To: US FDA Detroit District Office (DET-DO)
ATTN: Detroit District Director, DET-DO
Mr. Meng, Investigator, DET-DO
300 River Place, Suite 5900
Detroit, MI 48207

Re: Posting of FDA Form 483 Response

FEI: 3004575469, Health Dimensions, Inc.
EI: 07/31/2014 – 08/08/2014

Dear Sir,

Please accept this letter as authorization to post on the US FDA Internet website Health Dimensions, Inc.'s response to the FDA Form 483 Notice of Observations, dated 08/27/2014, as submitted to DET-DO, unredacted but without attachments. We understand this response will be posted under the FDA Form 483 Notice of Observations for Health Dimensions, Inc., issued on 08/08/2014 by Investigator Meng (DET-DO).

Thank you,

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Observation 1

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

A) Adequate aseptic process simulations (media fills) have not been performed under representative worst case aseptic processing conditions to assure the sterility of drug products. To date, media fills conducted for operators consist of drawing 25mL of non-sterile media into three 30mL syringes, transferring 5 mL from each syringe into three 10 mL vials as a control, aseptically attaching a 0.2um sterile filter and 20-gauge needle to each syringe, and injecting 10 mL of sterile filtered media from each syringe into two stoppered 10 mL vials for a total of six vials of sterile filtered media which are then incubated. Examples of aseptic processing operations at your firm that are not reflected in media fills include the following:

i. During production of Methylcobalamin injectable in 5mL vials lot 06242014+383669, the product is sterile filtered into open, unstoppered vials which are then manually stoppered.

ii. Production of impotence injections lot 07312014+387256 was observed to include the use of vent needles and filter sterilized process nitrogen gas after sterile filtration and filling the pre-stoppered vials via needle and syringe.

Observation 1.A. Response:

Health Dimensions will review and revise the media fill program accordingly to include, but not be necessarily limited to the following elements:

i. Transfer of preparation into "open" containers that are manually manipulated.
ii. Allocation of sterile preparation using different types of transfer methods.
iii. Consideration of the worst case conditions for exposure of sterile preparations to the aseptic environment.
iv. Various manipulations that are made during preparation of sterile compounded preparations.
v. Media fill SOP to be written/revised to include one media fill per process every 6 months.

Target Dates for Completion: Revise media fill SOP within 45 days; and complete media fill program within 6 months of revising the SOP.

Observation 1

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

B) The environmental monitoring (EM) program is inadequate in that:

i. Active viable EM is not performed during every drug production shift in the critical areas. Only one active viable air sample is routinely collected each week from each ISO 5 workbench.

ii. Non-viable particulate (NVP) EM is not performed during every drug production shift in the critical areas. Only one NVP sample is routinely collected each week from each ISO 5 workbench.

iii. Viable surface monitoring is not performed during each drug production shift in the critical areas. Only one surface sample is routinely collected each week from each ISO 5 workbench. However, sterile drug production activities routinely occur Mon-Fri approximately 7:00am-4:30pm.

Observation 1.B. Response:

The Routine Environmental Monitoring SOP will be modified and followed to include:

i. Active air sampling for viables and non-viables will take place, at a minimum, once per shift inside the ISO 5 workbench.

ii. Surface monitoring will take place at the end of one sterile compounding operation daily in the ISO 5 workbench at several locations determined to be the most susceptible to potential contamination.

iii. Alert and Action Levels will be defined; as well as steps that will be taken if an Alert or Action Level is reached.

iv. These requirements will be outlined in an SOP and all results will be trended to determine if more frequent monitoring is required.

Target Date for Completion: Revise Environmental Monitoring SOP within 45 days.

Observation 1

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

C. The materials sanitization and transfer procedures are inadequate in that no sanitation step occurs when materials are transferred from the ISO 7 buffer room environment to the ISO 5 workbenches. Prior to transfer into the ISO 7 buffer room, a sanitization of material surfaces is performed with a 2% bleach solution in the ISO 8 preparation room. Materials stored in the ISO 7 buffer room and waiting use are not additionally protected from the ISO 7 environment prior to transfer into the ISO 5 workbenches. A review of video of the recent smoke study of the ISO 7 buffer room revealed that air from the room HEPA filters does not uniformly sweep over materials and appears to eddy near areas where materials are temporarily stored.

Observation 1.C. Response:

Health Dimensions recognizes that materials have not been sanitized immediately prior to moving them from the ISO 7 area to the ISO 5 workbench. Procedure(s) will be written/revised to include specific instructions on how to sanitize materials that are stored in the ISO 7 area prior to transferring those materials into the ISO 5 workbench.

Target Date for Completion: Write/revise SOP(s) and implement within 30 days.

Observation 1

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

D. The gowning at your facility is inadequate in that the sterile garb worn by operators does not cover all exposed areas. Observation of operators working at the ISO 5 workbenches revealed that the gowning hood and mask do not provide adequate facial coverage allowing exposure of the skin around the eyes and forehead. Additionally, during two instances of personnel fingertip monitoring observed on 7/31/14, after contacting the media touch plates in the ISO 5 workbenches, operators removed and replaced their gloves within the workbench exposing the skin of their hands to the ISO 5 environment.

Observation 1.D. Response:

Gowning procedures will be modified and personnel will be monitored to ensure full gowning is appropriate when in ISO 5 environments. In addition, aseptic technique training will be performed and documented.

Specifically, Health Dimensions will adopt the following:

i. Use of full coverage goggles to eliminate skin exposure around the eyes and forehead.
ii. Double gloving will be implemented immediately to eliminate exposing the skin of hands to the ISO 5 environment.
iii. Training and observation of new procedures with personnel will be performed and documented.
iv. Aseptic technique review training and observation of personnel will be performed and documented on a quarterly basis.

Target Date for Completion: The appropriate SOP(s) will be written/revised and fully implemented within 30 days.

Observation 1

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

E. Viable surface EM and personnel fingertip monitoring is performed using TSA plates that do not contain disinfectant neutralizers. For example, TSA plate lot 1003233420.

Observation 1.E. Response:

TSA used for personnel monitoring and surface sampling will include neutralizers. Please see Exhibit 2 for evidence of compliance. Exhibit 2 includes a copy of Health Dimensions' invoice for the original purchase of the TSA containing neutralizers, as well as the Certificate of Analysis.

Target Date for completion: Completed.

Observation 1

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

F. Aseptic practices and techniques observed at your facility are inadequate that during processing of intrathecal product lot 07312014+387283, the operator was observed to rest their hand on the ISO 5 work surface followed by the performance of aseptic manipulations without sanitation of their hands.

Observation 1.F. Response:
Please see "D" above for additional aseptic technique training that will take place.

Observation 2
Time limits are not established when appropriate for the completion of each production phase to assure the quality of the drug product.

Specifically, maximum sterile hold times for preservative free stock formulation is not validated. For example, sterile, preservative free bupivacaine lot 05292014+381063 was produced on 5/29/14 in 10mL syringes with a BUD of 9/26/14. This lot was used, in part, to formulate intrathecal preparation lot 07312014+387283 which was then sterile filtered from a syringe into an open, unstoppered 50mL vial which was then manually stoppered, capped, crimped, and autoclaved.

Observation 2 Response:
Sterile hold times have been established. Please see attached Exhibit 4.

Target Date for Completion: Completed.

Observation 3
Aseptic processing areas are deficient regarding the system for monitoring environmental conditions.

Specifically, continuous differential pressure monitoring of the aseptic process suite is not performed. Differential pressure monitoring of the ISO 7 buffer room, ISO 7 ante room, and ISO 8 preparation room is only logged once per day.

Observation 3 Response:
Per section titled "Environmental Quality and Control", "Pressure Differential Monitoring" in the current USP <797>,

"A pressure gauge or velocity meter shall be installed to monitor the pressure differential or airflow between the buffer area and the ante-area and between the ante-area and the general environment outside the compounding area. The results shall be reviewed and documented on a log at least every work shift (minimum frequency shall be at least daily) or by a continuous

recording device. The pressure between the ISO Class 7 (see Table 1) and the general pharmacy area shall not be less than 5 Pa (0.02 inch water column). In facilities where low- and medium-risk level CSPs are prepared, differential airflow shall maintain a minimum velocity of 0.2 meters per second (40 feet per minute) between buffer area and ante-area ".

Data to support that we meet these USP <797> requirements have been collected, and a summary of the data for the past 7 months is provided as evidence of compliance with the <797> requirements (please see Exhibit 3). If we do not meet the daily requirements, corrective actions are taken. However, we recognize that specific corrective actions to be taken are not outlined in the current SOP and may include more extensive monitoring.

Corrective actions to be taken will be implemented and reflected in Health Dimensions' SOP 3.030 Environmental Monitoring of the Clean Room Facility.

Target Date for Completion: Revise SOP and implement within 30 days.

Observation 4

Laboratory controls do not include the establishment of scientifically sound and appropriate test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality, and purity.

Specifically, example of lots of sterile products produced that are not tested for potency, sterility and endotoxins.

i. Impotence injection lot 07312014+387256 in 1 mL vials with a lot size of 10 vials.
ii. Intrathecal (hydromorphone, bupivacaine, and clonidine) preservative free injection lot 07312014+387283 in a 50 mL vial with a BUD of 8/22/14. This intrathecal formula has a general BUD of 60 days after the compounding date if none of the BUDs of the stock components is earlier.

Observation 4 Response:

i. The Impotence Injection lot 07312014+387256, 1 mL x 10 vials, frozen, is dispensed per patient specific prescriptions and, we believe, meets the standards outlined in USP <797>.

The preparation of this lot meets the High-Risk Level CSP requirements as outlined in USP <797>, which states, "For a sterilized high-risk level preparation, in the absence of a passing sterility test, the storage periods cannot exceed the following time periods: before administration, the CSPs are properly stored and are exposed for not more than 24 hours at controlled room temperature (see General Notices and Requirements), for not more than 3 days at a cold temperature (see General Notices and Requirements), and for 45 days in solid frozen state between - 25° and -10°. [Note-Sterility tests for

autoclaved CSPs are not required unless they are prepared in batches of more than 25 units.]"

Lastly, the prescription is labeled with instructions to keep frozen and the patient is verbally consulted to this effect as well.

ii. Formulation lot 07312014+387283 is a single patient prescription order containing hydromorphone, bupivacaine, and clonidine in a 50 mL vial with a BUD of 8/22/14. This formula is terminally sterilized. The general BUD given of 60 days is established given these factors:

1. The preparation will crystallize when exposed to below room temperature, therefore must be stored at room temperature. The preparation is labeled with storage instruction to ensure compliance.
2. The vial container and closure integrity for the specified time period has been established based on data from a similar formulation that has undergone full testing for sterility. Exhibit 5 contains the data for this preparation (Edetate Calcium Disodium 300mg/mL injectable).

Target Date for Completion: The verification of the process for intrathecal closure system and BUD within 6 months.

Observation 5

Complaint procedures are deficient in that written complaint records are not maintained in a file designated for drug product complaints.

Specifically, there is no system to easily permit a systematic review of product quality complaints. Clear adverse events are captured within the CADER (compounding adverse drug event reporting) system. However, the majority of patient inquiries and communications regarding product quality are noted within each patient's individual electronic profile along with other miscellaneous information.

Observation 5 Response:

Health Dimensions recognizes that we require a more thorough and systematic manner of tracking preparation quality complaints.

i. SOP review/written to include specific instructions on addressing and filing of complaints so that they are easily retrievable for tracking and trending purposes.

Target Date for Completion: Revise SOP and implementation target within 30 days.