UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF OHIO
WESTERN DIVISION

(Electronically Filed)

ARTHUR RAY BOWLING, et al.,	:	CASE NO. C-1-91-256
Plaintiffs,	:	Herman J. Weber, Senior Judge
v.	:	
PFIZER, INC., et al.,	:	
Defendants.	:	

SUPPLEMENT TO THIRTY-FIRST REPORT OF THE SPECIAL MASTERS/TRUSTEES

The Trustees hereby submit the following supplement to Section 1(A) of the Thirty-First Report of the Special Masters/Trustees.

On July 28, 2009, a meeting of the Trustees, all members of counsel, the Claims Administrator and the Chairman of the Supervisory panel was conducted in Cincinnati, Ohio. The purpose of the meeting was to consider the future of the Settlement. During the meeting, Class counsel, Special counsel and Public Citizen stated their position that it is unlikely that further research will result in a diagnostic test or other meaningful benefit to the class. They asserted that it was time for the Supervisory panel to consider Section 5.5 of the Settlement Agreement, which provides: *"If the Supervisory Panel at any time determines that any money remaining in the Patient Benefit Fund cannot productively be spent for the specific purposes set forth herein, including payment of benefits for valve replacement surgery, it may recommend to the Court that such remainder should therefore be devoted to some other purpose for the benefit of the Settlement Class (other than direct distribution to class members). Subject to the approval*

of the Court, the Panel shall then direct the disposition of the remainder of the Fund. At such time, all of Shiley's and Pfizer's obligations under this section 5 shall cease, except to make any remaining unpaid required installments (up to a maximum of $75 million) into the Patient Benefit Fund."

The panel considered Section 5.5 and its future mission and has determined that it is time for active research to develop a diagnostic tool to stop, but that some activities of the panel should continue. One of the main issues the panel considered was the continuation of the work of ACES to develop a reliable diagnostic tool by conducting another series of clinical trials on patients using their testing technology. This was a close question for the panel to consider, but ultimately the majority of the panel members decided that it is highly unlikely that we could recruit enough class members to participate in the trials to make the results meaningful. More importantly, the panel did not think a sufficient number of those who did participate in the clinical trial that would undergo explantation of their valve in order to validate the ACES test. The following information provides the basis for the panel's decision to recommend that diagnostic device research should not be continued.

Review of Pertinent Data and Panel Observations.

The data provided below is regarding class members who were or still are implanted with the BSCC heart valve. With the exception of #3 below (outlet strut fractures over time), the data pertains to class members who are believed to be living with the valve still implanted who would potentially qualify for further benefits under the Settlement.

1. *Age and gender distribution of registered class members believed to be living with BSCC heart valves still implanted*: As of October 2, 2009 there were 7,045 registered class members believed to be living with BSCC heart valves still implanted (Exhibit 1). These

class members are divided into 3,736 males, 3,220 females, and 36 of unknown gender with another 53 class members whose date of birth is unknown. The aging of class members is evident as 84% of them are 60 years old and older, 63% are 70 years old and older, and 34% are 80 years old and older. These data are based upon records maintained by the Claims Administrator.

2. *Estimated number of living class members implanted with BSCC heart valves*: Applying the mortality experience of the US, UK, and the Dutch cohorts to all of the worldwide data, it was estimated that as of January 1, 2010, there will be between 9,600 and 12,300 patients living with 60° and somewhat less that 500 patients with 70° valves (Exhibit 2). This is based upon the work of Dr. Bill Blot, panel consultant.
3. *The number of Outlet Strut Fractures (OSF) over time*: As of November, 2009 there were reported 662 OSF's; the first occurrence was in 1978 and the last was in November, 2006. The occurrence of OSF increased over time since 1978 to reach a peak in 1983 and has declined ever since (Exhibit 3). These data were obtained by a review of the BSCC research database.
4. *The number of qualified Single Leg Separations (SLS) and valve replacement surgery claims over time*: From 1992 until the present, there were a total of 139 claims, divided into 39 SLS claims and 100 surgery claims processed through the Claims Administrator's office (Exhibit 4). The majority of the claims (60%) occurred by or before 1995, and only 2 claims were received after 2003.
5. *The frequency of SLS*: Using data maintained by the manufacturer and the results of examinations for SLS in explanted valves, it was estimated that SLS is prevalent in 6.8% (4.1-9.4% confidence intervals) of the class members. Using the estimated range of class

members reported in #2 above, this means we might expect somewhere between 393 and 1,156 patients worldwide to have the SLS condition in their valve. The mid-point in this range is 775 (Exhibit 5). This data is based upon a published study conducted by Dr. Bill Blot and others.

6. Known class members who qualify under the guidelines: As of November 11, 2009, there are 106 registered class members believed to be living who qualify for surgical benefits under the guidelines, 81 males and 25 females (Exhibit 6). These data are based upon records maintained by the Claims Administrator.

The data presented above provides somewhat of an overview of the makeup of the class members who are believed to be living and still implanted with the BSCC heart valve. We also know that the largest number of implanted class members who registered with the Claims Administrator was 13,351 in 1994 and this number has diminished to the current number of just over 7,000 who are believed to be living and still implanted with the BSCC heart valve. These registered implanted class members as a group are becoming older. As mentioned earlier, some 63% being age 70 and older. We know that cardiac output tends to decrease as one grows older, lifestyles tend to become less active and these factors among others often result in less stress on the cardio vascular system. Accordingly, the panel believes there is less risk of fracture of the BSCC heart valve and this is accounted for in our guidelines. In the guidelines we rely on the fact that the risk of valve fracture decreases as the person gets older. This is only one of the main two factors upon which the guidelines are formulated. The second is surgical mortality (the risk of death) and morbidity (the risk of serious complications) and the panel knows that as one grows older surgical mortality and morbidity rates increase. In other words, as one grows older they are less likely to be a candidate for elective valve replacement surgery.

Another observation is that outlet strut fractures, single leg separations and valve replacement surgery (VRS) claims have diminished significantly in recent years. We will take a look at each of those issues. There have been no reported or confirmed OSF cases since 2006. The first OSF occurred in 1978, and the number increased rapidly to reach a peak of 73 OSF in 1983. The number of OSF gradually declined to 32 in 1992 and continued to taper off to 10 cases in 1998, then less than 10 cases for the ensuing years until 4 cases occurred in 2006. There have been no reported OSF cases since November, 2006. The last claim for (SLS) was in 2007 and prior to that there were none dating back to 2001 when there was one case. There was one VRS claim in 2008 and prior to that none dating back to 2004 when there were 3 claims. These facts make sense to the panel given our understanding of decreasing stress placed on the BSCC heart valve as patients get older and the increased risk of elective surgery for older patients.

Is the panel saying there will be no more outlet strut fractures? No, we cannot positively assert that no fractures will occur. We do know from the data that there are likely to be a number of valves still implanted in class members with the SLS condition, by our best estimates somewhere between 393 and 1,156 of the estimated number of living patients with valves still implanted (if we consider only those registered implanted class members believed to be living the estimate of SLS prevalence is between 288 and 662). It is generally accepted that complete OSF is preceded by the SLS condition. Although some panel members believe that it is possible that fractures may increase since the valves have been implanted for over twenty years undergoing repetitive stresses, the diminishing numbers of observed OSF and SLS events, along with the rationale outlined above lead the panel to the conclusion that the number of OSF and SLS events going forward is likely to be minimal.

Current Status of Diagnostic Device Research

1. Advanced Computational and Engineering (ACES).

As stated earlier in this report, the panel decided not to continue research to develop the ACES diagnostic device. This was a close question for the panel to consider. Those who supported further research took the position that ACES is the best testing method we have; that a clinical trial can prove that ACES can detect the SLS condition of a valve in living people, and; that if they can detect SLS at the prevalence predicted in the Blot study provided in Exhibit 5, it would give confidence to its use as a diagnostic tool and would be a test to offer the class especially if there is an increase in the number of outlet strut fractures. The results of the test would be useful in the overall treatment plan of the patient. Those who oppose the clinical trials base their view on the fact that there is little ground truth to support the ACES method and it is not likely there ever will be. They assert a clinical trial of at least 200 patients would prove to be logistically difficult, if not impossible to implement and that it would not prove that ACES has a viable diagnostic tool. Finally, that its costs would outweigh its potential benefits. The following is an overview of the work of ACES and additional rationale for the panel's decision to discontinue its diagnostic device research.

The panel has sponsored and the court approved a series of acoustics-related research studies by ACES beginning in 2003. These studies were based on the premise that the acoustics of the operating BSCC heart valve in a living patient could be recorded and analyzed to determine if the valve were either intact or one leg of the outlet strut was separated. Dating back to the early 1990's, cardiologists and acoustical engineers determined that fracture of one leg of a BSCC heart valve would produce alterations in acoustical recordings that could be diagnostic. Numerous studies were carried out in high-risk patients and in sheep implanted with BSCC heart valves to assess these acoustical characteristics. Classic frequency spectra were determined for

intact outlet struts, for outlet struts that were completely fractured, and for outlet struts that were fractured but the two ends were touching. Over the past decade, these frequency studies have been reproduced by numerous investigators with a high degree of correlation. ACES developed what they called a "passive acoustic detection system" meaning that they were recording the resonant frequency of the working heart valve in its normal operation. They use an array of sensors or microphones by placing the sensor array on the chest of the patient in a way similar to how a doctor uses a stethoscope. It is a non-invasive method and the recording can be done in ten to fifteen minutes.

The ACES group did studies on six living sheep which were implanted with BSCC valves in early 2006. Some of the valves were intact and some were SLS, but ACES did not know the status of the valves as they completed the research. They correctly classified five out of six of the heart valves correctly upon initial studies. Later review of the study data led them to hypothesize on the existence of the second harmonic emanating from the valve as important in the correct classification of the valve in some cases. This second harmonic hypothesis led the panel to recommend a study to test this theory and the court approved a research study by the Hemolab Cardiovascular Engineering group in the Netherlands in 2009.

The ACES group also conducted a clinical trial at The Ohio State University in late 2006 in which twelve volunteer BSCC patients participated. Two of the patients had multiple valves so that fourteen valves in total were studied. All of these valves were classified by ACES as intact. Six of the valves studied were manufactured after April, 1984 and we would expect an intact status since we are not aware of any valve manufactured since then that has fractured. The other eight valves were in patients who were not qualified under the guidelines. We are not aware that any of these valves have been explanted so we do not know their actual condition

(intact or SLS).

The sheep and patient studies had an adequate degree of success and gave the panel confidence to pursue the work of ACES further, but we preferred to have additional testing data where they were able to accurately identify the status of the valve. To that end, the panel located some recordings of the heart valve as it operated in a number of patients who participated in the x-ray imaging studies at Stanford and Beaumont in the early 1990's. The panel knew the actual status of these valves because they had been explanted. In July, 2008 a study was approved by the Court for ACES to use their technology to study these valve recordings. Unfortunately, there were difficulties in converting the heart valve recordings into a medium which could be accurately read and analyzed by ACES. The difficulties in converting the acoustical signal from the earlier studies at Beaumont and Stanford were due to the fact that they had been recorded with acoustical sensors that were far less sensitive than those used by ACES in their studies and were frequently contaminated by a level of noise that made their conversion difficult. Thus, ACES was only able to provide us with data that their testing method was reliable in determining the status of the BSCC heart valve recordings in three of six valves on which analysis was possible.

The second harmonic or second frequency mode of the BSCC heart valve was mentioned above as a hypothesis put forward by ACES as they recognized the second frequency as potentially important in analyzing the valve as demonstrated in one of the valves tested in an implanted sheep and in three of the patients who participated in the clinical trials. In early 2009 the Hemolab Cardiovascular Engineering group was approved to study the second harmonic issue in an effort to verify its importance to the ACES analysis method. These studies were recently completed, and when the BSCC heart valves were studied in air a second harmonic was

recorded for each valve with frequencies that were almost exactly correlated with the values calculated and determined by ACES. On the other hand, when these same valves were studied in a pulse duplicator with conditions similar to functioning hearts in patients, the identification of acoustic signals for a second harmonic was inconclusive. The Panel is in the process of further questioning de Hart and his associate as to the meaning of the differences. It should be noted that the second harmonic research of HemoLab was still in progress when the panel was discussing its future mission in general and the possibility research by ACES in particular. Since we were trying to determine our future activities at that time the panel made the assumption that the HemoLab research would fully support the second harmonic hypothesis, which cast the possibility of continuing the ACES research in the best possible light.

This overview of the work of ACES brings us to the question of whether to continue to try to develop their testing method as a tool by which important information about the BSCC heart valve can be provided to the patient. The most meaningful way to determine the validity of the ACES technology is to conduct further clinical trials on volunteer patients. The surest way to determine the accuracy of the test results is to explant the valve from the patient and evaluate it as either intact or as having the SLS condition and compare the ground truth to the test result. The panel believes it is highly unlikely that enough test participants will undergo explant surgery in order to establish ground truth test data. This belief is based on the our observations provided earlier regarding the low number of valve replacement surgeries in recent years (one since 2004) as well as the low number of class members who qualify for valve replacement surgery under the guidelines (106 world-wide) and the ageing nature of the class (63% aged 70 and older).

The widely accepted measures of a medical test are known as *sensitivity* and *specificity*, which are measures of how good a medical test is. A medical test may have a positive result, for

example the person tested positive for the existence of a certain illegal drug in their system (a positive test meaning the drug was detected in the system) or a negative result (no indication the drug was in the system). There can also be false positives when the test indicates the presence of a condition that does not exist and false negatives when the test misses the presence of a condition. Sensitivity of a test measures the proportion of actual positives which are correctly identified as such (e.g. the percentage of sick people who are identified as having the condition). Specificity of a test measures the proportion of negatives which are correctly identified (e.g. the percentage of well people who are identified as not have the condition).

The best case scenario is when there is ground truth data supporting the test results. This means one can determine the sensitivity and specificity of the test by measuring the results of the test against the prevalence of the actual condition. In our case, the number of people who have either intact or SLS valves would be the ground truth. But, as stated above, it is highly unlikely we could get such ground truth on an adequate number of BSCC patients to provide reasonable sensitivity and specificity measures. In cases such as this, it is not uncommon to look for an alternative measure in lieu of ground truth data. This is just what the panel considered with regard to ACES. We had the estimated prevalence of SLS research completed by Dr. Blot which was referenced earlier at #5 under "Pertinent Data and Panel Observations" in which Blot estimated that 6.8% (around confidence intervals of 4.1-9.4%) of the population may have the SLS condition. Thus, the panel considered a clinical trial to be conducted by ACES to test enough patients to determine if they could detect SLS in 6.8% of the patients studied. The panel again relied on Dr. Blot to provide statistically relevant information regarding the number of patients for ACES to study. Blot reported that the number studied would depend on the degree of confidence intervals the panel wanted. Narrow confidence intervals of plus/minus 1% would

require approximately 1,000 patients; moderate intervals of plus/minus 2.5% would require approximately 500 patients, and; wide intervals of plus/minus 5% would require at least 200 patients. At the end of these clinical trials we would have proved or disproved the SLS prevalence estimate of 6.8% and indirectly proven the ability of the ACES technology to detect SLS.

The panel considered the difficulty of attracting enough volunteers to participate in such a study and the costs of carrying it out. In the earlier clinical trial completed by ACES, we solicited approximately 130 class members from within driving distance to Columbus, Ohio where the trials were completed. This yielded 12 volunteer class members to study. Therefore, we believe we may need to solicit as many as 2,000 class members to obtain 200 volunteers to participate in additional clinical trials. The panel considered that these trials could be done at other locations as long as Institutional Review Board approvals from accredited institutions were obtained. These logistical difficulties were considered but were not the major reason the panel decided against further trials. If the trials provided reasonable sensitivity and specificity measures to provide validation for the estimate of SLS prevalence in the population, the panel would have more confidence in the ability of ACES to detect SLS. However, without reasonable sensitivity and specificity measures on the ACES test itself we would not have sufficient confidence to ask patients and their doctors to rely on the ACES test result. The reason is the consequences of reliance on the test are too great and the potential for false positives and false negatives too real. In our case, a false positive (ACES test indicates SLS; explanted valve in intact) might mean an unwarranted surgery. A false negative (ACES test indicates intact; valve later fractures) might mean unwarranted assurance of the stability of the valve. For all of these reasons, the panel decided not to pursue the ACES technology.

2. The Hershey Imaging Program.

The panel has also decided not to continue this research program, mainly because only 7 out of 39 of the class members who participated in the study went on to have their valve explanted. Therefore, there has been insufficient ground truth data to validate this method as a diagnostic tool.

Study Background and Protocol for the Hershey Imaging Program. The Panel has sponsored several programs over the years which have used x-ray technology to observe the BSCC valve implanted in the mitral position in patients. Programs were conducted at Stanford University, Beaumont, Michigan and Glasgow, Scotland in the 1990's. These studies proved unreliable in that both the sensitivity and specificity were such that they could not be used as a basis for differentiating intact valves from those with single leg separation of an outlet strut. This is because there were some false positive results (the valve was imaged and thought to be separated, but upon explantation the valve was determined to be intact) and some false negative results (the valve was imaged and thought to be intact, but upon explantation was determined to be separated).

The improvement of the x-ray technology and the urging of Class Counsel led to the proposal to resume imaging studies from the Penn State University Milton S. Hershey Medical Center and in September, 2000 the Hershey Imaging Program commenced.

The program is and always has been a ***research study*** as outlined in the study protocol prepared by Penn State. The study has been available to those patients implanted with a valve in the mitral position who qualify for valve replacement surgery under the panel's guidelines. The purpose of the study is to conduct an x-ray examination of the Class member's mitral valve which will result in an imaging grade from I to V, with Grade I being "Apparently normal", or an