DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
8050 Marshall Drive, Suite 205 Lenexa, KS 66214 (913)495-5100 Fax:(913)495-5115	2/20/2017-3/24/2017* FEI NUMBER 1950222

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Thomas E. Handel , President and General Manager

FIRM NAME	STREET ADDRESS
Meridian Medical Technologies, Inc. a Pfizer Company	2555 Hermelin Dr
CITY, STATE, ZIP CODE, COUNTRY Brentwood, MO 63144-2504	TYPE ESTABLISHMENT INSPECTED Combination Drug/Device Manufacturer

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

The observations noted in this Form FDA-483 are not an exhaustive listing of objectionable conditions. Under the law, your firm is responsible for conducting internal self-audits to identify and correct any and all violations of the quality system requirements.

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

OBSERVATION 1

There is a failure to thoroughly review any unexplained discrepancy and the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed.

Specifically,

A. Your investigation of two complaints of 'Failure to Activate' for the EpiPen 0.3 mg Auto-injector finished product lot number 5FA665 did not extend to all potentially impacted lots. Your firm confirmed these complaints through investigations conducted under QAR Detail #PR ID: 22268 opened 5/9/16 and QAR Detail #PR ID: 28587 opened 2/23/17. These investigations identified manufacturing defects that resulted in distorted (b) (4) in the Power Pak (b) (4) of the Power Pak assembly. This assembly is used in both EpiPen and EpiPen Jr. Auto-injectors. Power Pak assembly lots (b) (4) (b) (4) were identified as potentially affected lots that were included in finished product lots. Your firm inspected all Power Pak (b) (4) for defects

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that were part of Power Pak assembly lots (b) (4) Your investigation implicated (b) (4) additional Power Pak assembly lots that were not utilized in finished product, (b) (4) You inspected lot (b) (4) and found up to 11 instances of flash near the (b) (4) and rejected this lot. Lot (b) (4) was also rejected but you did not evaluate or inspect the lot to determine if additional (b) (4) manufacturing defects were present. Your firm did not implement an inspection of complaint devices alleging similar failure modes for "failure to activate" / "difficult to activate" to determine if these devices had a distorted (b) (4) From your investigation, (b) (4) finished product lots remain on the market that contain potentially defective Power Pak (b) (4).

B. Your firm did not perform "(b) (4) testing" on the six (6) implicated lots identified in QAR PR 15815 prior to release of the lots. This QAR was opened when EpiPen Jr. lot 5GR446 failed functionality testing for low delivered volume due to (b) (4) defect. Your firm listed the most probable root cause of the (b) (4) defect as the presence of a non-homogeneous area in material. Your investigation for the other finished product using these (b) (4) was limited to batch record and testing record review. No additional physical tests were performed.

C. Your investigation PR 24844 did not fully address the issue of the large number of low fills for atropine in Lot 6M1454 of Atropine and Pralidoxime Chloride Injection (ATNAA). For this lot, your firm identified (b) (4) units with low fill in the front chamber (Atropine). The (b) (4) other batches inspected during the (b) (4) had a low fill range of (b) (4) units per batch. No new CAPAs were identified for the Lot 6M1454 investigation and your investigation concluded the filler was operating within its capabilities.

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OBSERVATION 2

Control procedures are not established which monitor the output and validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product.

Specifically,

A. Your procedures and practices allow your employees to repeatedly inspect lots of ATNAA to cull out defective units. These repeated 100% visual inspections however, do not remove all of the defective units.

1. Based upon review of production data, (b)(4)% of the batches from the ATNAA / DuoDote process (b)(4) out of (b)(4) batches inspected between 1 JAN 2015 and 21 FEB 2017) are not complying with the specified criteria for percent defect for critical, major, or minor defects during the 100% manual inspection. Your firm performed an additional 100% inspection for (b)(4) batches out of (b)(4), approximately (b)(4)% of the time. Additionally, there has been at least one batch, Lot 6M1133, which was subsequently rejected because it did not meet the criteria for a (b) (4) ; after the performance of a (b) (4) 100% inspection.
2. ANTAA Lot 6M1454, exceeded the alert limits for critical and minor defects during the initial 100% visual inspection. It passed the initial Acceptable Quality Limit (Visual (b) (4)) QA performs on (b)(4) of the "acceptable" units. Since this lot exceeded your defect alert limits, your firm performed a (b) (4) on (b)(4) of the "acceptable" units. During the (b) (4) the QA Inspector found one (1) unit with a low fill in the front chamber which is a critical defect. Therefore, your firm performed another 100% visual inspection and found 20 units with critical defects, 30 with major defects, and 907

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with minor defects. (b) (4) was performed on the "acceptable" units and three minor defects were found. This batch was released on 19 JAN 2017 by your Quality Assurance Unit.

B. Your manual visual inspection programs are deficient since:

1. There is no evaluation of the efficiency / effectiveness of an individual performing repetitive inspection over time for your basic units.
2. The (b) (4) certification process for detection of defects in your basic units is not currently performed at the end of the shift in order to evaluate the impact of fatigue, if any, upon defect detection capability.
3. The process for incoming (b) (4) " introduced into EpiPen manufacturing does not specify the maximum amount of time (b) (4) that an inspector is allowed to perform visual inspection. Current established practice does not limit inspection time to prevent errors caused by fatigue and loss of concentration. The operators do not have required break times and are not qualified for this inspection before being assigned and performing the (b) (4) evaluation task.

OBSERVATION 3

Procedures describing the handling of all written and oral complaints regarding a drug product are not established, written and followed.

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A. Your firm has not documented rationale why (b) (4) complaints of a similar nature on the same lot are necessary to identify a trend per your procedure Product Complaint Handling SOP-QLC-QLE-00702.

B. Complaint classifications, listed in GPB-QS1073 Prioritization of Pfizer Product Quality Complaints, are assigned prioritization classifications that are not commensurate with the associated clinical risk (e.g. no dose delivered) based on the alleged complaint. Three complaint prioritization classifications (Expedite, High, Normal) are assigned to complaint classifications. These prioritization classifications dictate the speed and thoroughness of the investigations conducted by your firm. There are at least ten product complaint classifications that do not adequately reflect the associated risk including, but not limited to, 'Spontaneous Activation' classified as Normal, 'Container Broken/Cracked/Leaking Prior to Use' classified as Normal, and (b) (4) (b) (4) classified as Normal.

C. No safety or risk assessment has been completed to establish the acceptability of the mean complaint rates received by Pfizer Corporate, which is utilized by your firm to establish the upper and lower confidence limits of complaint.

OBSERVATION 4

Procedures for identifying valid statistical techniques required for establishing, controlling, and verifying the acceptability of process capability and product characteristics have not been adequately established.

Specifically, insufficient statistical assessments were in place for establishing, controlling, and verifying process capability and product characteristics.

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A. Your firm provided no rationale for the acceptability of your sampling plan at lot release based on the risk associated with releasing defective product. The AQL (Acceptable Quality Limits) sampling plan and associated (b) (4) is not commensurate with the product risk based on intended use and design inputs of the product.

B. Your firm does not currently distinguish the failure modes of rejected components/units that are collected in reject bins on the EpiPen manufacturing assembly line. In addition, your firm does not currently track or trend the rejects from the EpiPen assembly manufacturing line and there are no action limits associated with the number or type of rejects.

C. Your firm failed to routinely evaluate ongoing state of control of the equipment and process. For example,
   1. The capability and suitability of equipment to produce conforming units was not assessed. Specifically, process capability evaluations did not reflect inherent capability of the process equipment to produce conforming units. Instead, you only calculated process capability after a large number of defects were inspected out of the batch.
   2. Your firm failed to adequately analyze data to determine process points in which excessive variation occurred and defective units were produced.
   3. Your firm lacked sufficient ongoing trending of numerous in-process attributes that are critical to the quality of the finished product. For example, there was insufficient ongoing trending to periodically assess (e.g. process trending reports, Annual Review) process performance to promptly detect atypical variability that may affect product quality.

OBSERVATION 5

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Records are not maintained so that data therein can be reviewed at least annually to evaluate the quality standards of each drug product to determine the need for changes in specifications or manufacturing or control procedures.

Specifically, your analysis of the quality data used to identify existing and recurring quality problems does not include an analysis of complaints based on finished product lots, manufacturing dates or component lots to identify existing or recurring quality problems. Your analysis is presented and discussed during management review meetings, is currently conducted by totaling complaints by .

OBSERVATION 6

Procedures for design input have not been adequately established.

Specifically,

A. The design inputs/requirements of the EpiPen, EpiPen Jr., and (b) (4) products are not appropriate for the intended use of the products in regards to the reliability of the delivery system. The reliability inputs/requirements of the device according to your PRD/TRD 16-001 Rev 1 do not include a system level reliability design input/requirement.
   1. Your inputs/requirements list an AQL (b) (4) for critical tests, which equates to establishing a certain confidence of no more than (b) (4) failures per (b) (4) products. (b) (4) failures of delivered dose, or other critical tests, per (b) (4) EpiPen, EpiPen Jr., or (b) (4) products does not give assurance of the level of reliability commensurate with the risk of failure of a critical test as defined by your firm (e.g. delivered dose, (b) (4), etc.).
   2. Your pharmaceutical / drug delivery performance inputs/requirements list the

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inputs/requirements for certain essential performance inputs/requirements being specified to an AQL of (b) (4), which establishes a certain confidence of no more than (b) (4) failures of an essential performance input/requirement, such as (b) (4), per (b) (4) products.

3. No rationale is provided for the acceptability of these design inputs/requirements based on the emergency use, life-saving intended use of the product.

B. The design inputs/requirements of the EpiPen, EpiPen Jr., and (b) (4) are conflicting. In PRD/TRD 16-001 Rev 1 the design inputs/requirements related to the 'Pharmaceutical / drug delivery performance' of the EpiPen, EpiPen Jr., and (b) (4) have specifications that are outside of the principal design attributes listed. As an example, the principal design attribute for the EpiPen for dose volume is (b) (4) mL. However, under input/requirement the delivered dose volume for the EpiPen is described as (b) (4) – (b) (4) mL @ AQL (b) (4), Not less than (b) (4) or greater than (b) (4) mL at AQL (b) (4).

C. The design inputs/requirements of the EpiPen, EpiPen Jr., and (b) (4) do not directly trace to a risk assessment of the product. It is unclear if the specifications listed under the 'Must' column of the document titled PRD/TRD 16-001 Rev 1 are appropriate for the intended use of the device and the user/patient needs, especially considering that many of the specifications are split into different levels of acceptability based on the confidence of a sampling plan.

D. Design inputs/requirement specifications of the EpiPen, EpiPen Jr., and (b) (4) utilize AQLs to describe the necessary confidence level associated with each range of a specification; however, AQLs do not consider the needs of the user/patient. As an example, in PRD/TRD 16-001 Rev 1 the (b) (4) input/requirement specification is described with two different AQLs for two ranges of values associated with (b) (4).

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E. Your firm has not established design inputs/requirements regarding the ability of the device to successfully inject through clothing as specified by the intended use of the product as defined by your firm's Injection Sites and Site Condition of the PRD/TRD 16-001 Rev 1 document.

OBSERVATION 7

Procedures for design output have not been adequately established.

Specifically,

A. Your firm has not established design outputs that allow an adequate evaluation of conformance to design input requirements. The design outputs as defined by your firm in the Design History File document titled DHF 17-001 Rev 1.0 include batch record tests, controlled drawings, QC test reports, and SOPs that do not establish acceptance criteria for any system level reliability requirements after (b) (4) given the intended use of the product.

B. The design outputs acceptance criteria do not reflect the risk associated with the failure of the specifications. The design output documents for the design input requirements allow for failures of 'major' functional requirements to occur such as delivered volume outside of the specification of (b) (4); – (b) (4) mL.

OBSERVATION 8

Procedures for design verification have not been adequately established.

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Specifically,

A. Your firm has not developed design verification testing that adequately tests that the design outputs meet the design inputs, specifically in regards to the reliability of the device at the end of the labeled date of expiry. No verification testing exists that is reflective of the design input requirement that the drug delivery performance must be acceptable at the end of product expiry.

B. The test methods for design verification testing are inadequate. (b) (4) ; of the final product is not done (b) (4) prior to functional verification testing according to your document PR-14719 titled 'Final Report – Component and Functional Qualification of the NGA EpiPen Sr. Auto-Injector using (b) (4) Plungers from (b) (4) ' for the (b) (4) . The same is true for the completed verification testing of the EpiPen and EpiPen Jr. products.

C. Verification testing demonstrated failures of design requirements according to PR-14719; however, these failures were deemed acceptable within the test report conclusions. Your firm confirmed that the same test failures would not be acceptable during lot release testing and would trigger the initiation of an investigation. For example, in PR-14719 one unit of the (b) (4) units tested during the (b) (4) test was noted to have a delivered volume of (b) (4) ml, which is outside of the delivered volume specification of (b) (4) – (b) (4) ml. The conclusion of the test was that it was acceptable to have up to (b) (4) delivered volume failures per the specification of (b) (4) – (b) (4) ml and still pass the acceptance criteria.

D. Essential performance requirements such as (b) (4) , activation force, dispensing time, and dispensing volume are listed to have a reliability of (b) (4) % in PR-14719 which is not

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commensurate with the listed design input requirements of PRD/TRD 16-001 Rev 1, nor is it commensurate with the risk associated with the intended use of the product.

OBSERVATION 9

Procedures for design validation have not been adequately established.

Specifically,

A. Your firm has not completed any validation testing of the design of the device in order to ensure that the devices conform to the defined intended uses. No validation testing was conducted to establish the device specifications conform with the intended use of the product to a degree of reliability commensurate with the risk associated with the device (e.g. no failure rate at product expiry has been established through design validation). Actual or simulated use conditions (e.g. activation orientation, environmental temperature, injection through clothing, etc.) are not part of the design validation plan. Validation testing has not been conducted on initial production units, lots, or batches for the EpiPen, EpiPen Jr., or (b) (4) products.

B. No validation testing has been conducted on the user interface of the EpiPen, EpiPen Jr., or (b) (4) products.

C. No risk analysis was conducted for the 'basic unit' subassembly of the EpiPen product line. Also, the document titled 'NGA Truject Autoinjector Risk Assessment' reference 8637935n FMEA Report has not been reviewed since its issuance in 2009.

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OBSERVATION 10

Laboratory controls do not include the establishment of 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.

Specifically, we witnessed functionality testing of EpiPen and observed the following:

A. The lot release test fixtures, which are used to perform the functionality testing of the final finished product, does not include assurance that all test surfaces are level. We also observed that the employee conducting the testing did not (b) (4) to ensure that the (b) (4) was not affected by the environment during testing. The (b) (4) the products during testing appeared damaged and currently there is no standard operating procedure for conducting preventive maintenance on this equipment.

B. We observed that drug product was accumulated on the (b) (4). We observed that the drug product inside the (b) (4) from previous testing can be transferred to the final finished product's (b) (4) after dispensing the drug product and prior to weighing the unit for the delivered dose measurement.

C. (b) (4) entry of (b) (4) and dispensed time relies on the operator to read the (b) (4) (b) (4) from a (b) (4) whereby the measurement of (b) (4) occurs (b) (4) (b) (4) of the

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device occurs.

D. Measurement results can be altered if a (b) (4) applied different forces to measurement tools. For example, the (b) (4) could be increased by applying more force to the device while (b) (4).

E. There have been no studies conducted to establish inter-operator and inter-test stand variation of the functional test results. Currently, your firm has (b) (4) and up to (b) (4) operators who are trained to conduct these tests.

F. The operator conducting functional testing on a production lot of final finished product was not listed as an operator trained to complete the functionality testing of NGA Auto-injectors or Auto-injectors according to your firm's records in document SOP-QLC-SQC-00307 & 00394. Additionally, the same operator is not included in the training record for conducting testing of Power Pak.

G. There is no risk assessment, failure mode analysis, or determination of analytical variation conducted for the functional lot release test procedure and testing process.

OBSERVATION 11

The quality control unit lacks the responsibility and authority to approve and reject all components, drug product containers, closures, in process materials, packaging material and drug products.

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8050 Marshall Drive, Suite 205 Lenexa, KS 66214 (913)495-5100 Fax:(913)495-5115	2/20/2017-3/24/2017* FEI NUMBER 1950222

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Thomas E. Handel , President and General Manager

FIRM NAME	STREET ADDRESS
Meridian Medical Technologies, Inc. a Pfizer Company	2555 Hermelin Dr
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Brentwood, MO 63144-2504	Combination Drug/Device Manufacturer

Specifically, Quality Assurance lacked a sufficient response to the positive sterility test of EpiPen (Epinephrine Injection, 0.3 mg) Lot 7GM063 that occurred on Friday 17 FEB 2017. The microorganism found was *Bacillus cereus*, a spore-former. For example, as of Thursday 24 FEB 2017:

A. (b) (4) batch operations continued on the Epinephrine line and other lines, with no extra controls mandated by QA to increase scrutiny of the aseptic processing operation.

B. Quality Assurance did not mandate a temporary suspension of batch release while the scope and possible cause of a sterility failure was being investigated.

C. Your procedure SOP-LAB-MIC-00416 Investigation of a Sterility Test Positive, Tested in the (b) (4), Version 9.0, only requires an evaluation of whether "(b) (4) lots and (b) (4)" should be rejected, rather than evaluating if a larger issue exists on the line that could have broader scope. There is no requirement that your firm considers whether other lots manufactured on the line and in the facility may have been affected by the route of contamination.

OBSERVATION 12

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established and followed.

Specifically,

A. We observed breaches in aseptic technique on the Epinephrine and ATNAA/DuoDote lines. For example:

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1. On 21 FEB 2017 during the filling of Epinephrine Injection 0.3mg, Lot 7GM163, an operator reached over exposed sterile barrels.
2. Your sterile operators introduce sterile barrels to the Epinephrine filling in an area with no barrier protection and completely open to the surrounding room, classified as Grade B. In addition, your smoke studies demonstrated turbulence in this area.
3. During filling operations of ATNAA Lot 7M1131 on 21 FEB 2017, your operators made interventions with their upper torso over units on the ATNAA line in two instances.

B. Regarding your media fill program:

1. For ATNAA, an operation that requires [redacted], the number of units were [redacted] as seen in the table below. The media fill for the Epinephrine line is also a [redacted].

Product	Target Fill	Media Fill	Media Fill	Media Fill
ATNAA	(b) (4) units	(b) (4) units 06 JAN 2017	(b) (4) units 11 NOV 2016	(b) (4) 21 DEC 2015
Epinephrine	(b) (4) units	(b) (4) units 05 JAN 2017	(b) (4) units 18 NOV 2016	(b) (4) units 22 JAN 2015

2. The number of media fills is not commensurate with the (b) (4) Although your firm operates on (b) (4), only (b) (4) media fills are required (b) (4) for both the Epinephrine and ATNAA lines. Your firm uses an approach that (b) (4) and is intended to cover (b) (4)

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[redacted].

3. Your firm aborted [redacted] media fill batches for ATNAA without the clear justification as required by procedure SOP- QLA-VAL-00020 Media Challenge of Aseptic Processes which states in part, "*** A media fill run shall be aborted (invalidated) only under circumstances in which written procedures require [redacted] Supporting data and justification shall documented [sic] in such cases***". Your firm had no production procedures that specified the conditions that were used to justify invalidate [redacted] media fill batches on the [redacted] (ATNAA) line.

OBSERVATION 13

Written production and process control procedures are not followed in the execution of production and process control functions and documented at the time of performance.

Specifically,

A. Epinephrine, as stated in the appropriate master batch records, is required to be [redacted] (b) (4) [redacted], however, controls within the inspection and assembly area [redacted] (b) (4) [redacted]) are deficient since:
   1) Units were observed in the inspection and assembly area being [redacted] (b) (4) [redacted] and were not [redacted] (b) (4) [redacted] during breaks.
   2) Your firm is not currently calculating the [redacted] (b) (4) [redacted] during all phases of production nor are you currently comparing the [redacted] (b) (4) [redacted] against a specified criteria.

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3) Your firm has not measured the impact of (b) (4)) and the duration and frequency of (b) (4) in the inspection and assembly area from:
   i. (b) (4) t used as (b) (4) as part of the (b) (4) process for the (b) (4)
   ii. (b) (4) used as (b) (4) as part of the (b) (4) process in (b) (4)
   iii. (b) (4) in (b) (4)
   iv. (b) (4) from (b) (4) of (b) (4) that is used as (b) (4) in order to aid in the inspection at the (b) (4)
   v. (b) (4) from (b) (4) from (b) (4)
   vi. (b) (4) from (b) (4) in Assembly Area in (b) (4)

4) Your firm is not currently evaluating the potential impact of epinephrine (b) (4) as part of the overall investigation process.

1. Based upon review of production data, Epinephrine Batch 6GM059 had been inspected (b) (4) in (b) (4) (b) (4)) and therefore (b) (4) (b) (4) (all units were (b) (4) This batch was subsequently released by the firm; and during commercial distribution received a complaint related to Liquids Atypical Color / Cloudy. The subsequent compliant investigation (MMT Complaint Number 2016-07-0037004-US) did not consider the atypical nature of the inspection process nor the potential (b) (4) as a root cause factor.

B. "SOP-QLA-GEN-00802, version 10.0, Management of Changes for Equipment, Facilities and Manufacturing Processes, Effective Date: 23 MAR 2016" fails to require documentation of

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effectiveness checks for completed change controls. Process validations are completed (b) (4) but are not evaluated or trended to determine impact to the overall manufacturing process; additionally, complete process validations for autoinjector manufacturing processes such as EpiPen and ATNAA/DuoDote have not been revalidated since the initial validations. Risk assessments are not required to be performed for every change. The aforementioned procedure does not define criteria or provide examples indicating when risk assessments are necessary to be completed for the change.

OBSERVATION 14

Employees engaged in the manufacture, processing, packing and holding of a drug product lack the training required to perform their assigned functions.

Specifically, your firm did not conduct training for employees involved in the visual inspection for (b) (4) used in EpiPen manufacturing. For example, your Site Lead reported there is no formal OJT for the visual (b) (4) evaluation (inspection) before the (b) (4) is introduced into the process. There are no job aides to assist operators in identifying defects and there are no visual examples of defects in the procedure. There is also not a defined time frame that the (b) (4) must be evaluated for the following defects: (b) (4) and (b) (4) The evaluation of the (b) (4) is not timed. The operators are not qualified for visual acuity or accuracy in discovering defects for this inspection before performing the (b) (4) evaluation task.

Annotations to Observations

Observation 1: Not annotated
Observation 2: Not annotated

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Observation 3: Not annotated
Observation 4: Not annotated
Observation 5: Not annotated
Observation 6: Not annotated
Observation 7: Not annotated
Observation 8: Not annotated
Observation 9: Not annotated
Observation 10: Not annotated
Observation 11: Not annotated
Observation 12: Not annotated
Observation 13: Not annotated
Observation 14: Not annotated

***DATES OF INSPECTION**

2/20/2017(Mon),2/21/2017(Tue),2/22/2017(Wed),2/23/2017(Thu),2/24/2017(Fri),2/27/2017(Mon),2/28/2017(Tue),3/01/2017(Wed),3/02/2017(Thu),3/03/2017(Fri),3/22/2017(Wed),3/23/2017(Thu),3/24/2017(Fri)

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