



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

WARNING LETTER

VIA FACSIMILE
VIA FEDERAL EXPRESS

D. Keith Grossman
President and Chief Executive Officer
Thoratec Laboratories Corporation
6035 Stone Ridge Drive
Pleasanton, California 94588

Dear Mr. Grossman:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has reviewed some of Thoratec Laboratories Corporation's (Thoratec's) promotional material for two of the company's products, the company's ventricular assist device (VAD) and its TLC-II™ device. The products are devices within the meaning of section 201(h) of the Federal Food, Drug and Cosmetic Act (the Act).

We have been advised that during the American Association for Thoracic Surgery Conference held in New Orleans from April 18-21, 1999, Thoratec ran a video on closed circuit television at the Hilton Riverside Hotel and possibly at some of the other hotels where people attending the conference were staying. The video contains numerous claims that the agency considers objectionable.

In the video, Thoratec made numerous comparative claims regarding its VAD and the ABIOMED, Inc. BVS-5000®. The claims are misleading. In addition, there are claims for use of the Thoratec VAD for viral myocarditis, which is not an approved use for the device. The video also promotes Thoratec's TLC-II™, which is currently under an approved investigational device exemption (IDE) and its promotion is in violation of the agency's regulations regarding the promotion of investigational devices.

The ABIOMED device is approved for "appropriate patient groups . . . likely to recover cardiac function after the myocardium is permitted to rest on circulatory support. Such patients include those who fail to wean from cardiopulmonary bypass following heart surgery, failed transplant patients who require ventricular assist following heart transplantation, patients who require right ventricular assist devices while on implantable left ventricular assist devices, patients suffering from acute cardiac disorders such as viral myocarditis."

The intended use for Thoratec's device is as follows:

“The Thoratec Ventricular Assist Device is indicated for:
Bridge to transplant patients who meet all of the following criteria:

1. Candidate for cardiac transplantation.
2. Imminent risk of dying before donor heart procurement.
3. Dependence on, or incomplete response to, continued vasopressor support.

Postcardiotomy recovery patients who are unable to be weaned from cardiopulmonary bypass.”

The video compares Thoratec’s VAD with ABIOMED’s BVS-5000 for use as an intermediate to long-term bridge to transplant. The comparison is misleading for several reasons. Bridge-to-transplant is not a use for which the ABIOMED device has been approved. Your comparisons imply that ABIOMED has studied the device for that use and has sought and received such a claim, and implies that the Thoratec device is better than the BVS-5000 for such an approved claim.

Further, Thoratec’s video quotes portions of information from two articles appearing in the Annals of Thoracic Surgery in 1995 and 1996. However, neither article reflects results from a controlled clinical trial conducted by either Thoratec or ABIOMED. Both articles instead reflect European clinical experience with circulatory support devices. The portions of the articles quoted are taken out of context and provide only the briefest statements of comparison between devices. Although such presentations may encapsulate the appearances of superiority for the Thoratec device that Thoratec apparently wishes to create, they are misleading presentations of clinical experience and conclusions.

There are other specific claims in the videotape that CDRH considers false and misleading. The video purports to indicate a survival rate for patients using the Thoratec VAD of 88.5% and a survival rate for patients supported by ABIOMED’s device as 50%. It appears to the agency that Thoratec has taken those data from Table 7 in Körfer R, El-Banayosy A, Posival H, Minami K, Körner M, Arusoglu, Breymann T, Kizner L, Seifert D, Körte H, Fey O. “Mechanical Circulatory Support: The Bad Oeynhausien Experience” Annals of Thoracic Surgery 1995; 59:S56-S63. Table 7 is entitled, “Results for 50 Bridged Patients”. Of the 14 patients who were bridged with the ABIOMED device, 7/14, or 50%, survived. Of the 26 patients who were bridged with the Thoratec device, 23/26, or 88.5% survived. However, as noted above, the ABIOMED device has not received FDA approval for use in bridging patients to transplant and your using the data from one article, which discusses a study not conducted by either company in support of agency approval, is misleading.

There is no mention of the rest of the discussion in the Comment section of the article, which continues that, “This may be due to our learning curve with bridging patients.” Instead, you also quote parts of the next two sentences, “Also, in patients with organ failure, pump output of the ABIOMED system (4.0 to 4.5 L) may not be high enough to prevent sufficient organ recovery. Another factor is the higher incidence of severe neurologic complications associated with the Abiomed system, resulting in increased morbidity. Therefore, the Abiomed device has been replaced by the Thoratec and the Novacor for bridging.” (Emphasis added.) We have discussed these issues with the Office of Device Evaluation (ODE). With regard to the issue of organ failure, it is

misleading to imply that the Thoratec device can reverse organ failure, but that the ABIOMED device cannot. There have been no data submitted to FDA to demonstrate that mechanical circulatory support can reverse actual end-organ failure. Again, you have merely quoted out of context one aspect of the experience of one clinical center. In addition, data submitted to FDA demonstrate that the pump output for the two devices are very similar; the ABIOMED device output is 6 liters/minute and the Thoratec device output is 6.5 liters/minutes. To use data from an article not submitted to the agency as though they are data that represent the demonstrated capacity of the device is not appropriate. Further, as you are probably aware, each of these devices can only pump the amounts of blood that it receives from the body and cannot induce the body to send it any more or less blood.

With regard to the comparison of neurological complications, your use of a comparison in a 1995 study not conducted by either company is inappropriate in this context as well. In addition, as noted above, the comment followed these comparisons with a statement that the ABIOMED device had been replaced by the Thoratec and Novacor devices for bridging; the ABIOMED device, as discussed above, has not been approved for use in bridging to transplant and for you to pick statements out of context is misleading.

It is also not clear that the comparisons of survival rates that appear in the videotape are based on statistically significant differences and it is misleading for the company to imply that the differences are meaningful if they are not and if the devices have not been directly compared with each other for a specific outcome.

The Thoratec video includes claims that promote the use of its VAD for myocarditis. The Thoratec VAD has not been approved for this claim and the company would be required to submit a premarket approval application (PMA) for this indication. The agency's regulations at 21 CFR 814.39 require that, after FDA approval of a PMA, an applicant submit a PMA supplement for review and approval by FDA before making a change affecting the safety or effectiveness of the device for which the applicant has an approved PMA, unless the change is of a type for which FDA has advised that an alternate submission is permitted. Among the changes that require a PMA supplement are new indications for use of the device.

In addition, several pieces of promotional material published and distributed by Thoratec make inappropriate claims and comparisons for the Thoratec device. In a piece called, "Patient and Device Selection Criteria Unique to Ventricular Assist Devices" that appears in Thoratec's "Current Issues in Circulatory Support" and copyrighted in 1998 (no specific date appears on the document), Thoratec purports to compare the various ventricular assist devices available in the United States. The comparisons are misleading. For example, the article presents as "limitations" the following aspects of the ABIOMED device: gravity system restricts patient mobility, transfer from intensive care unlikely, and pump components not appropriate for long-term use. However, these are relatively meaningless comparisons since the ABIOMED device is intended as a short term device and what you have described as limitations are essential aspects of the device's intended use and its functions.

In a piece entitled, "The Driving Force Behind Recovery," Thoratec promotes its device as being an aid to patient mobility by saying that "Unlike other systems, which force patients to be bedridden in the critical care unit, patients supported with the

Thoratec VAD System can realize a physical and psychological benefit of ambulation. In fact, patients are often put on exercise regimes to improve their rehabilitation.” As with the previous piece which states that the extracorporeal position of the ABIOMED device limits patients to the ICU and limits rehabilitative potential by keeping patients bedridden, this is misleading because patients on immediate postcardiotomy short-term care would be kept resting in the ICU anyway and would not be mobile or attempting immediate rehabilitation.

Another edition of Thoratec’s “Current Issues in Circulatory Support,” entitled, “Advancing the Standard in Postcardiotomy Circulatory Support: Thoratec® Ventricular Assist Device (VAD)” makes numerous inappropriate claims and comparisons. In the section called “Historical Perspective,” the company describes ABIOMED’s device as capable of only short-term support and referring to an average patient support time of 4.7 days. In fact, the device is approved for use for 7 days. Your article says that the device “in many cases does not allow for complete patient rehabilitation, including discontinuation of all inotropic support, removal of intravenous lines, and full recovery of end-organ function.” In fact, the device provides for adequate myocardial recovery to enable the heart to reverse end-organ dysfunction. You state that “[p]atients who survive long enough and are unable to be weaned from the BVS 5000 must be switched to a long-term VAD, if available, thus requiring a second operation.” However, there is no VAD approved for long-term use.

The “Device Overview” section contains a statement that the demand for mechanical circulatory assist devices has increased as . . . a shortage of donor organs remains. This implies that your device can be used for long term support as an alternative to medical therapy, since it does not clearly state that the device is used only until a donor organ becomes available and a patient can receive a transplant.

The list of criteria that you say “the ideal VAD” should meet includes reversible cardiomyopathy, an indication for which Thoratec’s VAD is not approved. This claim would require the submission by Thoratec of a PMA, as provided below.

Your Table 1 is misleading for the reasons discussed above about references to long-term use and references to transfer from ICU and patient ambulation, which are not relevant in the case of the ABIOMED device. In addition, the reference to the company’s Thoralon™ claims that the material provides enhanced strength, durability and superior thromboresistance properties. However, the company’s PMA indicates that 28% of Thoratec’s clinical trial subjects suffered thromboembolism, and the Center would like to know on what you base your claim for “superior thromboresistance.”

In the “Comparing Clinical Results” section, Thoratec purports to compare the clinical studies conducted by Thoratec and ABIOMED for their respective devices. The comparisons are inappropriate for several reasons. The statement that the ABIOMED hemodynamic criteria were less stringent than those used in the Thoratec study is a misstatement since ABIOMED’s Summary of Safety and Effectiveness (SS&E) describes the mean cardiac index for its device prior to support as 1.6, which is in fact less than 1.8. Further, a difference between ≤ 2 and 1.8 is meaningless in this context.

The “Adverse Events and Complications” section makes numerous inappropriate statements. You state that comparison of adverse events and complications between Thoratec and ABIOMED using ABIOMED’s adverse events-definitions showed significantly fewer Thoratec patients had bleeding complications and that bleeding was

defined as a blood loss of 1500 cc or more in a 12 hour period or a return to the operating room for reexploration for bleeding. CDRH is not aware of what you intend by the reference to ABIOMED's adverse event definitions and Thoratec's results can only be meaningfully described with reference to your own adverse event definitions as established for the purposes of your clinical protocol. Further, we are advised by ODE that the quoted definition of bleeding did not appear in your PMA or your SS&E and we are not aware of the source of this definition.

In addition, the statement that adverse events with Thoratec's VAD support are best characterized by a recent analysis performed at three centers in the United States is not appropriate, since data from this particular analysis were not presented in your PMA.

Figure 1 of that piece, Thoratec Postcardiotomy Voluntary Registry, represents statistical data in a way different from the way Thoratec was permitted to describe postcardiotomy data in the company's PMA and approved labeling. The numbers of patients discharged should be represented as a ratio of the number discharged over the number of patients enrolled in the study, not as a ratio of the number discharged over the number of patients weaned. Thus, for example, the percentage of BiVAD patients discharged should be 9/53, or 17%, rather than 9/19, or 47%. These figures are misleading. In addition, it is misleading to present conclusions from 151 patients, 122 of whom may not have met the PMA entrance criteria, since, even though the postmarket use of the device will reflect a broader population, the approved claims are based on the population included in the study. Similarly, discussing the 51 survivors in this piece is misleading since those patients may not have all met the PMA enrollment criteria.

The "Opportunity for Complete Patient Rehabilitation" section also contains misleading statements. The first sentence says "In addition to our postcardiotomy and bridge patients, we have another interesting subset of recovery patients who initially were thought to require transplantation. . . Generally these were young patients with non-ischemic cardiomyopathy." This is misleading because the Thoratec device is not approved for bridge to recovery and because an indication for cardiomyopathy would, as discussed earlier, require a PMA supplement.

The next page contains the following: "Nearly 50% of our reported postcardiotomy survivors were supported for more than seven days. These data indicate that time is required for patients to not only recover ventricular function but also fully recover other vital organ function. Devices such as the Abiomed BVS 5000 require a decision to be made at a time that might not be advantageous for the patient." This is a meaningless and misleading comparison because the Thoratec VAD appears to require more time than the ABIOMED device to accomplish the same level of patient cardiac function.

In the section "VAD System Cost Issues," the piece says "Thoratec's clinical experience has shown that as much as 50% of the postcardiotomy patient population will require extended support, some for possible bridge to transplantation. Therefore, the most appropriate VAD system should have the potential to provide support over a wide range of support durations. This is not possible with the Abiomed system since early weaning is required to prevent device-induced complications." The Center does not know what Thoratec means to imply by this discussion. As noted above, the ABIOMED device is designed for short term, i.e., 7-day use, so it is not intended for a wide range of support durations. There is no basis for a statement that leaving the ABIOMED device in

place will result in complications that would not result from use of the Thoratec device. In addition, the ABIOMED device generally is effective in providing its intended support within that 7 day period, so implying that the device is deficient because it cannot be left in for longer than 7 days is misleading. Further, as noted earlier, the patients in the Thoratec study were not patients who were both post cardiectomy and bridge to transplant patients. Your statement about Thoratec's clinical experience showing that up to 50% of the post cardiectomy population will require extended support, some for possible bridge to transplantation, is therefore inappropriate because it creates a new intended use for the device, a use requiring submission of a PMA supplement.

In the section "Advancing the Standard of Care," Thoratec claims that "in addition to Thoratec's own "bridge to recovery" patient group, other clinical studies have uncovered an interesting subset of patients in which ventricular chamber remodeling appears to stop and actually reverse, leading to eventual normalization of cardiac functions." There is no "bridge to recovery" patient group, as noted several times above, and the company has submitted to FDA none of the data in the studies it discusses and about which it draws preliminary conclusions. Once again, these are unapproved uses requiring the submission of PMA supplements.

Finally, with regard to this piece, the "Conclusion" includes a statement that "Mobility and system effectiveness permits [sic] early patient ambulation and rehabilitation, allowing for transfer out of the Intensive Care Unit." This is an inappropriate statement, as it is the system design that is related to these patient care aspects, not the effectiveness of the system in terms of its intended use.

In another promotional brochure, a "Clinical Update" with the title "Thoratec® VAD System: Introducing a Better Cardiac Support System for Postcardiectomy Myocardial Recovery," the company makes some of the same claims, as well as some other ones. In the first paragraph, there is a statement that Thoratec's VAD is the only circulatory assist device with FDA approval for both bridge to transplant and postcardiectomy bridge to recovery. However, as noted throughout this letter, the Thoratec device is not approved as a bridge to recovery or for long term support, as claimed later in the paragraph. Your introduction implies that removal of other devices after their prescribed short-term use is premature, when, in fact, those devices, are designed for short-term use. This promotional piece makes many of the same claims that we have addressed in your other publications. In addition, the section called "Advancing the Standard of Care" includes a statement that early weaning was preferred in the early 1980's because "it was thought there was a finite window of opportunity between myocardial recovery and device-induced complications." ODE believes that it is misleading to state this because the window of opportunity to which you referred was never considered finite; there was a sense that there was a somewhat uncertain window of opportunity between recovery and complications. However, you have used this statement as a lead-in to your promotion of your device for immediate and long-term use, when the device has not been approved for long-term use or for bridge to recovery.

Your statement, "The Thoratec VAD System is the only VAD System that provides the surgeon with the flexibility to provide virtually any duration of support with the same device" is again misleading and changes the product's intended use for the same reasons.

Thus, the Thoratec VAD is misbranded and adulterated within the meaning of sections 502(o) and 501(f)(1)(B), respectively, of the Act for the following reasons. It is misbranded within the meaning of section 502(o) because of Thoratec's failure to submit the notice and other information respecting the device required by section 510(k) of the Act. The company has failed to submit data to support several of the claims it makes for the device, including the viral myocarditis claim, the bridge to recovery claim, and the claim for long-term use. The failure to submit such data causes the product to be adulterated under section 510(f)(1)(B) because it is a class III device without an approved premarket approval application for the claims as required by section 515 of the Act or an approved investigational device exemption as required by section 520(g) of the Act.

The device is further misbranded within the meaning of section 502(a) because of the false and misleading representations made about Thoratec's device and the misleading comparisons made between the Thoratec device and the ABIOMED device. Section 801.6 of the agency's regulations provides that among representations in the labeling of a device which render it misbranded is a false or misleading representation with respect to another device.

The company is also in violation of the agency's regulations at 21 CFR 812.7, which prohibit the promotion of investigational devices. Thoratec's TLC-II™ Portable VAD Driver is an investigational device, currently being studied under an approved IDE. 21 CFR 812.7(a) prohibits a sponsor from promoting an investigational device until FDA has approved the device for commercial distribution and 812.7(d) prohibits a sponsor from representing that an investigational device is safe and effective for the uses for which it is being investigated. The video promotes the TLC-II, albeit with an attempted disclaimer that the device is as yet unavailable in the United States. In addition, as discussed below, the company's promotional literature, including its Heartbeat newsletter, distributed in the last year or so in the United States and materials on its website, make numerous claims for the device and promote it as safe and effective for particular uses.

CDRH would consider it appropriate for you to include on your website separate icons for your Canadian and European TLC-II™ products, as long as there is no link between the United States investigational product and the uses or claims approved in other countries.

This letter is not intended to be an all-inclusive list of deficiencies associated with Thoratec's devices. We have not addressed each appearance of each inappropriate statement since they are too numerous and many are repeated throughout several promotional pieces. It is your responsibility to ensure adherence to each requirement of the Act and the regulations. The specific violations noted in this letter may also be reflected in other promotion and advertising materials used by your company. You are responsible for investigating and reviewing all materials to ensure compliance with applicable regulations.

You should take prompt action to correct these violations. Failure to promptly correct these violations may result in FDA's initiating regulatory action without further notice. These actions include, but are not limited to, seizure, injunction and/or civil money penalties.

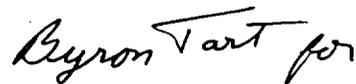
Please notify this office in writing, within 15 working days of your receipt of this letter, of the specific steps that you have taken to correct the noted violations. Your

response should include steps being taken to address any misleading information currently in the marketplace and to prevent similar violations in the future. If corrective actions cannot be completed within 15 working days, state the reason for the delay and the timeframe within which the corrections will be completed.

Direct your response to Deborah Wolf, Regulatory Counsel, Promotion and Advertising Policy Staff (HFZ-302), Office of Compliance, Center for Devices and Radiological Health, 2098 Gaither Road, Rockville, Maryland 20850.

A copy of this letter is being sent to FDA's San Francisco District Office. Please send a copy of your response to the District Director, San Francisco District Office, Food and Drug Administration (HFR-PA140), 1431 Harbor Bay Parkway, Alameda, California 94502-7070.

Sincerely yours,



Lillian Gill
Director
Office of Compliance
Center for Devices and
Radiological Health