

Establishment Inspection Report

MiMedx Tissue Services, LLC

Marietta, GA 30062-2254

FEI: **3005897621**

EI Start: 1/6/2016

EI End: 2/4/2016

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SUMMARY

The previous inspection of this Human Cells, Tissues, and Cellular Tissue-Based Products (HCT/Ps) firm was a comprehensive cGTP inspection conducted on 7/31-8/20/14 and classified as Voluntary Action Indicated (VAI). Form FDA 483 - Inspectional Observation was issued with the following observations: (1) Procedures for the cleaning and sanitizing of equipment were not followed and (2) HCT/P deviations relating to core CGTP requirements that occurred in your establishment were not reported to FDA. There were no items of discussion brought forth during the close out meeting with management.

The current inspection was conducted on 1/6-2/4/16, in response to FACTS Assignment: 11552451 (PAC 41B800) in accordance with Compliance Program 7345.848, Inspection of Biological Drug Products; and was initiated in response to a CBER assignment memorandum dated 11/17/15, which requested an unannounced, directed comprehensive GMP inspection. At the initiation of the inspection on 1/6/16, I presented credentials and issued the FDA 482 - Notice of Inspection to Parker H. Petit, Chairman and CEO of MiMedx Tissue Services (**Attachment 1**). The current inspection found that the firm continues to recover human tissue – specifically placental amniotic/chorionic membrane tissue, which undergoes (b) (4) . The focus of this inspection was the firm's micronized dehydrated injectable products. No refusals were encountered during this inspection. Documentary sample 806629 (**Attachment 3**) was collected to detail the interstate movement of the firm's micronized products.

An FDA 483 (**Attachment 2**) was issued at the conclusion of the inspection for (1) There are no written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess; (2)

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Written records of investigations into unexplained discrepancies do not include the conclusions and follow-up; (3) The statistical quality control criteria fail to include appropriate acceptance levels and rejection levels; (4) Written representation that processing methods reduce the risk of transmission of communicable disease by HCT/PPs was not based on a fully validated or verified process (5) Time limits are not established when appropriate for the completion of each production phase to assure the quality of the drug product; (6) Written procedures are not established that describe the in-process controls, tests and examinations to be conducted on appropriate samples of in-process materials of each batch; (7) Drug product component testing is deficient in that at least one specific test to verify the identity of each component is not performed; (8) Each batch of drug product required to be free of objectionable microorganisms is not tested through appropriate laboratory testing; (9) The accuracy of test methods have not been established; (10) The written stability program for drug products does not include reliable, meaningful and specific test methods; (11) Drug products do not bear an expiration date determined by appropriate stability data to assure they meet applicable standards of identity, strength, quality and purity at the time of use; (12) Drug product production and control records, are not reviewed and approved by the quality control unit to determine compliance with all established, approved written procedures before a batch is released or distributed; and (13) Batch production and control records do not include dates of each significant step in the manufacture, processing and packing of the batch for each batch of drug product produced. The firm had (b) lost products since the previous inspection. This issue was discussed with management during the close out meeting.

ADMINISTRATIVE DATA

Inspected firm: MiMedx Tissue Services, LLC
Location: 1775 W Oak Commons Ct
Marietta, GA 30062-2254
Phone: 770-651-9100
FAX: -
Mailing address: 1775 W Oak Commons Ct
Marietta, GA 30062-2254
Dates of inspection: 1/6/2016-1/8/2016, 1/11/2016-1/13/2016, 1/15/2016, 1/19/2016-
1/20/2016, 1/26/2016, 2/2/2016, 2/4/2016
Days in the facility: 12
Participants: **Kimberly C Delk-Brooks, Investigator**

INTERSTATE COMMERCE

The firm's micronized injectable dehydrated human amnionic/chorionic membrane (hereafter referred to as dHACM) products account for approximately (b) of the firm's business. Tissue utilized for manufacturing into micronized products is recovered from hospital sites in the S(b) (4) . Approximately (b) (4) were recovered

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in 2015. A complete list of recovery sites and recovery statistics is attached (**Exhibit 3-4**). The firm distributes approximately (b) of their micronized products into interstate commerce. A consignee list and distribution statistics are attached (**Exhibit 5-7**). Documentary sample 806629 (**Attachment 3**) was collected to detail the interstate movement of the firm's micronized products as well as support good tissue practice deficiencies observed and cited.

JURISDICTION

MiMedx Tissue Services (hereinafter referred to as MiMedx) maintains an active FDA 3356, Establishment Registration and Listing for HCT/Ps, under FEI 3005897621. The registration notes that the firm recovers, screens, packages, processes, stores, labels and distributes amniotic membrane and amniotic fluid that are "HCT/Ps Described in 21 CFR 1271.10". The firm's 361, minimally manipulated tissues as described in 21 CFR 1271.10 applies solely to their dehydrated sheet grafts. The firm also manufactures, stores, labels and distributes micronized injectable dHACM products, which are not listed as (b) tissues on the registration. All of the firm's micronized products are subject to CGMP inspection as those products are HCT/Ps regulated as Biological Drugs. Of note, one of the firm's micronized products, AmnioFix Injectable, is being manufactured as part of IND 16095 for the treatment of plantar fasciitis. The firm's other micronized products: EpiFix Micronized, AmnioFix Sports Med, AmnioOvo Injectable and Ambio Choice Plus do not have an IND and as such are subject to inspection under Compliance Program 7345.848 Inspection of Biological Drug products.

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED

There have been very few changes to the firm's upper management since the previous inspection. Mr. Parker H. Petit remains Chairman and CEO and most responsible person at the firm. He is responsible for all aspects of the organization's operations. Mr. William C. Taylor remains the firm's President and COO. He is second in command to the CEO and in conjunction with Mr. Petit, leads and directs all aspects of the firm's operations. Mr. Mark Rogers was promoted from Senior Director, Quality Assurance to Vice President, Quality Assurance and Regulatory Affairs. He continues to hold the Tissue Bank Director position. In this role he is responsible for oversight of all aspects of tissue bank operations including recovery, processing, storage and distribution of micronized injectable dHACM products. Other key operating personnel that were present during the course of the inspection, assisted by provided documents or answering questions were:

Brent Miller, Executive VP

(b) (6), General Counsel and Secretary

Doug Vine, VP Operations

Rebecca Brown PhD, VP Product Development

Dia Hill, Manager, Regulatory Affairs

Deborah Dean, Executive VP

(b) (6), Quality Assurance Supervisor

Mark Rogers, VP Quality Assurance and Regulatory Affairs and Tissue Bank Director

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All of the aforementioned individuals have the knowledge, duty and power to prevent, detect, and/or correct objectionable conditions and/or practices. Copies of the firm's position descriptions and organizational charts for the individuals listed above are attached (**Exhibits 1-2**).

All FMD-145 correspondence should be addressed to:

Mr. Parker H. Petit, Chairman and CEO
MiMedx Tissue Services
1775 W Oak Commons Ct.
Marietta, GA 30062

MANUFACTURING/DESIGN OPERATIONS

This inspection was a level 1 Biological Drug Product inspection that focused on the firm's quality system, donor eligibility system, production system and laboratory control system. The inspection consisted of a walk-through of the facility, a review of the firm's FDA registration, consignee list, recovery site list, distribution statistics, standard operating procedures, observance of micronized injectable dHACM product processing, labeling, storage and distribution; and review of the following records generated since the previous inspection: Donor recovery and processing records, training records, complaints, adverse reactions, environmental monitoring, biological product deviations, IND submissions, labeling, distribution records, viable and non-viable air monitoring, cleaning records, temperature monitoring records, BSC static and dynamic monitoring, incoming tissue inspection forms, discarded/rejected tissue tracking, processing suite maintenance logs, CLIA certificates, USP dHACM monograph, cleanroom certifications, equipment maintenance and repair records, dosimetry reports, incoming Bioburden testing, sieve calibration records, equipment IQ/OQ reports, and cleanroom analysis. The following quality trending reports were also reviewed: complaints, deviations, environmental monitoring actions, NCRs, CAPAs and CARs.

I reviewed the following validations: Disinfectant Efficacy (Vesphene) Study, Micronization Process Validation, Micronized Tissue Weigh Process Validation, Particle Size Analysis Protocol, Tissue Shipper Validation, Terminal Sterilization Validation, Gamma Sterilization Validation Protocol, Strength Testing, Tissue Product Packaging Study, 2006 Aging study and Real Time Shelf Life Stability Assessment.

MiMedx Tissue Services has had no recalls since the previous inspection. The firm was found to be clean and maintained in sanitary condition; all equipment was observed to be in good working order. No expired products or supplies were noted during the inspection.

MiMedx continues to contract with FDA registered, CLIA certified, (b) (4)

for infectious disease testing. (b) (4)

serves as the firm's backup testing facility. (b) (4)

) and (b) (4)

continue to be utilized for terminal sterilization.

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MiMedx Tissue Services has a secondary location (300 TownPark Drive, Suite 260, Kennesaw, GA 30144) that receives, processes, labels and stores dHACM sheet grafts. No micronized products are manufactured or stored at this location.

There has been no significant changes to the firm's recovery and manufacturing process since the previous inspection. A process flow diagram is attached (**Exhibit 8**). Review of the firm's donor eligibility system found that appropriate donor screening including testing for relevant communicable diseases is performed. (b) (4) of the recovered tissue is conducted. Recovered tissue is not released for processing until all test results are received and the donor is cleared for processing. I observed quarantined tissue pending release to be stored in a separate, controlled access refrigerator. A review of temperature monitoring records found the quarantined tissue to be stored at appropriate temperatures and properly identified with the donor identification number and quarantine warning. Recovered tissue can remain in quarantine storage for (b) (4). I confirmed that the firm does not release quarantined tissue for urgent medical need.

Cleared donor tissue undergoes processing, which includes (b) (4)

The (b) (4)

. The (b) (4)

It

is at this point (b) (4)

The firm will (b) (4)

. Once (b) (4)

. The firm (b) (4)

. Once the products (b) (4)

According to the firm, all micronized injectable dHACM products have (b) (4)

(b) (4) A review of the firm's Micronization validation (**Exhibit 9**), processing standard operating procedures (**Exhibit 53-58**), processing records (**Exhibit 10-14**), Real time shelf life stability assessment (**Exhibit 15-16**), pre-processing Bioburden testing (**Exhibit 19**), Terminal sterilization procedure (**Exhibit 52**), Gamma sterilization validation protocol (**Exhibit 20-21**) revealed significant deficiencies within the Micronization process. The most egregious violations were that the firm failed to fully validate their micronization manufacturing process and that there were failures during the validation that were not investigated. In addition, the firm (b) (4)

nor have they validated their pre-sterilization Bioburden testing. The firm has not established any acceptance criteria for their remnant tissue. They

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(b) (4) These deficiencies were all documented on an FDA 483 (**Attachment 2**), issued on 2/04/16.

During the course of the inspection, I had several in depth discussions with the firm regarding their Micronization Validation Process (**Exhibit 9**) and Sterilization Validation (**Exhibit 20-21**). The outcome of much of those discussions were captured in two documents provided to me by the firm which detailed their current practices for their micronized injectable dHACM products (**Exhibit 22**) as well their Terminal Sterilization Validation (**Exhibit 49**). These discussions revealed that, as it pertains to their AmnioFix Injectable IND product, the firm has implemented or is in the process of implementing (b) (4).

However, as detailed in **Exhibit 22**, very few of the Biological Drug requirements for the firm's micronized injectable dHACM products that are currently being manufactured and distributed have been implemented. The firm provided me with several documents (**Exhibit 23-26, 50-69**) which detail their plans for bringing their micronized products into compliance (b) (4).

According to management, the plan is (b) (4).

etcetera for their IND product first. The IND (AmnioFix Injectable) is to be used as a platform to build upon; and then implement the procedures across the board for all of their micronized injectable products within (b) (4).

Also during the course of the inspection, I conducted a review of deviations which revealed that the firm released the following EpiFix micronized injectable dHACM products for distribution on (b) (4).

(b) (4) and (b) (4). These products were manufactured from donor (b) (4) (**Exhibit 28**) and shipped to (b) (4) on (b) (4). According to (b) (4) (**Exhibit 27**), the products were implanted on/or before (b) (4). The final QA release was not performed by the QA department until (b) (4).

Review of (b) (4) (**Exhibit 29**) found that donor processing records (b) (4) and (b) (4) (**Exhibit 30-32**) were not submitted to QA for final review and release prior to the micronized dHACM grafts being shipped to (b) (4). Tissue samples from Donors (b) (4) and (b) (4) (**Exhibit 33-37**) were not submitted for (b) (4) and approved for release before being distributed to (b) (4) on (b) (4).

(b) (4) (**Exhibit 38**) revealed that the micronization processing technician did not document the day micronization was performed, the equipment used to micronize the tissue or the technician performing the micronization. (b) (4) (**Exhibit KDB 39**) documented that critical supplies including (b) (4).

, utilized during the micronization process were not recorded during (b) (4) (**Exhibit 40-48**).

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All of the aforementioned deviations were documented on the FDA 483, issued 2/04/16 (Attachment 2).

MANUFACTURING CODES

Donor records and recovered tissue are labeled with a donor identification number, which is unique to the donor and the hospital where the recovery took place (i.e., Donor ID (b) (4)). Once the recovered tissue is received in house at MiMedx and (b) (4)

(Manufacturing Donor ID (b) (4)). This manufacturing donor ID number will identify the tissue throughout processing. Processed tissue will be assigned a prefix that indicates product type (i.e., prefix MI12 – AmnioFix Injectable) and a suffix to identify each individual vial of product (i.e., suffix -003). The final tissue identification number for an AmnioFix micronized product manufactured from Donor (b) (4) intended for distribution is (b) (4).

The firm's SOP (b) (4) Identification and Traceability which also includes a coding breakdown for assigning donor IDs is attached (Exhibit 73).

OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE

Observations listed on form FDA 483

OBSERVATION 1

There are no written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess.

Specifically,

1. The firm failed to fully validate their micronization manufacturing process. The current process lacks validation of particle size and size distribution, product identity, safety and potency. Furthermore, the validation of antibiotic clearance and NaCl clearance has not been performed. Therefore, purity validation has not been completed. Under this micronization manufacturing process, the firm has manufactured and distributed (b) (4) micronized dehydrated human amnion/chorion membrane (dHACM) products in 2013; (b) (4) micronized dHACM products in 2014; and (b) (4) micronized dHACM products in 2015.
2. None of the firm's SOPs related to their micronization manufacturing process adequately address the identity, strength, quality or purity of their micronized dHACM products.

Reference: 21 CFR 211.100(a)

Supporting Evidence and Relevance:

The firm's Micronization validation is attached (Exhibit 9). The validation is deficient in that it does not address all critical attributes of Biological Drug Products. The validation was completed to meet the requirements of (b) (4) minimally manipulated HCT/PS, not Biological Drugs. The firm's micronization process SOPs are attached (Exhibit 53-58). The SOPs are deficient in that they also

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do not address the critical attributes of biological drug products. The SOPs were written to satisfy the requirements of 1271 HCT/Ps only.

Discussion with Management:

There were no questions or comments from management regarding this observation.

OBSERVATION 2

Written records of investigations into unexplained discrepancies do not include the conclusions and follow-up.

Specifically,

As part of the micronization validation, visual inspections of all grafts were conducted. A 100% visual inspection pass rate was required as part of the acceptance criteria for the validation. Deviation 1 was initiated for 9 visual inspection failures out of the 200 inspections conducted. Even though the 100% passing rate was not met, the micronization process was approved. There were no changes to the acceptance criteria or revalidation of the micronization process based on the failures; nor were additional details or further explanation provided in the deviation.

Reference: 21 CFR 211.192

Supporting Evidence and Relevance:

Exhibit 9, page 116. Deviation 1 addresses the visual inspection failures that occurred during validation. The firm established a 100% pass rate for the visual inspections. The products tested during validation did not meet this requirement. The firm did not conduct an investigation into the failures to determine a root cause. The failures were instead attributed to historical failure rates (b) (4). It is important to note that this validation went into effect (b) (4). However, the firm has been manufacturing and distributing micronized injectable dHACM products since 2011.

Discussion with Management:

Management stated that they conduct (b) (4) of their micronized products. I explained that trending does not address the failures that occurred during process validation. The expectation is that any deviation occurring during validation would be fully investigated to determine the cause of the failure. Once a cause is determined, new acceptance criteria should be set and the process revalidated.

OBSERVATION 3

The statistical quality control criteria fail to include appropriate acceptance levels and rejection levels.

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Specifically,

1. The firm failed to establish, validate and implement test methods by which the identity, purity and potency of their micronized dHACM products could be identified and verified.
2. (b) (4) performed on micronized dHACM products, (b) (4) Additionally, (b) (4) is not performed on micronized dHACM products, nor does it address bacteriostasis and fungistasis as the antibiotic clearance studies used to determine product purity have not been completed.

Reference: 21 CFR 211.165(d)

Supporting Evidence and Relevance:

Exhibit 22, pages 3-4: This document, provided by the firm, details the current acceptance criteria for their micronized injectable dHACM products. Currently, the acceptance criteria utilized for product release are (b) (4)

SOP (b) (4) Bacterial Acceptability Determination for Pre-Processing (**Exhibit 19**) and (b) (4) HCTP Final Release for Distribution (**Exhibit 18, page 1**) address the firm's current process for determining bacterial acceptability for pre-processing testing of incoming tissue and final release criteria for processed tissue. These are the only procedures that address the firm's current (b) (4)

do not currently conduct (b) (4) Management confirmed that they on their micronized injectable dHACM products.

Exhibit 22, page 6 indicates that (b) (4) have not yet been completed. The fact that this testing is not yet done further demonstrates that not only does the current (b) (4) not address bacteriostasis and fungistasis; but that validation for (b) (4) has not been performed, as the process cannot be adequately validated without addressing bacteriostasis and fungistasis.

Discussion with Management:

There were no questions or comments from management regarding this observation.

OBSERVATION 4

Written representation that processing methods reduce the risk of transmission of communicable disease by HCT/Ps was not based on a fully validated or verified process.

Specifically,

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(b) (4) for (b) (4) of the firm's micronized dHACM products has not been validated. Furthermore, the firm's (b) (4) fails to address bacteriostasis and fungistasis testing, as their antibiotics clearance studies used to determine product purity are not yet complete.

Reference: 21 CFR 1271.230(b)

Supporting Evidence and Relevance:

Exhibit 22, page 6 indicates that (b) (4) have not yet been completed. Failure to complete clearance testing is evidence that the current (b) (4) not address bacteriostasis and fungistasis; and that validation for (b) (4) has also not been performed, as the process cannot be adequately validated without clearance testing.

Discussion with Management:

Management stated that the firm conducts (b) (4). I explained (b) (4) Solely relying on the results of (b) (4) is not acceptable as it does not address (b) (4).

OBSERVATION 5

Time limits are not established when appropriate for the completion of each production phase to assure the quality of the drug product.

Specifically,

The firm has not established or validated a time frame, following dehydration, for storing remnant sheet graft tissue prior to micronization. Currently, remnant sheet graft tissue is stored (b) (4). The firm also failed to define a time limit in which stored remnant sheet graft tissue should be excluded from use in the micronization process.

Reference: 21 CFR 211.111

Supporting Evidence and Relevance:

SOP(b) (4) Micronized Amnion/Chorion Processing (**Exhibit 56**) and SOP(b) (4) Product Visual Inspection (**Exhibit 57**) do not address storage of remnant tissue that is utilized for micronization. The firm currently has no specifications established which define time windows that tissue can be stored and be considered acceptable for use; nor are time windows defined that would trigger rejection. According to management, tissue is currently stored (b) (4)

To date, no validation of the such has been conducted by the firm.

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Discussion with Management:

There were no questions or comments from management regarding this observation.

OBSERVATION 6

Written procedures are not established that describe (b) (4), tests and examinations to be conducted on appropriate samples of (b) (4).

Specifically,

The firm has failed to establish acceptance criteria for their micronized dHACM products including the performance of (b) (4). Currently, (b) (4) is performed on micronized dHACM products.

Reference: 21 CFR 211.110(a)

Supporting Evidence and Relevance:

The firm does not perform (b) (4), as such, there are no SOPs governing this observation.

Discussion with Management:

There were no questions or comments from management regarding this observation.

OBSERVATION 7

Drug product component testing is deficient in that at least one specific test to verify the identity of each component is not performed.

Specifically,

The firm failed to conduct (b) (4) of dHACM grafts prior to use in the manufacturing of micronized products.

Reference: 21 CFR 211.84(d)(1)

Supporting Evidence and Relevance:

The firm does not perform (b) (4) of dHACM grafts prior to micronization. Therefore, there are no SOPs or validations available that are related to this process.

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Discussion with Management:

There were no questions or comments from management regarding this observation.

OBSERVATION 8

Each batch of drug product required to be free of objectionable microorganisms is not tested through appropriate laboratory testing.

Specifically,

The firm does not perform (b) (4) on each batch of their micronized dHACM product prior to release and distribution.

Reference: 21 CFR 211.165(b)

Supporting Evidence and Relevance:

(b) (4) has not been validated and is not conducted on micronized injectable dHACM products prior to release. As such, there are no SOPs governing this process. (b) (4) (Exhibit 21), indicate that sterilization is performed post-processing.

Discussion with Management:

There were no questions or comments from management regarding this observation.

OBSERVATION 9

The accuracy of test methods have not been established .

Specifically,

The firm's endotoxin validation is inadequate in that the critical quality attribute selected for testing meets the specifications for an implantable device.

Reference: 21 CFR 211.165(e)

Supporting Evidence and Relevance:

Exhibit 22, page 5: the critical quality attribute listed for Endotoxin testing is (b) (4) " The firm manufactures Biological Drug products. As such, specifications for a device is not appropriate.

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Discussion with Management:

Management inquired why the specifications were not acceptable for the endotoxin validation. I clarified that their product is a biological drug and that basing the validation of their micronized products on that of a medical device are not appropriate for the product that they are attempting to validate.

OBSERVATION 10

The written stability program for drug products does not include reliable, meaningful and specific test methods.

Specifically,

The firm's Real Time Shelf Life Stability Assessment Protocol, (b) (4) is inadequate in that it does not utilize test methods that address critical attributes of micronized products including strength, quality, purity, identity, sterility, or level of degradation as it relates to product size.

Reference: 21 CFR 211.166(a)(3)

Supporting Evidence and Relevance:

(b) (4) Real Time Shelf Life Stability Assessment Protocol (**Exhibit 15**), assessed micronized injectable dHACM product's final packaging integrity by looking at the sterile barrier and physical characteristics. The sterile barrier integrity was assessed (b) (4)

(b) (4) It is unclear how assessment of the product's physical characteristics will determine sterility or stability (b) (4). Additionally, the protocol does not provide a definition of (b) (4)

Discussion with Management:

There were no questions or comments from management regarding this observation.

OBSERVATION 11

Drug products do not bear an expiration date determined by appropriate stability data to assure they meet applicable standards of identity, strength, quality and purity at the time of use.

Specifically,

1. The firm claims (b) (4) for its micronized dHACM products. However, the firm has only collected data for the (b) (4) through their Real Time Shelf Life Stability

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Assessment Protocol, (b) (4)

2. The firm failed to conduct the appropriate testing to establish an expiration date for their micronized dHACM products once they have been reconstituted.

Reference: 21 CFR 211.137(a)

Supporting Evidence and Relevance:

Exhibit 22, page 9: the firm has conducted its' stability studies in support of (b) (4) tissues, which the micronized injectable dHACM are not. Additionally, enough data has not been collected through Real Time Shelf Life Stability Assessment Protocol, (b) (4) (**Exhibit 15**).

The firm has not established an expiration date for their micronized injectable products once they (b) (4) in accordance with the instructions for use (**Exhibit 70**).

Discussion with Management:

Management inquired what was meant by "(b) (4)". I explained that their product is in a (b) (4). The mixing of those two materials is what is meant by (b) (4). The regulations require that an expiration date be provided for the product (b) (4).

OBSERVATION 12

Drug product production and control records, are not reviewed and approved by the quality control unit to determine compliance with all established, approved written procedures before a batch is released or distributed.

Specifically,

1. EpiFix Injectable products (b) (4) and (b) (4) manufactured from donor (b) (4) were released for distribution on (b) (4), shipped to (b) (4) on (b) (4) and implanted on/or before (b) (4). The final QA release was not performed by the QA department until (b) (4).
2. Donor processing records (b) (4) and (b) (4) were not submitted to QA for final review and release before grafts were shipped to (b) (4).
3. Tissue samples from Donors (b) (4) and (b) (4) were not submitted for (b) (4) and approved for release before being distributed to (b) (4).

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Reference: 21 CFR 211.192

Supporting Evidence and Relevance:

1. **Exhibit 27-28:** (b) (4) and processing records. Micronized products were not only distributed prior to QA final approval and release but also implanted. Failure to review all records and the final product before release pose a significant risk to the recipient.

2/3. **Exhibit 29-32:** (b) (4) and processing records. These micronized products were released before final QA approval, which poses a threat to potential recipients.

Discussion with Management:

There were no questions or comments from management regarding this observation.

OBSERVATION 13

Batch production and control records do not include dates of each significant step in the manufacture, processing and packing of the batch for each batch of drug product produced.

Specifically,

4. The processing technician that performed micronization of the dHACM grafts belonging to donor (b) (4) failed to document the (b) (4), the day the tissue was micronized or the technician performing the process.
5. Reagent usage information, including lot number and expiration dates of (b) (4) and (b) (4) were not documented during the Dehydration, Amnion, and Amnion and Chorion (b) (4).

Donor ID Number	Missing Reagent from Supply Usage Form	Date of Occurrence	Processing Step
(b) (4)			

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(b) (4)



Reference: 21 CFR 211.188(b)(1)

Supporting Evidence and Relevance:

1. **Exhibit 38:** (b) (4) and donor processing records are evidence of the firm's failure to document all steps in the manufacturing process, including the person performing the work and equipment used.

2. **Exhibit 39:** (b) (4) and donor processing records. Failure to document reagents used during processing prevents the firm from being able to properly conduct recalls or trace backs of effected products.

Discussion with Management:

There were no questions or comments from management regarding this observation.

GENERAL DISCUSSION WITH MANAGEMENT

A close out meeting was held with management on 2/04/16. The following individuals were present:

Parker H. Petit, Chairman and CEO
Bill Taylor, President and COO
Mark Rogers, VP of QA and RA/Tissue Bank Director
(b) (6), Quality Assurance Supervisor
Deborah Dean, Executive Vice President

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Rebecca Brown, PhD, Vice President, Product Development
(b) (6), General Counsel and Secretary

Prior to the issuance of the FDA 483, I provided an overview of the processes and records reviewed as well as explained the regulations that I focused on during this inspection which included:

- 21 CFR 1271, Current Good Tissue Practice Regulations (CGTP);
- 21 CFR 210 and 211, Current Good Manufacturing Practice Regulations (CGMP);

The FDA 483 was issued to Mr. Parker H. Petit, Chairman and CEO (**Attachment 2**). Prior to issuing the FDA 483, I informed Mr. Petit that I am not the final authority regarding the compliance status of MiMedx. The FDA 483, EIR and supporting documents will be reviewed by the Atlanta District and CBER Compliance Branches. I encouraged the firm to submit a written response to the observations listed on the FDA 483 and instructed them to address it to the Atlanta District Director at the address on the form. I advised Mr. Petit that if submitted within two weeks, the firm's response would be taken into consideration prior to the final classification of this inspection. Mr. Petit confirmed that they intended to respond in writing within two weeks from the date of our close-out meeting.

The FDA 483 was read aloud. If requested by the individuals present, regulatory cites and requirements related to the observation were given. Any significant discussion regarding the observation will appear under the item. After all questions were answered regarding the FDA 483 items, Mr. Petit excused all staff with the exception of his Senior Management, which included: Bill Taylor, Deborah Dean and (b) (6).

Discussion regarding regulatory actions available to the agency was also discussed. Mr. Petit inquired if the agency would exercise regulatory discretion and allow the firm to keep their micronized injectable products on the market while they work to bring the products into compliance. I advised Mr. Petit that the agency has multiple regulatory tools available that will be utilized if deemed necessary and that the agency cannot provide any assurance of enforcement discretion during this process. We discussed the fact that his product is a biological drug and as such must have an approved biological license in effect in order to be legally marketed and distributed.

Ms. Dean inquired to the likelihood of a conditional approval. I advised her that I could not speak on that matter.

(b) (6) asked me to explain the differences between an inspection that is classified as VAI versus OAI. I provided definitions of NAI, VAI and OAI classifications as well as gave a brief description of the review and recommendation process flow through the District Investigation Branch to District Compliance and on to the Center's Compliance. Lastly, (b) (6) inquired if the classification of an inspection can be downgraded. To which I replied that it is a possibility; and further explained that the final classification decision is made by the Center and District Compliance after careful review and consideration of all of the evidence presented by the Investigator. I reiterated the fact that the firm's timely response to the FDA 483 is helpful in that it gives them a

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chance to provide proposed corrections, justifications, etcetera that can be reviewed along with the complete EIR by Compliance and the Center prior to a decision being made.

Mr. Petit expressed concern regarding their product being pulled from the market as well as the effect of such actions on their stock values and shareholders. I again explained that I do not know what the final agency determination will be and cannot speak to rather or not their products will be pulled from the market. Mr. Petit then stated that other firms with similar products are not under the same level of scrutiny as his firm. To which I replied all firms that handle regulated product must register with FDA. I went on to explain that the time line by which we inspect those firms may not coincide with what he feels is appropriate. However, the agency's Investigators inspect all registered firms in accordance with the agency's established rules and regulations governing that process.

Ms. Dean inquired if the agency will tell them if their current time line for in-process testing validation is acceptable or if it needs to be changed. I replied that the agency will not establish a time line for validation of their products. As previously discussed, the micronized injectable product that is current going through IND has a different time line than that of the micronized products that are currently being manufactured and distributed. The expectation is that anything currently marketed will not only meet GMP standards, but will also have an approved Biologics license. Mr. Taylor then stated that they could be in compliance with GMPs but because their products are not licensed, it is still unacceptable. To which I replied yes because their micronized injectable products are biological drugs which require a valid biological license.

Lastly, Mr. Petit asked if they would hear from CBER directly. To which I responded that it is likely but that I did not know the time line for their response.

With no further questions from management, I thanked everyone for their time and cooperation and the inspection was concluded.

SAMPLES COLLECTED

Documentary sample 806629 (**Attachment 3**) was collected to detail the interstate movement of each of the firm's micronized injectable products as well as support good manufacturing practice deficiencies observed and cited. The referenced products are AmnioFix Injectable, EpiFix Micronized, AmnioFix Sports Med, AmniOvo Injectable and Ambio Choice Plus.

The sample, including the FDA 463a, photographs of packaging and labeling, donor recovery records, tissue processing records, MiMedx Packing List, and (b) (4) Proof of Delivery Letter was provided to John Mark Rogers, Vice President of Quality Assurance and Regulatory Affairs and Tissue Bank Director on 2/02/16. He reviewed all of the information in the FDA 463a, initialed and dated corrections and attested to the accuracy of all of the accompanying documents by signing the affidavit.

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ATTACHMENTS

- 1 FDA 482 issued 1/06/16, 3 pages
- 2 FDA 483, issued 2/04/16, 8 pages
- 3 Doc Sample CR 806629, 4 pages
- 4 Doc Sample 806629, 12 pages
- 5 Directed Inspection Assignment Request, 6 pages
- 6 MiMedx Directed Assignment Response Memo, 6 pages

EXHIBITS COLLECTED

- 1 Upper Management Position Descriptions, 23 pages
- 2 Organizational Charts, 21 pages
- 3 2016 Contracted Recovery Sites, 1 page
- 4 Recovery Statistics by Site, 1 page
- 5 Consignee List, 90 pages
- 6 Distribution by Micronized and Non-Micronized, 1 page
- 7 Distribution by State and Product Type, 28 pages
- 8 Manufacturing Process Flow Diagram, 4 pages
- 9 Micronization Process Validation, 116 pages
- 10 Donor Recovery Record (b) (4) Doc Sample, 70 pages
- 11 Donor Recovery Record (b) (4) Doc Sample, 76 pages
- 12 Donor Recovery Record (b) (4) Doc Sample, 65 pages
- 13 Donor Recovery Record (b) (4) Doc Sample, 81 pages
- 14 Donor Recovery Record (b) (4) Doc Sample, 67 pages
- 15 (b) (4) Real Time Shelf Life Stability Assessment Protocol, 10 pages
- 16 Real Time Shelf Life Stability Assessment Report, 12 pages
- 17 SOP(b) (4) HCT_P Release for Distribution, 6 pages
- 18 (b) (4) HCT_P Final Release for Distribution, 5 pages
- 19 (b) (4) , 4 pages
- 20 (b) (4) , 8 pages
- 21 (b) (4) 31 pages
- 22 Firm's Response to Micronization Validation Questions, 15 pages
- 23 SOP(b) (4) Endotoxin Testing, 3 pages
- 24 (b) (4) 3 pages
- 25 (b) (4) 4 pages
- 26 (b) (4) , 5 pages
- 27 (b) (4) , 7 pages
- 28 Tissue Processing Record (b) (4) 100 pages
- 29 DEV15-014, 12 pages
- 30 Tissue Processing Record (b) (4) 40 pages
- 31 Tissue Processing Record (b) (4) , 45 pages
- 32 Tissue Processing Record (b) (4) , 43 pages
- 33 Tissue Processing Record (b) (4) 33 pages

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34	Tissue Processing Record (b) (4)	, 49 pages
35	Tissue Processing Record (b) (4)	, 31 pages
36	Tissue Processing Record (b) (4)	, 31 pages
37	Tissue Processing Record (b) (4)	, 31 pages
38	(b) (4)	41 pages
39	(b) (4)	, 93 pages
40	Tissue Processing Record (b) (4)	, 51 pages
41	Tissue Processing Record (b) (4)	, 38 pages
42	Tissue Processing Record (b) (4)	32 pages
43	Tissue Processing Record (b) (4)	, 40 pages
44	Tissue Processing Record (b) (4)	, 40 pages
45	Tissue Processing Record (b) (4)	, 34 pages
46	Tissue Processing Record (b) (4)	38 pages
47	Tissue Processing Record (b) (4)	, 46 pages
48	Tissue Processing Record (b) (4)	, 40 pages
49	Firm's Response to Sterilization Validation Questions,	6 pages
50	(b) (4) Protocol for Simulated Distribution of Tissue Product Packaging,	9 pages
51	2006 Aging Study Summary Report,	5 pages
52	(b) (4)	, 12 pages
53	SOP(b) (4) 3 Amnion Chorion Processing,	26 pages
54	SOP(b) (4) Dehydration of Amnion Based Products,	7 pages
55	SOP(b) (4) Cutting Amnion Based Grafts,	8 pages
56	SOP(b) (4) Micronized Amnion Chorion Processing,	17 pages
57	SOP(b) (4) Product Visual Inspection,	8 pages
58	SOP(b) (4) Amnion Based Graft Packaging and Labeling,	5 pages
59	FDA Audit Summary Response - Upcoming Testing,	10 pages
60	Migration Assay Qualification Report,	40 pages
61	(b) (4)	102 pages
62	(b) (4)	, 12 pages
63	(b) (4)	, 16 pages
64	(b) (4)	, 10 pages
65	(b) (4)	, 27 pages
66	(b) (4)	, 37 pages
67	Route Administration for Rodent Injection - Upcoming Testing,	15 pages
68	(b) (4) Particle Size Analysis Test Method Validation,	11 pages
69	Particle Size Analysis Method Validation Protocol,	45 pages
70	Product Labeling Photocopies Taken by CSO,	21 pages
71	Photographs of Final Product Taken by CSO,	29 pages
72	Processing Photographs Taken by Firm,	4 pages
73	SOP(b) (4) Identification and Traceability,	6 pages

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X Kimberly C Delk-Brooks

Kimberly C Delk-Brooks

Investigator

Signed by: Kimberly C. Delk-brooks -S