessment of all Excel spreadsheets used to support CGMP operations to identify and investigate the extent of inaccuracies, such as incorrect formulas and other deficiencies. Include a detailed CAPA plan to address the noted deficiencies and to prevent recurrence. • A retrospective review and risk assessment of all test data for API within expiry and distributed in the United States using computerized systems that lack sufficient control to prevent modifications and deletions. If you obtain OOS results based on this assessment, indicate your action plan, such as notifying customers and/or initiating recalls. • A comprehensive independent assessment of your overall system for investigations of deviations, atypical events, complaints, OOS results, and failures. Your CAPA should include, but not be limited to, improvements in investigation competencies, root cause analysis, written procedures, and quality unit oversight.
6/26/2018	China	Foshan Jinxiong Technology Co. Ltd.	**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).** You lacked complete information related to the production and control of each lot. For example, you failed to have specific identification for each lot of component, and production equipment, used in manufacturing. You also failed to have unique lot or control numbers for the distributed drug product. You provided our investigator with a list of more than **(b)(4)** batches manufactured in 2017 that lacked this basic information. In your response, you described your new lot numbering system and how you revised your production records. You also provided a copy of the revised production record.
6/27/2018	China	Zhuhai United Laboratories	**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 lacked adequate procedures for investigating, and scientific justification to invalidate, OOS results. *OOS Results for Assay*

			You initiated an investigation of an initial OOS assay result for **(b)(4)** batch **(b)(4)**, which was found to be significantly below specification (**(b)(4)**–**(b)(4)**%). You also initiated an investigation of an initial OOS assay result for **(b)(4)** batch **(b)(4)**, which also yielded a test result below specification (**(b)(4)**–**(b)(4)**%). In both cases, your brief investigations found no anomalies and only stated that it was possible that the sample glassware was not thoroughly cleaned. Although you did not identify a laboratory error and lacked scientific justification, you invalidated the OOS results. Your firm released both batches based on passing retests. Your acceptance of the passing results based on an assumed laboratory error was insufficient to invalidate the original failing result and conclude the investigation. Re-analysis of the actual solutions, test units, and glassware is an integral part of an investigation to determine whether a laboratory error may have occurred. This assessment, in tandem with hypothesis testing if initial re-examinations do not reveal a root cause, is instrumental in determining whether there was a causative laboratory error. Whenever a laboratory investigation lacks conclusive evidence of laboratory error, it is essential that the investigation extends to a thorough investigation of potential manufacturing causes. Your response acknowledged that there was “no scientific justification or studies performed to evaluate or prove this hypothetical root cause.” Since our inspection, your indicated that you have shown that the API may degrade in the presence of residual detergent in glassware. However, your response did not include your study data. *OOS Results for Residual Solvent* You initiated investigation P201611001 for an initial OOS result of **(b)(4)** parts per million (ppm) in your **(b)(4)**residual solvent test (specification: not more than **(b)(4)** ppm) for **(b)(4)** API batch **(b)(4)**. The investigation did not reveal laboratory testing anomalies. You tested another sample preparation three times and obtained results very close to the specification upper limit (**(b)(4)**, and **(b)(4)** ppm). You invalidated the initial failing result, stating that your statistical analysis showed a significant difference between the original value and the retest results. Your investigation lacked further assessment of the root cause of the failing result.

			You released the batch to use as an intermediate in your in-house production of **(b)(4)** batches of **(b)(4)** API (batches **(b)(4)**). It is not appropriate to use an "outlier test" to invalidate your API test results. Such statistical treatments do not identify the cause of an extreme observation and are only of informational use. In this case, your investigation included multiple retests that were near the upper limit of **(b)(4)** ppm, similar to the original OOS result. Furthermore, your OOS investigation procedure, Q0100012.001, was inadequate because it did not adequately address the need to retest the original sample and specify when a new sample should be tested. We acknowledge receipt of your revised OOS investigation procedure. However, your response is inadequate because it does not meet CGMP. Your response stated that you can use an outlier test in determining whether to "waive the requirement for conducting appropriate laboratory investigation to determine definitive or potential root cause(s) for the atypical result(s)." It is inappropriate for your procedure to permit waiver of this requirement. Your OOS procedure should specify that outlier tests cannot be used for anything other than auxiliary, informational purposes. Your response also indicated that your firm was retrospectively assessing effects of previously-reported OOS results on your products. However, your response did not provide related records to document your review or summarize findings. It is unclear whether the retrospective review included an evaluation of your use of the statistical outlier test to invalidate OOS results. In response to this letter: • Provide a retrospective review of all invalidated OOS results obtained for products on the U.S. market. Assess whether the scientific justification and evidence was conclusive. For investigations that established the laboratory root cause conclusively, determine the adequacy of the corrective action and preventive action (CAPA) plan and ensure the other laboratory methods vulnerable to the same root cause have been identified for remediation. For any OOS results that had an inconclusive or no root cause identified in the laboratory, include a thorough review of production, such as batch manufacturing records, adequacy of manufacturing steps, process capability, deviation history, and batch failure history. Provide a CAPA plan that identifies the potential manufacturing root causes for each such investigation. Include process improvements where appropriate.

			• Evaluate all instances in which a statistical outlier test was used to invalidate OOS results. Determine the potential effect on drug quality. • Assess your overall system for investigating OOS results. Provide a CAPA plan to improve the quality of OOS investigations. Your CAPA should ensure that your revised OOS investigations procedure includes improved quality unit oversight of laboratory investigations, identification of adverse laboratory control trends, and investigation of potential manufacturing causes when a laboratory cause cannot be conclusively identified. • Comprehensive independent assessment of your overall system for investigations of deviations, discrepancies, complaints, OOS results, and failures. Your CAPA should include, but not be limited to, improvements in investigation competencies, root cause analysis, written procedures, and quality unit oversight. Also include your process for evaluating CAPA effectiveness. 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/guidances/ucm070287.pdf.
			2. Failure of your quality unit to ensure that critical deviations are investigated and resolved. You did not adequately investigate findings from your February 2015 retrospective review of analytical chromatography data irregularities (e.g., data deletion, sample trial injections, and missing audit trails). You did not sufficiently expand the scope of your limited review to a larger data set when you found significant data integrity lapses. Your investigation was also insufficient because your corrective actions failed to prevent recurrence of major data integrity deviations. For example, our investigators found that your firm deleted the initial chromatographic injection of **(b)(4)** API, batch **(b)(4)**, during batch release testing performed several months after the retrospective investigation. Your response stated that you performed a further retrospective review (protocol SD-Q0100011.000) of analytical chromatographic data and found further residual solvents results with inappropriate integration, system suitability testing data showing non-consecutive injections of the reference solution, and repeat injections. Your response was inadequate because you did not include sufficient details to demonstrate that you confirmed the validity of initial test results. Such detail would include retest sample testing dates and results, comparison of retest data to original data, and your "comprehensive review records" for the batches included in the assessment. Your response also lacked an assessment of the root

			cause of data integrity breaches and corrective actions for any products that failed to meet specifications. In response to this letter, provide: • a copy of the deviation investigation, GOV-2017001, initiated in response to our inspectional findings; • completed reports for all review stages in your retrospective review (protocol SD-Q0100011.000) including related annex documents; and • the additional information requested in the Data Integrity Remediation section of this letter.
7/5/2018	India	Baxter (Claris Injectables Ltd)	**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 invalidated out-of-specification (OOS) results without adequate investigation and scientific justification. Examples include: a. In January, 2017, you obtained OOS results for the **(b)(4)** impurity during stability testing of **(b)(4)** injection batches **(b)(4)**. Your OOS investigation reports stated that the postulated cause was "poor column efficiency," although no chromatographic abnormalities were noted and system suitability criteria were met. During the inspection, your lab management indicated that retention times, theoretical plates, and tailing factor appeared appropriate and no specific root cause had been demonstrated. You repeated the analyses, obtained passing results, and invalidated the OOS results. In March, 2017, you obtained OOS results for the **(b)(4)** impurity during stability testing of **(b)(4)** injection batches **(b)(4)**. You suspected the analyst may have incorrectly rinsed the HPLC vials. New samples prepared and tested by a second analyst using both the original column and a new column, as well as old and new vials, also yielded OOS results. Although you lacked sufficient evidence, your investigation concluded that the OOS results were due to sample vial contamination. You invalidated the OOS results after obtaining passing results from testing retain samples. After the conclusion of the inspection you initiated a voluntary recall of five batches of **(b)(4)** drug product due to failing **(b)(4)** levels, superpotent assays, and **(b)(4)**, all obtained during stability testing and including batches **(b)(4)**.

			Notably, you informed FDA that the apparent root cause of the **(b)(4)** assay failures was excessive **(b)(4)** from your **(b)(4)**. However, the investigation lacked an adequate assessment of all other batches distributed to the U.S. and within expiry that may be potentially affected by **(b)(4)**. b. Your OOS investigation of the failure of **(b)(4)** batches **(b)(4)** to meet the **(b)(4)** specifications under accelerated stability conditions was also inadequate. You obtained OOS results of **(b)(4)**% and **(b)(4)**%, respectively (specification Not More Than **(b)(4)**%). While the investigation lacked a demonstrated assignable root cause in the laboratory, you obtained passing results during repeat analysis and invalidated the OOS without a Phase II production investigation. After the inspection, you recalled eight batches of **(b)(4)** due to superpotent assay and **(b)(4)** results obtained during stability testing. While use of substandard **(b)(4)** that allow excessive **(b)(4)** again appears to have caused the specification failures, your response lacked sufficient relevant information on the root cause and scope of this major problem. In both of the above instances, you failed to expand your OOS investigations in a timely fashion to address potential manufacturing causes. When an investigation lacks conclusive evidence of laboratory error, a thorough investigation of potential manufacturing causes must be performed. Your acceptance of the passing results from testing a new set of samples based on an unproven hypothesis was insufficient to conclude the investigations. Your response stated that you will revise your *OOS Management* procedure and perform a retrospective review of your OOS investigations. Your response was inadequate because it lacked identification of root causes and implementation of effective corrective actions and preventive actions (CAPA). It also failed to address inadequacies in the **(b)(4)** you received from your supplier(s), and whether they are still considered qualified for use by your firm. Notably, your firm has had a worrisome history of recalls due to substandard **(b)(4)**. In 2017, you recalled **(b)(4)** parenteral drug products due to recurring **(b)(4)** complaints. In 2010, your firm conducted a Class I recall of all lots of four parenteral products due to loss of **(b)(4)** integrity and non-sterility. Also, while your firm has discussed adding a **(b)(4)** as a corrective action for **(b)(4)**, it would not resolve ongoing issues relating to quality of container-closure raw materials or **(b)(4)** fabrication. Durability and quality of your large volume parenteral container-closure systems is critical to ensure their robustness until administration at a clinical facility, who will remove **(b)(4)**, and can temporarily store and then transfer the **(b)(4)** within the facility before use. Your response lacks a commitment to thoroughly review your **(b)(4)** dependability with

			respect to both container-closure raw material quality and **(b)(4)** fabrication process weaknesses. In response to this letter, provide: • A retrospective, independent 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 establish laboratory root cause, determine adequacy of the CAPA, and ensure that other laboratory methods vulnerable to the same root cause are identified for remediation. For any OOS results with inconclusive or no root cause identified in the laboratory, include a thorough review of production (e.g., batch manufacturing records, adequacy of the manufacturing steps, raw materials, process capability, deviation history, batch failure history). • Provide a summary report of the retrospective review of all OOS investigations for product that remain within expiry. Include a CAPA plan that identifies manufacturing root causes and specifies meaningful improvements. Include the product name, date of the original result, initial and retest OOS results, detailed rationale for invalidating the OOS result, and the outcome of your thorough reassessment. Also, include any additional market actions you intend to initiate because of the retrospective review. • A fully remediated OOS investigation procedure, including but not limited to modifications to ensure investigations expand to manufacturing operations when a root cause is not conclusively identified in the laboratory. • Updated investigation into the root cause of container-closure system failures leading to increased **(b)(4)**. • Testing of retain samples of batches of all drug products within expiry in the U.S. market that used the **(b)(4)**suppliers (i.e., raw materials, fabricators) associated with excessive **(b)(4)**. • A comprehensive, independent assessment of the quality of all **(b)(4)** container-closure raw materials (parts such as **(b)(4)**, etc.) and adequacy of all sites who perform **(b)(4)** fabrication processes. This thorough assessment should also include an evaluation of the adequacy of your qualification program for suppliers of container-closure raw materials (**(b)(4)** part suppliers) and manufacturers of both **(b)(4)** and **(b)(4)**. • A full description of your **(b)(4)** material sourcing process and **(b)(4)** manufacturing process for both **(b)(4)** and **(b)(4)**. Include the roles and responsibilities of all parties involved in the **(b)(4)** supply chain and production. Specifically, for all lot of **(b)(4)** produced since July 1, 2015, provide a detailed summary of all suppliers and manufacturers that you used for your **(b)(4)** materials, and vendor lot numbers. In each case describe who performed the **(b)(4)** formation, fabrication, and final assembly

			(including the specific nature of any in-house operations, such as use of **(b)(4)** operations). Include any subcontractors or other parties involved with material supply or fabrication. • Vendor-generated Certificates of Analysis (COA) for **(b)(4)** part manufacturers and suppliers, as well as **(b)(4)**fabricators and assemblers. • An assessment of your overall system for investigations into deviations, discrepancies, complaints, OOS results, and failures. Your CAPA plan should include, but not be limited to, improved rigor in reviewing the sources of variation in your operation that may cause deviations, failures, or defects, as well as an extensive remediation of your capabilities to ensure CAPA effectiveness.
			2. 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 observed an operator recording unreliable data. Specifically, on July 27, 2017, our investigator observed your operator entering data in your *Visual Inspection Test (VIT) For* **(b)(4)** *Line* document for **(b)(4)**injection, USP, batch **(b)(4)** a day after the operation was completed. The document stated that the visual inspections were performed on July 26, 2017. In response to our question regarding how portions of the documentation had been completed without corresponding data, a senior manager at your site could not provide an explanation. We acknowledge your efforts to update SOPs and retrain personnel. However, your response is inadequate because you did not perform a retrospective assessment into other possible events in which data were not reported accurately or contemporaneously. In response to this letter, provide: • A comprehensive, independent risk assessment of production records including but not limited to your visual inspection documentation to determine the completeness, consistency, and accuracy of reported data. Indicate how you determined that the data you used to release product was attributable, legible, contemporaneously recorded, original or a true copy, and accurate. Include a re-examination of retain samples. • Provide a complete assessment of documentation systems used throughout your manufacturing and laboratory operations to determine where documentation practices are insufficient. Include a detailed CAPA plan that comprehensively remediates documentation practices, and ensures you retain complete, contemporaneously prepared, and accurate records.

7/23/2018	US	Milbar Laboratories Inc.	**2. Your firm failed to reject any lot of components that did not meet the appropriate written specification for identity, strength, quality, and purity (21 CFR 211.84(e)).** You used water from your **(b)(4)** purified water system with microbiological contamination that is objectionable in view of the component's intended use. This water is a component used in manufacturing your topical OTC drug products. On September 12, 2017, your aerobic plate count result for water was 8400 CFU/mL, exceeding the limit **(b)(4)**. You used water from this system as a component to manufacture multiple lots of OTC drug products without investigating and remediating the system. Several days later, your contract-testing laboratory tested a new sample from the system that passed the action limit. You accepted the passing result and released multiple lots of OTC drug products on September 21, 2017. Your contract laboratory's investigation, approved on October 4, 2017, found the growth to be gram-negative rods. The microbes were not speciated. The investigation concluded there was no assignable cause. Your response states that you now perform all water microbiological testing **(b)(4)**. You also implemented a cleaning and "sanitation" record for the **(b)(4)** water hose and water system, and perform **(b)(4)** water testing. In addition, you initiated a preventive maintenance schedule for your **(b)(4)** water system, updated your standard operating procedures (SOPs), and trained your staff. Your response is inadequate. Your response failed to adequately address the potential risk to your product posed by objectionable microbiological contamination in your water system. In response to this letter, provide a thorough investigation and root cause analysis of the sources of microbiological contamination in your water system. Also provide an enhanced program for ongoing control, maintenance, and monitoring to ensure the remediated water system consistently meets Purified Water, USP, monograph specifications and appropriately stringent microbial limits.
7/17/2018	Japan	Yuki Gosei Kogyo Co., Ltd.	1. **Failure to maintain complete data derived from all laboratory tests conducted to ensure your API complies with established specifications and standards.** Your firm does not ensure that complete data from testing of your API are included in the official batch record and reviewed by your quality unit. For example, you reported passing results for related substances testing of **(b)(4)** lot #**(b)(4)** analyzed starting at **(b)(4)** on July

			28, 2015. However, our investigator found unreported analyses including out-of-specification (OOS) results for the same lot acquired earlier on the same date, and on the next day as the reported results. You failed to include this data to be reviewed by your quality unit prior to the release of the lot. Our investigator documented the same pattern with other products not intended for the U.S. market. In your response, you explained that this "trial analysis" was performed on the sample solution for conditioning the high-performance liquid chromatography (HPLC) column. However, your explanation did not address why the "trial analysis" was performed using a sample solution instead of a standard solution, or why you ran this extra analysis in addition to the system suitability test, which verifies that a chromatographic system is adequate as set forth in USP <621>. You also acknowledged that a retrospective review conducted after the inspection found additional instances of unreported electronic data in original batch records. Your review only assessed laboratory data and did not assess all parts of your facility's operation where CGMP information is generated and maintained. In addition, you failed to provide details of your review criteria and methodology.
7/24/2018	Canada	Les Produits Chimiques B.G.R., inc.	**1. Failure to perform laboratory testing of API to ensure conformance to specifications and to accurately report results on certificates of analysis (COA).** Your firm distributed multiple lots of **(b)(4)** powder USP API without completing required release testing for identity. Your COA reported that these drugs met all required specifications. We reviewed your firm's COA and laboratory notebooks for **(b)(4)** powder USP lot #**(b)(4)**, as well as for multiple lots of this product dating back to at least 2015. The laboratory notebooks lacked the analytical data to support the information on your COA. Your firm confirmed to our investigator that, although your COA states that the identity tests "Passed," you did not perform the tests. Although you never performed the required testing, you distributed these API lots to the U.S. market with false information on the COA. In your response, you provided the identity test results for lots produced since 2015; you conducted these retrospective analyses only after our inspection identified that you had never performed the tests in the first place. Your response is inadequate. While you tested lots identified during our inspection that were manufactured since 2015, you did not test all distributed lots within expiry. In addition, you did not conduct a thorough review of all release records to determine whether the test results for other drug quality attributes were falsely reported.

			Customers and regulators rely on certificates of analysis for critical information about the quality and source of their ingredients. Unreliable information on a COA compromises supply-chain accountability and quality assurance, and may put consumers at risk. In response to this letter, provide the following. • A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Include a detailed description of the scope and root causes of your data integrity lapses. • A current risk assessment of the potential effects of the data integrity deviations on the quality of your API. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse of data integrity. • A management strategy for your firm that includes the details of your global corrective action and preventive action plan. The detailed corrective action plan should describe how you intend to ensure the reliability and completeness of all data generated by your firm, including laboratory data and manufacturing records.
			2. Failure of your quality unit to exercise its responsibility to ensure the API manufactured at your facility are in compliance with CGMP. Your quality unit failed to perform a number of critical functions to ensure that the **(b)(4)** powder USP API was manufactured according to CGMP. For example, your quality unit failed to ensure that the records it reviewed included complete data derived from all tests conducted to ensure compliance with established specifications and standards prior to the distribution of an API batch. Your quality unit did not document details such as sample weight and preparation for tests such as **(b)(4)** content, **(b)(4)**, **(b)(4)** or **(b)(4)** and **(b)(4)** content. Your quality unit also failed to ensure that samples intended for stability studies are stored with controlled temperature and humidity. Your firm kept retain and stability samples of **(b)(4)** USP in a cabinet in the quality control laboratory without monitoring temperature and relative humidity. In addition, your quality unit did not ensure the cleanliness of buildings and facilities used to manufacture API. You lacked sufficient controls to prevent the presence of pests in your packaging material storage area. At least twice, our inspector observed insects and spider webs in and on plastic-wrapped stacked containers used for packaging API. Your quality unit also did not ensure that your cleaning validation records are accurate and contain appropriate documentation. For example, you did not document rinse times in your study to validate cleaning of the **(b)(4)** you use to manufacture API.

			In your response, you stated that you would: • update your documentation procedure to clarify the information that is to be recorded in laboratory notebooks; • purchase a stability chamber and improve your stability program; • clean and transfer packaging materials to a location in the warehouse where you prevent entry of pests, and train personnel on packaging material inspection requirements; • repeat your cleaning validation with documented rinse times, and update corresponding cleaning procedures and checklists. Your response did not provide sufficient detail or evidence that your proposed corrective actions and preventive actions (CAPA) will bring your operations into compliance with CGMP. In response to this letter, provide the CAPA plans and procedures you have implemented to ensure that the roles and responsibilities of the quality unit are clearly defined and established. This should include but not be limited to assuring your quality assurance unit has the appropriate authority and resources needed to carry out its responsibilities. Also provide: • a revised documentation procedure that specifies the detailed information that must be recorded in laboratory notebooks; • evidence to demonstrate that you have purchased and qualified a stability chamber, as well as your updated stability protocol; • your procedures for appropriate storage and inspection of raw materials; • the report that summarizes your new cleaning validation studies; and • your revised cleaning procedures and checklists.
7/26/2018	China	Yicheng Goto Pharmaceuticals Co.,Ltd	**2. 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 perform adequate analytical tests for **(b)(4)** API. For example, you conducted assay, related substance, and residual solvent testing without performing system suitability tests and use of standards. In addition, your analysts performed manual integration on chromatograms without a written procedure.

			In your response, you state that you have established procedures that require your analysts to use standards, perform system suitability tests, and employ appropriate practices for chromatographic integration. However, you did not provide your procedures on the use of standards and system suitability. Your response also lacked a retrospective assessment of the effect of manual integration on data generated prior to implementing your new procedure. In response to this letter, provide: • An assessment of all test methods used by your firm to ensure they have appropriate instructions, method suitability criteria, and have been appropriately validated to determine whether they are fit for purpose. • A reanalysis plan for all batches within retest date that were analyzed using methods lacking system suitability or standards. • A comprehensive review of all instances of chromatographic manual integration. Provide scientific justification for the manual integration parameters you used for analysis. For integrations that lacked scientific justification, provide your plan for reintegration with appropriate reintegration parameters. Assess whether reintegration results comply with your established API acceptance criteria. If you identify out-of-specification (OOS) results, describe actions, such as customer notification and recalls, you have taken or will take to ensure the quality of marketed products and to protect patients. • Provide a comprehensive, independent review of your laboratory practices, methods, equipment, and analyst competencies. Based on this review, provide a detailed CAPA plan to fully remediate your laboratory system. Elements of your CAPA should include, but not be limited to, measures you will take to strengthen quality assurance oversight of review and approval of method validation and test results. Your plan should also include your process for evaluating the effectiveness of the implemented CAPA.
7/27/2018	India	JT Cosmetics & Chemicals Pvt Ltd	**1. 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 for each batch of drug product required to be free of objectionable microorganisms, appropriate laboratory testing, as necessary (21 CFR 211.165(a) and (b)).** Your firm released your OTC drug products without testing for the identity and strength of active ingredients. Without this testing you cannot determine whether your drug products conform to specifications.

			Your personnel also informed our investigators during the inspection that microbiological test results recorded on your certificates of analysis (COA) in support of your decision to distribute drugs were falsified, and the testing had not been performed. In addition, you lacked procedures for finished product testing that you do perform and records of your testing. In response to this letter provide: • all chemical and microbial test methods and specifications used to analyze each lot of your OTC drug products prior to a lot disposition decision; and • a summary of test results obtained from testing retain samples of all OTC drug products within expiry that have been distributed in the United States. Include test results for identity and strength of active ingredients, and all other appropriate chemical and microbial quality attributes.
			3. Your firm failed to establish and follow written procedures for the preparation of master production and control records designed to assure uniformity from batch to batch. 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 211.186(a) and 211.188). Your master and batch production records are inadequate. They do not include: • manufacturing instructions; • actual amounts of components weighed and added to the batch; • identification of major equipment and lines used; • sampling information; • yield; and • packaging and labeling records, including inspection of the area before and after use and information pertaining to containers, closures, and labels. In response to this letter, provide a risk assessment of products released to the U.S. market without adequate and approved production and control documentation. Also provide procedures you have implemented or revised to assure production records are completed as required and reviewed by your quality unit prior to release of products for distribution.
7/31/2018	US	Signature Formulations, LLC	**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 do not have stability data to support your firm's two-year expiration date for your OTC drug products, Herbal Muscle Gel, CBD Muscle Gel, and Herbal Muscle Mist. You failed to demonstrate that the chemical and physical properties of your drug products remain acceptable throughout the labeled two-year expiry period. Therefore, there is no assurance that your drug products can meet their label claims through their expiration period. In your response, you state that you conducted informal testing or observation to support the expiration date of your OTC drug products, and that you have now established a formal stability plan to evaluate and verify the stability characteristics of your formulation and container-closure system. Your response cannot be fully evaluated because you did not include your stability test results to demonstrate that each of your drug products met its specifications at the end of the labeled expiration period. In response to this letter, you should provide an adequate written stability testing program and results to support your assigned expiration dates.
8/9/2018	India	Apotex Research Private 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 investigations into out-of-specification (OOS) laboratory results and manufacturing deviations are insufficient and do not include scientifically-supported conclusions. For example: A. You tested **(b)(4)** for **(b)(4)** capsule samples collected at **(b)(4)** locations during the manufacture of **(b)(4)**capsules, **(b)(4)** mg, batch **(b)(4)**. The relative standard deviation (RSD) was OOS: **(b)(4)**% (specification is not more than **(b)(4)**%). You then tested reserve capsules and obtained additional OOS results for this batch. One unit assayed at **(b)(4)**% (specification is **(b)(4)**–**(b)(4)**%), and the RSD was **(b)(4)**% (specification is not more than **(b)(4)**%). Your firm excluded the individual sub potent assay OOS result and recalculated the RSD results as passing with a new value of **(b)(4)**%.

			You did not test the reserve capsules and investigate the failing **(b)(4)** capsule **(b)(4)** results until approximately one and a half months after you used the same batch of **(b)(4)** capsules for in-vivo bioavailability studies on December 17, 2016. Your response is inadequate. You attributed this failure to an "unknown lab error." You claimed that the low individual assay test result was an outlier and that the most probable root cause was analytical error. Outlier tests have no applicability in cases where the variability in the product is what is being assessed, such as for **(b)(4)**. You did not provide sufficient justification for disregarding the low result or supporting your unspecific conclusion of unknown laboratory root cause. B. You initiated an investigation into OOS and out-of-trend (OOT) assay results for **(b)(4)** tablets, **(b)(4)** mg and **(b)(4)** mg, three-month stability samples (batches **(b)(4)** and **(b)(4)**). Your May 2017 investigation states that you also obtained low OOT assay values at the one-month time point. You concluded the OOS and OOT results were due to analyst error during sampling preparation but lacked data to support your conclusion. Your testing associated with the investigation did not demonstrate that sample preparation caused the aberrant results as assay values did not differ substantially when you varied sample preparation. You did not extend the investigation to manufacturing, although your Site Incident Response Committee requested initiation of this part of the investigation. Notably, you performed the manufacturing phase of the investigation after our inspection. Your response explains that a third party performed a retrospective review of nine invalidated OOS investigations and that in "all cases, the investigations were found to be thorough and robust and the findings were sufficiently justified." However, this is not fully consistent with your third-party report. Regarding this specific OOS investigation, your third-party report says it "did not believe sufficient scientific evidence was presented in the laboratory OOS investigation process to justify retesting. Only retesting and obtaining passing results are the basis of conclusions." C. Variance investigation checklists (VIC) and variance investigation reports (VIR) used to investigate poor chromatography and failing results are inadequate. These VIC and VIR investigations are not subject to your OOS investigational procedures, and you do not track and trend them. Our inspection identified that you used test results obtained with your VIC and VIR investigations to replace original results. Further, your personnel stated that they

			retested a sample as part of a VIR investigation because they did not want to show low results to a customer. Your response is inadequate. You have not provided the retrospective review of all VIC and VIR investigations. D. On August 8 and 9, 2017, you observed capped and edge-worn tablets in two batches of **(b)(4)** tablets, **(b)(4)**mg. You rejected a substantial number of units from each batch due to these defects. You opened an investigation, which closed September 7, 2017, and concluded the most probable root cause was high **(b)(4)** force. You lacked scientific evidence to support this root cause as other batches had been successfully produced in that range. After observing a third batch with capped **(b)(4)** tablets, **(b)(4)** mg, in October 2017, you initiated another investigation. Your response acknowledges that the tablet defects may be due to multiple root causes and you continue to investigate the issue. However, your response lacks a detailed update on the investigations into the capped tablets. You also did not include corrective action and preventive actions (CAPA) initiated in association with the investigations. In response to this letter: • Explain why **(b)(4)** mg capsule batch **(b)(4)** was shipped and used for your bioequivalence studies before testing and investigational activities were completed. Also, describe whether your procedures require all testing and investigations to be completed prior to batch release. • Perform a three-year retrospective review to determine whether outlier tests have been used in previous OOS investigations, and determine whether you used them to improperly invalidate OOS results. • Provide the report and associated CAPAs for your retrospective review of all VIRs and VICs initiated since January 1, 2015. Include a third-party assessment of each of the VIRs and VICs, and of your firm's final report. • Assess the procedures you use to evaluate **(b)(4)** uniformity, including collecting and testing samples and evaluating results. • Provide a comprehensive, independent assessment of your overall system for investigations of laboratory and manufacturing-related deviations, discrepancies, complaints, OOS results, and failures. Your CAPA plan should include but not be limited to improvements in investigation competencies, root cause analysis, written procedures,

			and quality unit oversight. Also, include an improved process for evaluating CAPA effectiveness. 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/guidances/ucm070287.pdf.
8/10/2018	Japan	Kyowa Hakko Bio 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.** Your firm performed retesting or manipulated data after obtaining out-of-specification (OOS) or other unacceptable results. For example, investigation 2016-C-023 stated that the system suitability test (SST) was nonconforming and that "some data were manipulated to meet SST specification" for the high-performance liquid chromatography (HPLC) analysis of your raw material **(b)(4)**. You attributed the root cause to your firm's "lack of awareness of the seriousness" of CGMP deviations, and to an "environment where test data could be easily manipulated." Your investigation stated that you reanalyzed the crude sample and concluded that it met the specification. You provided no further details on the root causes and on the effect of using a system that failed SST to test your raw material. Your response stated that no product in distribution was found to be OOS, but you included no data to support this conclusion. Your response is inadequate. You identified additional data integrity issues, but failed to provide details regarding the corrective measures your firm has implemented. In response to this letter, provide a thorough assessment of your overall system for investigating deviations, discrepancies, OOS results, complaints, and other failures. In addition, provide a retrospective review of all distributed lots within expiry to determine whether your firm released lots not conforming to established specifications or appropriate manufacturing standards. For more information about handling failing, OOS, 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/guidances/ucm070287.pdf.

			2. Failure to exercise sufficient controls over computerized systems to prevent unauthorized access or changes to data, and failure to have adequate controls to prevent omission of data. Your firm's controls over your HPLC systems are inadequate. Some HPLC systems did not have audit trail capability or audit trails enabled. In addition, unique user names and passwords were not required to perform HPLC activities. You stated that you did not create unique usernames and passwords so that operators in different **(b)(4)** could continue what previous operators had initiated. In your annual product reviews, you used unprotected Excel worksheets to perform calculations and statistical evaluations of production data, such as standard deviation and process capability. These electronic files were not secured to prevent unauthorized changes, and have no change history. Your firm's lack of data control calls the reliability of your data into question. Your response stated that you stopped operating these HPLC systems without audit trail capability. Your response also stated that you will create a procedure for control of your electronic worksheets. Your response is inadequate because you have not assessed the effects of using data from uncontrolled HPLC systems or unsecured worksheets on your products. In response to this letter, provide a comprehensive, independent review of controls and procedures for electronic data generated from all of your laboratory equipment. Based on this review, provide a detailed corrective action and preventive action (CAPA) plan to remediate laboratory systems, including but not limited to data creation, modification, maintenance, retention, and system security. Your plan should also include the process you will use to evaluate CAPA effectiveness. Also see additional requests under the Data Integrity Remediation section below.
8/27/2018	China	Longood Medicine (Beijing) 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, including drug products manufactured, processed, packed or held under contract by another company. Your firm failed to establish a quality 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)).**

			Contractor Oversight You failed to ensure that your third-party contractor uses a validated terminal sterilization process, consistent with the requirements of 21 CFR 211.113(b), to sterilize your drug product, Chlora-Cleanze Proprep applicators, purported as sterile and labeled for "use prior to surgery." You released Chlora-Cleanze Proprep applicators without assurance of their sterility. For example, you were unable to provide adequate records demonstrating that your contractor terminally sterilized Chlora-Cleanze Proprep applicators lot 20170601, distributed to the United States. You also failed to provide evidence that your quality unit reviewed all appropriate records prior to releasing the lot. In your response, you acknowledged that your terminal sterilization contractor provided incomplete records for Chlora-Cleanze Proprep applicators (lot 20170601). Your response is inadequate. You failed to describe how your firm determined the lot was acceptable for release without complete documentation from your contractor. In addition, you failed to provide evidence from your contractor demonstrating this lot was terminally sterilized. Your response also provided terminal sterilization validation documentation for a different **(b)(4)** product (**(b)(4)**) to support the sterilization of Chlora-Cleanze Proprep applicators. Your response is inadequate in that it lacks sufficient validation data to support sterilization efficacy. You did not provide scientific rationale demonstrating validation studies for the **(b)(4)** sterilization process are representative of the sterilization process for Chlora-Cleanze Proprep applicators. **(b)(4)** drug product has a different formulation, including a different active ingredient. You failed to address whether you will validate the terminal sterilization process for the Chlora-Cleanze Proprep applicators. In your response to this letter, provide: • Your qualification procedures for assessing the suitability and competence of potential contractors before outsourcing, and for ongoing monitoring and review of the performance of the contract facility to identifying and implement any needed improvements; • A detailed plan for ensuring that the process your contractor uses to terminally sterilize all products, including Chlora-Cleanze Proprep applicators, is adequately validated; • Complete sterilization records from your contractor for Chlora-Cleanze Proprep applicators, lot 20170601. If you do not have sufficient evidence that the lot in question or any lot intended for the U.S. market was adequately sterilized, indicate the corrective actions you will take, such as customer notifications and product recalls.

			• A corrective action and preventive action (CAPA) plan to fully remediate your review and release procedures for finished drug products. Your procedures should require that third-party contractors provide sufficient production and control records to demonstrate compliance with established, approved written procedures and specifications before a lot is released or distributed by your quality unit. *Uncontrolled Documents* Our investigators found numerous uncontrolled and unofficial production and laboratory records associated with Chlora-Cleanze Proprep applicators (lot 20170601) during the inspection. These include duplicate records which contain incomplete fields and strike-throughs. In your response, you state that you will examine your document control procedures and provide training to management. Your response is inadequate. Training should include all employees involved in the manufacturing process. Additionally, you failed to indicate whether the uncontrolled and unofficial production and laboratory records for lot 20170601 were reviewed prior to release of the lot. Further, you did not perform a full retrospective review to determine the extent of the production and laboratory record deficiencies, and commit to a CAPA plan to comprehensively identify and address root causes. In your response to this letter, provide: • A comprehensive, independent assessment of documentation systems used throughout your manufacturing and laboratory operations to determine where documentation practices are deficient. Include a detailed CAPA plan that systemically remediates deficient documentation practices, and ensures you retain complete and accurate records. • A comprehensive CAPA for your training program to ensure all staff at your facility are fully trained in CGMP. Provide a fully remediated training program for your entire operation. Place special emphasis on assuring that all staff involved in any CGMP function are trained and competent in acceptable recordkeeping practices, such as retaining all records, completing records contemporaneously, documenting any error in records, and ensuring that all procedures are approved by quality unit.
8/29/2018	US	Pharmaceutical Laboratories and Consultants	**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)).**

			You recorded results for tests you admitted that you did not conduct. Your worksheets for total aerobic microbial counts and total yeast and mold counts report results for **(b)(4)** per test, as your microbial limits test procedure requires. However, our investigators found that you used **(b)(4)** per test. You acknowledged to our investigator that you only use **(b)(4)** and that reporting **(b)(4)** results is a "habit" your firm needs to "break." Your firm also failed to document critical information on microbiological worksheets. You did not record details of preparing microorganism suspensions for growth promotion testing. You neglected to record incubation times, laboratory materials, and equipment numbers for sample preparation. You did not note how much **(b)(4)** water you used in your growth media or how many containers you sterilized in the **(b)(4)** during media preparation. Customers rely on your laboratory data for information about the quality of drugs and their components. Your data reporting and documentation practices compromise supply-chain accountability, and may put consumers at risk. In response to this letter, provide a comprehensive investigation into your poor data, records, and reporting practices. Identify omissions, alterations, deletions, and other deficiencies. Provide a risk assessment summarizing the effect of incomplete and inaccurate data on assessing laboratory control and product quality. Also, provide a comprehensive corrective action plan, with target dates, to ensure that laboratory records are complete and reliable.
8/29/2018	Netherlans	Fargon BV	**1. Failure to transfer all quality or regulatory information received from the API manufacturer to customers.** Your quality unit omitted the names and addresses of the original manufacturers of your repackaged API on certificates of analysis (COA) you issued to your customers, and did not always include copies of original batch certificates. You generated your COA for repackaged API by replacing the original manufacturers' names and addresses with your own internal identification codes. In your response, you asserted that your current practice is sufficient. Your response is inadequate in that you do not commit to ensure that COA contain information on the original manufacturer, including a copy of their COA for the given batch. Customers and regulators rely on COA for information about the quality and source of drugs and their components. Omitting information from the COA compromises supply chain accountability and traceability, and may put consumers at risk.

			We observed similar failures to convey necessary information on COA during our November 2013 and April 2015 inspections. In a meeting on June 10, 2014, we informed you that you must include the original manufacturers' names and addresses on the COA. See *Guidance for Industry: ICH Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*for more information on how API, from original manufacturers as well as API repackagers and relabelers, should be labeled and clearly identify the original API manufacturer as the API moves through the supply chain. The guidance can be found at the following website: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/U CM073497.pdf In response to this letter, provide the following: • a remediated program for generating COA, including systems and procedures to assure that COA issued by your firm include necessary original manufacturer information; • a retrospective review to determine how your failure to provide required information may have affected drug quality, and indicate any actions you have taken or will take, such as notifying customers, or invalidating previously issued COA for any drugs still within their labeled retest dates; and • examples of recently-issued COA that include specific information regarding the original manufacturer, including a copy of their original batch certificate.
10/3/2018	South Korea	Hamlin Pharm Co., 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)).** Our investigator observed a quality control analyst and laboratory team leader signing and backdating a test record. In the microbiology laboratory, we also observed an analyst recording microbiological test results from environmental monitoring settling plates before reading the plates, as well as recording results for a previous day. Upon questioning by our investigator, the analyst stated the plate count data had been mistakenly omitted. CGMP activities must be documented at the time of performance. Your response acknowledged that your analysts lacked awareness of "Good Documentation Practice" and stated that you would perform self-audits and hire a consultant to perform related training. Your response is inadequate because you did not include a detailed CAPA

			plan with supporting documentation. In response to this letter, provide your CAPA plan as requested in the Data Integrity Remediation section of this letter below.
			4. Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records (21 CFR 211.68(b)). Three of your quality control team leaders had administrator privileges within your HPLC computerized laboratory software system. Because they review and approve CGMP data, their access level should preclude file deletion or modification. In addition, two of your laboratory software systems had unlocked time and date functions, which allowed users to change the recorded dates and times of analyses. FDA cited a similar CGMP violation regarding inadequate controls over your computerized laboratory systems in our July 2016 inspection. In your response, you stated you would grant administrator privileges to only an information technology employee not involved in laboratory testing. You also stated that you locked the time and date setting function for the system. Your response is inadequate because you did not evaluate whether CGMP data were improperly modified or deleted, and you did not include supporting documentation for your proposed CAPA plan. In response to this letter, provide a comprehensive, independent review of controls and procedures for electronic data generated from all of your laboratory equipment. Based on this review, provide a detailed CAPA plan to remediate laboratory systems, including but not limited to data creation, modification, maintenance, retention, and system security. Your plan should also include the process you will use to evaluate CAPA effectiveness.
10/29/2018	US	I Shay Cosmetics	**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).** You did not conduct adequate investigations into out-of-specification (OOS) test results. a. You did not investigate an epinephrine HCl assay OOS result for the over-the-counter (OTC) drug product **(b)(4)**, lot **(b)(4)**. The OOS result was **(b)(4)**% (specification was **(b)(4)** ± **(b)(4)**%), which is substantially less active ingredient than what is claimed on

			the label. Your certificate of analysis (COA) indicates that the product met the acceptance criteria. In your response, you stated the specification for epinephrine HCl will be "corrected to reflect [the] test result." Your response was inadequate because you did not explain how you determined the specification was incorrect. We note that other documents used the original specification, including the product label claim, your COA, and the specification used by the contract testing laboratory performing the assay analysis. b. On May 30, 2017, your customer, **(b)(4)**, reported bloated bottles of 3% hydrogen peroxide from lots **(b)(4)**, **(b)(4)** and **(b)(4)**. In August 2017, you manufactured and released lot **(b)(4)** while your investigation into this critical quality defect was pending. We note that in August 2017 you also manufactured but subsequently rejected lot **(b)(4)** due to the bloated bottle complaints associated with other lots. Labels on 3% hydrogen peroxide bottles state, "If the bottle expands, don't sweat it; it's natural." However, bloating of the bottles is a product quality defect and may be associated with degradation of hydrogen peroxide. In your response, you committed to continuing the investigation into the bloated 3% hydrogen peroxide bottles. We also note that during the FDA inspection, you committed to stopping shipment of this product until you concluded the investigation. c. Your firm did not assess the impact of OOS total dissolved solids testing results from the deionized water system that occurred from May through July 2016. The results were OOS on **(b)(4)** out of **(b)(4)** days. Your firm has a history of manufacturing finished drug products with water that does not meet the minimum quality standards for topical and oral drug products. Water is a major ingredient in many of your drug products, which include aqueous-based dosage forms. It is essential that you employ a robustly designed water system and that you effectively control, maintain, and monitor the system to ensure it consistently produces water suitable for pharmaceutical use. You reportedly modified your water system since relocating to your current facility, although it was not validated at the time of our inspection. In your response, you committed to evaluate the impact of these OOS results on finished products. However, you did not specify how you will perform this evaluation. We note you did not address in your response how you will ensure that the water you use in drug manufacturing will meet the requirements of the USP monograph for purified water and appropriate microbial standards. You did not submit protocols or timelines for your water

			system validation. You also did not assess how your failure to validate your water system affected the quality of products you released to the U.S. market that are within expiry. Your response is inadequate because you did not propose any corrective actions and preventive actions (CAPA) to address your repeated failure to conduct thorough investigations into OOS test results and unexpected discrepancies. For more information about handling failing, OOS, 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/guidances/ucm070287.pdf.
11/2/2018	US	Product Packaging West, Inc	**3. Your firm failed to maintain adequate written records of major equipment maintenance (21 CFR 211.182).** Your firm lacks records of cleaning, sanitizing, and inspecting the **(b)(4)** water system, **(b)(4)**, **(b)(4)**, and **(b)(4)** that are used in the manufacture of each batch of your finished drug products. In addition, you stated that there is no documentation identifying the products processed in each piece of equipment. In your response, you stated that you will create equipment logs for use, cleaning, and maintenance, and that you will write a new standard operating procedure (SOP) that includes provisions for periodic preventive maintenance and repair for each individual piece of equipment. Your response is inadequate because it does not include the SOP or timelines for writing, approval, and implementation of the SOP. You also failed to provide current equipment logs for use, cleaning, and maintenance. In response to the letter, provide: • New or revised SOP(s) that establish appropriate manufacturing equipment records. • Copies of the logs documenting any cleaning, maintenance, and repairs performed on all major manufacturing equipment since the FDA inspection.
11/6/2018	US	Surmasis Pharmaceutical	**2. 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 electronic data logs did not retain alarm messages indicating when certain manufacturing parameters exceed their limits during production operations. Specifically, you did not maintain electronic log records of the in-process control alarms for your **(b)(4)** hydrogel coating machine, your **(b)(4)** checkweigher, and your **(b)(4)** packager. Failure to record excursions of in-process limits for critical manufacturing unit operations, such as applying medicated gels to a fabric liner, rejecting over/underweight patches, and sealing packages, can pose an unacceptable risk to product quality. There is no evidence that you investigated all deviations for their effects on product quality. Specifically, any alarms that may affect manufacturing should be investigated as deviations, and appropriate action should be taken to address variability potentially introduced by the testing equipment or machine fault. In your response, you provided a list of equipment you will review for electronic data controls, but your response did not address the need to maintain a record of all deviations in the batch record in accordance with 21 CFR Part 211.188, and it lacked a global remediation to ensure electronic record retention. In response to this letter: • Provide a complete assessment of documentation systems used throughout your manufacturing and laboratory operations to determine where documentation practices are insufficient. Include a detailed CAPA plan that comprehensively remediates documentation practices and ensures that you retain complete and accurate records. This review should afford special focus to your electronic record retention and should ensure that electronic data are retained and deviations relevant to manufacturing are captured in your batch records for all manufacturing equipment with automated alarm functions. • Provide a retrospective review to determine whether potential breaches of your manufacturing parameters had any effect on the quality of products released to the market.
			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 used a texture analyzer to measure in-process gelatin bloom, to test elongation, and to test tensile strength of your **(b)(4)** patch. Your audit trails on the texture analyzer showed multiple occasions of additional testing that were not reported for your **(b)(4)** patch, your **(b)(4)** patch, and your **(b)(4)** patch. In addition, you performed instances of additional testing that were not reported on a number of products that could not be identified because

			your electronic data systems were inadequately controlled. Your systems allowed analysts to assign sample names such as “test1” and “test2,” which do not identify or describe analytical samples. You should maintain data throughout all batch record retention periods with all associated metadata required to reconstruct the CGMP activity. In your response, you stated that you opened deviations and retrained employees on CGMPs and data integrity. Your response is inadequate. We are unable to fully evaluate your response because you did not provide details on how you would correct your data management and oversight practices, including, but not limited to, audit trails and frequent performance of extra testing. See the Data Integrity Remediation heading immediately below.
11/27/2018	CHINA	Hangzhou Zhongbo Industrial 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 to the U.S. market without conducting finished product quality testing. You received a testing report from your contract laboratory, **(b)(4)**, dated March 23, 2018, for your **(b)(4)**. This testing was carried out on a small batch of your drug product. You used the results from this report to release Batch No. **(b)(4)** of your **(b)(4)**. Your records show that you began manufacturing Batch No. **(b)(4)** on April 2, 2018, more than a week after the date of your contract laboratory’s report. Further, this report contained results for microbial enumeration but not for assay testing. In your response, you stated that you will revise your procedure and ship batches after you complete production and after “a[n] overall inspection.” However, you did not indicate whether you will ship your product only after completing all required finished product tests using a representative sample. In response to this letter, provide your revised finished product release procedure. Your procedure should include the completion of manufacturing and product quality release testing before shipping. It should specify appropriate release tests of finished drug product samples that are taken at statistically appropriate intervals. In addition, provide testing by an independent CGMP-qualified laboratory of each finished product distributed to the United States within expiry, to demonstrate if they met established quality criteria before release. For any product that failed to meet established quality criteria

			before release, provide your detailed corrective action plan including notifying customers or recalling drug products.
11/29/2018	US	Genetech Inc	**5. Failure to retain the accompanying records with the HCT/Ps at all times following a donor eligibility determination including a statement whether, based on the results of screening and testing, the donor has been determined to be eligible or ineligible; and a summary of records used to make the donor-eligibility determination [21 CFR 1271.55(a)].** Specifically, all products distributed since your firm's manufacturing operation began in mid-2017, were distributed without a statement of donor eligibility and without a summary of records used to make a donor eligibility determination.
			6. Failure to retain documentation of the results and interpretation of all donor screening for communicable diseases in compliance with 21 CFR 1271.75 [21 CFR 1271.55(d)(ii)]. Specifically, you do not consistently receive relevant medical records, including the medical/social history interview and physical exams, from your umbilical cord blood suppliers in order to retain such records.