Warning Letter Bulletin

The Inside Alert to FDA Enforcement Activities, Inspections & Compliance Programs

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FDA released the following Warning and Untitled Letters, September to October 2016

DRUGS

DEVICES

DRUGS

Interpharm Praha A.S. Modrany, Czech Republic, Oct. 18 CDER

FDA found evidence of data manipulation among other GMP nonconformities during its Oct. 12-16, 2015, inspection of the **Interpharm Praha A.S.** drug manufacturing facility, in Modrany, Czech Republic, the agency said in a warning letter to the company.

During the inspection, FDA's investigator observed specific violations and deviations including, but not limited to, the following:

API Deviations

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

"Your quality control unit did not have basic controls to prevent changes to your electronically-stored laboratory data," the agency stated. "Your analysts had user privileges to the Empower-2 system used to generate and analyze chromatographic data that allowed them to eliminate failing, atypical and satisfactory results with no notification; alter peak areas; and add or eliminate samples from sequences without authorization."

During the inspection, the FDAer reviewed an audit trail from the Empower-2 system that stored 8,906 entries. "Of these, well over half indicated some form of data deletion or manipulation, including at least 1,441 instances of deleted results, at least 3,643 instances of manual integration and at least 194 instances of altered running sample sets," the letter detailed. "Your personnel confirmed that these actions are common during chromatographic data processing. We found that you did not have a procedure in place to indicate the requirements and level of restrictions for users of the automated system."

FDA explained that the firm's quality unit must review all pertinent analytical data when making batch release decisions. "However, your automated system permitted analysts to delete and alter test results without authorization," the letter noted. "As a result, your quality unit was presented with incomplete and inaccurate information about the quality of your drugs."

According to Interpharm's response to the 483, the company has now restricted access and permissions in the Empower 2 automated data system. However, FDA commented, "your response does not demonstrate how the specific controls you have implemented prevent deletion or alteration of data, nor have you shown how you will ensure that these permissions are documented, implemented, and followed. Finally, you have not shown how these controls ensure that records relied upon for batch release and other quality review decisions are complete and accurate."

2. Failure to ensure that test procedures are scientifically sound and appropriate to ensure that your API conform to established standards of quality and/or purity.

CODES

- **AE** — Adverse event reporting violations
- **510(k)** — Failure to file 510(k)
- **BiMo** — IRB, sponsor/monitor, CRO, clinical investigator issues
- **BLA** — Biologics License Application
- **CAPA** — Corrective/preventive action
- **C-H** — Complaint handling
- **Cal** — Calibration
- **Compound** — FDCA drug-compounding violations
- **Comp/Soft** — Computer software validation
- **Data**—Data integrity issues
- **Design** — Design controls
- **E-M** — Environmental monitoring
- **E-Sig** — 21CFR Part II, Electronic Signatures /Records Rule
- **F.A.R.** – Field action reporting
- **GDUFA** – Not filing user fees
- **F-B** — Lack of fair balance in promotions
- **Lab** — Laboratory
- **L**-B—Labeling issues
- **Mark** — Marketing and misbranding
- **MDR** — Medical Device Reporting violations
- **NDA** — Lack of new drug application
- **O-L Use** — Off-label use
- **OOS** — Out-of-specification results
- **Pak** — Packaging
- **PMA** — Lack of premarket approval
- **QC/QS** — Quality Control/Systems deviations
- **Stab** — Stability
- **Ster** — Sterility
- **Val** — Validation
- **Web** — Internet promotion irregularities

The firm's laboratory procedures allowed analysts to modify chromatographic sequences and delete results with no justification, the warning letter pointed out.

"During our review of chromatograms generated during impurities testing…we observed that your analysts conducted many manual integrations. We also found discrepancies in peak integrations, including inconsistent integrations, and peaks that were not integrated at all."

These peaks could represent impurities, the agency noted, but they were not included in data packages pre sented to the quality unit for batch release decisions. "Therefore, your quality review and product release decisions were based on incomplete data regarding the quality of your drugs."

The firm's 483 response stated that Interpharm has scheduled training on manual integration for all analysts who use Empower-2 software. However, FDA stated, "You have not shown how you will ensure that your test methods are appropriate to determine whether your API conform to established standards and specifications."

The agency instructed the company to respond to the warning with an "action plan for developing, validating and implementing chromatographic test methods to analyze the quality attributes of your drugs. Specify the procedures you will implement to process your chromatographic data related to all test results and audit trail functionality. Detail how you will review chromatographic results as part of the batch release procedure and documentation. Specify the controls you will implement to ensure that any manual integration steps are performed only under defined, limited circumstances according to a protocol approved and supervised by your quality unit."

Finished Product Violations

1. Failure 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.

The FDA investigator reviewed an audit trail for impurities testing conducted on a validation lot and found that the **"**audit trail revealed many deleted results and manual integrations. As discussed above, deleted and altered analytical test results mean that your quality unit is presented with incomplete and inaccurate information about the quality of your drugs."

2. Failure to establish laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling and drug products conform to appropriate standards of identity, strength, quality and purity.

"Your laboratory procedures allowed analysts to modify and delete chromatographic results without adequate justification, and to use manual integration in uncontrolled circumstances," the warning letter pointed out. FDA noted that its investigator found results deleted after repeated manual integrations for some stability lots. "Unjustified, repeated manual integrations and deletions indicate that your laboratory controls are not scientifically sound and appropriate to test your products," the agency added.

In response to the warning letter, FDA asked Interpharm to "describe all steps you will take to ensure that appropriate laboratory controls have been implemented to support product quality review and batch release decisions. Include the controls you will implement for the modification, deletion, and manual integration of chromatographic test results."

Data Integrity Remediation

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

The agency directed Interpharm provide the following in response to the warning letter:

"A. A comprehensive investigation into the extent of the inaccuracies in data, records and reporting. Your investi-

gation should include:

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

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

C. A management strategy that includes the details of your global corrective action and preventive action plan. Your strategy should include:

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

FDA also asked the firm to "Specify what you have done since our inspection to correct your violations and deviations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion." ***Data; E-Sig; Lab; QC/QS***

Teva Pharmaceutical Works Pvt. Ltd. Godollo, Hungary, Oct. 13 CDER

An FDA inspection of Teva Pharmaceutical's drug manufacturing facility, **Teva Pharmaceutical Works Pvt. Ltd**. in Godollo, Hungary, Jan. 21-29, 2016, revealed significant violations of GMP that resulted not only in the issuance of a warning letter to the firm, but also to the company's products being placed on import alert earlier this year.

FDA investigators observed the following specific violations:

1. Failure 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.

"You did not adequately investigate media fill and sterility test failures," the letter pointed out. "These failures indicate that there is a lack of adequate sterility assurance in your manufacturing facility."

a. Media Fills

"You did not adequately investigate media fill contamination in your aseptic manufacturing lines," FDA stated. For example, a media fill run performed Sept. 14-16, 2015, in the closed Restricted Access Barrier System (RABS) small volume parenteral line "yielded 31 contaminated units. In addition, media fills for other filling lines at your facility yielded one or more contaminants."

The warning letter commented, "You attributed the contamination in these media fills to aseptic technique breaches by different operators. Various breaches were identified relating to set-up, filling and changing of the filling tank. However, your investigations were insufficient."

For example, FDA noted, "you failed to identify the microorganisms found in the contaminated units. It is imperative that you determine the identity of microorganisms found in media filled units in order to adequately understand the potential sources and scope of the contamination.

"Any contamination in a media fill run indicates a potentially significant sterility assurance problem and should be thoroughly investigated."

b. Sterility Test Positive Investigations

Teva also did not thoroughly investigate sterility test positives, FDA found. For example, its investigation of a sterility test failure in one batch of drug product "did not adequately assess the hazards in the aseptic manufacturing operation that led to the sterility failure. You also did not determine whether other batches made on the same production line were affected."

In addition, the firm invalidated multiple sterility test positive results obtained during batch release testing, the inspection revealed. "However, we note that your firm uses a sterility test…as well as a sterility testing kit that minimizes potential for adventitious contamination that could cause false positives."

FDA found Teva's response to the inspection report inadequate and instructed the firm, in response to the warning letter, provide the following information:

- "a comprehensive review of all sterility positive and media fill failure investigations since January 2014 to reassess your root causes, corrections, conclusions and effect of your lack of aseptic processing control on the sterility of marketed commercial batches.
- revised media fill contamination investigation standard operating procedures (SOP), including but not limited to identification of microorganisms from each contaminated unit, thorough assessment of possible causes and assurance of appropriate corrective actions to prevent contamination.
- revised sterility failure investigation SOP, including but not limited to a thorough assessment of potential manufacturing root causes, identification of actions to prevent contamination and assurance that invalidation of a sterility positive does not occur unless there is a robust and conclusive laboratory root cause.
- a retrospective evaluation of videos of your aseptic manufacture of all in-date batches distributed to the United States to determine contamination hazards posed by deficient aseptic practices. Also review the video of the production activities associated with the injection sterility failure to help identify the source of contamination in that batch.
- a thorough assessment of the adequacy of your facility, equipment and process. Determine failure modes relating to design, control, and maintenance. Include a comprehensive corrective action and preventive action (CAPA) plan that fully identifies microbial contamination risks throughout your operation and describes improvements to assure high confidence in the sterility of your products."

2. Failure to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes.

a. Poor Aseptic Behavior

During the inspection, "our investigators observed poor aseptic processing techniques that had been previously videotaped at your facility," FDA stated. For example, video from Sept. 8 and 9, 2015, showed the following during the set-up and filling of a sterile injectable drug:

- "an operator passing a pen directly over the stopper bowl to another operator.
- an operator sitting on the clean room floor during set-up of the filling line and not changing the gown after standing up.
- operators leaning against the cleanroom walls.
- an operator leaving the RABS…open for extended periods of time during filling line set-up, even when he was not working in the immediate area."

Again, FDA found Teva's response to the 483 inadequate and asked the firm to provide in response to the warning letter:

- ✓ a risk assessment of the poor aseptic techniques observed during the inspection.
- ✓ a broader evaluation of any additional aseptic technique breaches that have occurred in your operation (e.g., through review of videos).
- ✓ updated information to demonstrate that each of your aseptic processing lines is in a state of control.

In addition to implementing enhancements to your aseptic processing operation design, describe how you will improve staff competencies, supervisory oversight of daily operations and other controls," the agency requested.

b. Mechanical Failure During Media Fill

FDA further found, "Your firm rejected numerous integral vials during media fill batches due to mechanical problems or other causes without appropriate justification." For example, the agency pointed out, one media fill batch was aborted due to a mechanical failure of the conveyor belt motor. "Although 3,696 integral vials had been filled, the vials were not incubated, and the media fill was invalidated without adequate justification. Your firm indicated that it would have released a commercial batch as a sublot under these circumstances."

Teva also did not have a procedure describing production and disposition practices after such a mechanical failure, the warning letter noted.

Finding its 483 response inadequate, FDA directed Teva to reply to the warning letter with:

- "a list of commercial batches rejected as a result of mechanical problems or other reasons and the CAPA that was implemented in each case.
- a list of all media fills conducted since January 2011 with fill date, number of units run, number of units incubated, number of positive units and annotation of whether the fill was aborted.
- descriptions of circumstances under which any portion of a media fill batch was incubated as a separate segment, and whether you detected any positive units.
- changes made to your written procedures to ensure that media fills accurately simulate actual production practices and to address when it is appropriate to abort a media fill run."

3. Failure to establish an adequate system for monitoring environmental conditions in aseptic processing areas.

The warning letter noted that Teva's SOP "System of Microbiological Environment Monitoring" includes microbial alert and action levels. This SOP sets limits for the number of colony forming units (CFU) "permitted on two hands in Grade A (ISO 5) areas where personnel perform critical interventions during filling, line set-up and other aseptic activities. In Grade B (ISO 7) areas, which are described as filling, filtration, capping or changing rooms," limits are set for CFUs permitted on two hands, and there is an alert level set for the number of CFUs.

However, FDA commented, "when our investigators observed operators performing activities which should adhere to Grade A levels (hands in open RABS and under laminar air flow), your firm officials stated that the operators were held to Grade B levels." Furthermore, Teva failed to justify allowing CFU on the operators who perform Grade A interventions that exceeded the SOP specifications without any potential follow-up. "Such instances should trigger an alert or action condition that, at a minimum, should lead to trending and may indicate the need for further investigation," FDA stated.

The agency asked Teva to "provide a comprehensive retrospective review and risk assessment of personnel and environmental monitoring data since Jan. 1, 2015. In addition, describe how future monitoring will be conducted in different classified aseptic processing areas to ensure that action and alert levels are commensurate with the operations being performed in the specified area."

4. Failure to establish laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling and drug products conform to appropriate standards of identity, strength, quality and purity.

FDA found that a suitability test Teva performed "failed to meet acceptance criteria for sterility testing. Specifically, a positive control sample did not exhibit growth" of the microorganism in during sterility testing. "Your firm did not investigate this failure of media to support growth. Unsuitable sterility test methods increase the probability that your quality control test will not detect a nonsterile product."

After finding the firm's response to this observation inadequate, FDA asked Teva to provide:

- a thorough investigation into the root cause of the positive control test failure, including your CAPA plan.
- a comprehensive investigation of each of your sterility test methods and their ability to reproducibly promote microbial growth in the presence of product.
- your latest plans for performing microbial testing (which was suspended during the inspection).

5. Failure to ensure that laboratory records included complete data derived from all tests necessary

to assure compliance with established specifications and standards.

"Our investigators observed colony counts for environmental and personnel monitoring that did not match your official records." For example, one contact plate from a Grade B area had a reported result that did not match the FDA investigator's count of CFUs on the plate. Five other plates had reported results that differed from the investigator's count of CFUs on the plate.

"Inaccurate reporting of environmental and personnel monitoring data undermines your ability to evaluate and maintain a state of control in your aseptic processing operation," the agency pointed out.

6. Failure 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.

"Your stand-alone computer systems lacked controls, such as routine audit trail review and full data retention, to prevent analysts from deleting data," the warning letter stated. "Although you implemented a procedure to begin reviewing audit trails of your high performance liquid chromatography (HPLC) Empower system on Jan. 11, 2016, you had not performed any reviews prior to our inspection."

FDA wrote, "We acknowledge your commitment to strengthening your procedures to assure user access restrictions and implement audit trails for computerized systems. However, simply activating audit trail functions and instituting user controls are insufficient to correct the data integrity problems observed at your facility and to prevent their recurrence."

In response to the letter, FDA requested that Teva "provide details of your retrospective review of the HPLC and other laboratory data, such as Fourier transform infrared spectroscopy, gas chromatography, UV spectrophotometry, and…analyzer data. Indicate the period covered in your review and your rationale for selecting that timeframe."

7. Failure to follow adequate written procedures for the preparation of master production and control records designed to assure uniformity from batch to batch.

The FDA investigators found quality-related documents in a waste bin, the warning letter noted. "Among these documents were an incomplete sterility test data sheet, a form used to track the movement of…samples, a media fill incubation card and others." The incomplete sterility test data sheet had been filled out to track information about a…sterility check. "After an error was observed on the original data sheet, the record was torn and discarded with no written explanation."

GMP Consultant Recommended

Based upon the nature of the violations identified at your firm, FDA stated, "we strongly recommend that your consultant, who should be qualified as set forth in 21 CFR 211.34, assist your firm in meeting GMP requirements. Your consultant should provide a thorough assessment of your entire operation to identify contamination hazards, assist in remediation of sterility assurance in your facility, improve your quality system and certify readiness."

The agency noted that Teva's "use of a consultant does not relieve your firm's obligation to comply with GMP. Your firm's executive management remains responsible for fully resolving all deficiencies and ensuring ongoing GMP compliance."

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

- A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing operations and systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude.
- Interviews of current and former employees to identify the nature, scope and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party.
- An assessment of the extent of data integrity deficiencies and record retention policies at your facility. Identify omissions, alterations, deletions, record destruction, noncontemporaneous record completion and other deficiencies. Describe all parts of your facility's operations in which you discovered data integrity lapses.
- A comprehensive retrospective evaluation of the nature of the testing data integrity deficiencies, including but not limited to investigation into your laboratory testing raw data, reported results and quality oversight for all products and process lines. We recommend that a qualified third party with specific expertise in the area where potential breaches were identified should evaluate all data integrity lapses. Provide a detailed report from your consultant."

FDA also requested that the firm provide 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."

Further, the agency asked Teva to provide a management strategy that includes the details of aglobal

corrective action and preventive action plan. This strategy should include:

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

Hebei Yuxing Bio-Engineering Co. Hebei, China, Sept. 6 CDER

FDA inspected the drug manufacturing facility, **Hebei Yuxing Bio-Engineering Co. Ltd.** at Xicheng District, Ningjin County, Hebei, from Aug. 17 to 21, 2015, and found significant deviations from current GMP for active pharmaceutical ingredients (API), plus data integrity problems.

FDA reviewed the firm's Sept. 9, 2015, response and subsequent correspondence, and largely said it was inadequate.

During the inspection, the FDA investigator observed specific deviations including, but not limited to, the following.

1. Failure to have laboratory control records that include complete data derived from all laboratory tests conducted to ensure compliance with established specifications and standards.

The quality control laboratory failed to record and maintain complete data from analyses of the **[redacted]** (**[redacted]**) API. For example: Prior to conducting official analyses, the quality control laboratory performed "experimental" analyses on product batches to assess whether the API met specifications, but failed to document these "experimental" tests in official laboratory records or to justify their exclusion.

The FDA investigator found the results of 2,404 high performance liquid chromatography (HPLC) injections in a folder titled "Experimental" on instrument SZG-002-006l. The quality unit indicated that these "experimental" injections were being conducted in all **[redacted]**chromatographic units in the quality control laboratory. The management provided different explanations in an attempt to justify the practice, including "fear" that the sample results would not pass.

FDA's review of the audit trails of chromatographic systems SZG-002-009, -010, -011 and -012 documented that the laboratory analysts deleted raw chromatographic data on multiple occasions. The firm indicated that analysts may have been testing the system and may have deleted associated files. The firm also indicated that the deleted files may represent aborted analyses. However, FDA documented that some audit trail entries of deleted raw data files contained batch numbers for actual batch samples being tested. There is no assurance that laboratory records and raw data are accurate and valid, the agency said.

FDA acknowledged the decision to revise the current procedure for the testing of **[redacted]**. In response to the letter, the agency asked the firm to provide a summary of how the chromatography procedures will conform to U.S. Pharmacopeia requirements, including those for the establishment of system suitability.

In addition to deciding to revise the **[redacted]** testing procedure, in the response the firm committed to acquiring additional chromatographic instruments, restricting certain chromatographic instruments to specific analyses, installing a new data control system, upgrading instrument software and enabling data integrity features included in the laboratory software.

The response is inadequate. "None of the explanations justify the failure to maintain complete records, nor do they support the practice of substituting repeat tests after failing results," FDA wrote. Acquiring new instruments, installing new and upgraded software and enabling various features on software are only effective if the firm has implemented appropriate procedures and systems to ensure that the quality unit reviews all production and control data and associated audit trails as part of the batch release process.

2. Failure to follow and document laboratory controls at the time of performance, and failure to document and explain any departures from laboratory procedures.

During the inspection, the firm provided the FDA investigator a chromatogram for an assay analysis of **[redacted]** batch**[redacted]** dated Aug. 30, 2014, at 9:46:39 a.m. The firm later submitted to FDA a different chromatogram corresponding to the same analysis, instrument, date, time and batch. The second chromatogram appears exactly the same as the one provided during the inspection, but it includes a different method file name, column type and serial number, and system temperature. Both versions of these documents cannot represent the actual assay analysis that the firm conducted for batch **[redacted]** on Aug. 30, 2014, at 9:46:39 a.m.

3. Failure of the quality unit to ensure that all critical deviations are investigated and resolved.

At the time of the inspection, the firm had documented 67 deviations regarding microbiological contamination found or related to the **[redacted]** step for **[redacted]**. These deviations occurred between Jan. 1 and Aug. 20, 2015, but FDA's investigation documented that microbiological contamination has been a persistent and unresolved problem at the firm since 2013. Over time, the firm has identified four potential causes:

- contaminated **[redacted]** supply due to inadequate **[redacted]** controls
- failing **[redacted]** of the **[redacted]** in the **[redacted]** tank **[redacted]** systems
- production operator errors
- inadequate sterilization of the supplement tanks used to store materials before they are discharged into the**[redacted]** tanks

However, the firm did not definitively identify the specific root causes(s) of the microbiological contamination problems, nor have the firm taken appropriate corrective actions and preventive actions.

In response to this letter, FDA asked to provide the report of the thorough investigation to identify the root cause(s) and the corrective action and preventive action plan.

Data Integrity Remediation

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

In response to this letter, provide the following.

A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. The 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 the operation that the firm propose to exclude.
- Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. FDA recommend that these interviews be conducted by a qualified third party.
- An assessment of the extent of data integrity deficiencies at the facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all
- A comprehensive retrospective evaluation of the nature of the testing data integrity deficiencies. FDA 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 the drugs. The 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 the firm that includes the details of the global corrective action and preventive action plan. The strategy should include:

- A detailed corrective action plan that describes how the firm intend to ensure the reliability and completeness of all of the data the firm generate, including analytical data, manufacturing records, and all data submitted to FDA.
- A comprehensive description of the root causes of the 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 the firm.
- Interim measures describing the actions the firm have taken or will take to protect patients and to ensure the quality of the drugs, such as notifying the customers, recalling product, conducting additional testing, adding lots to the 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 the company's data.
- A status report for any of the above activities already underway or completed.

FDA placed the firm on Import Alert 66-40 on July 8, 2016, and requested a response to the warning letter in 15 days.

Cheng Fong Chemical Co. Ltd. Taoyuan City, Taiwan, Sept. 15 CDER

FDA inspected the facility, which makes APIs, from April 18 to 22, 2016 and found significant deviations from current GMPs.

During the inspection, the FDA investigator observed specific deviations including, but not limited to, the following.

1. Failure to have an adequate maintenance procedure to prevent contamination or carry-over of a material that would alter the quality of the API.

The FDA investigator observed corrosion, pitting, dirt, and leaks, on and around the company's drug manufacturing equipment. For example, he observed pitting on the product contact surface of equipment used in the process of making certain APIs. The equipment names were not identified.

FDA requested a followup response, providing updated equipment line clearance and maintenance procedures, photos of cleaned or repaired equipment, and a list of batches potentially impacted by the poorly maintained equipment.

2. Failure to adequately conduct investigations and extend the investigations to other batches that may have been associated with the failure or deviation.

For example, FDA said, the facility did not adequately investigate customer complaints for black or foreign particles in finished ingredients.

For example, Cheng Fong was said to have received particulate complaints for batch , but rather than evaluating reserve samples for that batch, the firm evaluated a different batch of API (batch number). The firm found that one batch contained foreign matter, yet the facility did not determine the identity of the foreign particulates in either batch or implement adequate corrective action.

FDA said the response acknowledged that the foreign particle complaints are likely due to the poor condition of manufacturing equipment.

In addition, FDA said the company's internal investigations into poor equipment maintenance and foreign particles are inadequate as the facility did not identify the foreign matter in the API, nor sufficiently extend the investigations to other lots that may have been contaminated. Regarding the latter, reserve samples of all potentially-affected batches were not examined for presence of foreign matter.

3. Failure to properly maintain buildings used in the manufacture of API in a clean condition.

For example, the FDA investigator observed filth, insects, wet layers of unidentified material on the floors, and foul odors in the cold rooms used to store raw materials and intermediates used in the manufacture of finished API. Firm officials noted that the rooms had never been cleaned.

The agency reviewed Cheng Fong's May 13, 2016, response in detail and acknowledge receipt of subsequent correspondence. It acknowledged the company made some corrective actions, including cleaning, and adding the cold rooms to its pest control program.

In responding to the warning letter, FDA asked Cheng Fong to provide the following:

- An updated and comprehensive investigation into customer complaints
- A corrective action and preventive action (CAPA) plan that includes identification of the foreign particles, assessment of root cause, the impact on other potentially affected batches, and actions taken to prevent recurrence
- Updated and comprehensive assessment of the state of maintenance of all equipment that can be used in the manufacture of APIs for US supply
- A comprehensive assessment of the adequacy of the company's maintenance program
- An evaluation of the adequacy of the company's cleaning procedures

FDA requested a response within 15 days. The company's products were not put on import alert.

Mappel Industria de Embalagens, SA Sao Paulo, Brazil, Sept. 12 CDER

FDA inspected the drug manufacturing facility from April 11 to April 15, 2016, which told the agency "it did not comprehend" that OTC drugs were regulated by the agency. Thus, it ceased production.

The FDA investigator observed specific violations, including, but not limited to, the following.

1. The firm's quality control unit failed to approve or reject all procedures or specifications impacting on the identity, strength, quality, and purity of the drug product (21 CFR 211.22(c)).

2. The firm does not have, for each batch of drug product, appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release (21 CFR 211.165(a)).

3. The firm failed to follow written procedures for production and process control designed to assure that the drug products the firm manufacture have the identity, strength, quality, and purity they

purport or are represented to possess. (21 CFR 211.100(b)).

4. The firm failed to maintain production, control, or distribution records associated with a batch of a drug product for at least one year after the expiration date of the batch (21 CFR 211.180(a)).

According to the letter, FDA reviewed Mappel's May 31, 2016, response in detail and acknowledged receipt of subsequent correspondence.

In that response, the firm stated: "when Mappel began manufacturing -labeled products for the U.S. Market, it did not fully comprehend that such products were regulated by FDA as OTC drugs." You also stated: "Mappel has no intention of manufacturing OTC drug products for and should it decide to do so , it will notify FDA by filing a new drug establishment registration."

FDA recommended the company hire a consultant to straighten out its operations and notify FDA if it resumes export to the U.S.

Yangzhou Hengyuan Daily Chemical Plastic Co., Ltd. Yangzhou, China, Sept. 26 CDER

FDA inspected the company's drug manufacturing facility from Jan. 18-22, 2016, primarily finding inadequate procedures and drug specifications.

The company responded to the letter Jan. 30. According to the letter, FDA observed the following conditions at the plant:

1. The firm failed to provide adequate written production and control procedures which are designed to assure that the drug products produced have the identity, strength, quality and purity they purport or are represented to possess (21 CFR 211.101).

FDA collected samples of the company's batch # at the port of entry. FDA Laboratory analysis found that the company did not contain any of the labeled active ingredients. FDA denied entry of the shipment accordingly and notified the company's customer, which filed a complaint with the firm.

The company's subsequent investigation into the customer complaint for one batch revealed that Yangzhou added the wrong ingredient, instead of the active ingredient.

2. The firm does not have, for each batch of drug product, appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release (21 CFR 211.165(a)).

During the inspection, the firm acknowledged it had not tested all batches of finished drug product prior to release. For example, in 2015 the firm tested only five of the batches shipped to the United States. FDA noted the facility did not perform the active ingredient assay for one batch prior to release. FDA analysis showed this batch contained no active ingredient.

In the letter, FDA said the firm's "quality unit must review all production and control records, and ensure testing and conformance to all product specifications, prior to permitting release of a batch to the United States market." FDA acknowledged Yangzhou committed to test drug product batches for U.S. distribution in the future.

In addition, FDA said the company's investigation indicated the warehouse released the wrong active ingredient for another batch. This was the first of multiple errors that led to adding the wrong ingredient to the company's drug product.

In response to the letter, FDA asked Yangzhou to "provide an action plan to comprehensively evaluate the company's manufacturing operation to determine the root causes for these errors, and to prevent use of the wrong ingredient or other hazardous mix-ups for all of the company's drug products. Additionally, provide the revised master batch record for [redacted]. Describe all improvements to batch records, including addition of verifications for all critical manufacturing steps."

FDA also asked the firm to "describe the company's corrective actions and preventive actions (CAPA) to ensure that the company's finished drug products meet their specifications. Evaluate previous batches distributed in the United States within expiry to determine if they meet specification. As part of the company's CAPA plan, describe how the company's quality unit authorities and responsibilities will be enhanced to ensure ongoing oversight over the company's drug manufacturing operations. Also describe how the firm plan to measure the effectiveness of the company's CAPA and a timeline for completion of these actions."

Based on the nature of the violations FDA identified at the firm, FDA strongly recommended engaging a consultant.

FDA placed the firm on Import Alert 66-40 on Aug. 12, 2016, and asked for a response to the warning letter within 15 days.

Nippon Fine Chemical Co., Ltd Takasago City, Japan, Sept. 26 CDER

FDA said Nippon Fine Chemical "limited and/or refused" the investigator's ability to conduct the inspection of its Takasago City, Hyogo, finished dosage form plant when he arrived Dec. 15, 2015.

In the letter, FDA outlined what happened:

1. Barring access to areas

During the inspection, the firm limited the investigator's access to the quality control laboratory. The quality control manager directed employees to stand shoulder-to-shoulder, barring the FDA investigator from accessing portions of the laboratory and the equipment used to analyze drugs for U.S. distribution.

2. Refusal to provide copies of documents

The firm manufactures certain drugs for the Japanese and U.S. markets using the same equipment and processes, and divides lots for distribution between the two markets. During the inspection, the FDA investigator reviewed complaints the firm received about the company's drugs from the company's customers, including complaints that the company's drugs contained glass, hair, cardboard, metal, product discoloration, and a black spider. The firm limited the inspection by refusing to provide FDA copies of these records.

3. Limiting photography

During the inspection, the FDA investigator attempted to take pictures of the apparatus used to manufacture drugs for U.S. distribution. The company's quality assurance manager impeded the inspection by preventing the FDA investigator from photographing this piece of equipment.

The agency reviewed the company's responses dated Jan. 5, 2016, April 25, 2016, the two letters from Aug. 18, 2016, and correspondence from counsel dated Sept. 14, 2016, in detail.

The firm was placed on Import Alert 99-32 on Aug. 8, 2016, and requested a response to the warning letter in 15 days.

DEVICES

Nanchang, China, July 19 CDRH

An FDA inspection of **Beyond Technology Corporation Nanchang** Nov. 9- 11, 2015, resulted in FDA issuing a warning letter to the firm, which manufactures teeth whitening and dental floss products, that the agency "is taking steps to refuse entry of these devices into the United States, known as 'detention without physical examination,' until these violations are corrected."

These nonconformities include:

1. Failure to establish and maintain procedures to prevent contamination of equipment or product by substances that could reasonably be expected to have an adverse effect on product quality.

"For example, the buildings used in the manufacturing process were infested by rodents," FDA's letter stated. "Fresh excrement was observed on the bags of raw materials and on the windowsills" in some rooms of the facility.

FDA reviewed the firm's response and concluded that it was not adequate because it "did not provide a copy or summary of documentation in English."

2. Failure to establish and maintain procedures to control product that does not conform to specified requirements.

The inspection found that there were no written procedures for documenting or investigating manufacturing deviations or out-of-specification results, FDA noted. "Manufacturing deviations or out-of-specification results were not investigated, as there were no procedures or requirements for documenting these events."

The response was again found inadequate for lack of summary or documentation in English.

3. Failure to establish procedures for identifying training needs and ensure that all personnel are trained to adequately perform their assigned responsibilities.

FDA noted that "There were no written training procedures to define job specific training requirements for manufacturing operators. Completed training records lack specific details of the job-related trainings. No records of GMP training were provided."

The warning letter stated, "Given the serious nature of the violations of the Act, devices manufactured by your firm are subject to refusal of admission…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, FDA explained, "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 responses and the need to reinspect your firm's facility to verify that the appropriate corrections and/or corrective actions have been made."

The firm's response, FDA stated, should detail "the specific steps your firm has taken to correct the noted violations, including an explanation of how your firm plans to prevent these violations, or similar violations, from occurring again. Include documentation of the corrections and/or corrective actions (which must address systemic problems) that your firm has taken. If your firm's planned corrections and/or corrective actions will occur over time, please include a timetable for implementation of those activities. If corrections and/or corrective actions cannot be completed within fifteen business days, state the reason for the delay and the time within which these activities will be completed. Please provide a translation of documentation not in English to facilitate our review." ***QC/QS***

Trimed, Inc.
Santa Clarita, CA, June 30
Los Angeles District

A March 7-18, 2016, inspection of **TriMed, Inc**., which manufactures implantable bone fixation systems including plates, screws, nails and wires intended to treat bone fractures of extremities, and instruments and drills used to implant these products during surgeries, revealed nonconformities with GMPs for medical devices, FDA stated in a warning letter to the company.

The violations observed included:

1. Failure to review, evaluate and investigate complaints involving the possible failure of a device, labeling and packaging to meet any of its specifications where necessary.

The firm maintains an Error Log for Returned Good Authorizations (RGAs) that references failures of its devices' labeling and packaging to meet specifications, FDA noted. A number of these "were not documented as complaints, and were not investigated," the letter pointed out. "Additionally, your firm found that 17 Perimeter Bone Plates, Part #WHV-4, had oversized threaded holes, which could allow the nonlocking screws to go through the plate. There was at least one instance where your firm received communication that this occurred in a clinical setting, and your firm did initiate a complaint file for this event."

Trimed's response was not adequate, FDA stated. "You have not completed the corrective actions referenced in this response, nor have you provided a timeline for the completion of these activities. Additionally, in your response to FDA-483 Observation 9, you stated that you would initiate a complaint file for MRB #0121, which referenced the oversized threaded holes in your Perimeter Bone Plates, Part #WHV-4; however, you did not demonstrate you had initiated this corrective action."

2. Failure to conduct a complete risk analysis.

FDA found "the failure mode of nonlocking screws passing through the hole of bone plates during surgeries has not been documented in the risk analysis for your Supracondylar Elbow Implant System."

The agency again found the firm's response inadequate. In the response, Trimed "stated that risk analysis for all bone plates would be updated to address the possibility of screws, locking and nonlocking, passing through the hole of the plate. Your firm has not completed this corrective action, nor have you provided a timeline for the completion of this activity."

3. Failure to adequately establish procedures for corrective and preventive action.

The firm's CAPA procedures "do not include a requirement to analyze sources of quality data such as complaints documented in your Error Log, nonconformances documented in your Material Review Board Log, and returned products documented in your Returned Goods Authorization Log to identify existing and potential causes of nonconforming product, or other quality problems," the agency found.

In addition, a CAPA initiated to address complaints of nonlocking SMTP-10 screws that were passing through the hole of the SMTP-10 plate. "The CAPA is referenced as implemented on 10/2/15 and effective on 2/9/16; however, there is no documentation to demonstrate the corrective action of revising the dimension of the screw hole was effective," FDA noted. "Furthermore, the 'Corrective Action (Plan)' references that other bone plates using the same threaded screw hole may be affected by the same issue, but CAPA #0293 does not refer to the products affected, nor is there documentation to show that effective corrective actions have been implemented for all products affected."

The firm's response stated that it would upgrade its procedure "to include the requirement to analyze all sources of quality data, but did not reference which specific sources will be included, nor did you provide a time line for these corrections. You stated that a verification of effectiveness for CAPA #0293 will be created, as well as documentation to show effective corrective actions have been implemented for all affected products; however, you have not completed these activities, nor have you provided a timeline for their completion," FDA stated in explaining why this response was deemed not adequate.

4. Failure to adequately establish procedures to control product that does not conform to specified requirements.

Trimed's Control of Nonconforming Products procedure "does not require nonconformances to be evaluated to determine if an investigation is needed, and does not require the documentation of any investigation conducted," FDA pointed out. The firm's Material Review Board-Rework records referenced several reports of

nonconformances "that did not include documentation that they were evaluated to determine whether an investigation was needed. If any investigations were performed, the investigations were not documented."

The company's response stated that it would "review and revise your procedure and your process for nonconforming products to conform with FDA regulations, and that MRB files will be re-evaluated to determine if documentation of whether additional investigation will be required," FDA acknowledged. "You stated a product complaint record will be initiated for MRB #121. You have not completed these activities, nor have you provided a timeline for their completion." As a result, FDA found this response inadequate.

5. Failure to adequately establish procedures for device history records.

Finished products shipped to a customer "did not include records that demonstrated the activities required in the device master record for your Wrist Fixation System, your Radiocarpal Fusion System and your Ulnar Osteotomy System were completed," FDA commented. "We reviewed your response, dated April 7, 2016 and find it is not adequate. This response references your firm will review and revise your QOP for device history records to meet FDA requirements. You have not completed these activities, nor have you provided a timeline for their completion."

6. Failure to submit a report to FDA no later than 30 calendar days after the day that your firm received or otherwise became aware of information, from any source, that reasonably suggests that a device that it markets may have caused or contributed to a death or serious injury.

Based on the information included for a complaint, FDA found that Trimed "became aware on Feb. 19, 2015, of an event that associates the breakage of the implanted fixation plate to the patient necessitating surgery to remove the broken device. Your firm has not submitted an MDR for the referenced event."

As of the issuance of the warning letter, FDA noted, the firm had not yet submitted an MDR for the referenced complaint "and there is no evidence that it has implemented corrective actions that will allow your firm to meet the required reportability timeframes for the future submission of MDR reportable events."

7. Failure to submit a report to FDA no later than 30 calendar days after the day that your firm received or otherwise became aware of information, from any source, that reasonably suggests that a device that it markets has malfunctioned and this device or a similar device that your firm markets would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Based on the information included for two complaints, FDA determined that Trimed became aware of events "on May 11, 2015, and Sept. 10, 2015 respectively, that associate your firm's osteotomy device and your firm's pin plate with a malfunction. The malfunction of long-term implantable devices is reportable. There is no evidence to justify whether the malfunctions would not be

likely to cause or contribute to a death or serious injury, if they were to recur. Your firm did not submit MDR reports within 30 days of receiving or otherwise becoming aware of the referenced events."

Because the firm had not yet "submitted evidence of implemented corrective actions that will allow your firm to meet the required reportability timeframes for the future submission of MDR reportable events," FDA found its response to this observation inadequate.

8. Failure to implement written MDR procedures.

After reviewing the firm's MDR procedure, titled "Medical Device Reporting," FDA found the following deficiencies:

The procedure does not establish internal systems that provide for timely and effective identification, communication, and evaluation of events that may be subject to MDR requirements. For example, FDA noted that the procedure includes definitions for the terms "caused or contributed," "malfunction," "MDR reportable event," and "serious injury," and the definition for the term "reasonably suggests," found in 803.20(c)(1). The procedure omits definition of the term "become aware" from 21 CFR Part 803.3. "The exclusion of the definition for this term from the procedure may lead your firm to make an incorrect reportability decision when evaluating a complaint that may meet the criteria for reporting under 21 CFR 803.50(a)," the agency commented.

The procedure does not establish internal systems that provide for timely transmission of complete medical device reports. Specifically, FDA found, the following are not addressed:

- "The circumstances under which your firm must submit supplemental or follow-up reports and the requirements for such reports.
- How your firm will submit all information reasonably known to it for each event. Specifically, which sections of the FDA Form 3500A will need to be completed to include all information found in the firm's possession and any information that becomes available as a result of a reasonable follow up within its firm."

The procedure also does not describe how Trimed will address documentation and record-keeping requirements, including:

- Documentation of adverse event-related information maintained as MDR event files.
- Information that was evaluated to determine if an event was reportable.
- Documentation of the deliberations and decision-making processes used to determine if a device-related death, serious injury or malfunction was or was not reportable.
- Systems that ensure access to information that facilitates timely follow-up and inspection by FDA.

Further, FDA explained, "Please note your firm's MDR procedure does not provide information about MDR reports in electronic format. Effective Aug. 14, 2015, MDRs should be submitted to FDA in an electronic format that FDA can process, review and archive. Paper submissions will not be accepted, except under special circumstances directed by the FDA. Your firm should revise its MDR procedure accordingly to include a process for submitting MDRs."

FDA also noted that "The adequacy of your firm's response dated April 7, 2016 cannot be determined. Your firm plans to address the issues noted in the current MDR procedure. However, your firm did not provide an updated MDR procedure for review. Therefore, the adequacy of your firm's response could not be determined at this time."

9: Failure to submit a written report to FDA of any correction or removal of a device initiated to remedy a violation of the Act caused by the device which may present a risk to health.

For example, FDA found, Trimed initiated a CAPA Sept. 29, 2015, "referencing nonlocking semi-tubular screw plate screws that were passing through the hole of the Semi-Tubular Bone Plates…allowing the screws to pass through the plates. You received SMTP-10 plates from the field from Sept. 1-28, 2015. Your firm did not submit a written report to FDA of the removal, as required by 21 CFR 806.10."

In its response to FDA, Trimed "stated that you will generate a justification to demonstrate that the removal does not require Recall. However, CDRH classified a similar recall, where a bone screw went through a hole in a bone plating system. As of June 7, 2016, there is no record of Trimed, Inc. submitting a Report of Correction or Removal to FDA." ***C-H; CAPA; MDR; QC/QS***