8/29/2018 Pharmaceutical Laboratories and Consultants, Inc.

Pharmaceutical Laboratories and Consultants, Inc.
Product: testing laboratory
Date:8/29/18<p>
This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See 21 CFR, parts 210 and 211.

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

Data Integrity Remediation

Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. In response to this letter, provide the following:

A. A comprehensive investigation into the extent of the inaccuracies in data, records, and reporting, including results of the data review for drugs distributed to the United States. Include a detailed description of the scope and root causes of your data integrity lapses.

B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse of data integrity, and risks posed by ongoing operations.

C A management strategy for your firm that includes the details of your global corrective action and preventive action plan. The detailed CAPA plan should describe how you intend to ensure the reliability and completeness of all data generated by your firm, including all laboratory data, manufacturing records, and all data submitted to FDA.

<p>
FDA District: Detroit

8/10/2018 Kyowa Hakko Bio Co., Ltd

Yuki Gosei Kogyo Co., Ltd.
Product: drug manufacturing facility
Date:8/10/18<p>

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.

Data Integrity Remediation

Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. We acknowledge that you are using a consultant to audit your operation and assist in meeting FDA requirements. Each third-party consultant used by your firm must be qualified for their specific assigned function, including data integrity remediation.

In response to this letter, provide the following.

A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Your investigation should include:
A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude.
Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party.
An assessment of the extent of data integrity deficiencies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies.
Describe all parts of your facility's operations in which you discovered data integrity lapses.
A comprehensive retrospective evaluation of the nature of the testing, manufacturing, and other data integrity deficiencies. We recommend that a qualified third party with specific expertise in the area where potential breaches were identified should evaluate all data integrity lapses.
B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analysesof the risks to patients caused by the release of drugs affected by a lapse of data integrity, and risks posed by ongoing operations.

<p>
FDA District: CDRH

7/17/2018 Yuki Gosei Kogyo Co., Ltd.
Yuki Gosei Kogyo Co., Ltd.
Product: drug manufacturing facility
Date:7/17/18<p>
Data Integrity Remediation

Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. We strongly recommend that you retain a qualified consultant to assist in your remediation.

In response to this letter, provide the following.

A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Your investigation should include:
A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude.
Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party.
An assessment of the extent of data integrity deficiencies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies.
Describe all parts of your facility's operations in which you discovered data integrity lapses.
A comprehensive retrospective evaluation of the nature of the testing, manufacturing and other data

integrity deficiencies. We recommend that a qualified third party with specific expertise in the area where potential breaches were identified should evaluate all data integrity lapses.
B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analysesof the risks to patients caused by the release of drugs affected by a lapse of data integrity, and risks posed by ongoing operations.

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

7/5/2018 Baxter (Claris Injectables Ltd.)
Baxter (Claris Injectables Ltd.)
Product: drug manufacturing facility
Date:7/5/18<p>
Data Integrity Remediation

Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. In response to this letter provide the following.

A. A comprehensive investigation into the extent of the inaccuracies in data, records, and reporting, including results of the data review for drugs distributed to the United States. Include a detailed description of the scope and root causes of your data integrity lapses.

B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse of data integrity, and risks posed by ongoing operations.

C. A management strategy for your firm that includes the details of your global corrective action and preventive action plan. The detailed corrective action plan should describe how you intend to ensure the reliability and completeness of all data generated by your firm, including microbiological and analytical data, manufacturing records, and all data submitted to FDA.
<p>
FDA District: CDRH

6/12/2018 Henan Lihua Pharmaceutical Co. Ltd.
IDT Australia Ltd.Henan Lihua Pharmaceutical Co. Ltd.
Product: drug manufacturing facility
Date:6/12/18<p>
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.
Data Integrity Remediation

Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. We acknowledge that you committed to using a consultant to assist in meeting FDA requirements. In response to this letter, provide the following.

A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Your investigation should include:
A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude.
Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party.
An assessment of the extent of data integrity deficiencies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility’s operations in which you discovered data integrity lapses.
A comprehensive retrospective evaluation of the nature of the testing and manufacturing data integrity deficiencies. We recommend that a qualified third party with specific expertise in the area where potential breaches were identified should evaluate all data integrity lapses.
B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analysesof the risks to patients caused by the release of drugs affected by a lapse of data integrity, and risks posed by ongoing operations.

C. A management strategy for your firm that includes the details of your global corrective action and preventive action plan. Your strategy should include:
A detailed corrective action plan that describes how you intend to ensure the reliability and completeness of all of the data you generate, including analytical data, manufacturing records, and all data submitted to FDA.
A comprehensive description of the root causes of your data integrity lapses, including evidence that the scope and depth of the current action plan is commensurate with the findings of the investigation and risk assessment. Indicate whether individuals responsible for data integrity lapses remain able to influence CGMP-related or drug application data at your firm.
Interim measures describing the actions you have taken or will take to protect patients and to ensure

the quality of your drugs, such as notifying your customers, recalling product, conducting additional testing, adding lots to your stability programs to assure stability, drug application actions, and enhanced complaint monitoring.
Long-term measures describing any remediation efforts and enhancements to procedures, processes, methods, controls, systems, management oversight, and human resources (e.g., training, staffing improvements) designed to ensure the integrity of your company's data.
A status report for any of the above activities already underway or completed.
<p>
FDA District: CDRH

5/23/2018 IDT Australia Ltd.
IDT Australia Ltd.br>
Product: drug manufacturing facility
Date:5/23/18<p>
Data Integrity Remediation

Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. We strongly recommend that you retain a qualified consultant to assist in your remediation.

In response to this letter, provide the following.

A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Your investigation should include:
A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude.
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An assessment of the extent of data integrity deficiencies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies.
Describe all parts of your facility's operations in which you discovered data integrity lapses.
A comprehensive retrospective evaluation of the nature of the testing data integrity deficiencies. We recommend that a qualified third party with specific expertise in the area where potential breaches were identified should evaluate all data integrity lapses.
B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse of data integrity, and risks posed by ongoing operations.

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

A status report for any of the above activities already underway or completed.
<p>
FDA District: CDRH

5/9/2018 Nox Bellcow Cosmetics Co., Ltd.
Nox Bellcow Cosmetics Co., Ltd.br>
Product: drug manufacturing facility
Date:2/2/2018<p>
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)).

Data Integrity Remediation

Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. We strongly recommend that you retain a qualified consultant to assist in your remediation.

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

2/2/2018 Cosmecca Korea Co., Ltd.
Cosmecca Korea Co., Ltd.
Product: drug manufacturing facility
Date:2/2/2018<p>
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.
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.
Data Integrity Remediation

Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. We acknowledge that you are using a consultant to audit your operation and assist in meeting FDA requirements.

In response to this letter, provide the following.

A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Your investigation should include:
A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude.
Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party.
An assessment of the extent of data integrity deficiencies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility's operations in which you discovered data integrity lapses.
A comprehensive retrospective evaluation of the nature of the testing data integrity deficiencies. We recommend that a qualified third party with specific expertise in the area where potential breaches were identified should evaluate all data integrity lapses.
<p>
FDA District: CDRH

12/18/2017 Prosana Distribuciones S.A. de C.V.
Prosana Distribuciones S.A. de C.V.
Product: drug manufacturing facility
Date:12/18/2017<p>
This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See 21 CFR, parts 210 and 211.
Your March 29, 2017, response to FDA's inspectional observation was inadequate and did not provide sufficient evidence of corrective actions to bring your operations into compliance with CGMP. For

example, you failed to provide:
A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility's operations in which you discovered data integrity lapses, and evaluate the nature of the data integrity deficiencies.<p>
FDA District: CDRH

11/14/2017 Bayer AG
Bayer AG
Product: drug manufacturing facility
Date:11/14/2017<p>
Your firm failed to ensure that laboratory records included complete data derived from all tests necessary to assure compliance with established specifications and standards (21 CFR 211.194(a)).

When reviewing audit trails, our investigator observed unreported data from in-process tablet weight checks. You programmed your in-process weight checker not to report values that varied more than (b)(4)% from the tablet target weight.

In your response, you committed to suspend this procedure, investigate any such values, and perform a retrospective assessment of tablet weight checker data. However, your retrospective tablet weight assessment was limited to all rejected measurements from February 1 to March 15, 2017, and about 8,000 rejected measurements representing an unspecified percentage of the total number of rejected measurements from August 1, 2016, to February 1, 2017. There was no commitment to revisit equipment qualification(s) and process validation(s) to ensure they included complete data.

In response to this letter, as part of your retrospective tablet weight assessment, explain whether your findings impact data supporting tablet manufacturing equipment qualification and manufacturing process validation studies. Provide a summary listing of equipment qualification and process validation documents that you reviewed.
Data Integrity Remediation

FDA acknowledges that, before our inspection, you began a data integrity remediation program. Our investigator documented that, as part of your data integrity remediation program, you discontinued the practice of performing “test” injections as a result of an internal assessment in June 2016. However, we noted that you only reviewed chromatographic data for (b)(4) and (b)(4) generated between January 1, 2015, and June 23, 2016.

Your action plans submitted on May 11, 2017, and August 10, 2017, did not include an assessment of other products manufactured and tested at your facility. Additionally, the retrospective review did not include data generated before January 1, 2015, used in support of drug applications submitted to FDA. Further, your retrospective review only focused on the laboratory. You did not investigate potential data integrity lapses in other manufacturing systems.

In response to this letter, provide your revised action plan. In your summary report, include other products manufactured and tested at your facility and identify any data generated before January 1, 2015, that was used to support drug applications submitted to FDA. Also, include your protocol and methodology. Summarize all laboratories, manufacturing operations, and systems covered by the assessment. Specify whether a qualified independent consultant performed interviews to ensure that the nature and scope of the problem was fully determined. Discuss the role of the independent consultant in auditing the integrity of your data and assisting with CAPA. Justify why you excluded any part of your operations or systems.
<p>
FDA District: CDRH

11/14/2017 TELEMED
TELEMED
Product: diagnostic ultrasound systems
Date:11/14/2017<p>
Failure to establish and maintain adequate procedures for receiving, reviewing, and evaluating complaints, as required by 21 CFR 820.198(a). Specifically,

A) Your firm's complaint handling procedure, QP-85-03, Customer Complaints, Revision D., was deficient in that:

1. It did not include the elements required to be part of an investigation record including, but not limited to results of our investigation and any reply to the complainant. Your Vice President/Computer System Administrator stated he receives all customer calls / emails, some of which are considered complaints. The next step is to perform remote diagnostics to determine if the issue is user, software, or hardware related. If the complaint is resolved over the phone, no other record is completed other than a note on an uncontrolled electronic list of calls / emails. Additionally, none of the complaint records reviewed included a reply to the complainant.
Failure to establish and maintain procedures to control environmental conditions, as required by 21 CFR 820.70(c). For example:
Your firm did not monitor or control the temperature in the production areas where phantoms, which are affected by temperature variations according to the user guides, were used for routine testing activities. Additionally, discrepancies in the temperature readings of the phantoms for (b)(4) test area and for software testing ((b)(4), respectively) were observed. Your firm's user manuals for the (b)(4) phantom and Doppler Flow phantoms both contain the following statement: "….(b)(4)." No documentation was available for review to determine if utilizing the phantoms at conditions higher than room temperature would adversely affect the testing results. <p>
FDA District: CDRH

10/16/2017 Kim Chemicals Private Ltd.
Kim Chemicals Private Ltd.
Product: drug manufacturing facility
Date:10/16/2017<p>
This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See 21 CFR, parts 210 and 211.

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).
Your firm failed to ensure that laboratory records included complete data derived from all tests necessary to assure compliance with established specifications and standards (21 CFR 211.194(a)).

You had no records to support the analytical testing results reported on your certificate of analyses. Your firm indicated to our investigator that you document finished product analysis on a pad of paper, transcribe the test results onto a certificate of analysis, and then destroy the piece of paper. There is no assurance that the testing was conducted in the first place, and there is no record that any associated calculations were performed.

Data Integrity Remediation

Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. We strongly recommend that you retain a qualified consultant to assist in your remediation.

In response to this letter, provide the following.

A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Your investigation should include:
A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude.
Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party.
An assessment of the extent of data integrity deficiencies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility's operations in which you discovered data integrity lapses.
A comprehensive retrospective evaluation of the nature of the data integrity deficiencies. We recommend that a qualified third party with specific expertise in the area where potential breaches were identified should evaluate all data integrity lapses.
B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analysesof the risks to patients caused by the release of drugs affected by a lapse of data integrity, and risks posed by ongoing operations.

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

9/7/2017 Wuxi Medical Instrument Factory
Wuxi Medical Instrument Factory.
Product: drug manufacturing facility
Date:9/7/2017<p>
This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See 21 CFR, parts 210 and 211.

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).
Your firm does not exercise appropriate controls over computer related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel [21 C.F.R. 211.68(b)]. For example:
Your firm failed to maintain adequate written records of major equipment maintenance (21 CFR 211.182).

During the inspection, you provided our investigator with records documenting (b)(4) sanitization of your (b)(4) loop. The records, covering January to March, 2017, were signed by two employees, and indicated that sanitization had been completed and verified contemporaneously throughout this period.

However, our investigator found that these operations were not documented at the time of their actual performance, but were instead created and completed on March 7, 2017, the second day of the inspection.

Your response acknowledges this data integrity issue and indicates that you have taken some remediation steps. In response to this letter, provide:

A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility's operations in which you discovered data integrity lapses, and provide an evaluation of the nature of the data integrity deficiencies.

B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs.

C. A management strategy for your firm that includes the details of your global corrective action and preventive action plan. Your strategy should include: a comprehensive description of the root causes of your data integrity lapses, the interim measures you have taken or will take to protect patients and to ensure the quality of your drugs while remediation is ongoing, and the long-term measures you will take to ensure the integrity of your company's data. Include a status report for any of the above activities already underway or completed.

<p>
FDA District: CDRH

5/17/2017 Med-Pharmex

Med-Pharmex.
Product: drug manufacturing facility
Date:5/17/2017<p>
Your firm does not exercise appropriate controls over computer related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel [21 C.F.R. 211.68(b)]. For example:
A. Your "Processed By" dates and times listed on printed chromatograms do not always show the same "Processed By" dates and times listed on the system chromatograms.

B. Your data in the audit trails does not always show the same data listed on your printed chromatograms.
Your response states you have not observed any test result data discrepancies between your printed versions of the test results. However, this does not address adequate electronic data controls to prevent inconsistencies between the printed and electronic data. Your responses for 2A and 2B above are not adequate in that your firm did not provide any corrective action addressing the assessment of all relevant data in the audit trails.
<p>
FDA District: Los Angeles District Office

4/3/2017 Mylan Pharmaceuticals, Inc.

Mylan Pharmaceuticals, Inc.
Product: drug manufacturing facility
Date:4/3/2017<p>
Your firm failed to establish an adequate quality control unit with the authority to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated (21 CFR 211.22(a)).

Your quality unit failed to monitor and investigate error signals generated by the computerized systems that you use for high performance liquid chromatography and gas chromatography. These signals

indicated the loss or deletion of original CGMP analytical data. However, your quality unit did not comprehensively address the error signals or determine the scope or impact of lost or deleted data until after these problems were reviewed during our inspection.

For example, our investigator reviewed audit trails from August 2016 assay testing on (b)(4) batch (b)(4) and dissolution testing for (b)(4) tablets batch (b)(4). The audit trail for these tests included the message, “deleted result set,” but neither of these two incidents were recorded in the analytical packages for these batches of drug products, nor were they reviewed or investigated by the quality unit.

In addition, during the inspection, our investigator observed that your Empower 3 system audit trail displayed many instances of a “Project Integrity Failed” message, which indicates that injections were missing from the results of analytical testing. For example, in (b)(4) analysis for (b)(4) tablets batch (b)(4) conducted on June 20, 2016, no chromatogram was rendered for the initial run of testing. The data package for this testing clearly shows that the initial run is missing, but your quality unit did not investigate the incident.

Although you showed our investigator isolated examples of interrupted, missing, deleted, and lost data for which you had opened investigations, you reached similar conclusions in many of these investigations regarding the root cause of your loss of data integrity but failed to take appropriate corrective action and preventive action in response. Our investigator observed that you attributed numerous incidents to power interruptions, connectivity problems (disconnection of the Ethernet or power cord), and instrument malfunctions. You could not explain why these events occurred with frequency in your laboratory, nor had you undertaken a comprehensive investigation into the problem or sought to correct it and prevent its recurrence.

In your written response dated February 17, 2017, you identified seven samples from a single week of testing for which original results were lost following data acquisition interruptions at the time of initial analysis. Instead of uniformly initiating an investigation into the root cause of each interruption when it occurred or even documenting it for later review and investigation by the quality unit, you explained in your response that you retested the samples immediately after the interruptions.

Your response is inadequate because you have not identified and investigated each instance in which data acquisition was interrupted. While you assessed a limited number of error codes from a seven day period, you did not evaluate the effects of other error codes identified in your simulation exercise report on the reliability, accuracy, or completeness of the data you use to evaluate the quality of your drugs. Although you have submitted multiple responses, you have not yet:
shown exactly how widespread these problems are;
evaluated their full effects on the quality of your drugs;
explained why these events occurred with frequency in your laboratory;
or demonstrated how you will ensure that your quality unit reviews, investigates, and acts upon codes that affect the reliability of your CGMP data.
In response to this letter, provide your validation of laboratory instrument error codes. Identify the specific codes that may impact product quality and the reliability of CGMP data, and provide your procedures to demonstrate how your quality unit will review, investigate, and respond to these specific codes.

Data Integrity Remediation
Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. We acknowledge that you are using a consultant to audit your operation and assist in meeting FDA requirements. In response to this letter, provide the following.

A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Your investigation should include:

o A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude.
o An assessment of the extent of data integrity deficiencies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility's operations in which you discovered data integrity lapses.
o A comprehensive retrospective evaluation of the nature of the testing data integrity deficiencies.

B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analysesof the risks to patients caused by the release of drugs affected by a lapse of data integrity, and risks posed by ongoing operations.

<p>
FDA District: CDRH

3/10/2017 USV Private Limited
USV Private Limited
Product: drug manufacturing facility
Date:3/10/2017<p>
Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records (21 CFR 211.68(b)).

For example, during inspection of the sterile manufacturing and QC microbiology areas, our investigators observed:

A. Deletion of at least six (b)(4) and (b)(4) tests in the audit trails for two instruments used to test sterile (b)(4). Your systems allowed operators to delete files. You had no procedure to control this practice or to ensure a backup file was maintained. When you reviewed the audit trail data further, you identified a total of 25 deleted (b)(4) test results. In your response, you state that the production staff now only have "view and print" privileges. However, your response is inadequate because it lacks details of how appropriate oversight will be exercised over data backup to ensure it is appropriately retained.

B. No restricted access to the microbial identification instrument. Further, you lacked restricted access to the external hard drive used for backup of this instrument. All users could delete or modify files. In your response, you commit to limit access to the system and external hard drive. However, your response is inadequate because you did not provide a retrospective risk assessment of the impact and scope of inadequate system controls at your firm.,P>
Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. We acknowledge that you are using a consultant to audit your operation and assist in meeting FDA requirements.

In response to this letter, provide the following.

A. A comprehensive retrospective investigation into the extent of the inaccuracies in data records and reporting.

B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analysis of the risks to patients caused by the release of drugs affected by a lapse of data integrity, and risks posed by ongoing operations.

C. A management strategy for your firm that includes the details of your global corrective action and preventive action plan.
<p>
FDA District: FDA

2/23/2017 Denttio, Inc.
Company: Denttio, Inc.
Product: digital x-ray image receptors and intraoral microscope/cameras
Date:2/23/2017<p>
Failure to perform device software validation and risk analysis as required by 21 CFR 820.30(g). For example, you do not have records to demonstrate that your Imaging Software used with the Tio-H Digital X-Ray Sensor has been validated. You do not have records to demonstrate that your firm has conducted a risk analysis to identify potential hazards and control measures with the Tio-H Digital X-Ray Sensor System.
<p>
FDA District: Los Angeles District

2/17/2017 Morton Grove Pharmaceuticals, Inc.
Company: Morton Grove Pharmaceuticals, Inc.
Date:1/17/2017<p>
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)).
Data Integrity Remediation

Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. We acknowledge that you are using a consultant to audit your operation and assist in meeting FDA requirements.

In response to this letter, provide the following.

A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Your investigation should include:
A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude.
Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party.
An assessment of the extent of data integrity deficiencies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility's operations in which you discovered data integrity lapses.
A comprehensive retrospective evaluation of the nature of the testing data integrity deficiencies. We recommend that a qualified third party with specific expertise in the area where potential breaches were identified should evaluate all data integrity lapses.

Our investigators observed that information technology (IT) staff at your facility share usernames and passwords to access your electronic storage system for (b)(4) data. Your IT staff can delete or change directories and files without identifying individuals making changes.After a previous inspection in which FDA observed similar deficiencies, you committed to eliminate these and other data integrity vulnerabilities.

In response to this letter:
Provide your detailed plan to ensure that each current and future employee will have a unique username and password to allow traceability of changes to electronic data back to specific authorized personnel.
Describe the specific changes made to your software and electronic systems to ensure the effectiveness of your corrective actions.
Include a detailed description of the role of your quality unit to ensure that the corrections are appropriately implemented and sustainable.

<p>
FDA District: Chicago District Office

1/13/2017 FACTA Farmaceutici S.p.A Ltd.
FACTA Farmaceutici S.p.A
Product: drug manufacturing facility
Date:1/13/2017<p>
1. 1. Your firm failed to ensure that laboratory records included complete data derived from all tests necessary to assure compliance with established specifications and standards (21 CFR 211.194(a)).

For multiple sterile drug product lots, your original data showed failing results, but data you reported showed passing results. This discrepancy was not adequately explained.

You stored original data in an “unofficial” and uncontrolled electronic spreadsheet on a shared computer network drive. Your analyst stated that original data was first recorded in this “unofficial” spreadsheet and transcribed later to an “official” form. This spreadsheet showed failing results above the limits you established in your procedure, PCH 035 Visible Particle Determination in use prior to September 1, 2014.
In response to this letter, provide the following.

A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Your investigation should include:
A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude.
Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party.
An assessment of the extent of data integrity deficiencies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility’s operations in which you discovered data integrity lapses.
A comprehensive retrospective evaluation of the nature of the manufacturing and laboratory data integrity deficiencies. We recommend that a qualified third party with specific expertise in the area where potential breaches were identified should evaluate all data integrity lapses.

B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analysesof the risks to patients caused by the release of drugs affected by a lapse of data integrity, and risks posed by ongoing operations.

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

<p>
FDA District: CDRH

1/6/2017 Sato Yakuhin Kogyo Co., Ltd.
Sato Yakuhin Kogyo Co., Ltd.
Product: drug manufacturing facility
Date:1/6/2017<p>
1. Your firm failed to ensure that laboratory records include complete data derived from all tests necessary to assure compliance with established specifications and standards (21 CFR 211.194(a)(4)).

Reliance on incomplete data
Our investigator reviewed the audit trails generated by your high performance liquid chromatography (HPLC) system for impurities testing that you conducted on (b)(4) (lots (b)(4), (b)(4), (b)(4)). The audit trail showed that you performed this testing in duplicate. The audit trail indicated that you conducted a chromatography sequence analyzing impurities on samples of these lots beginning at (b)(4) on April14, 2014. The audit trail showed that a new sequence was started approximately 24 hours later, at (b)(4) on April 15, 2014, for impurities testing that again included samples for lots (b)(4), (b)(4), and (b)(4). None of the 19 chromatograms generated in the first sequence were maintained and available for review. Only the second set of chromatograms was maintained and relied upon in releasing lots (b)(4), (b)(4), and (b)(4) for use in the manufacture of products for the U.S. market. You could not provide any rationale for not maintaining the original data, and you failed to document a scientific justification for repeating the analysis.

Failure to appropriately maintain data
You do not maintain electronic data on your ultraviolet-visible spectrophotometer UV SP-502 which you use for content uniformity and identity testing of (b)(4) capsules, and it does not have an audit trail.

In your response, you acknowledged that your data integrity controls were deficient. You stated that the chromatography software version was upgraded and that you are retaining all electronic data as of June 1, 2016. You also committed to upgrade UV SP-502 and to appropriately control access to data for this instrument. In addition, you provided the revised procedure, Procedure on Testing Records (QC Standard 3-C-017), which stipulates, “All the data generated from any analytical devices should be kept as records.” However, your response is inadequate. You have not conducted a retrospective review to determine how your failure to maintain complete records affected the quality of your drugs. Moreover, you have not shown how your revised laboratory procedures prevent the deletion, manipulation, or exclusion of data from the records relied upon for batch release and other quality review decisions.

2. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).

Your analysts told our investigator that, until June 1, 2016, they were permitted to perform repeat testing without scientific justification or documentation. They also told our investigator that they were not required to maintain the data from the original results when performing investigations of system suitability failures, suspected errors, or out-of-trend results. Our investigator reviewed records of your investigations for a two-year period and found that you recorded only two minor deviations in the production area and no out-of-specification investigations.

In your response you stated, “The analysts will not make the decision to perform re-analysis at their discretion and the investigation shall be conducted on the initial failure and the testing results shall be verified.” In addition, you stated that you will revise your procedure (Procedure on Unexpected Testing Results (OOT), QC Standard 3-C-006) to require that records be retained. However, you failed to describe the role of the quality unit in this procedure. Include this procedure as a part of your response to this letter.
Data Integrity Remediation

Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. We strongly recommend that you retain a qualified consultant to assist in your remediation. In response to this letter, provide the following.

A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Your investigation should include:
A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude.
Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party.
An assessment of the extent of data integrity deficiencies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies.
Describe all parts of your facility's operations in which you discovered data integrity lapses.
A comprehensive retrospective evaluation of the nature of the testing data integrity deficiencies. We recommend that a qualified third party with specific expertise in the area where potential breaches were identified should evaluate all data integrity lapses.
B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analysesof the risks to patients caused by the release of drugs affected by a lapse of data integrity, and risks posed by ongoing operations.

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

12/5/2016 Zyno Medical LLC
Zyno Medical LLC
Product: infusion pumps
Date:12/5/2016<p>
Failure to establish and maintain procedures to control product that does not conform to specified requirements, and to address the identification, documentation, evaluation, segregation, and disposition of nonconforming product, as required by 21 CFR 820.90(a). For example:
Your firm did not open a non-conforming report (NCR) on 7/30/15, when over (b)(4) Z-800F infusion pumps had a flow rate outside your specification when tested at Test Station (b)(4).
Your NCR dated 8/12/15 documented that (b)(4) Z-800F and (b)(4) Z-800 Infusion Pumps received from your contract manufacturer had the wrong software installed. The rework performed on these units was not documented.
Your response is not adequate to address the above violation. We acknowledge you will be updating

your procedures, re-trained your staff and performed a retrospective review of previous NCR activities. In response to the Warning Letter, you should provide us with a summary of your retrospective review as well as a description of any required corrective actions taken as the result of your review. We will need to verify during a re-inspection that your revised procedures will be implemented effectively.

5. Failure to establish and maintain procedures for acceptance activities that include inspections, tests, or other verification activities, as required by 21 CFR 820.80(a). For example, a review of acceptance testing performed at your facility revealed the following inconsistencies:
The IFU for your Z-800 Infusion Pump recommends that the battery be replaced after one to two years, however, your repair and maintenance work instructions indicates that if the pump is less than (b)(4) years old, the battery does not need to be replaced.
The Flow Rate Accuracy testing for new pumps includes a total test time of (b)(4) minutes but the Flow Rate Accuracy testing for pumps returned for service, includes only (b)(4) minutes total test time.
The Z-800 Testing & Calibration Work Instruction does not include instructions to verify that the current software version is installed on devices received from your contract manufacturer. <p>
FDA District: New England District Office

11/8/2016 Sekisui Medical Co., Ltd.
Sekisui Medical Co., Ltd.
Product: drug manufacturing facility
Date:11/8/2016<p>
1. Failure to maintain complete data derived from all laboratory tests conducted to ensure compliance with established API specifications and standards.

Our investigator found that you failed to maintain complete data from all laboratory analyses, and that you relied on the incomplete information to determine whether your drugs met established specifications. For example:

a. Numerous data files were found in the recycle bin folder on the computer connected to gas chromatography instruments GC-4 and GC-6. Specifically, our investigator found deleted data for residual solvent testing for (b)(4) lot (b)(4) in the recycle bin. Your records show that you retested the lot without documented justification or an investigation. You retained only the final test result.

b. During the inspection our investigator requested residual solvent release test data for two of your API, (b)(4) and (b)(4). You were unable to retrieve this data.

Any data created as part of a CGMP record must be retained so that it can be evaluated by the quality unit as part of release criteria and maintained for CGMP purposes.

We acknowledge that you commit to revising your SOP for archiving data. Your response is inadequate because it does not explain your failure to maintain complete records prior to the inspection. You also did not address validation of the systems you use to archive your data.

2. Failure to prevent unauthorized access or changes to data, and failure to provide adequate controls to prevent omission of data.

Our investigator observed that your laboratory systems lacked controls to prevent deletion of and alterations to electronic raw data. You do not have adequate controls for seven of (b)(4) high performance liquid chromatography (HPLC) systems and one of (b)(4) gas chromatography systems. For example, the audit trail on HPLC 15 did not record the (b)(4) batch (b)(4) assay. Your records indicate that the assay was performed on March 3, 2014, but your audit trail shows no assays performed between February 28 and March 4, 2014. Moreover, your analyst demonstrated to our investigator that he could change the data, including injection time and date, without the changes being captured in the audit trail, prior to printing the results.

We acknowledge that you have committed to upgrading your analytical systems to be compliant with CGMP requirements. However, procuring new instruments, installing new and upgraded data acquisition software, and enabling various features on software are not sufficient alone. These steps will be effective only if you implement appropriate procedures and systems to ensure that your quality unit reviews all production and control data and associated audit trails as part of the batch release process.
Data Integrity Remediation
Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. We strongly recommend that you retain a qualified consultant to assist in your remediation. In response to this letter, provide the following.

A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Your investigation should include:
A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude.
Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party.
An assessment of the extent of data integrity deficiencies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility's operations in which you discovered data integrity lapses.
A comprehensive retrospective evaluation of the nature of the testing data integrity deficiencies. We recommend that a qualified third party with specific expertise in the area where potential breaches were identified should evaluate all data integrity lapses.
B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analysesof the risks to patients caused by the release of drugs affected by a lapse of data integrity, and risks posed by ongoing operations.

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

8/3/2016 Spiegelberg Gmbh & Co. KG
Spiegelberg Gmbh & Co. KG
Product: intercranial pressure monitoring products
Date: 8/3/2016<p>
This inspection revealed that these devices are adulterated within the meaning of section 501(h) of the Act, 21 U.S.C. § 351(h), in that the methods used in, or the facilities or controls used for, their manufacture, packing, storage, or installation are not in conformity with the current good manufacturing practice requirements of the Quality System regulation found at Title 21, Code of Federal Regulations (CFR), Part 820.

Failure to ensure that when computers or automated data processing systems are used as part of production or the quality system, the manufacturer shall validate computer software for its intended use according to an established protocol, as required by 21 CFR 820.70(i). For example: your firm uses (b)(4) use.

We reviewed your firm's response and conclude that it is not adequate. The response indicates your firm will follow the guidance of "Off-The-Shelf Software Use in Medical Devices" (b)(4), and if necessary, perform a validation. However, your firm did not provide sufficient details describing its corrective actions for assessment. <p>
FDA District: CDRH

8/2/2016 Adamson Analytical Laboratories, Inc.
Adamson Analytical Laboratories, Inc.
Product: finished pharmaceuticals
Date: 8/2/2016<p>
This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals, 21 CFR parts 210 and 211, and significant deviations from CGMP for active pharmaceutical ingredients (API).
Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records (21 CFR 211.68(b)).

Specifically, your high performance liquid chromatography (HPLC) and gas chromatography (GC) data acquisition systems did not have sufficient controls to prevent deletion or alteration of raw data files. During the inspection, our investigators observed that your laboratory personnel use a shared password to access the HPLC (b)(4) computer system and that your GC (b)(4) computer system requires no password for access.

In addition, multiple instruments had no audit trail function to record information about each analytical test, such as:
type of injection
date and time
identity of analyst
reason for action taken (for example, modifying a record)
This is a repeat observation from our February 7, 2013, inspection. In 2013, you committed to augmenting the security of your computer systems within six months. However, based on our 2015 inspection, it appears that you have not made appropriate corrective actions such as installing audit trails and ensuring that analysts have unique user names and passwords for your computerized systems.

It is essential that your firm keep track of all changes made to your electronic data. The use of audit trails for computerized analytical instrumentation helps to ensure that all additions, deletions, or modifications of information in your electronic records are authorized. It also allows you to verify the quality and integrity of the electronic data your contract testing laboratory generates for your customers.

We acknowledge your commitment to install and configure appropriate electronic controls to ensure that access to your computerized systems and data is restricted to authorized personnel with access rights specified for each individual. However, your response is inadequate as you did not provide an action plan describing the interim security measures in place prior to your installation of electronic controls. Your response also lacked details regarding the type of electronic controls to be installed, and you did not describe how you will evaluate the effectiveness of these computerized system changes.
<p>
FDA District: Los Angeles District

6/1/2016 86 Harriet Ave. Corporation DBA General Devices

86 Harriet Ave. Corporation DBA General Devices.
Product: Carepoint EMS WorkStation/GEMS Series 4000, EIM- lOS Prep-Check, EIM-107-20A Prep-Check Plus, Rosetta-Lt, and Rosetta-Rx
Date: 6/1/2016<p>

This inspection revealed that these devices are adulterated within the meaning of section 501(h) of the Act, 21 U.S.C. § 351(h), in that the methods used in, or the facilities or controls used for, their manufacture, packing, storage, or installation are not in conformity with the current good manufacturing practice requirements of the Quality System regulation found at Title 21, Code of Federal Regulations (CFR), Part 820.

Failure to adequately establish design change procedures, as required by 21 CFR 820.30(i). For example:

A. Unsigned SOP titled "Change Notification System," dated 8/16/94, does not require that design changes be verified or validated prior to implementation.

B. There is a lack of a documented software validation for releasing the following Carepoint.exe versions for resolving issues from one customer site, which include, but are not limited to:

- #10089, dated 5/21/14: The unit kept alarming for an incoming ECG, but the ECG did not appear on the screen.
- #9169, dated 12/11/13: The unit continued to alarm audibly after a 12 Lead ECG came in.
- #8429, dated 05/21/13: The unit kept having audible alarms for an incoming 12 Lead ECG, but the 12 Lead ECG did not show up on the screen after the user selected View 12-Lead ECG.

C. Issue Ticket# 9808, dated 4/2/14, indicated that the audio between an iPad and Carepoint EMS WorkStation, Serial No. 0464, was not working. The unit's (b)(4) program was upgraded to version 1.01.26 to resolve the issue. There is a lack of documented software validation for the (b)(4) release.

We reviewed your firm's written responses; however, the adequacy of your firm's responses cannot be determined at this time. We acknowledge that your firm's initial response, dated June 29, 2015, stated that your firm will conduct an in-house audit of the firm'squality system and initiate corrective actions which were expected to be completed within 90 days "from receipt of official report." In your subsequent response, dated September 11, 2015, your firm outlined its implementation of corrective actions to address each of the noted observationsin the Form FDA 483. However, the response did not provide any supporting documentation to demonstrate how your firm corrected each deficiency. <p>
FDA District: New Jersey District

5/27/2016 Zimmer Biomet Holding, Inc.

Zimmer Biomet Holding, Inc.
Product: iAssist Knee System
Date: 5/27/2016<p>

8. Failure to submit a Report of Correction or Removal for a medical device correction or removal initiated to reduce a risk to health or to remedy a violation of the Act caused by the device, which may present a risk to health, as required by 21 CFR 806.10. For example:

a. Your firm initiated a correction in November 2007 and May 26, 2008, for the Orthosoft Knee Universal CAS Software 2.3.2, due to a complaint relating to Right/Left knee Selection issues, Extension/Flexion Gap Assessment issues, and the SKS incorrect offset parameter value. Your firm conducted a correction or removal of these devices; however, no report was filed to FDA within 10 working days of initiating this correction.

b. Your firm initiated a removal in June 2008, of Sesamoid Plasty CAS workstation/base and column

assemblies 52 1.025 in the field, because the workstation could potentially collapse and fall on a user if an attempt was made to fold the workstation without first removing the camera and arm. Your firm conducted a removal of these devices; however, no report was filed to FDA within 10 working days of initiating this removal.

c. Your firm initiated a removal in 2008, of Unicondylar Digitizer 108.098 instruments from the field, due to feedback received from surgeon that the newly modified software application was incompatible with the Unicondylar Digitizer instrument, causing large off-scale errors. Your firm conducted a removal of these devices; however, no report was filed to FDA within 10 working days of initiating this removal.

d. Your firm initiated a correction in July and August 2008, for the Magnetic Offset Paddle 108.117, due to a complaint relating to Anterior Cortex Digitization, Implant Tolerance Interpretation Issues, and Software Issues. Your firm conducted a correction of these devices; however, no report was filed to FDA within 10 working days of initiating this correction.

e. Your firm initiated a removal in October 2010, of NDI P7 Position Sensors, because the camera components of the sensor could potentially malfunction, resulting in an interruption of the CAS system, and causing the display of positional data to stop during surgery. Your firm conducted a removal of these devices; however, no report was filed to FDA within 10 working days of initiating this removal.

f. Your firm initiated a correction in December 2011 for the Orthosoft Knee Universal CAS Software 2.3.2, due to a complaint that the software can malfunction, resulting in stalling during the preoperative calibration of the Universal Holding Platform, which in tum causes a delay in surgery or the need to complete the surgery using a conventional surgical technique. Your firm conducted a correction of these devices; however, no report was filed to FDA within 10 working days of initiating this correction.

Your firm's response did not address this deficiency.<p>
FDA District: CDRH

5/16/2016 BBT Biotech Gmbh
BBT Biotech Gmbh.
Product: pharmaceutical manufacturing facilities
Date: 5/16/2016<p>
Failure to exercise sufficient controls over computerized systems to prevent unauthorized access or changes to data, and to provide adequate controls to prevent omission of data.

Our investigator found that your (b)(4) system used for (b)(4) and (b)(4) testing lacked access controls and audit trail capabilities. For example, all employees had administrator privileges and shared one user name, so actions could not be attributed or traced to specific individuals. This exposed your electronic data to manipulation and/or deletion without traceability.

Our investigator also noted that your firm copied raw data to a CD (b)(4), and then deleted the data from the (b)(4) system to free space on the hard drive. Files copied to the CD were selected manually; the selection process was not supervised. Without audit trail capabilities or supervised file selection, there was no assurance that all raw data files were copied to the CD before they were permanently deleted from the system.

We acknowledge your commitment to hire a third-party expert to install audit trails and other controls to ensure that data cannot be deleted from this electronic system. However, your response was inadequate. Simply preventing data deletion is not sufficient. You did not show how these steps will ensure that your firm retains and evaluates all data, including laboratory data, created as part of a CGMP record prior to release of your API.

In your response to this letter, investigate your retention and review of CGMP data and provide the results. Focus on your firm’s review and retention of laboratory raw data. In addition, provide your

interim plan for reviewing and retaining data while your firm is in the process of implementing access controls and audit trail capabilities. <p>

5/12/2016 Tai Heng Industry Co., Ltd.
Tai Heng Industry Co., Ltd.
Product: pharmaceutical manufacturing facilities
Date: 5/12/2016<p>
Failure to prevent unauthorized access or changes to data, and to provide adequate controls to prevent manipulation and omission of data.

During the inspection, an FDA investigator discovered a lack of basic laboratory controls to prevent changes to your firm's electronically stored data and paper records. Your firm relied on incomplete records to evaluate the quality of your drugs and to determine whether your drugs conformed with established specifications and standards.

Our investigator found that your firm routinely re-tested samples without justification, and deleted analytical data. We observed systemic data manipulation across your facility, including actions taken by multiple analysts and on multiple pieces of testing equipment.

Specifically, your Quality Control (QC) analysts used administrator privileges and passwords to manipulate your high performance liquid chromatography (HPLC) computer clock to alter the recorded chronology of laboratory testing events.
<p>
FDA District Office: CDRH<p>

5/5/2016 F.P. Rubinstein Y Cia SRL
F.P. Rubinstein Y Cia SRL
Product: laser powered surgical instruments
Date: 5/5/2016<p>
This inspection revealed that these devices are adulterated within the meaning of section 501(h) of the Act, 21 U.S.C. § 351 (h), in that the methods used in, or the facilities or controls used for, their manufacture, packing, storage, or installation are not in conformity with the current good manufacturing practice requirements of the Quality System regulation found at Title 21, Code of Federal Regulations (CFR), Part 820. These violations include, but are not limited to, the following :

3. Failure to establish and maintain procedures for validating the device design, as required by 21 CFR 820.30(g). For example:

a. Your firm has not performed software validation (b)(4). These programs are used in the Starlight laser product family.

b. The software validation for (b)(4) is inadequate, in that the (b)(4). This message occurs when either the maximum voltage (6V) is exceeded, or the actual voltage is higher than the reference voltage associated with the intensity selected by the operator.
6. Failure to validate computer software for its intended use according to an established protocol, when computers or automated data processing systems are used as part of production or the quality system, as required by 21 CFR 820.70(i). For example, your firm has not validated the following software used in its quality system:

a. (b)(4), used for complaint handling;
b. (b)(4), used for complaint handling by your firm's sales force; and
c. (b)(4), used for data analysis.
8. Failure to establish and maintain procedures to ensure that all purchased or otherwise received product and services conform to specified requirements, as required by 21 CFR 820.50. For example:

a. Your firm has not documented the qualifications of its suppliers, consultants, or contractors.

b. Your firm's approved supplier list does not include three contractors/consultants used for software development and internal audits.<p>
FDA District: Center for Devices and Radiological Health

4/11/2016 Polydrug Laboratories Pvt. Ltd. Corporate Office

Recipient:Polydrug Laboratories Pvt. Ltd. Corporate Office
Product:Pharmeceuticals
Date: 4/11/2016<p>
Failure of computerized systems to have sufficient controls to prevent unauthorized access or changes to data.

Your firm’s computer system for entering test results and storing certificates of analysis (CoA), which document whether a drug meets specifications, does not have sufficient controls to prevent unauthorized changes to a CoA after quality unit approval.
Your firm’s computer system for entering test results and storing certificates of analysis (CoA), which document whether a drug meets specifications, does not have sufficient controls to prevent unauthorized changes to a CoA after quality unit approval.

During the inspection, our investigator reviewed (b)(4) CoA stored on computer #16, all of which were approved by the quality unit. A manager demonstrated for our investigator how results on an already finalized CoA could be manipulated after the formal quality unit approval. Also, the quality unit’s electronic signatures on these CoA were uncontrolled images of signatures rather than certificate-based electronic signatures.

Your response states that your firm plans to implement an enterprise resource planning system. Your response is inadequate because you did not provide sufficient detail about how this system will prevent unauthorized access or data manipulation, nor did you indicate your timeframe for installing and validating the system. In addition, you failed to review and confirm authenticity of CoA data for products you have already released under the deficient conditions described above. <p>
FDA District: CDRH <p>

3/22/2016 FDA Guidance Genetic Tests for Heritable Markers

FDA "Guidance on Pharmacogenetic Tests and Genetic Tests for Heritable Markers" is at the link provided. Section III.D addresses Software and Validation of Instrumentation. In addition to referring to the general software submission guidance it specifically states: "If applicable, you should describe how computational concerns such as probe saturation level, background correction, normalization, etc., are addressed by the software."

3/16/2016 FDA Inspection Observation Summary for 2015.

FDA issued "2015 Annual FDA Medical Device Quality System Data Inspections, FDA Form 483 Observations, and Warning Letter Citations". The full report is at the link provided. <p>
This report identifies numbers of observations and inspections by country as well as obervations by Quality subsystem. FDA noted that the number of Foreign inspection has increased. Production and Process Controls and CAPA continue to be the most frequently cited. <p>
The most frequent Design Control citiations were Design Validation by a large margin then Design Changes followed by Design Verification with a much lower number related to other elements of Design Control.

2/16/2016 Implants International Ltd.
Implants International Ltd.
Product: orthopedic implants
Date: 2/16/2016<p>
This inspection revealed that these devices are adulterated within the meaning of section 501(h) of the Act, 21 U.S.C. § 351(h), in that the methods used in, or the facilities or controls used for, their manufacture, packing, storage, or installation are not in conformity with the current good manufacturing practice requirements of the Quality System regulation found at Title 21, Code of Federal Regulations (CFR), Part 820.
Failure to establish and maintain adequate procedures to ensure that the design input requirements are documented, as required by 21 CFR 820.30(c). For example, your firm's design history file (DHF) does not include all design inputs for the Ring Lok Hip system. Specifically:
The DHF includes computer aided design (CAD) testing for range of motion; however, there is no design input documented for range of motion.
<p>
FDA District: CDRH

1/29/2016 pca Laboratories Ltd.
pca Laboratories Ltd..
Product: pharmaceutical manufacturing facilities
Date: 1/29/2016<p>
1. Failure to have computerized systems with sufficient controls to prevent unauthorized access or changes to data.

During the inspection, FDA investigators discovered a lack of basic laboratory controls to prevent changes to your firm's electronically stored data. Your firm relied on incomplete records to evaluate the quality of your drugs and to determine whether your drugs conformed with established specifications and standards.

Our investigators found that your firm routinely re-tested samples without justification, and deleted analytical data. We observed systemic data manipulation across your facility, including actions taken by multiple analysts, on multiple pieces of testing equipment, and for multiple drugs. You are responsible for determining the causes of these deviations, for preventing recurrence, and for preventing other deviations from CGMP.

During the inspection, our investigators examined the computerized instrumentation and systems you used to conduct chromatographic analyses of your drugs and found that laboratory analysts had PC administrator access that they utilized to manipulate raw data and test results. We found that controls on your computerized chromatographic instrumentation were not adequate to prevent analysts from manipulating processing parameters in order to obtain passing results. We also found that your computerized systems lacked controls to prevent the back-dating of test data.

For example, we reviewed the (b)(4) API 12-month (b)(4) Commercial Stability assay test for residual solvent by gas chromatography (GC). For batch #(b)(4) US-DMF ((b)(4)), you reported an (b)(4)% result for (b)(4) residual solvent (specification (b)(4)-(b)(4)%) obtained on July 18, 2013.

We documented that the original peak had been integrated inconsistently. Standards and samples had been processed using different integration parameters with no documented reason; there were no controls in the software to prevent analysts from manipulating integration settings in order to obtain passing results that you relied on to evaluate the quality of this product. When our investigator asked you to reprocess the chromatograms using appropriate integration parameters, an out-of-specification (OOS) value of (b)(4)% was obtained.. In the (b)(4) stability interval assay test of the same API, batch #(b)(4) US-DMF ((b)(4)), you reported an (b)(4)% result for (b)(4) residual solvent (specification: (b)(4)-(b)(4)%) obtained on June 12, 2013. We again found that the original sample peaks had been re-reintegrated inconsistently. There were no controls in the software to prevent the inappropriate

manipulation of integration parameters. When our investigator asked you to reprocess the chromatograms using appropriate integration parameters, the result was an OOS value of (b)(4)%.

For the same test, we found that on and after June 18, 2013, the date and time of the chromatographic injections for the (b)(4) stability test appear to have been set back to June 12, 2013. The data was reprocessed to obtain a passing result, upon which you relied to evaluate the quality of this drug.

In addition to these examples of computerized systems that permitted inappropriate manipulation of integration parameters and backdating, our investigators also found several instances of computerized data systems that failed to prevent the deletion of original injections. For example, our investigators reviewed the GC audit trail for (b)(4) (finished API batch #(b)(4)) and found that the original sample injection for related substance was on June 4, 2013 at (b)(4). This injection was aborted with no justification and the computerized system that your laboratory used to capture raw data did not retain the original results. The sample was re-injected at (b)(4)., which automatically deleted the original sample result. Passing results from the re-injection were reported for individual and total impurities. You used these incomplete results to evaluate the quality of this drug.

The High Performance Liquid Chromatography (HPLC) audit trail for (b)(4) (finished API batch #(b)(4)) shows that the first sample injection for aliquot #2 assay test was on May 28, 2013 at (b)(4). This injection result was deleted without justification. The sample was re-injected at (b)(4). A passing assay result was reported from the re-injection. As with the GC system discussed above, the electronic system your laboratory used to capture HPLC results lacked sufficient controls to prevent the deletion of data without justification, and failed to retain the original data. You relied on these incomplete results to evaluate the quality of this drug.

These practices appear to be commonplace in your analytical laboratory. During the inspection, our investigators spoke with an analyst who reported that "…if we find a failure, we set back the date/time setting and re-integrate to achieve passing results…" The analyst explained that deleting, overwriting, changing integration parameters, and altering PC date and time settings were done for raw materials, in-process testing, and finished API drugs.

In your response you stated that the stand-alone chromatographic instruments in the Quality Control and Stability laboratories are no longer under full control of individual analysts and have been connected to a network-based laboratory system. You also acknowledged that you did not identify all instances of data manipulation that may have led to inaccurate conclusions regarding product quality. However, your response still lacks a comprehensive assessment and retrospective review of data generated from all of your computerized laboratory systems. This includes but is not limited to a risk assessment that evaluates all potentially-affected test data.<p>
2. Failure to adequately investigate and resolve critical deviations.

Our inspection documented that your firm's quality unit was aware of the lack of controls in your computerized systems to prevent the manipulation and deletion of quality-related data. Your site's senior management failed to take sufficient corrective action and prevent the recurrence of these problems. For example, an anonymous email dated August 5, 2013 notified your quality management about data falsification and manipulation in your laboratory. This email stated: "…[t]here is no control of data in the department…Falsification is going on…Take action as early as possible..." Although you investigated your GC and HPLC equipment, the multi-part investigation that you opened on August 10, 2013 (CD/RTM/QA/001/2013) was incomplete and did not resolve the underlying problems of data falsification and manipulation.

Phase I: GC Investigation
Your GC Investigation was limited to review of audit trails for batches analyzed on GCs #052 and #202 between January and August, 2013. Although your investigation found multiple examples of deficient data management and retention practices, you concluded that none of the deviations were considered

critical. You also concluded that there was no product or patient risk associated with these deviations. You closed this phase of the investigation on November 27, 2013, without implementing effective corrective actions and preventive actions.

Our investigator reviewed the same data and audit trail records that you included in your own investigation. In the limited time available during the inspection, our investigator found serious deficiencies and questionable data management practices that your own four-month investigation did not identify, including:
altering time and date settings of computerized equipment using the software administrator's access

1/5/2016 DiamoDent
DiamoDent.
Product: class II dental prosthetic permanent and temporary implants and abutments
Date: 1/5/2016<p>
This inspection revealed that these devices are adulterated within the meaning of section 501(h) of the Act, 21 U.S.C. § 351(h), in that the methods used in, or the facilities or controls used for, their manufacture, packing, storage, or installation are not in conformity with the current good manufacturing practice requirements of the Quality System regulation found at Title 21, Code of Federal Regulations (CFR), Part 820.
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ailure to adequately validate software used as part of production and quality systems for its intended use according to an established protocol, as required by 21 CFR 820.70(i). Specifically, you did not validate any software programs of your (b)(4) machines used to manufacture all your devices. Per your employee, there are hundreds of tooling programs to make hundreds of different device parts as specified in your product catalogue. Examples include, but are not limited to, software and tooling programs for the following devices: Cement-On Post HEXED, TiteFit (Part no. 13347), Cement-On Post 4mm COLLAR, 4.5mm PROFILE (Part no. 13040) and Implant Analog Aluminum (Part no. 11013-01).

We reviewed your response and conclude that it is not adequate since you did not provide complete documentation of your corrections and not enough details of your proposed corrections were submitted for our review, such as the scope of the software validation and which devices are covered under the software validation. We understand that you are implementing your "Process Validation" SOP-25, Rev. B and planned to complete software validation by October 30, 2015. In response to this Warning Letter, you should provide us with an update of these activities, including details of specific devices involved.<p>
FDA District Office: Los Angeles District<p>

12/31/2015 Zhejiang Hisun Pharmaceutical Co., Ltd.
Zhejiang Hisun Pharmaceutical Co., Ltd..
Product: pharmaceutical manufacturing facilities
Date: 12/31/2015<p>
We identified significant deviations from current good manufacturing practice (CGMP) for the manufacture of active pharmaceutical ingredients (API).

These deviations cause your drugs to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B), in that the methods used in, or the facilities or controls used for, their manufacture, processing, packing, or holding do not conform to, or are not operated or administered in conformity with, CGMP.
Our investigators observed specific deviations during the inspection, including, but not limited to, the following.
1. Failure to prevent unauthorized access or changes to data, and to provide adequate controls to prevent manipulation and omission of data.

During the inspection, FDA investigators discovered a lack of basic laboratory controls to prevent changes to your firm's electronically stored data and paper records. Your firm relied on incomplete

records to evaluate the quality of your drugs and to determine whether your drugs conformed with established specifications and standards.

Our investigators found that your firm routinely re-tested samples without justification and deleted analytical data. We observed systemic data manipulation across your facility, including actions taken by multiple analysts, on multiple pieces of testing equipment, and for multiple drugs. You are responsible for determining the causes of these deviations, for preventing recurrence, and for preventing other deviations from CGMP.

a. During the inspection, we reviewed the electronic log for high performance liquid chromatography (HPLC) system #36 and determined that the audit trail was disabled on February 6, 2014. One of your analysts executed 80 HPLC injections for assay and impurity tests of validation stability batches (b)(4) of (b)(4) API.

Because the audit trail was disabled, neither your quality unit nor your laboratory staff could demonstrate that records for these batches included complete and unaltered data. All supporting raw data was discarded, including sample solution dilutions and balance weight printouts. Sample analyses were not recorded in the instrument use logbook. Test results were deleted from the hard drive and all supporting chromatograms were discarded. Audit trail functions were re-enabled on February 8, 2014, and the same analyses were repeated. You submitted the February 8th test results to the FDA in March 2014 in support of Drug Master File (DMF) (b)(4).

During the inspection, we asked the analyst who generated the data submitted to the FDA whether audit trails could be disabled. The analyst stated that another employee, who was no longer with the company, had disabled the audit trails. Your firm could not explain why the audit trail was disabled or why the original data was deleted, nor could you demonstrate whether the original results were within specification.

In your response, you assumed that the original raw data was deleted because a system suitability failure invalidated the data. You acknowledged that the data should not have been invalidated without an investigation of the laboratory event. However, your response is inadequate. There is no evidence to support invalidation of the original data on the grounds of a system suitability failure because your firm deleted all of the original records associated with these analyses.

c. While reviewing the audit trail on HPLC system #28, we determined that one of your analysts performed trial HPLC injections during assay and impurities testing for batches of (b)(4) API ((b)(4) and (b)(4)). These trial injections were performed on May 4-6, 2014. The data for the sample set was deleted from the system. Testing was not recorded in the instrument use logbook. All supporting electronic raw data was discarded. Testing results for these batches were then recorded on May 7, 2014, when the analyses were repeated using HPLC system #32.

During our inspection, one of your analysts provided the original analyses worksheets to review. According to this analyst, tests were repeated because of poor column efficiency. The analyst neither initiated an investigation of the laboratory event nor documented the original analyses in the instrument use logbook. The analyst did not respond when we asked why the initial chromatograms were deleted.

However, in your written response, you claimed that this analyst later recalled deleting the data (chromatogram) because column inefficiency may have invalidated the data. Your quality unit must review all pertinent analytical data when making batch release decisions. When analysts delete nonconforming test results, the quality unit is presented with incomplete and inaccurate information about the quality of the products. Your response does not demonstrate how your laboratory procedures prevent the deletion of data or how the quality unit ensures that the records relied upon for batch release and other quality review decisions are complete and accurate.

Our concerns about deletion of data are heightened by the significant number of customer complaints

for subpotency and out-of-specification (OOS) impurity levels from 2012-2014. We observed data deletion in your laboratory related to assay and impurity levels during this time period. During the inspection, we asked to review your lab's raw analytical data of the lots associated with four of the 61 complaints. However, you were unable to provide the raw data because it had been deleted. Without raw test data for the lots associated with these complaints, your firm could not adequately investigate the complaints, nor could you expand your investigation to determine whether other lots were affected by the same problems or take corrective actions, such as recalling drugs if appropriate.

We acknowledge your commitment to hire a third-party consultant, set up user access restrictions, and upgrade computerized systems with audit trails. However, simply activating audit trail functions and instituting password controls are insufficient to correct the broad data manipulation and deletion problems observed at your facility and to prevent their recurrence.

Your management is responsible for the assuring that the scope and extent of the third party audit is adequate, including a full evaluation of sophisticated electronic systems and their potential for manipulation. Your management is also responsible for fully documenting and preserving records.<p>
FDA District Office: CDRH<p>

12/23/2015 Cadila Healthcare Limited
Cadila Healthcare Limited.
Product: pharmaceutical manufacturing facilities
Date: 12/23/2015<p>
Our investigators observed specific violations during the inspection, including, but not limited to the following.
Your firm failed to exercise sufficient controls over computerized systems to prevent unauthorized access or changes to data.

a. Your firm failed to adequately control the use of computerized systems in the quality control laboratory. Our inspection team found that the laboratory manager had the ability to delete data from the Karl Fischer Tiamo software. During our limited review of your Karl Fischer data, we found that one file had been deleted. However, because the audit trail function for the Karl Fischer Tiamo software was not activated, and because eight different analysts share a single username and password, you were unable to demonstrate who performed each operation on this instrument system. You do not have a record of the acquisition of all data, nor do you have records of changes to or modifications of such data.

<p>
FDA District Office: CDRH<p>

12/17/2015 Sun Pharmaceuticals Industries Ltd..
Sun Pharmaceuticals Industries Ltd..
Product: pharmaceutical manufacturing facilities
Date: 12/17/2015<p>
Our investigators observed specific violations during the inspection, including, but not limited to the following.
6. Your firm failed to establish appropriate controls over computers and related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel (21 CFR 211. 68(b)).

You lacked audit trails or other sufficient controls to facilitate traceability of the individuals who access each of the programmable logic controller (PLC) levels or Man-Machine Interface (MMI) equipment. You had no way to verify that individuals have not changed, adjusted, or modified equipment operation parameters.

Access to production equipment used in parenteral manufacturing and solid (b)(4) dosage forms used a

password shared by four or five individuals to gain access to each individual piece of equipment and access level. During our inspection, your Executive Production and QA manager confirmed that the password was shared. Neither your operators nor your supervisors had individual passwords.

During our inspection, firm officials also confirmed that you had not established or documented a control program to describe the roles and responsibilities of production equipment system administrators. There was also no record documenting the individuals who have access to the production equipment or the manner in which individual personnel access production equipment.

In your response, you indicated that you have performed a comprehensive review of the PLCs and manufacturing equipment associated with the production of parenteral and solid (b)(4) dosage forms to assess your access controls and traceability to individual operators. You suggested that traceability to the individual operator could be determined through a hybrid system using the batch manufacturing record and equipment logbook. However, because you used shared login credentials that did not permit identification of a specific person using the shared login, you have not shown how your hybrid system could link specific actions to a specific operator.

In your response, you also stated that you will conduct a retrospective risk assessment to evaluate the effects of your deficient computerized system controls on the quality of the products manufactured using this automated equipment. However, you did not indicated the timeframe for your review, your criteria for evaluating the effects of these deficiencies on your products, or any actions needed for products within expiry.

Finally, in your response, you indicated that you planned to (b)(4). Your response is inadequate because you did not indicate what controls you will implement in the interim to assure that only authorized personnel change your production or other records.

In response to the letter, provide your retrospective review and risk assessment of lots manufactured using equipment with shared passwords. Explain how you will identify which operators or personnel performed and recorded specific activities, your criteria for evaluating how manufacturing and quality of your products has been affected by your deficient controls, and any actions needed to assure the quality, safety, and efficacy of products within expirry. <p>
FDA District Office: CDRH<p>

11/5/2015 Dr. Reddy’s Laboratories Ltd.
Dr. Reddy’s Laboratories Ltd.
Product: pharmaceutical manufacturing facilities
Date: 11/5/2015<p>
At Dr. Reddy’s Laboratories Limited CTO Units VI and V facilities, we identified significant deviations from current good manufacturing practice (CGMP) for the manufacture of active pharmaceutical ingredients (APIs). At Dr. Reddy’s Laboratories Limited Unit-VII facility, we found significant violations of CGMP regulations for finished pharmaceuticals, Title 21, Code of Federal Regulations, Parts 210 and 211.

These deviations and violations cause your APIs and finished drug products to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), 21 U.S.C. 351(a)(2)(B). The methods used in, or the facilities or controls used for, their manufacture, processing, packing, or holding do not conform to, or are not operated or administered in conformity with, CGMP.

We reviewed your firm’s responses of December 15, 2014, February 19, 2015, and March 27, 2015. We note that they lack sufficient corrective actions. We received your additional correspondence of January 31, April 9, May 13, May 21, July 14, and September 14, 2015.

Our investigators observed specific deviations and violations during the inspection, including, but not

limited to, the following.
2. Failure to prevent unauthorized access or changes to data, and to provide adequate controls to prevent omission of data.

During the inspection we found the following examples of uncontrolled access to electronic systems used to generate data in your Product Development Laboratory (PD Lab).

a. Your HPLC systems are configured so that no passwords are required to log in. Credentials are unverified. Anyone who accesses the system can use software administrator privileges, which means that there is no electronic or procedural control to prevent manipulation of data.

b. Your HPLC system had no access controls to prevent alteration or deletion of data. Furthermore, your HPLC software lacked an audit trail feature to document all activities related to the chromatographic analysis. Because of this failure, neither your quality unit nor your laboratory staff could demonstrate that HPLC records included complete and unaltered data. They were also unable to verify that there had been no alterations or deletions.

c. One of your analysts stated that another, unknown individual had logged into the system using the analyst's credentials. This unknown individual performed injections and deletions without the analyst's knowledge. <p>
FDA District Office: CDRH<p>

9/30/2015 Merge Healthcare, Inc.
Merge Healthcare, Inc.)
Product: software used in clinical settings to manage patient data
Date: 9/30/2015<p>
inspections revealed that your firm's devices are adulterated within the meaning of section 501 (h) of the Act, 21 U.S.C. § 351 (h), in that the methods used in, or the facilities or controls used for, their manufacture, packing, storage, or installation are not in conformity with the current good manufacturing practice requirements of the Quality System (QS) regulation found at Title 21, Code of Federal Regulations (CFR), Part 820.
Failure to adequately establish procedures for design validation, as required by 21 CFR 820.30(g). Specifically, QS-57532 (Rev. 2.0, ?WI-Customer Validation Process?) allows for devices that have not yet fully completed design validation, including software validation, to be shipped to end users for clinical use on patients in a ?Limited Availability? basis for the purpose of collecting additional feedback prior to the completion of design validation activities. Further, the Merge HEMO V10.0 was shipped to (b)(4) end users for clinical use in cardiac catheterization procedure labs as part of the firm?s design validation plan as a ?Limited Availability? release; these devices had not been fully validated. Additionally, document number HEMO-6830 (Rev. 1.0, ?Customer Validation Plan Merge Hemo 10.0) describes the customer validation process conducted at the two end user facilities during the ?Pre-Release/Limited Availability? release timelines where it is indicated the software will be used in a ?production environment,? i.e. for patient use.

We have reviewed your response dated August 12, 2015. We acknowledge your commitment to updating your design validation procedure. However, your response is inadequate in that you have not provided an updated procedure for review, nor have you provided a timeframe for implementation of your new design validation process. It is also unclear whether other in-progress design projects may be affected by your elimination of the ?Limited Availability? release, including whether any of your devices are currently being utilized by end users prior to completion of design validation. <p>
FDA District Office: Minneapolis District<p>

9/28/2015 Unimark Remedies Ltd
Unimark Remedies Ltd
Product: active pharmaceutical ingredients
Date: 9/28/2015<p>
Failure to prevent unauthorized access or changes to data and to provide adequate controls to prevent omission of data.

Your laboratory systems lacked access controls to prevent raw data from being deleted or altered. For example:

a. During the inspection, we noted that you had no unique usernames, passwords, or user access levels for analysts on multiple laboratory systems. All laboratory employees were granted full privileges to the computer systems. They could delete or alter chromatograms, methods, integration parameters, and data acquisition date and time stamps. You used data generated by these unprotected and uncontrolled systems to evaluate API quality.

b. Multiple instruments had no audit trail functions to record data changes.

We acknowledge your commitment to take corrective actions and preventive actions to ensure that your laboratory instruments and systems are fully compliant by January 15, 2015. In response to this letter, provide a copy of your system qualification to demonstrate that your electronic data systems prevent deletion and alteration of electronic data. Describe steps you will take (e.g., installing better systems or software) if your qualification efforts determine that the current system infrastructure does not assure adequate data integrity. Explain the archival process your firm has implemented to address these issues and how you will evaluate the effectiveness of these corrections. Provide a detailed summary of the steps taken to train your personnel on the proper use of computerized systems. <p>
Failure to maintain complete data derived from all testing, and to ensure compliance with established specifications and standards.

Because you discarded necessary chromatographic information such as integration parameters and injection sequences from test records, you relied on incomplete records to evaluate the quality of your APIs and to determine whether your APIs conformed with established specifications and standards. For example:

a. During the inspection, the investigator found no procedures for manual integration or review of electronic and printed analytical data for (b)(4) stability samples. Electronic integration parameters were not saved or recorded manually. When the next samples were analyzed, the previous parameters were overwritten during the subsequent analyses.

b. We found that some analytical testing data was inadequately maintained and reviewed.

i. Your HPLC 14 computer files included raw data for undocumented (b)(4) stability samples analyzed on December 30, 2013, but no indication of where these samples came from and why they were tested.
ii. In a data file folder created on May 22, 2013, 23 chromatograms were identified as stability samples for (b)(4) lots (b)(4), and (b)(4). Results were not documented. More importantly, the acquisition date was July 7, 2013, more than six weeks after the samples were run.
iii. (b)(4) lots (b)(4) and (b)(4) were not in your stability study records at the time of inspection. Additionally, there were no log notes of any samples from the three lots removed from the stability chamber.

You responded that ?the probable reason for this inconsistency in data acquisition was due to some malfunction in the computer system at the time of data acquisition.? Your response is inadequate because you have provided neither evidence to support this conclusion, nor a retrospective review of the effects your incomplete analytical data records may have had on your evaluation of API quality.

In response to this letter, provide your revised procedures and describe steps you have taken to retrain employees to ensure retention of complete electronic raw data for all laboratory instrumentation and equipment. Also, provide a detailed description of the responsibilities of your quality control laboratory management, and quality assurance unit for performing analytical data review and assuring integrity (including reconcilability) of all data generated by your laboratory. <p>
FDA District Office: CDRH<p>

8/12/2015 Hoya Corporation (PENTAX Life Care Division)

Hoya Corporation (PENTAX Life Care Division)
Product: endoscopes and endoscope accessories.
Date: 8/12/2015<p>
inspections revealed that your firm's devices are adulterated within the meaning of section 501 (h) of the Act, 21 U.S.C. § 351 (h), in that the methods used in, or the facilities or controls used for, their manufacture, packing, storage, or installation are not in conformity with the current good manufacturing practice requirements of the Quality System (QS) regulation found at Title 21, Code of Federal Regulations (CFR), Part 820.
Failure to establish and maintain procedures for implementing corrective and preventive action, as required by 21 CFR 820.100(a). For example: <p>
FDA District Office: CDRH<p>

8/7/2015 Cardiac Designs, Inc.

Mylan.
Product: ECG Check Application and ECG Check Wireless Lead Cardiac Monitor
Date: 8/7/2015<p>
1. Failure to establish and maintain design validation procedures to ensure that devices conform to defined user needs and intended uses and shall include testing of production units under actual or simulated use conditions, as required by 21 CFR 820.30(g).

1. Your firm?s ?Design Validations? procedure Revision 1 dated May 22, 2015, states software should be tested according to a test plan and requires the results of this software validation to be maintained in the design history file (DHF). Your firm does not have any records demonstrating the ECG Check Application software was validated.
2. Failure to establish procedures for receiving, reviewing, and evaluating complaints by a formally designated unit, as required by 21 CFR 820.198.

a. Your ?Customer Requirements and Complaints? procedure revision 2 dated August 24, 2014, is inadequate. Your firm is currently using a contractor to receive and initially document all communications; however, your complaint handling procedure does not address this practice. Further, your procedure does not address how you will receive, review, and verify complaints are being forwarded from your contract complaint handling company, to conduct the complaint investigations.

b. Your ?Customer Requirements and Complaints? procedure revisions 1 and 2, dated May 22, 2013 and August 24, 2014, respectively; require all complaints be documented on your ?Customer Complaint Report Form?. However, your complaint log showed your firm received at least 87 complaints between April 4, 2014 and June 15, 2015 and these complaints were not documented on your ?Customer Complaint Report Form?. Further, there are no records showing these complaints were reviewed to determine if an investigation was necessary or if they were evaluated to determine if they were reportable events as defined in 21 CFR 803.

c. On December 16, 2014, your firm received a complaint indicating a possible failure of your ECG Check Monitor and software to detect an abnormal heart condition. There is no record this complaint was evaluated to determine if it was reportable under 21 CFR 803. In addition, there is no record for this complaint demonstrating the nature and details of the complaint, whether the device failed to meet

specifications, or the relationship of the device to the event.<p>
FDA District Office: Dallas district<p>

8/6/2015 Mylan
Mylan.
Product: pharmaceutical manufacturing facility
Date: 8/6/2015<p>
Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel can change master production and control records, or other records (21 CFR 211.68(b)).

Your Siemens computer-based BMS and NVPMS do not require passwords to access the network and servers. Your contractors? access is uncontrolled. Responsibilities for system administrators are undefined.

This violation is recurrent. On September 9, 2013, we cited your firm in Warning Letter 320-13-26 for failure to exercise appropriate controls over computer or related systems<p>
FDA District Office: CDRH<p>

7/13/2015 Mahendra Chemicals
Mahendra Chemicals..
Product: pharmaceutical manufacturing facility
Date: 7/13/2015<p>
Failure to prevent unauthorized access or changes to data, and to provide adequate controls to prevent omission of data.

Your laboratory systems lacked access controls to prevent raw data from being deleted or altered. For example,

a) There is no assurance that you maintain complete electronic raw data for your Gas Chromatography (GC) instrument. FDA investigators observed multiple copies of raw data files in the recycle bin connected to the GC instrument QC-04 even in the presence of ?Do Not Delete Any Data? notes posted on two laboratory workstation computer monitors.

b) Employees were allowed uncontrolled access to operating systems and data acquisition software tracking residual solvent, and test and moisture content. Our investigators noted that there was no password functionality to log into the operating system or the data acquisition software for the GC, the High Performance Liquid Chromatography (HPLC) instrument QC-17, or the Karl Fischer (KF) Titrator QC-13.

c) HPLC SpinChrome and GC Lab Station data acquisition software lacked active audit trail functions to record changes in data, including original results, who made changes, and when.

In your response, you state that your laboratory GC, HPLC and KF systems are now password-protected and that you have begun drafting analytical software password procedures for the GC, HPLC and KF laboratory instruments. However, your response does not state whether every analyst will have their own user identification and password. You also mention plans to install a validated computer system. However, you did not provide a detailed corrective action and preventive action (CAPA) plan or conduct a review of the reliability of your historical data to ensure the quality of your products distributed to the U.S. market.

Inadequate controls of your computerized analytical systems raise questions about the authenticity and reliability of your data and the quality of your APIs. It is essential that your firm implements controls to prevent data omissions or alterations. It is critical that these controls record changes to existing data, such as the individuals making changes, the dates, and the reason for changes. <p>

FDA District Office: CDRH<p>

5/27/2015 VUAB Pharma a.s.
VUAB Pharma a.s..
Product: pharmaceutical manufacturing facility
Date: 5/27/2015<p>
ailure to prevent unauthorized access or changes to data and to provide adequate controls preventing data omissions.

Our inspection noted that your firm did not retain complete raw data from testing performed to assure the quality of (b)(4), API. Specifically, our inspection revealed your firm did not properly maintain a back-up of HPLC chromatograms that form the basis of your product release decisions. Our inspection revealed discrepancies between the printed chromatograms and the operational qualification protocol for the High Performance Liquid Chromatography (HPLC) system, which is intended to demonstrate correct operation of the HPLC. These discrepancies included injection sequences and values to calculate relative standard deviation (RSD).

While investigating these discrepancies, our investigator requested the original electronic raw data. Your quality unit, after consulting with the Information Technology (IT) department, stated they were unable to retrieve the original electronic raw data because back-up discs were unreadable. Your quality unit then stated that back-up disks have been unreadable since at least 2013. Your HPLC system is used to test (b)(4), API for batch release. However, without complete, accurate, reliable, or retrievable raw data about the HPLC system?s qualification, you lacked complete assurance that the system was operating as intended.

You also failed to have proper controls in place to prevent unauthorized manipulation of your laboratory?s raw electronic data. Our inspection revealed your HPLC system did not have access controls to prevent alteration or deletion of data. Your HPLC software lacked an audit trail recording any changes to the data, including: previous entries, who made changes, and when changes were made. During the inspection, we also noted that all laboratory employees shared a common log-in and password to access the system.

This lack of control over the integrity of your data raises questions about your analytical data?s authenticity and reliability, and about the quality of your APIs. We note that the September 2008 FDA inspection uncovered concerns over your handling of raw analytical data, including discrepancies between laboratory notebooks and printed chromatograms.

Your response states you are qualifying a new HPLC system which allows operator-specific passwords and has audit trial and back-up functions. Your response also states you will implement a new electronic back-up system in your QC chemistry department.
However, your response lacks sufficient detail about systems and controls you will implement. Simply activating audit trail functions and instituting password controls is inadequate. In addition, you failed to review historical data to ensure the quality of your products distributed to the US market.
In your response to this letter, provide a comprehensive corrective action plan for computer system controls over all laboratory and manufacturing instrumentation and equipment. This response should include but not be limited to:

Information regarding changes in the reliability of your information technology infrastructure, including but not limited to improved computer systems, systems validation, revised procedures, and appropriate retraining of employees that will be implemented immediately to ensure your firm creates and retains complete and accurate electronic raw data.
Your firm's procedure for the establishment, issuance, and control of passwords used to access your analytical instrumentation. All access levels for computerized systems should be clearly defined and documented in a written procedure.
A detailed summary of the steps taken to train your personnel on the proper use of computerized

systems.<p>
FDA District Office: CDRH<p>

4/30/2015 Soft Computer Consultants, Inc.
Soft Computer Consultants, Inc.
Product: Class I/II software systems
Date: 4/30/2015<p>
1. Failure to adequately establish procedures for CAPA as required by 21 CFR 820.100(a). Specifically,
A. Product Change Controls (PCCs) which are corrective and preventive actions for handling software coding defects do not always include investigating the cause of all nonconformities relating to product, processes and the quality system, and identifying action(s) needed to correct and prevent recurrence of nonconforming product and other quality problems. For example;
i. PCC-54168 dated 4/25/14 was a CAPA for investigating a software defect in (b)(4) for clients using the Results Reporting interfaces to send results to an (b)(4) or (b)(4)
system. The defect was that the interface fails to send the abnormal flags for Reference Lab test results. This affects the flag that indicates the result is abnormal. Caregivers, who rely on the abnormal flag rather than the results may come to an incorrect conclusion. The PCC- 54168 identified a software coding error as the assignable cause of this problem. Your firm also identified that the software interface between your software and other software was not fully tested. A mandatory software Hot Fix was created due to the severity of the failure mode. The mandatory Hot Fix led to a correction and removal (1058332-10/13/2014-002- C). This PCC did not include the following:
a. An analysis to determine if other software products manufactured have had similar failure modes due to lack of testing of software interfaces.
b. Software testing that was created for verifying this corrective action was not included in the repository of tests known as (b)(4) tests as required by your (b)(4) Testing Procedure, SOP TST_P005, to allow these tests to be run for future software changes.
http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2015/ucm448655.htm 2/8
6/3/2015 2015 > Soft Computer Consultants, Inc. 4/30/15
ii. PCC-52730 dated 12/31/13 was a CAPA for investigating a software defect in (b)(4) version (b)(4) when used with (b)(4) version (b)(4). The problem was that when an isolate is resulted without a SNOWMED code, the isolate information in the downstream system may be incomplete or missing. As a result, there is a potential for the delay or omission of patient treatment updates. Your firm identified a software error as the assignable cause of this problem. Your firm also identified that the software interface between the (b)(4) system and (b)(4) was not fully tested which would have identified the software defect. A mandatory software Hot Fix was created due to the severity of the failure mode. The mandatory Hot Fix led to a correction and removal (1058332-10/13/2014-001-C). This PCC did not include the following:
a. An analysis to determine if other software products manufactured have had similar failure modes due to lack of testing of software interfaces.
2. Failure to adequately establish procedures to ensure that all purchased or otherwise received product and services conform to specified requirements as required by 21 CFR
820.50. Specifically,
A. Quality contracts for the design contractors ((b)(4) & the (b)(4)) who perform design of software do not include a provision that the design contractors agree to notify your firm of changes in the product code or service so that your firm may determine whether the changes may affect the quality of the product provided.
B. According to the VP of Administration and the VP of Genetics and Anatomic Pathology (AP) who are both responsible for conducting supplier audits of the contractors in (b)(4) and in the (b) (4), the supplier audits of the facilities are reportedly to be conducted (b)(4). The supplier audits are divided into two categories Administrative and Technical. Administrative audits covered reviewing the Quality contract, verifying employee training and experiences are suitable at the respective contract facilities. Technical audits include auditing design projects, adherence to design control requirements, and adherence to standard operating procedures. Review of the documents provided identified the following:
i. There is no documented evidence that Technical supplier audits for the (b)(4) contract facility were conducted for 2012 and 2013. The Technical supplier audit conducted for September 2014 for the

(b)(4) facility has not been reviewed or approved as required by your Conducting External Quality Audits Procedure, SOP AUD_P003.
ii. There are no corresponding Quality Audit Plans as required by SOP for any Technical supplier audits for the (b)(4) contracting facility for 2012, 2013, or 2014.
3. Failure to establish and maintain procedures for design change, as required by 21 CFR 820.30(i). Specifically,
A. The software changes made by your firm and the (b)(4) and (b)(4) contractors are not assessed by your firm to confirm that the design changes meet their intended use and conform to all of your requirements including all verification and validation activities. The following are examples:
i. The Hot Fixes used to correct design defects for (b)(6) that were part of the correction and removal submitted to FDA on or about 12/10/14. The software changes were made by the (b)(4) contractor.
ii. The Hot Fixes used to correct design defects for (b)(6) that were part of the correction and removal submitted to FDA on or about 11/4/14. A portion of the software changes were made by the (b)(4) contractor.
iii. The Hot Fixes used to correct design defects for (b)(6) that were part of the correction and removal submitted to FDA on or about 2/17/14. The software changes were made by your firm.
B. User requirements (design inputs) are not required by either your firm or any of your contracting organizations for any software custom scripts created that can be used as part of a software Hot Fix (software correction made to a customer). Hot fixes are used as an emergency or high priority change that needs to be made when the client or your firm cannot wait for the normal patch process for any product manufactured by your firm.
For example, the Hot Fix utility used to identify the design defects for (b)(6) did not include documentation of user requirements (design inputs) for the Hot Fix utility 1.18021.1. This Hot Fix utility for the (b)(4) software was used to identify defective records in the customer's database and was a part of the correction and removal submitted to FDA on or about 12/11/14. Your Hot Fix Process, SOP G01D072, does not include any requirements for documenting design inputs for
http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2015/ucm448655.htm 5/8
6/3/2015 2015 > Soft Computer Consultants, Inc. 4/30/15
custom scripts.
4. Failure to establish and maintain procedures for design review as required by 21 CFR 820.30(e). Specifically,
There was no evidence to demonstrate that the Release notes for Hot Fix utility 1.18021.1 used to identify defective records in the customer's database for software package (b)(4) were reviewed and approved. Under section 5.2d of your Release Note Processing Workflow Procedure, G04S1082, the product specialist or designee is required to review the release notes and place them in the published status prior to going live (release). This Hot Fix utility was part of a correction and removal submitted to FDA on or about 12/11/14. The Release notes are provided to the customer or your personnel for all software changes.
<p>
FDA District Office: Florida District<p>

4/11/2015 Quality Electrodynamics, LLC
Quality Electrodynamics, LLC..
Product: cois used in conjunction with MRI scanners .
Date: 4/10/2015<p>
Failure to document validation activities, as required by 21 CFR 820.75(a). Specifically,

The setting (temperature and line speed) used during the validation studies for the reflow oven, which is part of the SMT (Surface Mount Technology) line, to determine the optimum settings were not documented. Therefore, it is unknown if you are currently operating the reflow oven within your validated parameters.

Your response dated March 26, 2015 cannot be assessed at this time. The response states that you have placed all 176 oven reflow profiles under the change control process and revised your ?Validation of Processes and Software? procedure, SOP 021; and training is ongoing. You are also working with an

SMT (Surface Mount Technology) expert to aid in monitoring the process capability and control of the SMT line. Additionally, you have ordered new process monitoring equipment. Please provide an update on the progress of these corrective actions. <p>
FDA District Office: Cincinnati District<p>

4/6/2015 Yunnan Hande Bio-Tech. Co. Ltd.
Recipient: Yunnan Hande Bio-Tech. Co. Ltd..
Product: active pharmaceutical ingredients .
Date: 4/6/2015<p>
Our investigators observed specific deviations during the inspection, including, but not limited to, the following:

1. Failure to prevent unauthorized access or changes to data and to provide adequate controls to prevent omission of data.

You lacked controls to prevent the unauthorized manipulation of your laboratory's electronic raw data. Specifically, your infrared (IR) spectrometer did not have access controls to prevent deletion or alteration of raw data. Furthermore, the computer software for this equipment lacked active audit trail functions to record changes to data, including information on original results, the identity of the person making the change, and the date of the change. Audit trails that capture such critical data about the quality of your batch production should be reviewed as part of the batch review and release process.

We acknowledge your commitment to upgrade the IR software by adding full audit trail capabilities in compliance with CGMP. In your response, you also commit to obtain information about the (b)(4) archival of all data obtained on laboratory computerized systems, and to evaluate software upgrades to other instrumentation. However, your response is inadequate because you have not specified how you will ensure the integrity of raw analytical data or maintain data before you complete your planned corrective actions and preventive (CAPA) actions.

In response to this letter, provide your comprehensive CAPA plan for ensuring that electronic data generated in your manufacturing operations, including laboratory testing, cannot be deleted or altered. It essential that your firm implement controls that prevent the omission of data, and record information about changes to existing data, such as the date of the change, identity of person who made the change, and an explanation or reason for the change. Any such changes should be made in accordance with an established and appropriate procedure. Your response should address your laboratory equipment and any other manufacturing-related equipment that may be affected by the lack of adequate controls to prevent data manipulation <p>
FDA District Office: CDRH<p>

3/31/2015 Hospira S.p.A.
Hospira S.p.A..
Product: Hospira S.p.A.
Date: 3/31/2015<p>
Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records (21 CFR 211.68(b)).

Specifically, your high performance liquid chromatography (HPLC) and gas chromatography (GC) data acquisition software, TotalChrom®, did not have sufficient controls to prevent the deletion or alteration of raw data files. During the inspection, the investigator observed that the server that maintains electronic raw data for HPLC and GC analyses (the J drive) contains a folder named ?Test,? and that chromatographic methods, sequences, and injection data saved into this folder can be deleted by analysts. The investigator also found that data files initially created and stored in the ?Test? folder had been deleted, and that back-up files are overwritten (b)(4).

In addition, because no audit trail function was enabled for the ?Test? folder, your firm was unable to verify what types of injections were made, who made them, or the date or time of deletion. The use of audit trails for computerized analytical instrumentation is essential to ensure the integrity and reliability of the electronic data generated.

Your response indicates that you have added computer controls to prevent the deletion of folders and files in the J drive for electronic raw data. However, you provide no evidence demonstrating how your firm will prevent deletion of newly created folders and files in each of your computer systems. We acknowledge your commitment to hire a third party consultant to address the inadequacies of your data systems. However, your response is inadequate as it fails to address how you will enable and review audit trail functions for all of your analytical computer systems.

In response to this letter, provide specific details about the comprehensive controls in place to ensure the integrity of electronic raw data generated by all computer systems used to support the manufacture and testing of drug products. Your response should demonstrate an understanding of your processes and the appropriate controls needed for each stage of manufacture that generates electronic raw data, as well as for your laboratories. <p>
FDA District Office: CDRH<p>

2/27/2015 Novacyl (Thailand), Ltd.
Novacyl (Thailand), Ltd.
Product: active pharmaceutical ingredients (APIs)
Date: 2/27/2015<p>
3. Failure to prevent unauthorized access or changes to data and to provide adequate controls to prevent omission of data.

The inadequate controls over access to your data raise questions about the authenticity and reliability of your data and the quality of the APIs you produce.
Specifically,

a. Your firm did not have proper controls in place to prevent the unauthorized manipulation of your laboratory?s raw electronic data. Your HPLC computer software lacked active audit trail functions to record changes to analytical methods, including information on original methodology, the identity of the person making the change, and the date of the change. In addition, your laboratory systems did not have access controls to prevent deletion or alteration of raw data. During the inspection, your analysts demonstrated that they were given inappropriate user permissions to delete HPLC data files.

b. Moreover, the gas chromatograph (GC) computer software lacked password protection allowing uncontrolled full access to all employees.

Your response states that you commit to upgrading your HPLC systems to have audit trails and your GC system to have password protection by July 31, 2014. However, your response lacks sufficient detail of the systems and controls you will implement. Simply turning on audit trail functions is inadequate. In addition, you failed to review historical data to ensure the quality of your products distributed to the US market.

In response to this letter, provide specific details about the comprehensive controls in place to ensure the integrity of electronic raw data generated by all computerized systems during the manufacture and testing of your drugs. Your response should demonstrate an understanding of your processes and the appropriate controls needed for each stage of manufacturing and testing that generates electronic raw data. Your response should also describe the controls and procedures you will implement to retain and archive the raw data you generate. <p>
FDA District Office: CDRH<p>

2/20/2015 XZeal Technologies, Inc.
XZeal Technologies, Inc.
Product: XZeal Dental X-Ray Unit Z70
Date: 2/20/2015<p>
1. Failure to establish and maintain procedures for validating the device design, as required by 21 CFR 820.30(g). For example:
b. Your firm has not established and maintained documentation in support of Section 4.6 - Design Validation of the Product - Conception and Development, PR0-04.01, Ver. 00, concerning software validation of the embedded software for the device. Specifically, you stated to our investigator that your firm is not responsible for the software because your firm does not manufacture it. You also stated to our investigator your firm did not know what, if any, validation activities were performed by your firm?s Chinese supplier for this software.

In addition, your firm?s Risk Analysis Report ? Software, Ver. 00, Technical File, does not adequately access the risk presented by the software controlling the XZeal Dental X-Ray Unit Z70 as a moderate risk to users and patients. For example, the report indicates a ?No? to the questions: ?Could a malfunction of, or a latent design flaw in the Software Device lead to an erroneous diagnosis or a delay in delivery of appropriate medical care that would likely lead to Moderate Injury? and ?Does the Software Device control the delivery of potentially harmful energy that could result in death or serious injury, such as radiation treatment systems, defibrillators and ablation generators.?

Your firm?s October 7, 2014 response includes reference to assembly operational checks or functional (Black-box) testing of the XZeal Dental X-Ray Unit Z70. Adequate software validation of the XZeal Dental X-Ray Unit Z70 software would require more than functional testing, including but not limited to a description of software (i.e.: Title, Manufacturer, Version Level, Release Date, etc.); control of capabilities of end user; reliability of functionality; maintenance and control of software versions; and adequate software hazard analysis. <p>
FDA District Office: Florida District<p>

2/19/2015 Inovo, Inc
Inovo, Inc
Product: AccuPulse Model 6505 oxygen conserver, Bonsai Velocity oxygen conserver, Evolution oxygen conserver, Evolution with Motion oxygen conserver, SmartDose oxygen conserver, Smart Does Mini oxygen conserver, Oxymizer Disposable oxygen conservers, and oxygen Regulators.
Date: 2/19/2015<p>
4. Failure to establish and maintain procedures for validating the device design, as required by 21 CFR 820.30(g). Specifically,

a. Your software development /validation:

i. does not include written procedures covering the development/validation of the software used in your devices;

ii. documentation for your Evolution Oxygen Conserver device does not include structural testing at the code level (use of static code checkers, independent code review, etc); and

iii. software product testing procedure, Database/Software Controls IQP 030 Rev A dated 10/20/08, does not require structural testing and does not include provisions for the adequate description of regression testing.
We reviewed your firm?s responses and conclude that they are not fully adequate.

a) The revisions to your software procedures and the initiation of the added testing requirements do not appear to timely relative to the criticality of this deficiency.<p>
FDA District Office: Florida District<p>

1/30/2015 Apotex, Inc.
Apotex, Inc.
Product: intercranial pressure monitoring products
Date: 1/30/2015<p>
Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records (21 CFR 211.68(b)).

QC personnel created unauthorized folders on laboratory computerized systems without appropriate oversight. Our review of the HPLC Empower III data collected in 2013-2014 in the commercial QC laboratory found a data folder entitled “WASH.” According to your management, the folder was intended for column wash injections using blank solvent prior to and following sample runs, although you have no standard operating procedure (SOP) detailing this process. One of your laboratory analysts stated that this folder does not contain any standard or sample injection results. However, our investigator found that this folder contained a total of 3,353 injection results, some of which appeared to be samples.
<p>
FDA District: CDRH

1/9/2015 Micro Labs Limited
Micro Labs Limited
Product: pharmaceutical manufacturing facility
Date: 1/9/2015<p>
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)).
a) During the inspection, your management admitted that employees in both of your Quality Control (QC) laboratories had frequently conducted unauthorized ?trial? High Performance Liquid Chromatography (HPLC) injections prior to additional injections that were used in the reported test results. Although your management stated that this practice ended in February 2014, FDA investigators discovered evidence that this practice continues. The inspection found that the names assigned to each sequenced injection were often changed during testing, obscuring the traceability of repeated injections. The data from ?trial? injections was not reviewed or considered in determining batch quality. For example,

1) For the related substances analysis of (b)(4) USP (b)(4) mg Tablets batch (b)(4) conducted on February 25, 2013, there were three sample injections of vial 1_8, all named ?TEST,? which were run prior to the reported sample injections. The ?TEST? injection data was stored in the ?Trial? folder located on a personal computer (PC) with no audit trail linked to the HPLC instrument.
5) The audit trail for the dissolution analysis of the 9-month long-term stability sample of (b)(4) USP (b)(4) mg Tablets batch (b)(4) conducted on March 22, 2014, showed a single manual injection that was not included in the official test results package. A manual ?trial? sample injection from vial position (b)(4) at 12:29 pm was injected between the Set (b)(4) and Set (b)(4) analytical sequences. No deviation was documented regarding the extra sample injection. In addition, the original injection data obtained for vial position (b)(4) was overwritten and not saved. Because the original data was overwritten, you did not review and evaluate it as part of your batch release decision.
b) The inspection also found similar unreported and unexplained sample data acquired during your gas chromatography (GC), ultra violet (UV) spectroscopy and (b)(4) analyses. The extra GC data was stored in the ?Trial? folder located on a PC with no audit trail linked to the GC instrumentation. The extra UV and (b)(4) data was stored on the instrument hard drives. This unreported and unexplained data was not reviewed when assessing batch quality and making product disposition decisions. For example,

1) For the (b)(4) analysis of the 9-month long-term stability sample of (b)(4) USP (b)(4) mg Capsules ((b)(4) drug product) batch (b)(4) conducted on January 10, 2014, three extra analyses that were run prior to the reported sample were found on the instrument hard drive. During the inspection, the calculations that you performed showed that two of the extra analyses were OOS ((b)(4)% & (b)(4)%, as

compared to the specification of NMT (b)(4)%).

Notably, there were no test sample weight records for the three extra (b)(4) tests. The extra sample data was not reviewed when assessing batch quality and product stability.<p>
2. Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records (21 CFR 211.68(b)).

FDA investigators discovered a lack of basic laboratory controls to prevent changes to electronically stored data. The following examples show that you lack effective control of the integrity of instrument output data:

a) The ten Shimadzu HPLC instruments in the QC ?commercial? laboratory were configured to send acquired injection data to PCs without audit trails.

b) There was a lack of controls to prevent substitution or overwriting of data. The (b)(4) audit trail dated January 6, 2014, for HPLC MLG/QC/12/026 and the (b)(4) audit trail dated January 15, 2014, for HPLCs MLG/QC/12/031 and MLG/QC/12/027 each showed sample injections marked with the same small graphic symbol. For each of these entries, you replaced the original injection sequence data with data from a single manual injection and failed to save the original sequence data.

In your response to this letter, include a chronology of Chromeleon audit trail information that shows all single manual sample injections that replaced data collected during HPLC testing.

c) A ?File Note? dated February 10, 2014, signed by the QC Head, established that the printed data used for batch disposition decisions from the Metrohm Titrando Instrument MLG/QC/12/048 hard drive was not necessarily the complete data for a batch. Our inspection found that data on the instrument was selected for use and was not protected from change and deletion. Notably, the audit trail capability of this QC ?commercial? laboratory instrument was not enabled, even aftercreation of the ?File Note.? <p>
FDA District Office: CDRH<p>

12/19/2014 Novacyl Wuxi Pharmaceutical Co., Ltd.
Novacyl Wuxi Pharmaceutical Co., Ltd. .
Product: pharmaceutical manufacturing facility
Date: 12/19/2014<p>
1. Failure to manage laboratory systems with sufficient controls to ensure conformance to established specifications and prevent omission of data.
Our inspection revealed serious deficiencies related to your documentation practices, including missing raw data. It is a basic responsibility of your quality unit to ensure that your firm retains the supporting raw data that demonstrates your APIs meet specifications that they are purported to possess.

For example, during the inspection, our investigator found a chromatogram related to (b)(4), API in the trash, dated October 15, 2013, which reported an additional chromatographic peak when compared to the standard. During the inspection, your firm stated that the analyst discarded the chromatogram because it was present in the blank injection. However, the analyst was unable to retrieve the blank chromatogram from the system because it was overwritten by a subsequent injection.

In addition, the inspection documented that your firm made changes to integration parameters for the impurities test without appropriate documentation or justification. Your firm relied upon hand written notes on a chromatogram discovered in a drawer at the laboratory as the documentation for this change. Furthermore, your firm implemented this change without an audit trail that would have captured the date of the change and who made the change.
Other significant deficiencies noted in your laboratory system include:

a) Failure to have a written procedure for manual integration despite its prevalence.
b) Failure to use separate passwords for each analyst?s access to the laboratory systems.
c) Use of uncontrolled worksheets for raw analytical data in your laboratory.
d) Presence of many uncontrolled chromatograms, spreadsheets and notes of unknown origin found in a drawer.

The lack of controls on method performance and inadequate controls on the integrity of the data collected raise questions as to the authenticity and reliability of your data and the quality of the APIs you produce.

Your firm?s response, dated November 06, 2013, stated that your firm will create a validation program for all uncontrolled computer systems, create a new standard operating procedure (SOP), and retrain all analysts performing analytical tests. However, observations found during the most recent inspection regarding the inadequacy of your HPLC system raises questions regarding your ability to implement sustainable corrective and preventive actions, as previous commitments made to the agency were not fulfilled. Please provide specific milestones and your detailed plan on how you intend to implement the appropriate corrective actions. We will also encourage you to submit monthly reports to the agency of your progress.

As part of your response, provide a complete validation plan for your laboratory computerized systems. This plan should include an audit trail component and other appropriate controls to prevent deletion and overwriting of data. In addition, include a retrospective review of the analytical data and batch records for all of the APIs distributed that remain within expiration, along with an evaluation of data that may have been generated to support a drug application, including any Drug Master File. This investigation should include a review of all APIs manufactured at your site. Furthermore, provide details of the systemic corrective actions taken to prevent recurrence of these deficiencies. .<p>
FDA District Office: CDRH<p>

12/18/2014 Moor Instruments Ltd.
Moor Instruments Ltd.
Product: Laser Doppler Blood Flow Monitor devices
Date: 12/18/2014<p>
This inspection revealed that these devices are adulterated within the meaning of section 501(h) of the Act, 21 U.S.C. § 351(h), in that the methods used in, or the facilities or controls used for, their manufacture, packing, storage, or installation are not in conformity with the current good manufacturing practice requirements of the Quality System regulation found at Title 21, Code of Federal Regulations (CFR), Part 820.
Failure to establish and maintain procedures for changes to a specification, method, process, or procedure, as required by 21 CFR 820.70(b). For example, your firm completed design change note 798 to modify the moorVMS-LDF device and updated the software from version 1 to version 2. Work instruction procedure, ?(b)(4)?, states that version 1 is uploaded onto the device during the main board testing operation. However, your firm did not update the work instructions to address the software version change.
Failure to establish and maintain procedures for quality audits and conduct such audits to assure that the quality system is in compliance with the established quality system requirements and to determine the effectiveness of the quality system, as required by 21 CFR 820.22. For example, your firm?s Internal Audit Procedure does not require quality audits to be conducted by individuals who do not have direct responsibility for the matters being audited. During the 2011 and 2012 internal audits, your firm's Quality and Regulatory Representativeaudited matters that were under her direct responsibility, including customer complaints implemented by your firm?s Customer Feedback procedure.

We reviewed your firm?s response and conclude that it is not adequate. Your firm?s response did not address this observation.

Given the serious nature of the violations of the Act, devices, including moor VMS-LDF and moor

VMS-LDF-HP Laser Doppler Blood Flow Monitor devices,manufactured by your firm are subject to refusal of admission under section 801(a) of the Act, 21 U.S.C. § 381(a), in that they appear to be adulterated. As a result, FDA is taking steps to refuse entry of these devices into the United States, known as ?detention without physical examination,? until these violations are corrected. In order to remove the devices from detention, your firm should provide a written response to this Warning Letter as described below and correct the violations described in this letter. We will notify you regarding the adequacy of your firm?s response and the need to re-inspect your firm?s facility to verify that the appropriate corrections and/or corrective actions have been made.<p>
FDA District Office: CDRH<p>

12/9/2014 Customed Inc.
Customed Inc.
Product: medical devices, including convenience packs for surgical procedures
Date: 1/9/2015<p>
Failure to validate the defined user needs and intended uses of the (b)(4) used as part of the quality system according to an established protocol, as required by 21 CFR 820.70(i). Specifically, your firm implemented (b)(4) to track product inventory (incoming materials, finished/released products and quarantine items), however the software was not validated. In addition, the status of lots of finished products and incoming materials in the warehouse failed to match the (b)(4) system inventory.

Your firm?s response dated August 21, 2014, is not adequate. Your firm initiated CAPA (b)(4) to prepare a software validation protocol, however, you failed to initiate a corrective action to identify and address pertinent quality system and production software that have not been appropriately validated. Further, your firm failed to provide the executed (b)(4) validation protocol and summary report for review. <p>
FDA District Office:San Juan Office<p>

8/11/2014 Spacelabs Healthcare, Inc.
Spacelabs Healthcare, Inc..
Product: patient monitoring devices
Date: 8/11/2014<p>
1. Failure to establish and maintain procedures for implementing corrective and preventive action (CAPA), as required by 21 CFR 820.100(a).

a. Your firm failed to implement corrective and preventive actions needed to correct and prevent identified quality problems. Specifically, several CAPAs identify corrective actions but were closed without implementation of the corrective actions. For example:

i. Your firm opened CAPA 31920 on July 22, 2013, to address the shipment of an outdated version of Élance Central software. Your firm?s root cause investigation determined the ECO did not address which version of the software to scrap, and that the latest version of the software was not checked prior to shipment. Your firm identified the following corrective and preventive action plan, (b)(4) CAPA 31920 was closed on September 9, 2013, even though the action plan was not implemented.

ii. Your firm opened CAPA 24340 on January 29, 2013, to address ICS G2 units that were released when they were covered by a stop ship that was intended to prevent their shipment. In CAPA 24340, your firm documented that a (b)(4).? Your firm opened the follow-up CAPA 24356 on January 29, 2013, but then closed it without further corrective actions on February 1, 2013, because it was documented as a duplicate of CAPA 24340. CAPA 24340 was closed on October 2, 2013, and documented as effective, even though your firm did not make changes to the stop/ship purge process to prevent the issue from reoccurring.

b. Your firm failed to verify or validate its corrective and preventive action to ensure such action is effective and does not adversely affect the finished device. For example, CAPA 31363 was opened on July 8, 2013, to address language bill of materials (BOMs), which called for a previous version of Elance

software to be installed on monitors instead of the latest software version. Your firm documented several corrective and preventive actions including the requirement to add the software to the bill of materials with the engineering change order (ECO) PR034750. Under your firm?s confirmation of results section, your firm states ?PR034750 has been implemented? as its verification and validation of effectiveness results, but your firm does not document how it verified or validated the actions to ensure that the actions were effective. Your firm later updated its corrective actions to require the deletion of bedside software from Elance language bill of materials. Under ?Was the plan effective?? your firm states ?yes? without documenting activities performed for verification or validation of effectiveness.

Your firm?s response is not adequate. Your response indicated your firm revised its CAPA process and is implementing a CAPA management system to support the changes. Your firm plans to provide training to personnel on several revised procedures and to conduct a retrospective review of closed CAPAs. Your firm has not explained how its new CAPA system will ensure that follow-up CAPAs are documented and tracked to allow for proper processing. Your firm has not submitted an update to or implementation plan for CAPA 24340 or your firm?s plan for verifying or validating the effectiveness of its corrective actions for CAPA 31363. Your firm should complete the remaining corrective and preventive actions and submit evidence of implementation. We note that these violations have been observed previously during FDA inspections. <p>
3. Failure to establish and maintain procedures for receiving, reviewing, and evaluating complaints by a formally designated unit, as required by 21 CFR 820.198(a). For example, your firm failed to follow its procedure, Complaint Handling, 1100-0012, Rev. K, which defines a complaint as ?any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device after it is released for distribution? and requires that a complaint be entered into an electronic database as a complaint record. Your firm failed to initiate a complaint record for service calls including, but not limited to: CA822459 on April 23, 2013; CA831398 on September 25, 2013; and CA833691 on November 4, 2013. CA822459 was for three 91496 modules that would not boot up after a software change. CA831398 was for a neurology monitor with a non-volatile random access memory failure. CA833691 was for a monitor that would not power on.

The adequacy of your firm?s response cannot be determined at this time. Your firm has entered CA822459, CA831398, CA833691, and other service records into the complaints system. Your firm plans to complete a retrospective review of service calls to determine if they are complaints and to provide training to field personnel regarding the revised complaint handling process. However, evidence of implementation of these corrective actions was not provided for review. We note that these violations have been observed previously during FDA inspections. <p>
6. Failure to establish and maintain procedures for validating the device design to ensure that devices conform to defined user needs and intended uses, as required by 21 CFR 820.30(g). For example, your firm?s software validation testing for the Qube compact monitor (part number 91390) was conducted according to Design Validation Plan 91390 Salish Compact Monitor,819-0011-00, Rev. A, for the English and foreign language packs. There were multiple test case failures, yet your firm reported in Design Validation Report, 816-0099-02, that ?the test results showed the product is acceptable and it meets the user requirements for patient monitoring.? Failures include, but are not limited to: (b)(4) out of (b)(4) test case failures for Level 0 Alarm (Suite 80) in the Czech language on January 26, 2012; (b)(4) out of (b)(4) failures for Level 0 Admit Patient (ADT) (suite 78) in the Polish language on January 12, 2012; and (b)(4) out of (b)(4) failures for Level 0 Alarm (Suite 80) in the Portuguese Brazilian language on January 24, 2012. The Qube compact monitor device was released for general distribution on June 18, 2012.

Your firm?s response is not adequate. Your firm revised Design Controls, 1100-006, to Revision F to include a requirement that the validation protocol define expected results and acceptance criteria, including the criteria to pass or fail an activity. Your firm plans to provide training to appropriate personnel on the revised procedure. Your firm plans to perform a retrospective review of its patient monitoring design projects to confirm that change requests are accepted prior to product release and

do not include non-conformances against product requirements. Your firm did not submit a current adequate validation for the software cited for the Qube compact monitor. Additionally, your firm should complete and submit evidence of implementation of its corrective and preventive actions.<p>
FDA District Office: Seattle District<p>

7/7/2014 Trifarma S.p.A.
Trifarma S.p.A.
Product: active pharmaceutical ingredients (APIs)
Date: 7/7/2014<p>
1. Failure to maintain complete data derived from all testing and to ensure compliance with established specifications and standards pertaining to data retention and management.

Your firm did not retain complete raw data from testing performed to ensure the quality of your APIs. Specifically, your firm deleted all electronic raw data supporting your high performance liquid chromatography (HPLC) testing of all API products released to the U.S. market. In addition, your firm failed to retain basic chromatographic information such as injection sequence, instrument method or integration method for the tests. Your firm?s lack of data control causes us to question the reliability of your data.

In addition, your laboratory management was unaware of, and therefore did not follow, the written procedure detailing the review of analytical data. Furthermore, your management confirmed that the review of analytical data did not include evaluating the system suitability parameters to ensure proper column performance.

Your response states that your firm has been researching backup systems since July 2013 and will have a backup system online by the third quarter of 2014. Your response also states you have begun provisionally storing backup data on each computer, including the integration method as part of that data. However, you do not address the backup of the injection sequence, the instrument method or audit trails. In addition, your response does not address how your firm will ensure that electronic files are not deleted prematurely from local computers.

In response to this letter, provide a comprehensive corrective action plan addressing the foregoing concerns. Include information regarding system-wide changes, revised procedures, and appropriate retraining of employees that will be implemented immediately to ensure retention of complete electronic raw data for all laboratory instrumentation and equipment.
2. Failure to prevent unauthorized access or changes to data and to provide adequate controls to prevent omission of data.
Your firm did not have proper controls in place to prevent the unauthorized manipulation of your laboratory's raw electronic data. Specifically, your laboratory systems did not have access controls to prevent deletion or alteration of raw data. The inspection noted that all laboratory employees were granted full privileges to the computer systems.

In addition, prior to January 7, 2014, HPLC and gas chromatograph (GC) computer software lacked active audit trail functions to record changes to data, including information on original results, the identity of the person making the change, and the date of the change.

Your response statesyour Agilent GC system and HPLC systems now have audit trails, with (b)(4) more GC systems to be upgraded by the second quarter of 2014. However, your response did not describe the audit trails for the processing of the data on your Agilent systems. Your response also states your firm has begun to retain electronic raw data on the local hard drive, but without proper safeguards to ensure they cannot be deleted prematurely. Such safeguards will not be implemented until the third quarter of 2014.

In response to this letter, provide your corrective action plan to prevent deletion and alteration of electronic data. In addition, describe with more detail your firm?s new archival process and provide

assurance that it will consistently function to prevent the types of failures described above from recurring in the future.

We also note that your firm lacked electronic raw data supporting cleaning, method and process validations. In response to this letter, provide a corrective action plan to review all related test methods associated with products distributed to the U.S. in light of the lack of supporting raw data. <p>
FDA District Office: CDRH<p>

6/27/2014 Zynex Medical, Inc.
Zynex Medical, Inc..
Product: NesWave and IF8000 electrical stimulators
Date: 6/27/2014<p>
This inspection revealed that these devices are adulterated within the meaning of section 501(h) of the Act, 21 U.S.C. § 351(h), in that the methods used in, or the facilities or controls used for, their manufacture, packing, storage, or installation are not in conformity with the current good manufacturing practice requirements of the Quality System regulation found at Title 21, Code of Federal Regulations (CFR), Part 820. These violations include, but are not limited to, the following:
Failure to establish procedures for design verification as required by 21 CFR 820.30(f).

Specifically, your firm did not conduct a complete design verification of the software requirements of your NexWave multimode electrical stimulator. Your verification testing of the software did not include verifications to ensure all your software requirements were met. For example, verification testing did not include testing of the control/reset of the treatment timer, idle shut off functionality, and the treatment data storage functionality.

We have reviewed your response and have concluded it is inadequate. Your response states you will update the design control SOP and verify detailed software specifications. However, you did not include evidence to show a comprehensive review of the verification activities of other aspects of your NexWave device. In addition, you did not provide sufficient details of the planned corrections to your design control procedures to allow for evaluation at this time.
Failure to establish procedures for internal audits as required by 21 CFR 820.22.

Specifically, you did not complete your scheduled internal auditing activities as required by your 2013 auditing schedule. You did not conduct audits of your training, document control, management responsibility, CAPA, complaints, calibration, purchasing, or servicing systems during 2013.

We have reviewed your response and have concluded that the adequacy of your response cannot be determined at this time. Your firm has committed to drafting new internal audit procedures; until you have completed internal audits and we can review these procedures, we cannot determine the adequacy of your response. <p>
FDA District Office: Denver District Office<p>

6/16/2014 Apotex Pharmachem India Pvt Ltd
Apotex Inc.
Product:pharmaceutical manufacturing facility
Date: 6/16//2014<p>
These deviations cause your APIs to be adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 USC § 351(a)(2)(B), in that the methods used in, or the facilities or controls used for, their manufacture, processing, packing, or holding do not conform to, or are not operated or administered in conformity with, CGMP.
Our investigators observed specific deviations during the inspection, including, but not limited to, the following:
1. Failure to maintain complete data derived from all laboratory tests conducted to ensure compliance with established specifications and standards.
Your firm lacked accurate raw laboratory data records for API batches shipped by your firm. The

inspection revealed that batch samples were retested until acceptable results were obtained. In addition, your quality control (QC) laboratory failed to include complete data on QC testing sheets. Failing or otherwise atypical results were not included in the official laboratory control records, not reported, and not investigated. For example,

A review of the Gas Chromatograph (GC) electronic records from July 13, 2013, for (b)(4) USP batch #(b)(4) revealed an out-of-specification (OOS) result for the limit of residual solvents that was not reported. However, the QC test data sheet included passing results obtained from samples tested on July 14, 2013 and July 15, 2013. The inspection documented that your firm discarded sample preparation raw data related to the OOS results. In your response you indicate that the electronic chromatographic data and the weighing log books were available and reviewed during the inspection. However, the raw data and sample preparation information used for the calculation of the test results that were found OOS or disregarded were not in fact available for review.
A review of the High Performance Liquid Chromatograph (HPLC) electronic records from July 3, 2013, for (b)(4) batch #(b)(4) revealed an Out-of-Trend (OOT) result. The sample preparation raw data was discarded and not reported. A QC analyst indicated that these results were discarded due to some small extra peaks identified in the chromatogram fingerprint and an unexpected high assay result. The QC test data sheet reported two new results that were obtained from samples tested on July 4, 2013 and July 5, 2013, using a different HPLC instrument.

A review of the Karl Fischer electronic records from November 21, 2013, for (b)(4) EP batch #(b)(4) revealed an OOS result that was not reported. The passing results reported on the data sheets were generated from another sample tested an hour after the initial OOS results were obtained on the same day, November 21, 2013. <p>
2. Failure to investigate and document out-of-specification results.
Your firm?s investigation of the data from the Empower software identified instances where additional testing was performed but not properly documented in laboratory records. This investigation was limited in scope to only a short timeframe, the month of August 2013, and to only one type of laboratory instrumentation, <p>

FDA District Office: CDRH<p>

6/2/2014 HeartWare, Incorporated
HeartWare, Incorporated.
Product:HeartWare Ventricular Assist Device (HVAD) system
Date: 6/2/2014<p>
The inspection revealed that this device is adulterated within the meaning of section 501(h) of the Act, 21 U.S.C. § 351(h), in that the methods used in, or the facilities or controls used for, its manufacture, packing, storage, or installation are not in conformity with the current good manufacturing practice (cGMP) requirements of the Quality System (QS) regulation found at Title 21, Code of Federal Regulations (CFR), Part 820.
Our investigators observed specific deviations during the inspection, including, but not limited to, the following:
Failure to validate computer software for its intended use according to an established protocol when computers or automated data processing systems are used as part of production or the quality system, as required by 21 CFR 820.70(i). For example, your firm did not validate software used with the (b)(4) tester prior to implementation of the new test, as required by SOP00090, ?(b)(4).? According to Section 2 of SOP00090, this procedure applies to ?any software used to automate device design, testing, component acceptance [?] or to automate any other aspect of the quality system.? Section 6 of this SOP requires software validation. The software for the (b)(4) tester was changed as part of a corrective action to address premature battery failure issues. The new test was implemented on July 23, 2013, before the modified software was validated in September 2013. This change was related to 238 complaints and 119 MDR events.

The adequacy of your firm?s responses cannot be determined at this time. Your firm indicated that it

will revise its procedures, perform training, and retrospectively conduct software validation of the battery testers. However, without evidence of implementation of these activities, FDA cannot determine adequacy., <p>

FDA District Office: Florida District<p>

5/22/2014 Steris Isomedix Services
STERIS Corporation
Product:facility sterilizes medical devices
Date:5/22/2014<p>
1. Failure to establish and maintain adequate procedures for implementing corrective and preventive action, as required by 21 CFR 820.100.
Your CAPA procedure, PROC-00007, Revision 19, is deficient in that it does not adequately describe how to identify, correct and prevent the recurrence of nonconforming product and other quality problems, including any actions necessary to mitigate such risk. For example, the investigation, NC-05731, opened on July 29, 2013 to investigate data manipulation/falsification at the inspected facility where product was overdosed but was subsequently made to appear within specification, did not include a review of all potentially affected products. Specifically, NC-05731 excluded:
all runs that were not suspected overdosed runs. This would include all dosimeters that are read following the possible manipulation of the spectrophotometer to improperly zero the instrument which is not stored in the instrument?s audit trail. If the spectrophotometer is not properly zeroed,
8. Failure to adequately validate software used as part of production and the quality system for its intended use according to an established protocol, as required by 21 CFR 820.70(i). Specifically, actions were not taken to ensure that computer errors would not result in the loss of dosimetry and run dose data from the Dosimetry Measurement Application (DMA) module of (b)(4). For example,

a. The inspection found that 2,900 records were missing from the main table of the DMA module of (b)(4) between the time that it was installed at the Libertyville North facility on November 4, 2011 and November 6, 2013. Each missing record represents an attempt at creating a dosimeter record.

b. Of the 2,900 missing records, 1,623 records/dosimeters (representing (b)(4) irradiation runs) contained dosimetry data and were intentionally deleted from the DMA module. These records contained a calculated dose when they were deleted, and 192 of the dosimeters (representing (b)(4) unique runs) were out-of-specification low (under-dosed).

c. The (b)(4) and DMA systems are set up to automatically discard any dosimeter absorbance readings outside the set operating range of (b)(4) to (b)(4) absorbance units.

We have reviewed your responses to sub-points (a) through (c) and have determined that the adequacy of the responses cannot be determined at this time because your firm?s corrective actions are either on-going or documentation was not provided to allow for FDA review. For example, your responses indicated that the (b)(4) software and system documentation will be remediated, and a full revalidation of the (b)(4) system will be performed; however, this is not complete. In addition, your responses indicated a number of corrective actions to address the specific issues listed above; however, no documentation was included with the responses to verify these actions. <p>
FDA District Office:Chicago District<p>

5/7/2014 Sun Pharmaceutical Industries Limited
Sun Pharmaceutical Industries Limited
Product: pharmaceutical manufacturing facility
Date:5/7/2014<p>
1. Failure to ensure that laboratory records included complete data derived from all tests necessary to ensure compliance with established specifications and standards.
our firm frequently performs ?unofficial testing? of samples, disregards the results, and reports results from additional tests. For example, during stability testing, your firm tested a batch sample six times and

subsequently deleted this data.

Our investigators found your practice of performing initial ?trial? sample high performance liquid chromatography (HPLC) analyses prior to acquiring the ?official? analyses. The ?trial? sample results were subsequently discarded. ?Trial? HPLC analyses for (b)(4) USP ((b)(4)) were apparently run as part of the 12-month long-term stability studies on batch #(b)(4) for related substances. The inspection revealed that on August 26, 2011, your employee ran an HPLC analysis sequence with the sample names (b)(4) and subsequently deleted the raw data files. It was noted that the assigned names for the sequence injections indicates that your quality control staff named the samples using the last three digits of the batch numbers to link the "trial" injections for the batches with the official assay analyses. Your Senior Quality Control (QC) Officer confirmed that these were analyses of batch samples. Furthermore, we found that on August 27, 2011, this batch was analyzed for unknown impurities and the results were reported to be within specifications. However, the chromatographic data showed that the "trial" injection data for this batch failed the unknown impurities specification of (b)(4)% in multiple cases.

Your Senior QC Officer confirmed that QC laboratory employees had frequently practiced the use of ?trial? injections at your facility. Significantly, in addition to the example above, our inspection found 5,301 deleted chromatograms on a computer used to operate two HLPC instruments in your QC laboratory. Many of these files were ?trial? injections of batches.
n addition, the inspection revealed numerous examples of deleted GC electronic raw data files on the computer controlling the GC instruments that were replaced with identical ?official? chromatogram file names. The identically named GC data files that were deleted had been created at different times and contained disparate data. Also, it appeared that data was not consistently archived to the central server.

Your response is inadequate in that you did not conduct an adequate investigation into the pervasive practice of deleting files. In the reports provided in your response, you did not identify what criteria you used to designate each type of HPLC and GC data files (e.g. blanks, standards, samples, and system suitability runs). The response does not identify any impurity standards used in your procedures and does not provide the procedures that your firm was using to conduct the ?trial? and ?unofficial? runs. In addition, your investigation found 47 instances of apparent trial injections of samples for which the results were out-of?specification (OOS), and some of these batches were distributed to the U.S. market. The investigation failed to adequately examine why your analysts hid or deleted these runs. Your response only explains that your firm chose to retest samples from the implicated lots, but does not address the causes of the original OOS results, or justify the basis of your decision to invalidate the original failing result and accept the passing retest result. Such an investigation is necessary for any OOS event. Refer to the FDA?s guidance on OOS investigations Guidance for Industry, Investigating Out-of-Specification (OOS), Test Results for Pharmaceutical Production.

The above examples suggest a general lack of reliability and accuracy of data generated by your firm's laboratory, which is a serious CGMP deficiency that raises concerns about the integrity of all data generated by your firm. We are concerned that your laboratory allowed the practice of "trial" injections and deletion of both GC and HPLC files to persist without implementation of controls to prevent data manipulation until at least September 2013. Your company?s executive management is responsible for ensuring the quality, safety, and integrity of your products. Implementing adequate controls and systems to prevent manipulation of laboratory data is at the foundation of fulfilling this critical responsibility.<p>
Our investigators also observed significant violations regarding the finished drug product manufacturing operations at your facility, including, but not limited to, the following:

1. Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records (21 CFR 211.68(b)).

The investigator identified numerous deleted raw data files on computers used for your GC instruments in your quality control laboratory. The software (?GC Solutions?) on the computers used to control the GC instruments allowed your analysts to delete files from the computer?s hard drive with no audit trail or other adequate form of traceability in the operating system to document the deletion activity. The software as configured assigned sequential, numerical names to raw data files within the same folder. When a raw data file was deleted or moved out of the designated folder, the next file recorded into the folder would be saved with an identical name as the deleted file. As a result, data can be manipulated so that saved files appear to be in sequence even if they were not generated sequentially. Due to the basic lack of audit trail and data security, an analyst could delete analytical files without traceability of this unacceptable practice.

The inspection revealed that you stored GC raw data files in multiple folders on the hard drives in the QC laboratory. Your Senior QC Officer stated you had no written procedure describing the management of GC raw data file storage. According to your firm's electronic data archival SOP IT-001, each QC analyst manually transferred individual raw data files to the central server at (b)(4). Your procedure did not address how this data transfer by QC analysts could be reliably verified, and whether proper computerized system controls will be implemented by your company.

We acknowledge your firm?s commitment to amend the data handling system of your GC instruments to implement controls that ensure that analyses performed by employees are maintained as accurate, with data integrity and traceability. In your response to this letter, describe your detailed systemic improvements, training activities, and other actions implemented to provide evidence of the effectiveness and sustainability of these changes.<p>
FDA District Office: Center for Drug Evaluation and Research<p>

5/7/2014 Gold Standard Diagnostics, Inc.
Gold Standard Diagnostics, Inc.
Product: Gold Standard Diagnostics test kits for the detection of infectious pathogens
Date:5/7/2014<p>
Quality System
This inspection also revealed that these devices are adulterated within the meaning of section 501(h) of the Act, 21 U.S.C. § 351(h), in that the methods used in, or the facilities or controls used for, their manufacture, packing, storage, or installation are not in conformity with the current good manufacturing practice requirements of the Quality System regulation found at Title 21, Code of Federal Regulations (CFR), Part 820
1. Failure to establish procedures for design changes as required by 21 CFR 820.30(i). For example, your design and development procedure does not address software changes, or describe how they will be defined, documented, or implemented. You do not describe the types of changes that require software verification or validation. In response to Complaint # CC0159 you made changes to the Thunderbolt GUI software. You were unable to provide documentation to show the verification or validation of this software change when our investigator asked you for it.

2. Failure to establish requirements that must be met by suppliers as required by 21 CFR 820.50(a). For example, you have no documentation of the design responsibilities your Thunderbolt analyzer software supplier (supplier ?A?) must meet and there is no documentation that you or your supplier have validated or verified the analyzer?s software; and according to your management representative, you evaluated supplier ?B? solely on years of doing business with them and executive management knows them. Supplier ?B? provides reagents, antigens, and antigen coated plate components for your infectious disease devices.

3. Failure to perform a risk analysis as required by 21 CFR 820.30(g). For example, our investigator asked you for and you were unable to produce a risk analysis for the following in vitro diagnostic kits you manufacture: Brucella IgM, Borrelia burgorferi B31 IgG and IgM, and Entamoeba histolytica IgG; and you failed to mitigate the risk of patient misdiagnosis in your Thunderbolt Risk Analysis. Your Thunderbolt Risk Analysis Summary, RMP-0001-3 requires items (b)(4) to have control measures to

reduce the probability of occurrence; however, you have assigned a (b)(4) to the general ?Operational? hazard that may lead to patient misdiagnosis and have not mitigated the hazard.<p>
FDA District Office: San Francisco District<p>

3/6/2014 Smruthi Organics Ltd
USV Limited
Product: pharmaceutical manufacturing facility
Date:3/6/2014<p>
1. Failure to maintain complete and accurate laboratory test data generated in the course of establishing compliance of your APIs to established specifications and standards.

a. There was no written explanation for deletion events observed on audit trails for your standalone HPLC units. Your standard operating procedures (SOPs) did not include instructions for the retention of electronic raw data. In response to this letter, provide your procedures describing requirements to maintain complete data
Audit and identify the extent of this activity in your laboratory and manufacturing operations and provide an update to your investigation into this matter. .<p>
FDA District Office: CDRH<p>

2/6/2014 USV Limited
USV Limited
Product: control laboratory testing facility
Date:2/6/2014<p>
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 C.F.R. §211.68(b)).

Your firm failed to have adequate procedures for the use of computerized systems in the quality control (QC) laboratory. Our inspection team found that current computer users in the laboratory were able to delete data from analyses. Notably, we also found that the audit trail function for the gas chromatograph (GC) and the X-Ray Diffraction (XRD) systems was disabled at the time of the inspection. Therefore, your firm lacks records for the acquisition, or modification, of laboratory data.

Moreover, greater than (b)(4) QC laboratory personnel shared (b)(4) login IDs for (b)(4) high performance liquid chromatographs (HPLC) units. In addition, your laboratory staff shared one login ID for the XRD unit. Analysts also shared the username and password for the Windows operating system for the (b)(4) GC workstations and no computer lock mechanism had been configured to prevent unauthorized access to the operating systems. Additionally, there was no procedure for the backup and protection of data on the GC standalone workstations.

In your response, you indicate that your firm performs periodic back-ups of data, however your firm lacks assurance that the periodic backed up data includes all of the original data generated. Your response to this deficiency does not discuss how you will ensure that data audit trails will not be disrupted in the future and lacked a computer life cycle approach to, for example, assure routine verification of access controls in computer systems.

In your response to this letter provide a comprehensive computer life cycle program to assure that appropriate controls are always exercised over computer or related systems to comply with 21 CFR 211.68. .<p>
FDA District Office: CDER<p>

1/29/2014 ConMed Corporation
ConMed Corporation
Product: medical devices used for open and laparoscopic surgical procedures
Date:1/29/2014<p>
The inspection revealed that these devices are adulterated within the meaning of section 501(h) of the

Act [21 U.S.C. § 351(h)], in that the methods used in, or the facilities or controls used for, their manufacture, packing, storage, or installation are not in conformity with the current good manufacturing practice requirements of the Quality System regulation found at Title 21, Code of Federal Regulations (CFR), Part 820. These violations include, but are not limited to, the following:
Procedures for design change have not been adequately established, per 21 CFR 820.30(i). Your Design Verification & Validation procedures, SOP #168 (Rev. 1 & 2) require an evaluation of the impact of changes to a released design on the device function and performance. However, your firm failed to fully and adequately evaluate design changes to Altrus Tissue Fusion System 5mm and 10mm Handpieces to ensure that verification and/or validation activities were complete. For example:
b. Your firm failed to adequately evaluate a revision to the Altrus Tissue Fusion System Controller Software which (b)(4). Specifically, after your Impact Analysis determined that the software change would (b)(4) tests, these protocols were repeated; however, numerous deficiencies were observed with the design verification protocols, including:

i. No documentation of any (b)(4) tests to evaluate (b)(4) on the 5mm handpieces.
ii. (b)(4) handpieces (5mm) tested for (b)(4) failed the (b)(4) acceptance criteria (b)(4) test points (combined total), yet the (b)(4) were not investigated and the Design Verification Report results were marked as ?Pass?.
iii. The Design Verification Reports, 5mm Handpiece (b)(4) and (b)(4) report show that the design verification tests were conducted with (b)(4), not the (b)(4).
iv. The Design Verification Protocol, approved on 12/21/12 and executed on 12/24/12, shows that multiple tests were ?Not executed per (b)(4); however, that document, (b)(4), was not approved until 2/26/13, approximately two months after the executed protocol. Furthermore, Impact Analysis (b)(4) does not include any justification for omitting certain tests (b)(4).
v. Design Verification report, (b)(4), shows that your firm used data from a previous design verification study (b)(4) which showed failing results for (b)(4) handpieces tested for (b)(4) and which stated, (b)(4).However, there was no documentation that the failing test results were addressed.

c. Design verification for a software change (b)(4) was incomplete. Design control deficiencies included:

i. No documentation of any (b)(4) tests to evaluate (b)(4).
ii. The Impact Analysis record for the 10mm handpieces (b)(4) identified (b)(4) of the 10mm handpiece that were affected by the (b)(4); however, test data showed that the (b)(4) Test for (b)(4) only tested the (b)(4), not the specified (b)(4). The results were marked as ?Passed.?
iii. (b)(4) handpieces (b)(4) tested for (b)(4) failed the (b)(4) verification acceptance criteria (b)(4) test points (combined total), yet the (b)(4) were not investigated and the Design Verification Report results were marked as ?Pass? on the Design Verification Report.
iv. The Design Verification Report (b)(4) summarizes results from the executed Altrus Handpiece Design Verification Protocol (b)(4) which indicated that both 5mm and 10mm handpieces were to be evaluated for (b)(4); however, there was no documentation that 10mm handpieces were subjected to these tests.
v. Portions of the Installation Qualification for the (b)(4), applicable to the configuration file were (b)(4) in the 10mm handpiece (b)(4). However, the associated Performance Qualification was not re-executed (b)(4)<p>
Acceptance activities were not documented and maintained as part of the device history record as required by 21 CFR 820.80(e). For example:
(b)(4) device history records reviewed for Altrus (b)(4) failed to include documentation of all required in-process acceptance activities.<p>
FDA District Office: Denver District<p>