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

intact valve and Grade V being "Definite SLS" with other gradations between. Due to the angle and position of the aortic valve, it cannot be readily imaged using the x-ray technology.

The study was designed to determine the effectiveness or ineffectiveness of x-ray imaging as a minimally-invasive detection device in those patients who have the mitral valve imaged ***and*** have their valve explanted. This is clear from reading the protocol for the study approved by the Court. Section 3 of the Hershey study protocol outlines the purpose of the study and reads as follows: "It is believed that most of these patients will undergo re-operation within 30-90 days following imaging and, thus, we will be able to establish the sensitivity and specificity of imaging for SLS detection in this high-risk population. In addition to providing valuable information for these patients, the imaging will be of benefit to the remaining class. This imaging program will confirm or negate our impressions of the value of imaging for SLS detection."

Results of imaging sessions at Hershey. The panel has never seen sufficient data from this study to verify the validity of the x-ray imaging technology. Without such sensitivity and specificity data, the panel has little confidence in the imaging result as a diagnostic device or tool for patients or their physicians. The results of the Hershey imaging study have not satisfied the panel that the method is reliable for differentiating intact valves from those with SLS of an outlet strut. This is mainly because most of the patients who have participated in the study have not had their valve explanted so that a ground truth comparison of the actual valve status to the imaged valve status could be made. During this study there have been 59 imaging sessions of 39 patients. Seven of the patients have had their valve explanted. Of the seven explants there was one false positive, one false negative and two correctly identified as intact. There were three where the grade of the x-ray was not confirmed when the valve was explanted, but in two of those cases a

significant period of time had elapsed between the test and the explantation of the valve. See Exhibit 7 for more details.

The issue of continuing the Hershey imaging program was considered by the Court in August, 2005. The panel took the position that the program should not be continued for the reasons provided above. On or about October, 2005, the Court decided to continue the program for two years or until $160,000.00 was expended. Since then the panel has continued to recommend six-month extensions of the program because we thought it would provide some corroboration of the ACES test in the event we completed additional clinical trials using their testing method. Although we understood that neither the Hershey or ACES test had sufficient ground truth testing data, we believed that if both tests provided consistent classification of the valve, the information would be valuable to the class member and his/her physician in formulating a treatment plan. As the panel has now decided to cease further research by ACES, the need to maintain the Hershey program no longer exists.

Recommended future activities of the supervisory panel.

The conclusion of diagnostic device research will not end all panel activities. The panel will continue to have a number of responsibilities and will need funds to support them as well as other purposes set forth in Section 5 of the Settlement Agreement. The panel recommends that money from the Patient Benefit Fund be budgeted for the following functions:

- to pay for uninsured surgical claims as outlined in the Settlement Agreement;
- to provide for claims administration for the class;
- to continue its protocol of quarterly monitoring and surveillance of issues relating to the guidelines and its review of scientific literature relevant to the BSCC heart valve (the panel will amend this protocol to include the review engineering and clinical literature relating to advances in acoustics and imaging which might lead to improved techniques for assessing BSCC heart valves);

- to obtain an annual review of BSCC research database and the risk factors contained in the guidelines;
- to obtain updated surgical mortality and morbidity data;
- to develop and distribute an amended version of the guidelines should the data support the need to do so;
- to provide notice to class members in the event that a diagnostic test is developed in the scientific community, and;
- to continue to maintain the website and document repository.

The panel believes it is essential to budget for the need to pay for uninsured surgical claims of class members and to preserve adequate funding with which to provide the claims administration service to the class.

We also believe it is important to ensure the guidelines continue to appropriately assess the risk of valve fracture and the risk of explant surgery mortality and morbidity so that only those patients for whom a gain in life expectancy would occur if they underwent elective explant surgery qualify for monetary benefits. To do this, we must monitor the class for events such as single leg and outlet strut fracture and deaths to ensure the risk factors in the guidelines are valid; periodically verify that the surgical mortality and morbidity rates on which we rely in the guidelines are correct; review the medical/scientific literature, and; as a panel, evaluate the data periodically to ensure no changes to the guidelines are appropriate. The panel believes it is unlikely that a revision to the guidelines will be necessary, but if one is needed it will occur by the end of 2015.

The panel also suggests budgeting for the cost of providing the class notice of a diagnostic test. Part of the monitoring and surveillance work of the panel is the review of worldwide medical and scientific journals for the purpose of ensuring that we are aware of new research or developments that might benefit our class. There is the potential that a diagnostic test

or technology may be developed outside of the auspices of the panel that would be useful to our class. An amount of money is budgeted to provide notice to the class in this eventuality. Finally, we have budgeted funds to maintain the website and the document repository.

An estimate of the amount needed to pay for uninsured surgical claims has been developed, as has a budget for the activities of the panel proposed above. The panel is working with the Trustees, Claims Administrator and members of counsel to finalize the amounts needed to fund these purposes. The amounts will be provided to the Court as part of the Joint Status Report to be filed on January 29, 2010.

Respectfully submitted,

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CERTIFICATE OF SERVICE

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Exhibit 1

October 2, 2009

TRUSTEES FOR THE BOWLING-PFIZER HEART VALVE SETTLEMENT FUNDS

Registered Class Members Believed to be Living
With BSCC Heart Valve(s) Still Implanted
Grouped By Their Ages In 2009

Age	Total	Male	Female	Unknown
24 - 29	4	2	2	0
30 - 39	49	25	23	1
40 - 49	287	210	74	3
50 - 59	739	441	297	1
60 - 69	1,464	790	669	5
70 - 79	2,053	1,044	1,002	7
80 - 89	1,994	1,033	946	15
90 - 99	388	185	199	4
100 - 105	14	6	8	0
	6,992 (1) (2)	**3,736**	**3,220**	**36**

(1) It is likely that there are Class Members included who are deceased that we are not aware of being deceased and that some of them may have had explant surgery that we are not aware of the surgery.

(2) There are 53 registered Class Members whose dates of birth are unknown, for a total of 7,045 Class Members.

*458 of the above Class Members are implanted with BSCC heart valves that were manufactured after April 1984.

**226 of the Class Members are implanted with BSCC conduit heart valves.

Estimates of the number of living BSCC patients
April, 2008 (Revised October, 2008)

Exhibit 2

The following statistically-derived estimates were provided to the panel by Dr. Bill Blot. In the past, these estimates were done by Dr. Ron Brookmeyer, who recently has taken a diminished role in consulting for the panel. Each consultant used a different method to provide the panel with the estimate. However, the results from both are broadly consistent. Below is a summary of the work of Dr. Blot.

The data from the United States (US), United Kingdom (UK) and Dutch cohort follow up studies was used as a basis for the prediction model. While the UK and Dutch follow up studies are believed to have included all BSCC patients in those countries, this is not so for the US cohort. The US cohort follow up did not begin until the mid-1990's and included only patients who had survived until 1991. Therefore, an estimated range of between 55% and 75% of the patients were located and included in the US cohort study.

Dr. Blot looked at the number of patients living at the end of each cohort study. He then used accepted mortality rate figures to project how many patients would have survived to January, 2008. The assumption was made that the experience of class members in the rest of the world is similar to the experience of those in the three cohorts. He was also able to extrapolate those predictions out to 2025 with several increments in between provided.

Since about 95% of all valves manufactured were 60° valves, and since the US cohort study only included 60° valves, Dr. Blot's estimates focus on those valves. Since the method used by Dr. Blot included the use of a range of living patients in the US cohort, the estimates will also be provided as a range.

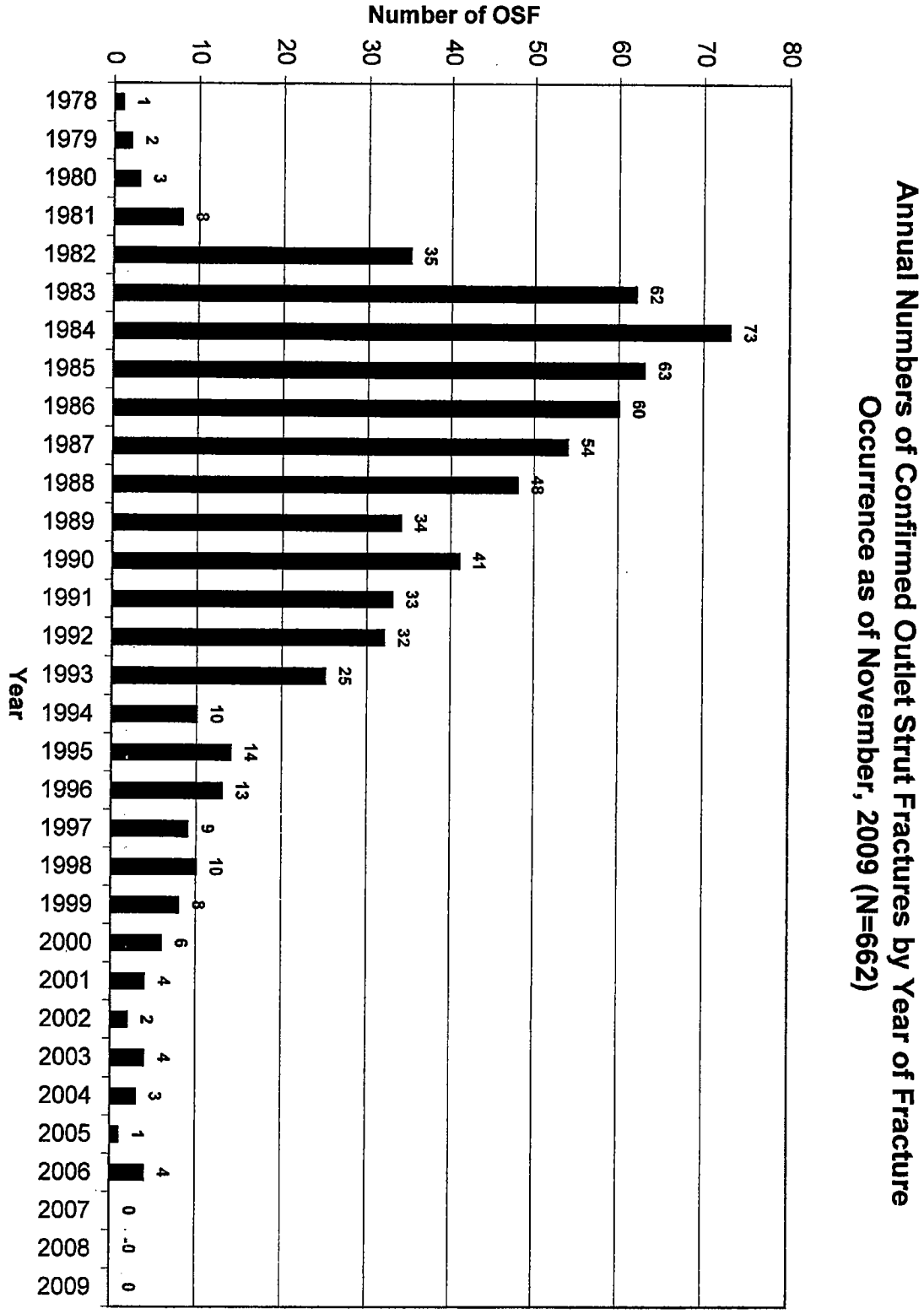
Here are the predictions for numbers of patients with 60° BSCC valves alive as of:

January 2008	11,500-14,700
January 2010	9,600-12,300
January 2015	6,000-7,700
January 2020	3,700-4,800
January 2025	2,300-2,900

Dr. Blot also estimates approximately 500-700 BSCC patients with 70° valves are living as of January 2008.

DEM

Exhibit 3



Annual Numbers of Confirmed Outlet Strut Fractures by Year of Fracture Occurrence as of November, 2009 (N=662)

Exhibit 4

July 22, 2009

TRUSTEES FOR THE BOWLING-PFIZER HEART VALVE SETTLEMENT FUNDS

Breakdown of SLF & VRS Claims by Year

Year	Total	SLF	VRS
1992	25	8	17
1993	19	5	14
1994	18	6	12
1995	21	13	8
1996	8	2	6
1997	1	1	0
1998	5	1	4
1999	8	0	8
2000	8	1	7
2001	14	1	13
2002	3	0	3
2003	4	0	4
2004	3	0	3
2005	0	0	0
2006	0	0	0
2007	1	1	0
2008	0	0	1
	139	**39**	**100**

Single Leg Separation Prevalence among Explanted Björk-Shiley Prosthetic Heart Valves

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Background and aim of the study: **Björk-Shiley convexo-concave (BSCC) prosthetic heart valves are believed to have been implanted in over 86,000 patients worldwide. Limited data are available on the prevalence of single leg separations (SLS) of the valves' outlet struts, a potential precursor to complete valve fracture.**

Methods: **Data maintained by the manufacturer, including results of examinations for SLS in explanted valves, were merged with available information on the characteristics of the valve. The prevalence of SLS in the examined valves was calculated according to valve angle, size, position, and study.**

Results: **Among 343 examined valves, the overall prevalence of SLS was 8.2%, but this varied significantly by valve size, being three-fold higher among 29+ mm valves than among smaller valves, with statistically non-significantly higher prevalences among mitral than aortic, and among 70° than 60° valves. By applying the size, position and angle-specific SLS prevalences to the worldwide valve distribution, it is estimated that SLS may be present in 6.8% (95% confidence limits 4.1-9.4%) of all BSCC valves.**

Conclusion: **These findings suggest that SLS may affect between 820 and 1,880 of the almost 20,000 BSCC valves among surviving patients worldwide. Such estimates help frame the context for potential patient screenings, should imaging and acoustic techniques to detect SLS become available.**

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The Björk-Shiley convexo-concave (BSCC) prosthetic heart valve was introduced during the late 1970s as an improved mechanical replacement for diseased native valves (1,2). In Figure 1, the BSCC valve is shown with its tilting disc held in place by a large fixed inner strut and a smaller, welded outlet strut. Incidents of fractures of the BSCC valve's outlet struts, and escape of the disc - resulting in embolization, massive regurgitation and often death - were first reported shortly after the valve's introduction, and led eventually to the valve being withdrawn from the market in 1986. The natural history of the fractures - which have continued to occur into the present decade - is unknown, but appears first to involve a separation of one of the two legs of the outlet strut, commonly designated as a single leg separation (SLS) (Fig. 2) (3-6).

At present, very few data exist on the prevalence of SLS or other valve abnormalities among the near-

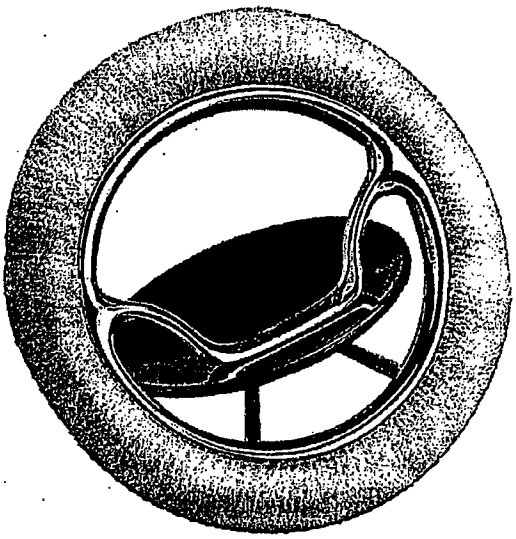

Figure 1: The Björk-Shiley convexo-concave (BSCC) prosthetic heart valve.

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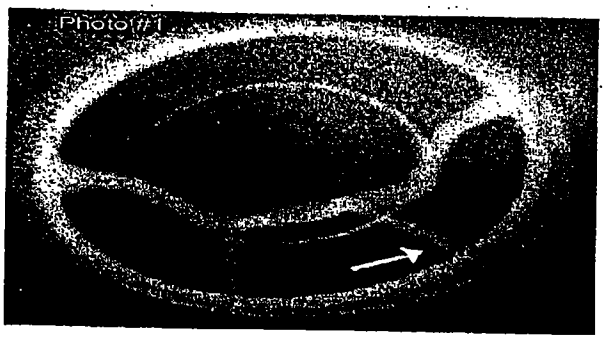

Figure 2: Photographic image of a single leg separation fractured BSCC prosthetic heart valve (http://www.bowling-pfizer.com/photos.shtml).

20,000 living patients with BSCC prosthetic heart valves. To date, no 'gold standard' diagnostic test has been devised that can detect SLS with high sensitivity and specificity, identifying almost all those patients who actually have an SLS in their valve, and with a low false-positive rate. Cineradiographic methods have been employed to diagnose SLS (3), and ongoing research is assessing potential new acoustic and imaging techniques which have yet to be applied in patient populations. In lieu of the direct evidence which would arise from applying a reliable diagnostic test to large numbers of patients, estimates of the prevalence of SLS must be approximated from other sources. One such resource exists in data maintained by the manufacturer (Pfizer) on valves which have been explanted from BSCC patients and then subjected to microscopic or other physical examination to detect SLS. Herein, information from this resource is reviewed, and estimated SLS prevalence rates computed according to valve size, position, and angle.

Materials and methods

Computerized listings were obtained from the manufacturer containing information on 769 returned valves that had been examined in-house, and on 359 returned valves examined by a company with expertise in metallurgical analyses which had been commissioned by the manufacturer to conduct microscopic examinations of the BSCC valves. The listings provided the valve serial number as well as examination results classified as Intact, SLS, or outlet strut fracture (OSF). The present analyses considered only those valves designated as Intact or SLS. Information on risks of OSF has recently been summarized elsewhere (2).

The Intact and SLS valves in the manufacturer files (hereafter referred to as 'Examined' valves) were matched by valve serial number against the BSCC Research Database, a file which contains manufacturing and limited other information on all 85,756 valves believed to have been implanted in patients worldwide. The Examined valves that were recorded in the BSCC Research Database were identified, and their characteristics compared with the general population of BSCC valves. SLS prevalence rates were then computed among the Examined valves overall and for large (29+ mm) versus smaller, 70° versus 60°, and mitral versus aortic valves. Chi-square tests for proportions were used to test for the significance of differences in the prevalences (7). Logistic regression analyses were conducted to compute the odds ratios (OR) and corresponding 95% confidence intervals (CI) of SLS prevalence associated with valve size, angle, and position (8). These OR-values represent the relative increases in SLS prevalence associated with each of the three factors adjusted for the others.

The Examined valves were also matched against those recorded in an earlier X-ray imaging study, a file containing information on approximately 1,100 valves from 903 patients who participated in an SLS screening survey during the early to mid-1990s in the United States and United Kingdom (3,4). The prevalences of SLS were computed among Examined valves included versus not included in the X-ray study.

In order to obtain estimates of the overall prevalence of SLS among the total population of BSCC heart valve patients, weighted averages of the prevalences among Examined valves were calculated across strata defined by valve angle, size and position, with the weights defined by the percentages of all BSCC valves in these strata.

Results

A total of 1,113 distinct valve serial numbers was included in the file of valves returned to the manufacturer. Of these valves, 221 had OSF and were deleted from any further consideration. Among the remaining 892 Intact or SLS valves, only 452 (51%) had serial numbers which were recorded in the BSCC Research Database. The large majority of the 440 non-matching valves had been returned to the manufacturer for credit when all BSCC heart valves were withdrawn from the market in 1986, although 44 were Spherical or Delrin valves.

The percentage distribution by valve angle, size, and position of the 452 Examined valves classified as Intact or SLS, the serial numbers of which were listed in the BSCC Research Database, are shown in Table I. For comparison, the distribution of all BSCC valves in the Database by these characteristics is also shown.

Over half of the Examined valves were large (29+ mm), whereas less than one-third of all BSCC valves

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Table I: Position, size, angle and characteristics of 'Examined' valves and all valves in the BSCC Research Database.

Position	Size (mm)	Examined (%)		Total BSCC (%)	
		60° (n = 408)	70° (n = 44)	60° (n = 81,709)	70° (n = 4,047)
Aortic	≤23	15	14	28	27
	25	13	7	15	16
	27	8	16	8	8
	29+	8	16	4	4
Mitral	≤23	1	0	1	<1
	25	3	2	5	3
	27	5	4	12	14
	29+	46	41	27	28

were large, and about 10% of the Examined valves were of 70° angle, whereas only 5% of all BSCC valves were 70°. Among the 452 Examined valves, 69% were registered in the United States, compared to 36% of all valves in the BSCC Research Database. The differences between the Examined and BSCC Research database distributions with respect to valve size, position, angle and country were highly statistically significant ($p < 0.01$).

Among the Examined valves reported in Table I, 11% were designated as SLS. The percentage of Examined valves with SLS varied according to valve characteristics, and tended to be over three-fold higher among 29+ mm than among smaller valves (a highly significant difference ($p < 0.01$). The overall prevalence of SLS also tended to be higher among mitral than aortic, and among 70° than 60° valves, but the differences were not statistically significant.

A total of 109 Examined valves was available from participants in the X-ray imaging study. Of these valves, 22 (20%) were SLS. The prevalence of SLS among the remaining 343 Examined valves after the valves included in the X-ray imaging study were excluded is shown in Table II. Removal of the X-ray imaging study patients resulted in the overall percentage of Examined valves with SLS declining from 11.1% to 8.2%. The percentages of examined valves with SLS still varied significantly ($p < 0.05$) by valve size, again being three-fold higher among 29+ mm valves than smaller valves (OR = 3.1, 95% CI = 1.1-8.3%), with non-significantly higher prevalences among mitral (OR = 1.4, 95% CI = 0.5-3.5%, $p = 0.51$) and 70° valves (OR = 2.1, 95% CI = 0.8-5.5%, $p = 0.12$).

Among the 60° valves, the percentages with SLS for <29 mm aortic valves, 29+ mm aortic valves, <29 mm mitral valves and 29+ mm mitral valves, respectively, were 3.5%, 7.1%, 5.1%, and 13.2%. If these percentages

Table II: Prevalence of single leg separation (SLS) among Examined valves, with valves from the X-ray imaging study removed, according to valve angle, size and position.

Angle (°)	Position	Size (mm)	Total valves (n)	No. with SLS*
60	Aortic	<29	141	5 (3.5)
		29+	28	2 (7.1)
	Mitral	<29	39	2 (5.1)
		29+	91	12 (13.2)
	Total		299	21 (7.0)
70	Aortic	<29	16	1 (6.3)
		29+	7	2 (28.6)
	Mitral	<29	3	0 (0)
		29+	18	4 (22.2)
	Total		44	7 (15.9)
Total			343	28 (8.2)

*Values in parentheses are percentages.