



DEPARTMENT OF HEALTH & HUMAN SERVICES

HFI-35 (Purged)

Public Health Service

94960d

AUG 12 2004

Food and Drug Administration  
Center for Devices and  
Radiological Health  
2098 Gaither Road  
Rockville, MD 20850

WARNING LETTER

VIA CERTIFIED MAIL  
RETURN RECEIPT REQUESTED

Mr. Perry S. Melton  
Vice President of Operations  
Westmed de Mexico, S.A.  
Blvd. Encino #100, Praque Industrial  
Tecate, B.C.  
Mexico C.P. 21400

Dear Mr. Melton:

An investigator from the Food and Drug Administration (FDA) conducted an inspection of your firm located in Tecate, B.C., Mexico C.P., from March 8-11, 2004. Your firm manufactures various model Arterial Blood Gas Sampling Kits which are intended to obtain arterial blood samples from a patient for blood gas determinations. Under Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act), these products are medical devices because they are intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body.

Our inspection disclosed that your various model Arterial Blood Gas Sampling Kits are adulterated within the meaning of Section 501(a)(2)(A) of the Act, in that they have been prepared, packed, or held under insanitary conditions whereby they may have been contaminated with filth.

Our inspection also disclosed that your various model Arterial Blood Gas Sampling Kits are adulterated within the meaning of Section 501(h) of the Act, in that the methods used in, or the facilities or controls used for manufacturing, packing, storage, or installation do not conform with the Good Manufacturing Practice (GMP) requirements set forth in the Quality System Regulation, Title 21, Code of Federal Regulations (CFR), Part 820.

Your firm was issued a FDA 483 Notice of Inspectional Observations at the close of the above referenced inspection. Mr. Lynn Hayse, Vice President of Regulatory Affairs and Quality Assurance at your firm responded to this notice by letter to the FDA dated March 22, 2004.

The following are violations of the Quality System regulation observed during the inspection, and we are providing our assessment of the adequacy of each of Mr. Hayse's associated responses:

1. Failure to establish and maintain procedures to control environmental conditions that could reasonably be expected to have an adverse effect on product quality, including periodically inspecting environmental control systems to verify that the system, including the necessary equipment, is adequate and functioning properly, as required by 21 CFR 820.70(c). For example:
  - a. Appropriate specifications have not been established for controlling environmental conditions in the unclassified cleanroom. Specifically, there are no specifications for humidity, temperature, HEPA filter air flow, and airborne particle count and size.
  - b. The Air Handling System for the cleanroom, including both Air Handling (Intake) Filters' and HEPA Filters' performances, has not been qualified.
  - c. There are no written procedures for, and there is no evidence of, Air Handling System maintenance, including Air Handling (Intake) Filter and HEPA Filter maintenance.
  - d. The <            >Temperature Monitor, the <        > Digital Humidity Monitor, and/or the <        >Chart Recorder for temperature and humidity were not calibrated since the temperature and humidity readings between them did not reasonably match.
  - e. In the clean room, 1 live beetle-like winged insect was observed near the window on the East wall, and more than 20 dead beetle-like winged insects were observed inside 8 fluorescent light covers directly above the manufacturing area.
  - f. Ten fluorescent light covers' exterior surfaces had a blackish moldy substance growing on them above the manufacturing area.
  - g. The air supply duct is not maintained as holes were observed in the supply (outside air) downstream from the primary particulate [air handling intake] filters.

Mr. Hayse's March 22, 2004, response is not adequate.

- Reference Item 1.a.

Specifications now put forth for temperature, relative humidity, and airborne particle count and size, and considerations for future HEPA Filter air flow, all derived from the initial qualification of the Arterial Blood Gas (ABG) Control Room (cleanroom) are not appropriate because this qualification was not adequate for numerous reasons:

- The Bio-burden Test on Surfaces and Air was not adequate. The study did not include testing for total yeast and molds (TYM) using, for example, Sabraoud Dextrose Agar. The testing for airborne bacteria contamination of air using < > was not adequate because these < > would have only captured heavier, and not lighter, microbe containing particles. A Slit Sampler or equivalent should have been used to collect the particles because it does not discriminate between lighter and heavier particles. The < > used for surface bacterial contamination were not adequate because they did not contain Lecithin and Polysorbate 80 to counter surface cleaning agent residues; hence, microbial counts would not be accurate as possibly false low counts would be obtained. No justification was provided for using < > < > for surface testing. The < > "facility validation protocol" used to identify sample points was not provided for evaluation. The use of RODAC plates would be a better choice.

With respect to page 6, Table 1a. and Table 2b., inadequate information and evidence was provided. Further acceptance criteria was not established in the test protocol(s).

- The Air Particle Count and Size Distribution Test was not adequate because the particles counted were limited to < > microns or lower in size. Bacteria can be attached to larger particles, so all particle sizes should have been counted.
- The Average Air Velocity at HEPA Filters and Hampers Test was not adequate. The testing appears to have been conducted arbitrarily based on the conditions of the HEPA Filters at the time of testing, which conditions were not recorded. It was apparently not recognized that the air velocity will degrade over time as the HEPA Filters collect particulates, such that a lower limit of air velocity that would no longer support the desired cleanliness of the room should have first been identified, such that testing would not be conducted near, at, or below this limit. The percentage of relative humidity was only tested at one unidentified location in the room, which is not adequate because the lack of a central humidification system and the use instead of < > portable humidifiers does not ensure even distribution of humidity.

- As recognized in Mr. Hayse's response, the qualification did not include seasonal impact. The tests were conducted in the < > during which time the outside air would present less of a challenge of particulate matter (e.g., pollen) to the Air Handling and HEPA Filters. Mold problems would also be less compared to the summer when the humidity would be higher.

Even if the qualification had been adequate, some specifications identified for temperature and percentage of relative humidity in the "ABG Packaging Control Room Specifications and Testing" fall well outside those used during the qualification. The selected temperature specification is a high of < >°, yet the temperature range during the qualification was < >. The selected percentage of relative humidity specification is a low of < >%, yet the percentage of relative humidity range during the qualification was < >%.

No justification was identified in the "ABG Packaging Control Room Specifications and Testing" for the acceptable high level of less than < > [airborne] particles of < > microns and for the ideal level of less than < > particles of < > microns – both inside the unclassified cleanroom, and for the acceptable high level of less than < > particles of < > micron at each HEPA Filter face. Under Federal Standard 209E, the lowest quality "cleanroom" is Class 100,000 that allows no more than 100,000 airborne particles of .5 microns or higher per cubic foot. Since your specifications do not prohibit particles higher than < > microns (assume per cubic foot), your specifications would allow particle counts of more than 100,000 and < > particles of .5 microns or higher. So your firm can not consider this area to be a cleanroom, unclassified or otherwise, because it would not meet any class cleanroom standard. Your specification does not identify the volume of air the count is taken from.

As recognized in Mr. Hayse's submission, Air Flow Velocity has not yet been determined.

Note: The qualification of the ABG Control Room needs to be repeated for the reasons specified above because the bacterial samples collected would not be an accurate representation of the bacterial bio-burden in this cleanroom, and yeast and mold bio-burden were not collected.

- Reference item 1.b.

The information provided on the qualification of the ABG Control Room does not adequately qualify the performance of the HEPA Filter. Only particles < > microns down to < > microns were measured and counted. All particle sizes need to be measured and counted. No comparison was made of the HEPA Filter manufacturer's specification. To do an adequate

validation of a HEPA Filter, a dioctyl phthalate (DOP) Integrity Test must be done.

While Mr. Hayse states that your firm has scheduled an additional test of the HEPA Filter by an outside service specializing in this technology, as outlined under its Exhibit D, the Purchase Request Form only identifies a "HEPA filter efficiency study," not specifically a DOP Integrity Test. Two of the four pages under the exhibit are in Spanish and could not be fully evaluated. Your firm should ensure that associated bio-burden studies to be done do not have the same problems identified above under Reference 1.a., first small square bulleted item.

Your firm needs to further address the above deviation regarding the Air Handling System, including the Air Handling (Intake) Filters' performance not being adequately qualified, which was not listed on the FDA 483. Mr. Hayse's statement that your firm's engineers and outside service personnel totally reevaluated the effectiveness of the Air Handling System and found it to be more than adequate is not satisfactory. This includes a determination as to whether the new Air Intake Filters (which are separate from the HEPA Filters) your firm is now using meet their specifications.

It is recognized that Mr. Hayse has stated that bio-burden, particulate count, HEPA Filter performance, and room air change testing will be conducted once identified room improvements are complete.

- Reference item 1.c.

For the proposed written procedures for HEPA Filter and Air Handling Filters Preventative Maintenance, under section 4.5.2, there is no justification for the referenced option to replace the HEPA Filter at the end of a < > year period per manufacturer's specification, which is one of considerations on when to change the filters. The procedures do not yet specify under section 4.4.1 the specific air velocity that is to be verified at the face of each HEPA Filter referenced under "ABG Packaging Control Room Specifications and Testing" (TMXXX). The procedures reference under section 4.4.2 verifying a particle count in TMXXX, which as specified above under Reference 1.a. is not justified. The procedures under section 4.5.2 identify that one criteria to replace the Air Handling Filters is when air flow velocities reach less than the specifications called out in TMXXX, which is a HEPA Filter face velocity. So there may be a problem with the HEPA Filter, such that the Air Handling Filter does not need to be replaced.

While Mr. Hayse stated that on March 12, 2004, your engineers and outside service personnel totally re-evaluated the effectiveness of the < > HEPA Filters, and found the system to be more than adequate, no information was provided on whether any maintenance was a performed.

Your firm needs to address the above deviation regarding no written procedures for Air Handling System maintenance (i.e., areas other than Air Handling and HEPA Filter maintenance), which was not listed on the FDA 483.

- Reference item 1.d.

Your firm needs to address item 1.d. above which was not listed on the FDA 483.

- Reference item 1.e.

While Mr. Hayse identified facility improvements your firm has taken to further limit "contaminant access," there is no evidence that your firm conducted an investigation to determine how the flying insects got into the cleanroom, so your firm could take measures to specifically address this problem.

Your firm's purchase of an "air insecticide" to be placed in the gowning room area of the cleanroom to further deter airborne insects is not appropriate. As noted on this product distributor's website, this type of insecticide that flying insects should not be used in food handling areas because of the possibility of pieces of dead insects contaminating food and food handling equipment. Likewise, it should not be used in a gowning area because of the possibility of gown, shoe cover, etc., contamination and resultant device contamination.

- Reference item 1.f.

It is the investigator's position the blackish substance on the outside of the fluorescent lights is mold, based on its growth pattern and surface texture, and not residual latex paint as reported by Mr. Hayse in his March 22, 2004, response. Your firm needs to determine what is causing the mold and needs to take appropriate measures to prevent it from recurring.

- Reference item 1.g.

While your firm has sealed the gaps in the outside ducts with silicone, and has procedures for preventative maintenance of Air Handling and HEPA Filters, including inspecting areas immediate to these filters, there is no assurance that your firm will maintain the ductwork or other areas of the Air Handling System, e.g., the forced air fan. This is because your firm does not have written procedures for Air Handling System maintenance, as identified above under "Reference item 1.c."

2. Failure to establish and maintain procedures for the identification, documentation, validation or where appropriate verification, and review of design changes before their implementation, as required by 21 CFR 820.30(i). For example:
  - a. Primary sterile packaging was changed from a metal foil to a paper package in December 2003. There is no documentation evaluating how the change impacted the sterilization process or the integrity of the packaging, to determine if revalidation was necessary.
  - b. There is no documentation of the design change.

Mr. Hayse's March 22, 2004, response is not adequate.

- Reference Item 2.a.

Your firm can not use the fact that other manufacturers use the same material that it uses to support that sterility revalidation is not necessary, for the same reasons it can not use the < > packing revalidation discussed below.

The referenced current bank of tests being conducted by < > for Westmed's < > sterility dose audit for 2004 would need to test for the sterility of the heparin also.

Your firm needs to address the above deviation regarding the integrity of the packaging which was not listed on the FDA 483.

- Reference Item 2.b.

Your firm needs to address item 2.b. above which was not listed on the FDA 483.

3. Failure to establish and maintain procedures for validating the device design to ensure that devices conform to defined user needs and intended uses, as required by 21 CFR 820.30(g). For example:
  - a. There is no evidence of stability testing to demonstrate that the Arterial Blood Gas Sampling Kits meet the 2 year expiration date for sterility (device and Heparin drug).
  - b. There is no evidence to demonstrate product functionality within the 2 year expiration at the maximum sterility dose (device and Heparin drug).

Mr. Hayse's March 22, 2004, response is not adequate.

- Reference Items 3a. and b.

Your firm can not rely on the < > packaging revalidation showing that a sterility barrier of 2 years was maintained. These products were manufactured in a different facility (different bioburden), using different equipment, different procedures, a different component supplier, probably a different raw material supplier, and probably a different contract sterilizer. So the < > products are not representative of Westmed products, and, therefore, any tests on those products would not apply to Westmed products.

The referenced current "Preliminary Study" is not adequate for several reasons. It uses retained samples from production runs manufactured by (< >) and by an unnamed manufacturer (< >), which would be < >. These products can not be used to represent Westmed products for the reasons specified above. Retained samples when Westmed started production in < > should have been used with accelerated testing. Also, the Preliminary Study did not include sterility testing for the device or the heparin drug, nor did it include potency testing for the Heparin.

The referenced ongoing "Full Study" is not adequate because it does not include sterility testing for the device or for the heparin drug.

Finally, no specific information was provided on the referenced additional testing being conducted by reputable external laboratories.

4. Failure to establish and maintain procedures to validate a process with a high degree of assurance and approve it, where the results of a process cannot be fully verified by subsequent inspection and test, as required by 21 CFR 820.75(a). For example, the sterilization process validation is inadequate because there is no evidence documenting that the 3cc syringe with needle and luer cap, product 3302, represented the greatest challenge to the < > sterilization process identified as < > Protocol for Validating < > Sterilization, dated January 16, 2003.

Mr. Hayse's March 22, 2004, response is not adequate

Your firm selected the product with the < > and < > as being the greatest challenge to the < > sterilization process. Mr. Hayse did not provide a scientific justification for this method, or indicate that this is a method recognized by the scientific community or by any scientific body or organization. It is not clear if your firm looked at all known products or < >. For example, the product brochure collected by the

investigator lists 36 product kit configurations, but your firm's Exhibit L, Appendix A, lists only 18 kit descriptions. The product brochure lists a 5cc syringe device, but only 1cc and 3 cc syringes are listed by your firm. The product brochure lists a "Grasshopper Needle Protection" option, but your firm's Appendix B list of all components does not list this as a component.

5. Failure to monitor production processes to ensure that a device conforms to its specifications, as required by 21 CFR 820.70(a). For example, required  
< > dose verification audits were not conducted for the < >  
< > accordance with < > protocol For Validating < >  
< > Sterilization and < >

Mr. Hayse's March 22, 2004, response is not adequate.

The fact that early qualification studies were conducted in late 2002, and the Multivac, room, and process validations were not completed until early March 2003, does not justify Mr. Hayse's position that there was no need for a < > sterility dose audit.

Mr. Hayse did not submit the results of the referenced 3rd quarter sterility dose audit.

6. Failure to establish procedures for quality audits and to conduct such audits to assure that the quality system is in compliance with the established quality system requirements and to determine the effectiveness of the quality system, as required by 21 CFR 820.22. For example:
  - a. Internal Audits were not conducted in 2003 in accordance with SOP 118, Compliance Verification, Section 4.2, "Scheduled QMS Compliance Verification (Internal Audit)."
  - b. Internal Audits were not conducted in 2003 in accordance with Section 4.3, "GMP Check list Evaluation/Quality Walk (Internal Audit)."

Mr. Hayse's March 22, 2004, response is not adequate.

He provided inconsistent information in that he stated during the inspection that no Quality Audits were conducted at the Tecate facility [in 2003], yet in his response, he stated that < > during calendar year 2003 the plant was personally audited by Miguel Menza (Tecate Quality Manager) and himself. His response does not state which audit requirement was met by Mr. Menza and himself. Formal System Audits (i.e., tier 2 documentation) for the Tecate, Mexico facility conducted at the Westmed Tucson, Arizona facility would not comply with the 21 CFR 820.22 audit requirements. Any audit of the Tecate facility must be conducted at the Tecate facility to confirm,

for example, that documentation procedures are being followed. No evidence was provided of the referenced audit that was conducted at Tucson.

7. Failure to establish and maintain procedures for management with executive responsibility to review the suitability and effectiveness of the quality system at defined intervals and with sufficient frequency to ensure that the quality system satisfies the requirements of 21 CFR Part 820, as required by 21 CFR 820.20(c). For example, the < . . . > 2003 Management Review was not conducted in accordance with the Quality Manual, QMS-100, Section 4.1.3.

Mr. Hayse's March 22, 2004, response is not adequate.

The Second Quarter Quality Review is not dated. He provided inconsistent information in that he stated during the inspection that no management reviews were conducted in 2003, yet he stated in his response that all reviews since April 2003 have been on schedule.

This letter is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence to each applicable requirement of the Act and FDA's regulations. The specific violations noted in this letter and in the Form FDA 483 issued at the conclusion of the inspection may be symptomatic of serious underlying problems in your firm's manufacturing and quality assurance system. You are responsible for investigating and determining the causes of the violations identified by the FDA. If the causes are determined to be systems problems, you must promptly initiate permanent corrective actions.

Given the serious nature of these violations of the Act, all sterile Arterial Blood Gas Sampling Kits, a Clear Bacterial/Viral Filter, sold separately as Product Number 6216, and all products that include this filter as a component, i.e., certain separately manufactured Anesthesia Circuits, Conventional Respiratory Circuits, Neonatal Nebulizer Adapters, and Heated Wick Circuits, manufactured by your firm that are imported or offered for import are subject to refusal of admission under section 801(a) of the Act, 21 U.S.C. § 381(a), in that they appear to be adulterated. As a result, FDA may take steps to refuse these products, known as "detained without physical examination," until these violations are corrected.

In order to remove the devices from this detention, it will be necessary for you to provide a written response to the charges in this Warning Letter for our review. After we notify you that your response is adequate, we will request an establishment re-inspection. As soon as the re-inspection has taken place, the implementation of your corrections has been verified, and you are notified that your corrections are adequate, your devices may resume entry into this country. In addition, U.S. federal agencies are advised of the issuance of all Warning Letters about devices so that they may take this information into account when considering the award of government contracts.

Please notify this office in writing within fifteen (15) working days from the date you receive this letter, of the specific steps you have taken to correct the noted violations, including an explanation of how you plan to prevent these violations, or similar violations, from occurring again. Include all documentation of the corrective action you have taken. If you plan to make any corrections in the future, include those plans with your response to this letter as well. If the documentation is not in English, please provide an English translation to facilitate our review.

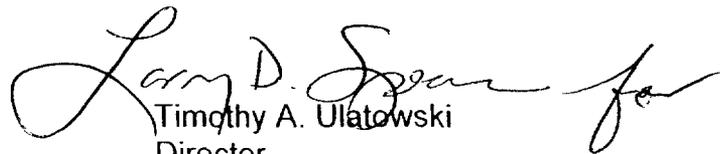
Please direct your response to:

William C. MacFarland, Chief  
Orthopedic, Physical Medicine and Anesthesiology Devices  
Division of Enforcement B, Office of Compliance  
Center for Devices and Radiological Health  
Food and Drug Administration  
2098 Gaither Road, HFZ-343  
Rockville, MD 20850

Finally, you should understand that there are many FDA requirements pertaining to the manufacture and marketing of medical devices. This letter pertains only to issues that relate to the Quality System Regulation and the manufacture of devices under insanitary conditions, and does not necessarily address other obligations you have under the Act. You may obtain general information about all of FDA's requirements for manufacturers of medical devices by contacting our Division of Small Manufacturers, International and Consumer Assistance at (800) 638-2041 or through the Internet at <http://www.fda.gov>.

If you have more specific questions about how FDA marketing and other requirements affect your particular device, or about the content of this letter, please feel free to contact William F. Defibaugh at (301)-594-4660 ext. 121.

Sincerely yours,



Timothy A. Ulatowski  
Director  
Office of Compliance  
Center for Devices and  
Radiological Health