UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF OHIO

WESTERN DIVISION

IN RE:	:	Case No. C-1-91-256
BOWLING-PFIZER LITIGATION	:	(Judge Spiegel)

FIFTH REPORT OF THE SPECIAL MASTERS/TRUSTEES

COVERING PERIOD FROM JUNE 14, 1996 TO DECEMBER 13, 1996

SPECIAL MASTERS/TRUSTEES

Hon. Robert L. Black, Jr.
Peter J. Strauss, Esq.

AGENDA

FIFTH REPORT OF THE SPECIAL MASTERS/TRUSTEES

In Re: Bowling-Pfizer Litigation

Case No. C-1-91-256

December 13, 1996
10:00 A.M.

Hon. S. Arthur Spiegel

1. Introductory remarks by Judge Spiegel.
2. Report of the Special Masters/Trustees.
3. Comments from Counsel:

   Class Counsel.
   Counsel for Defendants.

4. Questions and comments from those in attendance.
5. Request for date of next report of Trustees.
6. Closing remarks of Judge Spiegel.

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FIFTH REPORT OF THE SPECIAL MASTERS/TRUSTEES

To the Honorable S. Arthur Spiegel, Judge, United States District Court:

Your Special Masters/Trustees respectfully present their fourth periodic report, covering activities from June 14, 1996 to December 13, 1996.

I. APPLICATION FOR ADDITIONAL ATTORNEYS' FEES AND EXPENSES

In the Court's "Memorandum and Order on Applications for Attorneys' Fees and Expenses" journalized March 1, 1996 by Hon. John F. Nangle (Document 800) as amended by Order journalized March 12, 1996 (Document 802), the Special Masters/Trustees are directed to "file a written report and recommendation to this Court indicating whether Counsel's application [for additional fees and expenses payable from the defendants' annual payments of $6,250,000 into the Patient Benefit Fund] should be granted in whole or in part, or denied." Class Counsel has duly filed an application for such additional fees and expenses related to the first annual payment of $6,250,000 (without specifying an amount). Amicus

Public Citizen and Class Members Gary Crane, et. al., have filed a memorandum stating opposition to Class Counsel's application, and in addition have filed their own application for additional fees and expenses. Class Counsel opposes payment of additional fees and expenses to Public Citizen.

The Special Masters/Trustees respectfully submit that because the fee Order as amended (Documents 800 and 802) is now on appeal to the Court of Appeals for the Sixth Circuit, they should be directed to withhold their report and recommendations until the Court of Appeals renders its decision on the appeal.

II. CONSULTATION FUND

Under Section 6 of the Settlement Agreement, the Consultation Fund, initially $80,000,000, is intended to provide Claimants with funds to obtain medical and psychological consultation as they deem best. It is to be divided equally among Claimants after paying or providing for fees and expenses to be paid out of this Fund. In addition, a $10,000,000 fund was established to be paid, after fees and expenses, equally among all Claimants who are spouses of Class Members.

The final deadlines for filing Consultation Fund claims were March 31, 1996 for Class Members resident in the United States, and May 31, 1996, for Class Members resident in all other countries. To date, 13,178 claims have been received and approved, 298 claims are pending approval, and 2,394 claims have been rejected for various reasons (such as, lack of reasonable proof of a BSCC valve,

implantation of another type of valve, death before January 23, 1992, etc.). Distributions have been made as follows: $3,000 to implantees, and $500 to spouses, or a total of $43,812,500.

The Special Masters/Trustees are prepared to make further distributions from the Consultation Fund when and as approved by the Court. The defendants have questioned whether any further distributions should be made until the current appeals have been resolved. Class Members Gary Crane et.al., Amicus Public Citizen and Special Counsel James T. Capretz have filed a Motion and Memorandum for an additional partial distribution. The Special Masters/Trustees await the Court's decision.

III. PATIENT BENEFIT FUND

Under Section 5 of the Settlement Agreement, the Patient Benefit Fund was established for the following purposes, briefly stated: to conduct research on the diagnosis of the risks of strut fracture and the risks of surgical replacement of valves, to establish guidelines for valve replacement surgeries, and to create a publicly accessible repository of appropriate information concerning the status of research and the risks of valve fracture and valve replacement.

A. Guidelines. The Supervisory Panel has been working hard to be in a position to establish new guidelines for valve replacement surgeries. While progress has been made and a method of evaluating risks established, it has not been possible to

complete the necessary scientific research and to finalize a proposal for the Court's consideration at this time.

The Guidelines Committee met in Vienna, Austria, on October 10 and 11, 1996, under the chairmanship of Dr. Tom Ivey. The Guidelines Committee was furnished with the best available scientific data and information by the Supervisory Panel. After consideration thereof, the Guidelines Committee approved a method of determining how to identify "those circumstances in which prophylactic replacement of a [BSCC] heart valve would reasonably offer a meaningful extension of life expectancy because of the risk of strut fracture," in accordance with Section 5.4.4.2 of the Settlement Agreement (as supplemented by Document 290). The Guidelines Committee ordered certain revisions and refinements. When those are accomplished and reviewed by the restructured Guidelines Subcommittee, the complete recommendation will be reported to the Supervisory Panel. These steps will be completed as promptly as humanly possible.

As reported to the Court in the Fourth Report, the Guidelines Committee has been restructured as the Guidelines Subcommittee of the Supervisory Panel, consisting of three members, with former members of the Guidelines Committee as consultants.

The Supervisory Panel will give careful consideration to the new method of identification of the risks of fracture and the risks of reoperation. The Panel will follow the requirements for consultation with various governmental and scientific organizations as required by Section 5.4.4.2 of the Settlement Agreement. The

Panel will of course ask for the comments of Class Counsel and Counsel for Defendants. Thereafter, the Supervisory Panel will be in a position to consider final adoption of the new guidelines, which will, as promptly as possible, be submitted to the Court for approval.

B. Research Program. The Supervisory Panel continues to pursue its program of research in the three lines of investigation (epidemiological, radiographic and acoustics), and in addition has under consideration new lines of research that are being pursued to determine whether they hold promise of benefit for the Class Members.

The epidemiological studies in the United Kingdom and in The Netherlands are progressing according to the agreed schedules, which call for final reports at the end of 1997. A pilot study is underway to asses the feasibility of conducting a cohort study of American implantees, but certain delays have pushed the expected completion date into 1997. See "Ongoing Cohort Studies of Patients with BSCC Valves" dated September 30, 1996 attached as Appendix 1.

The imaging and acoustics studies have not, to date, produced a medically acceptable diagnostic technique to identify implantees with a significant risk of strut fracture. However, the Supervisory Panel has concluded that it is in the best interests of the Class to pursue these lines of investigation further, and to consider initiating certain new studies, with the expectation that a medically acceptable diagnostic technique can reasonably be developed in the future. The report of Donald C. Harrison, M.D.,

Chair of the Subcommittee on Imaging and Acoustics, is attached as Appendix 2.

C. Repository. To initiate the creation of a publicly accessible repository of appropriate information about research and the risks of valve failure and replacement, the Chairman of the Supervisory Panel is seeking the advice and counsel of Supervisory Panel members, Class Counsel, Counsel for Defendants, and persons and organizations with skill and experience in this field. Care must be taken to preserve the confidentiality of files and records with information about individual patients. A report will be made to the Court and the final plan, when developed, will be submitted to the Court for approval.

D. Valve Replacement Surgery Claims and Fracture Claims. As previously reported, the Claims Administrator has been processing claims for valve replacement surgery and strut fracture claims. As of December 6, 1996, 309 claims have been received. There are 44 qualified outlet strut fracture claims, 28 qualified single leg fracture claims and 33 qualified valve replacement surgery claims. The remaining claims have been reviewed and they either do not qualify or additional information is needed and has been requested from the claimants.

IV. FINANCIAL INFORMATION

At October 31, 1996, the total balance of cash and cash equivalents was $46,408,208 for the Consultation Fund (class member portion and spousal portion) and $9,969,999 for the Patient Benefit

Fund. These amounts include net interest earned from January 28, 1992 through October 31, 1996, in the aggregate amount of $15,970,543 for the Consultation Fund and $1,093,730 for the Patient Benefit Fund.

An unaudited balance sheet as of October 31, 1996 and an unaudited statement of income, benefit payments and funds balance for the ten months ended October 31, 1996 which includes the budgeted amounts for expenses for the period January 1, 1996 through December 31, 1996, are attached as Appendix 3.

The Trustees have received the audit report for the years ended December 31, 1995 and 1994 from Deloitte & Touche. A copy of their independent auditor's report is attached as Appendix 4.

V. COMMUNICATIONS

The Claims Administrator and the Trustees' office are in daily contact with individual Class Members, but no mass communication with the Class is contemplated until a distribution from the Consultation Fund is approved or a change in the Guidelines is approved by the Court.

VI. APPROVALS

Your honor, the Special Masters/Trustees request that the Court approve this Report and the actions specifically referred to herein, and approve or provide further direction with respect to each of the Appendices to this Report. We ask that the Court fix the date of the next Report.

Respectfully submitted,

Dated: December 13, 1996

_____
Hon. Robert L. Black, Jr.

_____
Peter J. Strauss, Esq.

ONGOING COHORT STUDIES OF PATIENTS WITH BSCC HEART VALVES

September 30, 1996

Followup of patients with BSCC heart valves is currently ongoing in cohort studies in the Netherlands and the United Kingdom, and is being considered in the United States. These investigations are ascertaining the mortality experience of the patients and will provide estimates of the rates of valve fracture as a function of both valve and patient characteristics.

The Dutch study, led by Dr. Yolanda van der Graaf, involves a continuation of research begun in the 1980s (with results through 1990 described in Lancet 339:257-261, 1992). In brief, patients with 2,309 60^0 and 279 70^0 valves are being tracked for mortality and valve fracture. Special attention is being placed on a review of the original manufacturing records for these valves, in a search for new clues to aspects of the manufacturing process that might predict valve failure. Rates of mortality and valve fracture in the entire cohort are being updated through 1996, of importance because in the past the highest rates of fracture have been reported from the Netherlands and have led to acceptance of the notion that fractures elsewhere in the world are being underdetected. Information on mortality following elective replacement of the BSCC valves is also being compiled. Initial results are expected in early 1997.

The UK cohort study, led by Professor Ken Taylor and initiated in 1996, involves the followup of approximately 3,600 patients with 4,000 BSCC valves (almost all 60^0 valves). Medical records at the time of implant are being abstracted to determine patient characteristics for later examination of their effect on valve fracture. Complete ascertainment of all deaths is possible through national vital statistics registration in the United Kingdom, and post mortem examination data and medical records for deaths with suspicion of valve-related etiology are being obtained to evaluate potential underreporting of valve fractures. A manufacturing record review may be initiated should the Dutch study indicate its advisability . In addition, the UK Heart Valve Registry, a systematic recording of all artificial heart valve patients since the mid 1980s, is being accessed to provide estimates of in-hospital vs 90-day mortality associated with reoperations to replace artificial heart valves. Results are expected in late 1997.

In the United States, a pilot study is nearing completion to assess the feasibility of conducting a cohort study among American BSCC patients. The study would utilize Medic Alert records on approximately 12,000 BSCC patients and ascertain mortality during the period 1991-96. The full-scale study would help evaluate the postulated nearly 50% underreporting of valve fracture in the United States, and provide direct estimates of risk in the 1990s. The pilot study, evaluating access to and followup of the patients, is expected to be completed in late 1996.

MEC

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DONALD C. HARRISON, M.D.
PRESIDENT

LAURA M. HARRISON
MANAGER

DATE: December 10, 1996

TO: Kermit Smith

FROM: Donald C. Harrison, M.D.

Attached is the revision which you needed. I believe the Appendices A, B, C1, C2 should be included, but I have removed Appendix D. Appendix E is now relabeled Appendix D. I have also removed the Repository section.

Hope this is satisfactory.

MEC

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DONALD C. HARRISON, M.D.
PRESIDENT

LAURA M. HARRISON
MANAGER

DATE: December 10, 1996

TO: J. Kermit Smith

FROM: Donald C. Harrison, M.D.

RE: Report of the Bowling-Pfizer Supervisory Panel
Subcommittee on Imaging and Acoustics

Introduction

This memorandum is a report of the activities of the subcommittee during the past several months. Our intent is to report on our monitoring of the ongoing research project in the area of imaging and acoustics to provide an analysis of a meeting held at Livermore which brought together all of the groups working on acoustics. It will also outline the likelihood of proposals for future research. These results will be discussed in detail at the Supervisory Panel meeting January 3-4, 1997.

This summary report is accompanied by appendices which are the more detailed reports presented by the research groups carrying out the work.

Acoustic Studies

The acoustic studies fall into two major project areas. First, an analysis of 70 recordings from patients and sheep where the ground truth is known for the status of the valve. These recordings were made with the Tracor instrumentation in the patient sites at Beaumont, Glasgow, and Stanford, and in the sheep, at the Hershey site. Some of the recordings were made with digital techniques allowing a full spectral range for the data, and some were recorded on digital acoustic tapes with filters which limited the spectral range of the data recorded. In addition, the sheep recordings proved to be impossible to analyze because of a poor signal-to-noise ratio likely resulting from the difficulty in carrying out sound recordings in sheep.

The second major set of studies relates to the planned anechoic studies by the Livermore group

utilizing an anechoic chamber in Santa Barbara, which is the property of the U.S. Navy. These studies should have been carried out years ago to get the basic data needed to develop appropriate analysis algorithms for clinical data. A detailed description of these anechoic studies will follow.

SAI Studies

Allen Eberhardt and his colleagues have completed the analysis of the 50 human acoustical recordings which were given to them in a blind analysis study. Their studies were carried out on the closing sound as the primary focus of the analysis. Their report is attached as Appendix A. The sensitivity and specificity for their analysis both were in the low 80% range. This can be interpreted to mean that they had a false-positive rate of approximately 20% and a false-negative rate in the same range. Upon careful analysis, the reasons they missed in their identification was the fact that the Glasgow data proved to be the cause of the largest number of errors. Their training set had not included data from Glasgow.

Livermore Report

The results of the Livermore studies on the 50 tapes presented in a blind fashion are attached in Appendix B. The sensitivity and specificity for the Livermore studies were quite similar to that of SAI. However, the largest group of misses for the 20% false-positive and 20% false-negative were from Stanford. The analysis from this group focused largely on the opening sound, but in the more recent runs, also included the closing sound. The full report for the committee is attached for review.

Combined Conference with SAI and Livermore on November 24-25, 1996

The subcommittee convened a meeting at Livermore, California with the two acoustical analysis groups. Appendices C1 and C2 present the attendees at the meeting and the agenda which was followed. The focus of the discussion was on the combined studies and what factors were important in the correct and incorrect detections. There was general agreement on the area in the sound spectrum which contained important information for differentiation between SLS and normal valve sounds. Additional focus was on the lessons learned, the most important being that the training set of 24 total valves, 14 normals and 10 SLS, was inadequate to develop appropriate detection methods across a wide spectrum of potential patients' sound recordings from those that have BSCC valves in place.

The group projected collaborative programs to improve the analysis algorithms, and criteria were developed to define what level of sensitivity and specificity would make the acoustical analysis useful for patients. The primary detection methodology must be greater than 95% specific, that is, presenting a very small number of false-positive tests in order to prevent recommending patients with normal valves for explantation. Further analysis of the combined

algorithm programs developed by the two groups can, at this time, reach a specificity in the high 80% range, but will require extensive work to become more accurate.

Anechoic Studies

Livermore has now planned anechoic studies with 24 valves. As pointed out earlier, these studies should have been carried out long ago so that the sound characteristics without external noise could have been identified. By doing anechoic studies on normal and SLS valves, patterns of abnormal sound spectra can be developed. Based upon such programs, techniques to determine sensitivity and specificity by analyzing different parts of the sound spectrum of both the closing and opening sounds may be possible. If the anechoic studies demonstrate that an appropriate sensitivity and specificity can be developed which would allow differentiation of normal from SLS valves with a high probability of being correct, then better recording techniques will have to be developed. A new recording system need not be planned until the anechoic studies have been completed. If indeed, under the best of conditions it is not possible to develop spectral analyses or feature extractions from the spectra which allow both sensitive and specific detection to occur, there will be no need to develop new acoustical recording equipment.

This project will be followed closely by the subcommittee. It is intended that studies will be completed by the end of January 1997. The one major recommendation of the subcommittee would be to obtain as many other valves as possible for anechoic studies, since that would give a higher probability of developing analytical techniques for the detection of abnormal sound from the broad spectrum of patient groups. This will require additional work on the part of Livermore and would require extending their budget and the time for them to complete the studies. We intend to work on this before they have completed their studies at Santa Barbara.

Cleveland Clinic Studies

As previously outlined in my earlier reports, there are three objectives to the Cleveland Clinic studies. Considerable progress has been made on each of these. The basic summary findings are:

1. The ability to digitize all of the signals from images acquired at Stanford, Glasgow, and Beaumont would be important in putting these data into a centralized database. This would allow many more investigators to interact with them and to potentially develop image enhancement techniques which would be useful to the patient groups.

2. No clear identification of a time in the cardiac cycle in which images are most likely to reveal SLS was possible with the quality of the data and the infrequent ability of X-ray to detect SLS.

3. Image enhancement techniques used alone are not likely to increase the sensitivity of the diagnostic techniques utilizing X-ray. These remain at approximately the 30% level and further enhancing of the images which were acquired does not seem to be a profitable pursuit.

Coordination of Activities with Dr. Thomas Ivey on Guidelines

Our group has reviewed the data presented at the Vienna meeting of the Guidelines Committee and of their recommendation. We have also been made aware of the work Ron Brookmeyer has been doing to develop algorithms to identify patients with the potential for further study of the status of the BSCC valves. The segmentation of groups and priorities for their consideration seem important to us. We look forward to the opportunity to review his entire database and their conclusions at the January 1997 meeting of the Advisory Panel.

As a committee, we have also reviewed the mortality data from the explant surgeries which are available to us. It is clear that age and the status of heart failure in these patients will be important in stratifying recommendations for explant. Further work in this area is indicated and may be part of the follow-up studies which we will be proposing at a later date.

Quantum Magnetics Proposal

After completing preliminary studies utilizing the principles of magnetometry, the Quantum Magnetics group has made an extensive proposal for furthering their magnetic studies. Our subgroup arranged for Dr. John Wikswo to review this proposal. Dr. Wikswo is Professor of Physics a Vanderbilt University who has worked with magnetic signals from the heart and its structures for more than 20 years. He coordinated his review with a mathematical analysis by Dr. John Newell of the Massachusetts General Hospital. Appendix D is the full analysis of the proposal by Wikswo and Newell. They detect some possibility that magnetic techniques might be useful. However, they believe that the presently-constituted Quantum Magnetics proposal is far too ambitious until more preliminary and pilot studies are accomplished. They have recommended funding for parts of the proposal and for providing the Quantum Magnetics group with the critique and recommendations. It is essential that this evaluation and critique remain confidential, since Dr. Wikswo has other ongoing projects with the Quantum Magnetics group.

We will present a series and summary of recommendations to the entire panel at its January 1997 meeting.

Follow-up Study Proposal

As we have previously discussed, the Imaging and Acoustics Subcommittee believes that a

follow-up study of patients imaged at Beaumont, Glasgow, and Stanford is absolutely essential. While there are logistic problems with Pfizer as to the assumption of the cost of previous studies at Beaumont which might limit the scope of this study, we still believe that this group is the best defined clinical group we have available. The nearly 1000 carefully-studied patients will provide important clinical insights into the course of patients with BSCC valves, not only including outlet strut fracture, but also including the other major complications of risk. Embolic and stroke risks, the development of endocarditis, perivalvular leak, the importance of advanced heart failure, and the subsequent development in elderly patients of coronary artery disease are far more important that outlet strut fracture in determining the clinical course of patients with BSCC valves. Important clinical guidelines can be developed from such a database, which we feel to be extremely important.

Dr. Gary Grunkemeier and Dr. Donald Harrison are developing a proposal for presentation to the Supervisory Panel for such a follow-up study. The proposal will be modified in accord with the directions from Shiley and from class council, and within the logistical capabilities of funding as part of the ongoing research.

Kermit, I believe this summarizes and provides you with back-up material for what this group has been doing. I will provide my separate appraisal of the new proposed Dutch epidemiological study and the Xiao proposals from Texas A&M University. You should regard what I am providing as draft material, since I am submitting it to my other subcommittee members for any corrections they might have. I trust this will be useful to you for the court hearing.

cc: Robert Black
Peter Strauss
Arthur Weyman
Robert White

p:\dch\bprpt2

APPENDIX A

Acoustic Classification of BSCC Heart Valve Condition

Executive Summary, Structural Acoustics, Inc.

December 5, 1996

1. Results

A classifier has recently been applied to evaluate outlet strut condition for a set of 50 blinded data sets (35 valves) received from the Bowling-Pfizer Research Management Group. This classifier was developed in April of 1994 by Structural Acoustics, Inc. at the completion of the first stage of a project to acoustically classify BSCC heart valve outlet strut condition. In developing the classifier, ten (10) SLS valves, and fourteen (14) IOS valves were used for identification of spectral features, and for training to separate the two classes using a Volterra expansion based on the identified features. Because two sets of recordings were made for four of the SLS valves and for seven of the IOS valves, a total of fourteen (14) SLS and twenty-one (21) IOS recordings were used in the development of the classifier (35 total recordings). When the classifier was applied to these original 35 recordings, using a leave-one-out method, results were as follows:

Leave-One-Out Training Results (1994)

Sensitivity: 100%

Specificity: 100%

When 19 additional blinded data sets were included, performance was reduced to the following:

Leave-One-Out and Blinded Testing Results (1994)

Sensitivity: 96%

Specificity: 93%

When it was revealed that the blinded data included multiple recordings of individual valves, combining the data sets for each valve again produced a sensitivity of 100% and a specificity of 100%.

In August of 1996, this same (1994) classifier was applied to 50 new blinded data sets with performance results as follows:

Blinded Testing Results (50 data set basis) (1996)

Sensitivity: 70%

Specificity: 73%

Because two sets of recordings were made for five of the SLS valves and for ten of the IOS valves, the twenty (20) SLS and thirty (30) IOS recordings, were produced from 15 SLS and 20 IOS valves. When the same classifier was applied to the new blinded data of August 1996, but on a valve-to-valve basis, the performance for the 35 individual valves is as follows:

Blinded Testing Results (35 valve basis) (1996)

Sensitivity: 80%

Specificity: 80%

2. Existing Problems

Both in 1994 and in 1996, performance improves if multiple data sets for each valve are used. There are a number of likely contributors to the change in performance on the new blinded data as follows.

1. The spectral features for separation of the two classes were identified in 1994 using a Mahalanobis technique on all available explanted (gold-standard) valves (10 SLS and 14 IOS). These same valves were then used to train the Volterra classifier. Due to the small number of valves available for identification of the feature set, and the small number of data sets available for training, neither the features nor the weights are sufficiently robust.

2. The recent data, analyzed in August of 1996, were all recorded on Digital Audio Tape (DAT), with inadequate checks on signal quality, whereas all data used in the original training and almost all data used classification testing were recorded (on disk) only after passing a qualification check by the acquisition system for signal level, and subsequent adjustment by the auto gain control (AGC) circuitry. The DAT is perceived as a 'backup system' by Shiley; analysis of clipping and under-range data reveal the poor quality.

3. The data used for training was acquired using 8-pole elliptic anti-alias filters set to a 22 kHz low-pass cutoff. The Stanford system was recently discovered to have 4-pole anti-alias filters set at 15 kHz. This lowered cut-off alters all features above 15 kHz, including key features at 18 kHz and at 22 kHz.

4. Robustness is poor due to lack of multiple auscultation points on each patient, resulting in dropout of key features due to the directivity of the source above 10 kHz. Multiple recordings can be more robust than a single record if a slight shift is introduced in the location of the recording microphone. A change of less than two centimeters can alter the classification results.

5. Changes in microphone location of a few centimeters across a set of five recording positions in vitro produced a significantly different result for each position, producing in an incorrect classification for one of the five measurements.

3. Requirements for 95% Performance

It is reasonable to expect sensitivity and specificity in the range of 95% if improvements in the process are made. These improvements require the following actions:

1. The original training was done with only 10 SLS and 14 IOS valves; this is a very small number of the total universe of valves. More training data is necessary, through human opportunistic recordings, in vitro studies, or both.

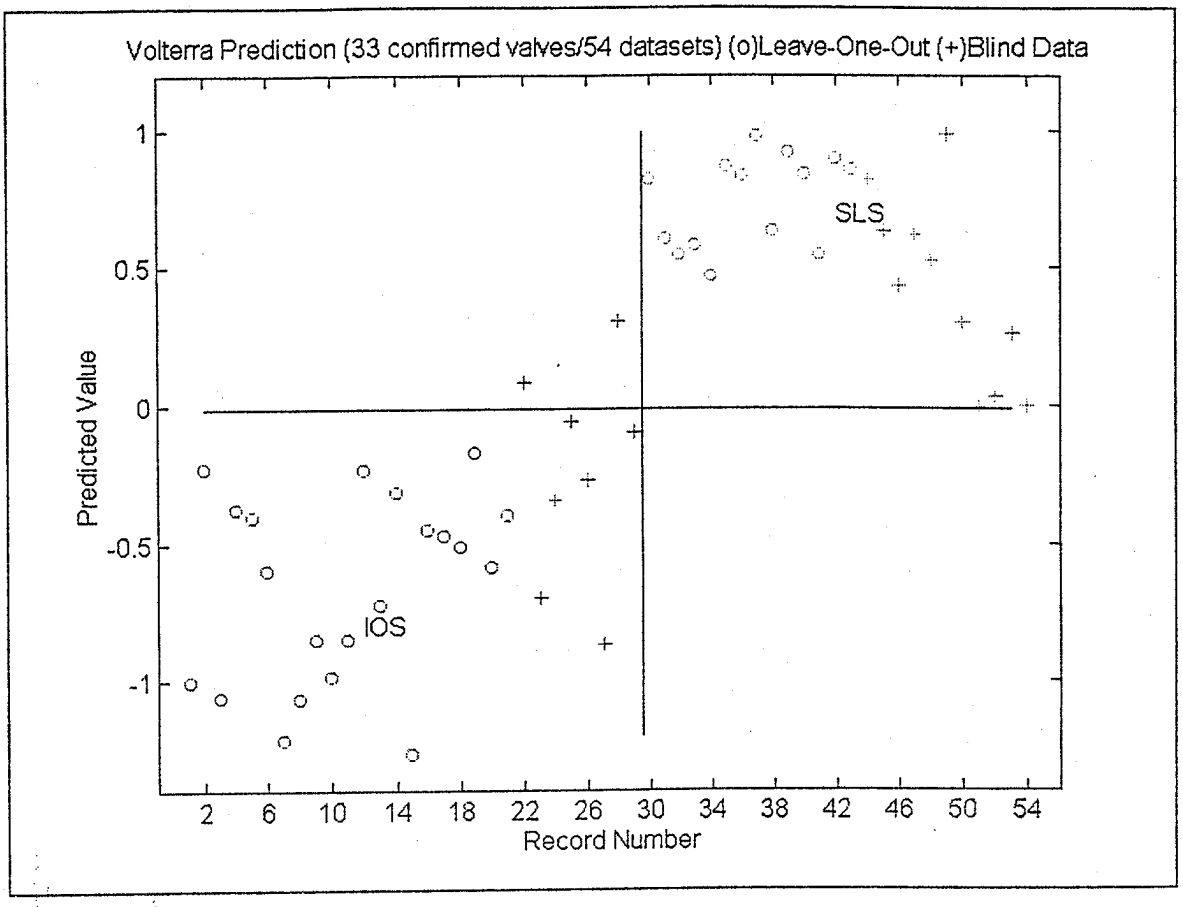
2. Valve acoustic emissions are directional for all frequencies of interest. Multiple auscultation points on each patient, whether obtained simultaneously or sequentially, are essential.

3. Acoustic data should be acquired via digital recording through a computer interface, with qualification and rejection of under-range, noisy, clipped, or unrecognizable signals.

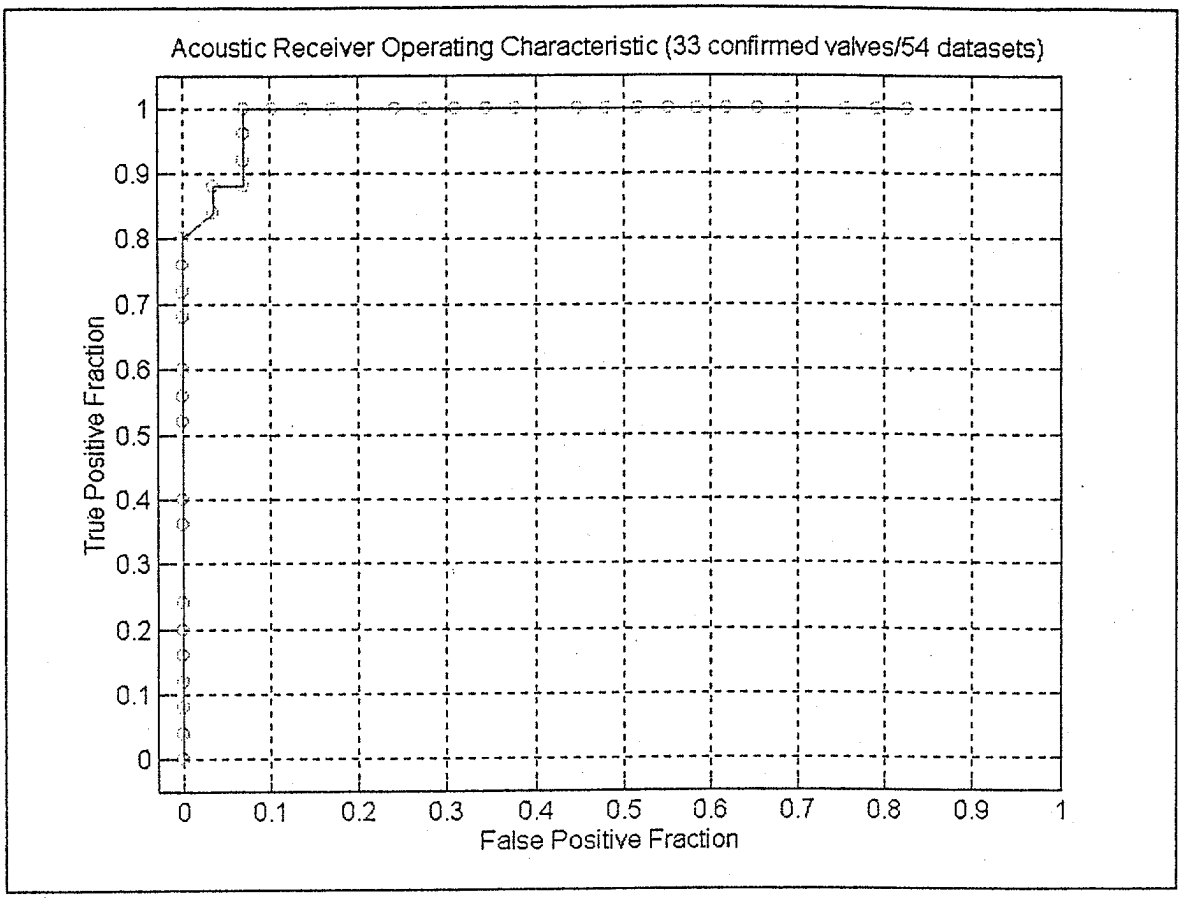
4. Filtering must be performed using appropriate 'brick-wall' anti-alias filters at no less than 23 kHz cut-off frequency.

These requirements can be completed in a time frame of less than eighteen months.

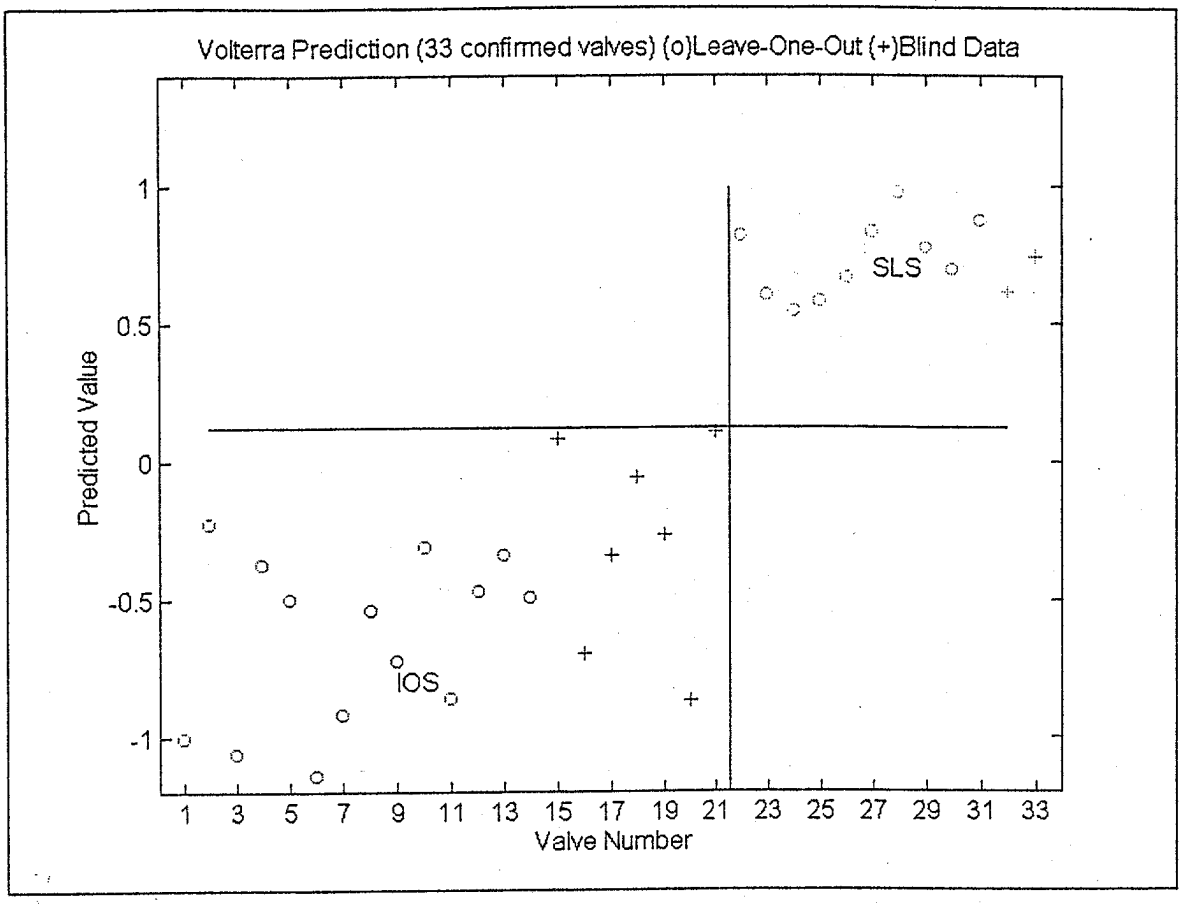
Accompanying figures show the results of classification of individual data sets, individual valves, and for a single SLS valve recorded at five distinct microphone positions.



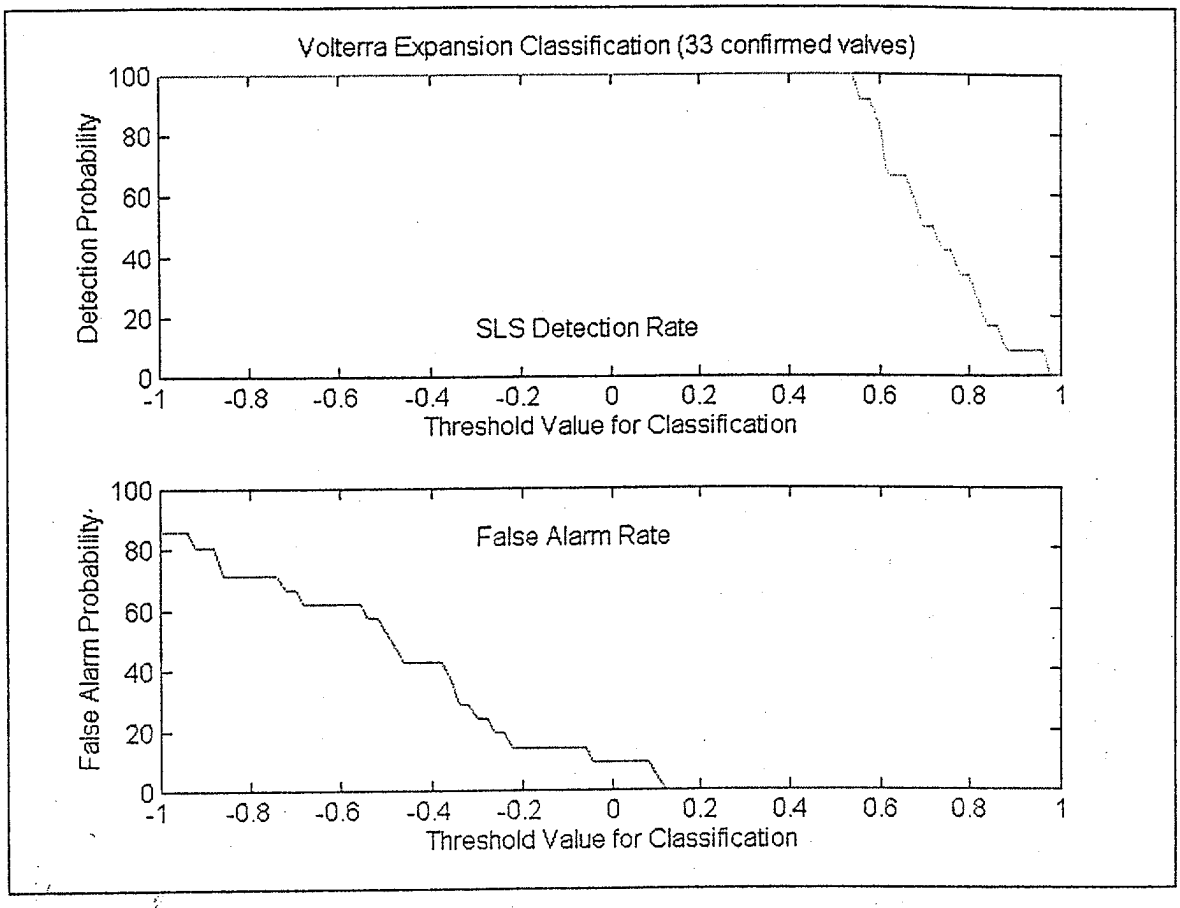
Separation of 54 data sets of 1994 leave-one-out and blinded data.



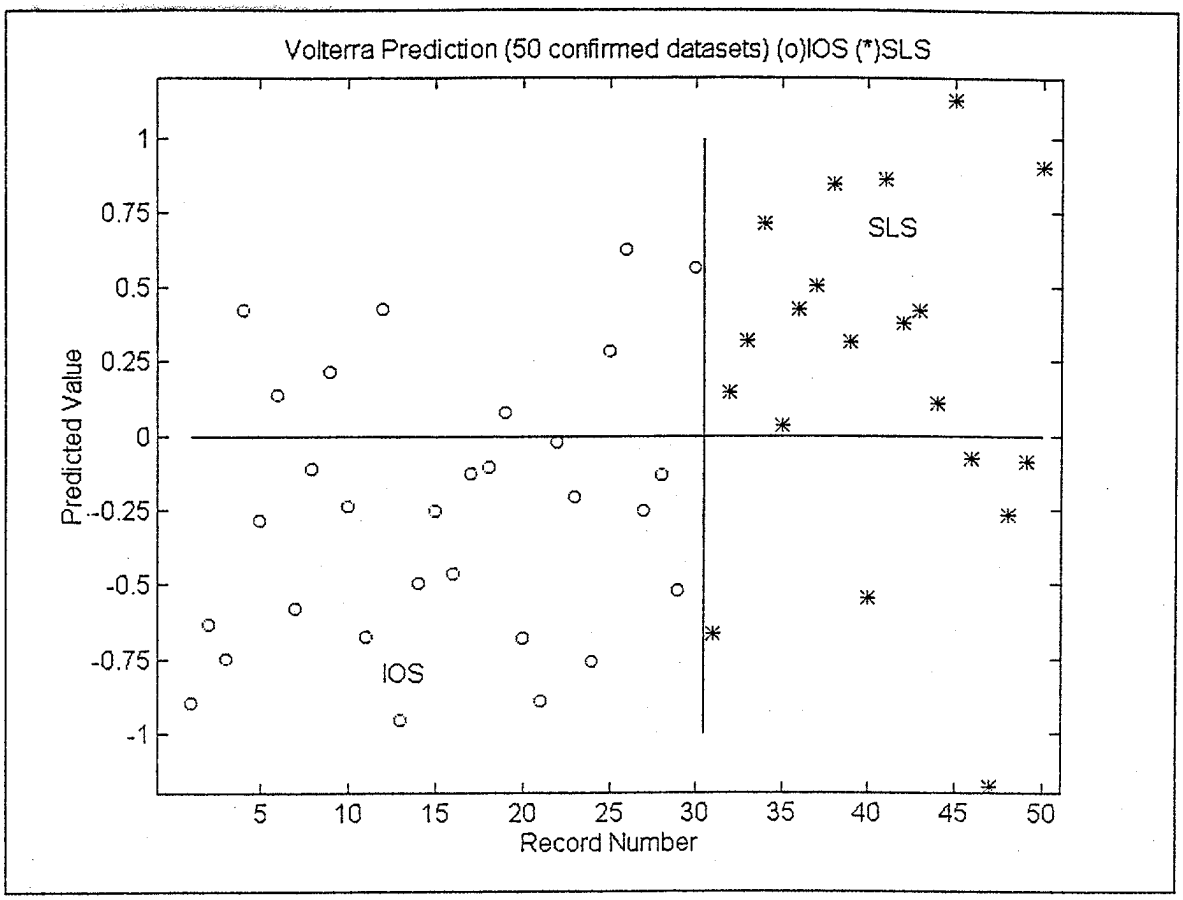
ROC curve for 54 data sets of 1994 leave-one-out and blinded data.



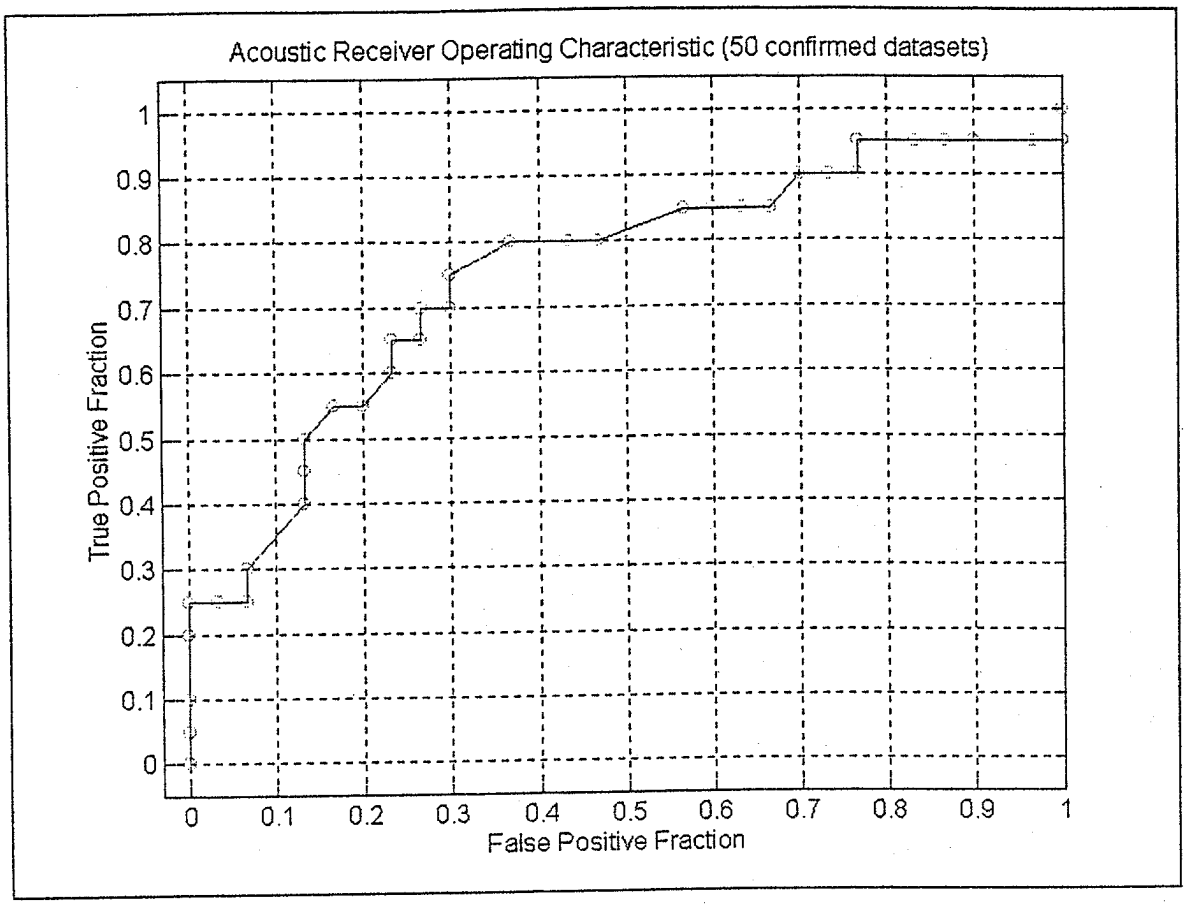
Separation of the 33 valves of 1994 leave-one-out and blinded data.



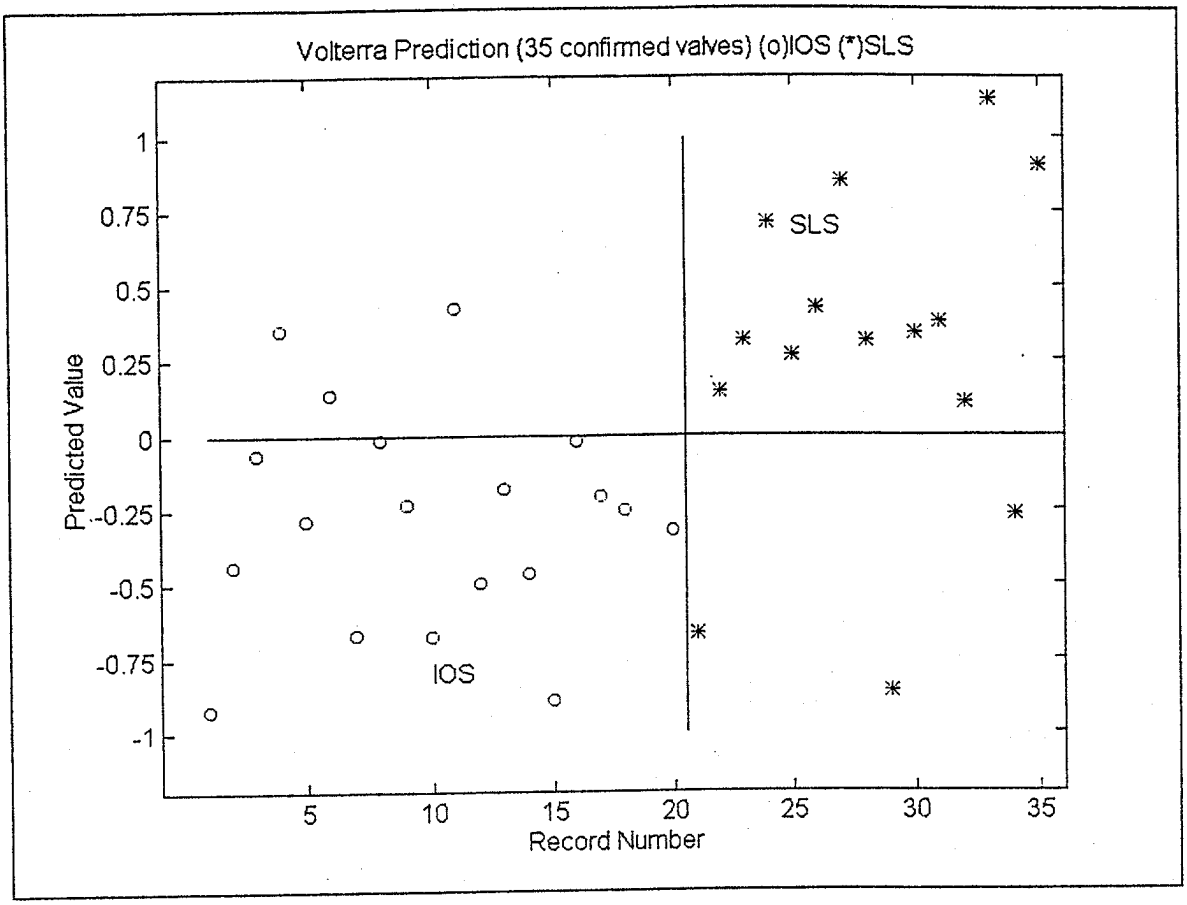
Threshold effect on the 33 valves of 1994 leave-one-out and blinded data.



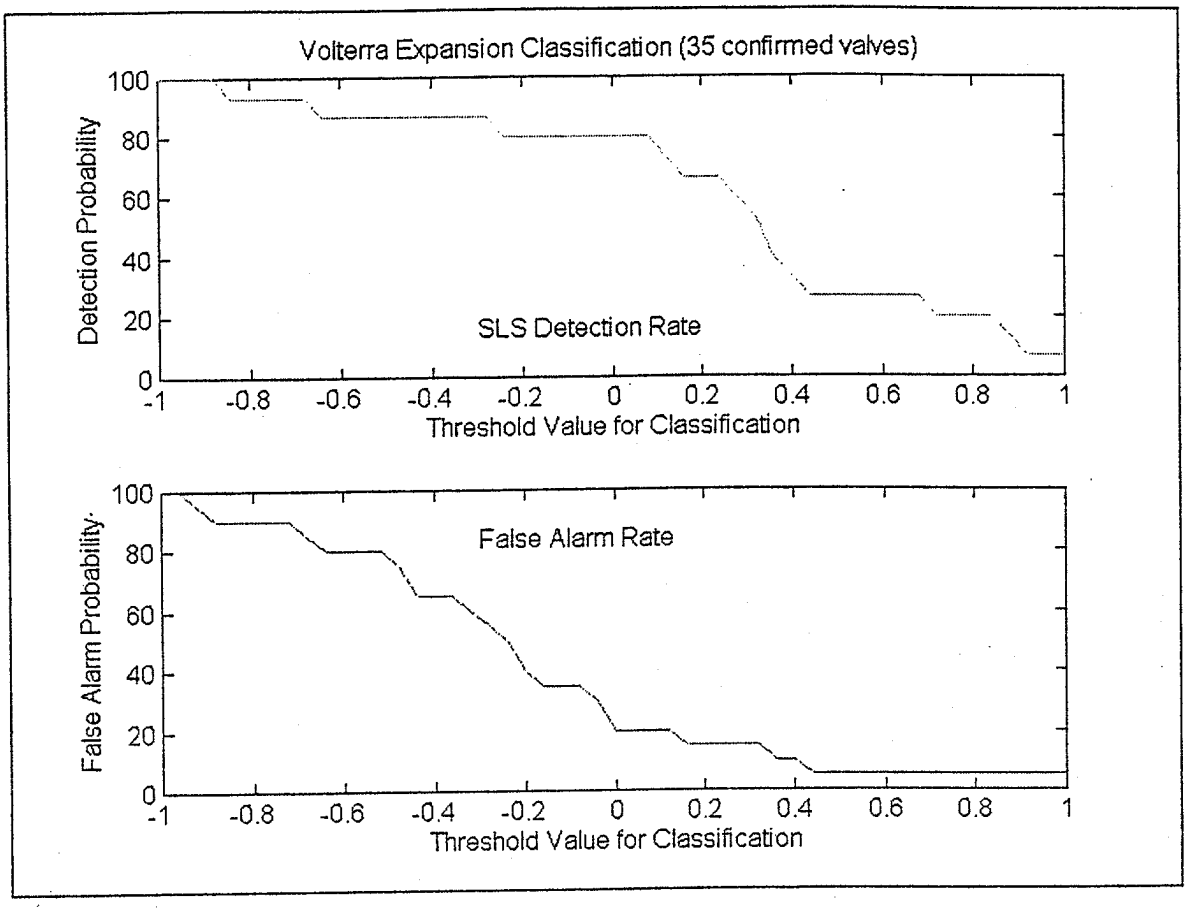
Separation of 50 data sets of 1996 blinded data.



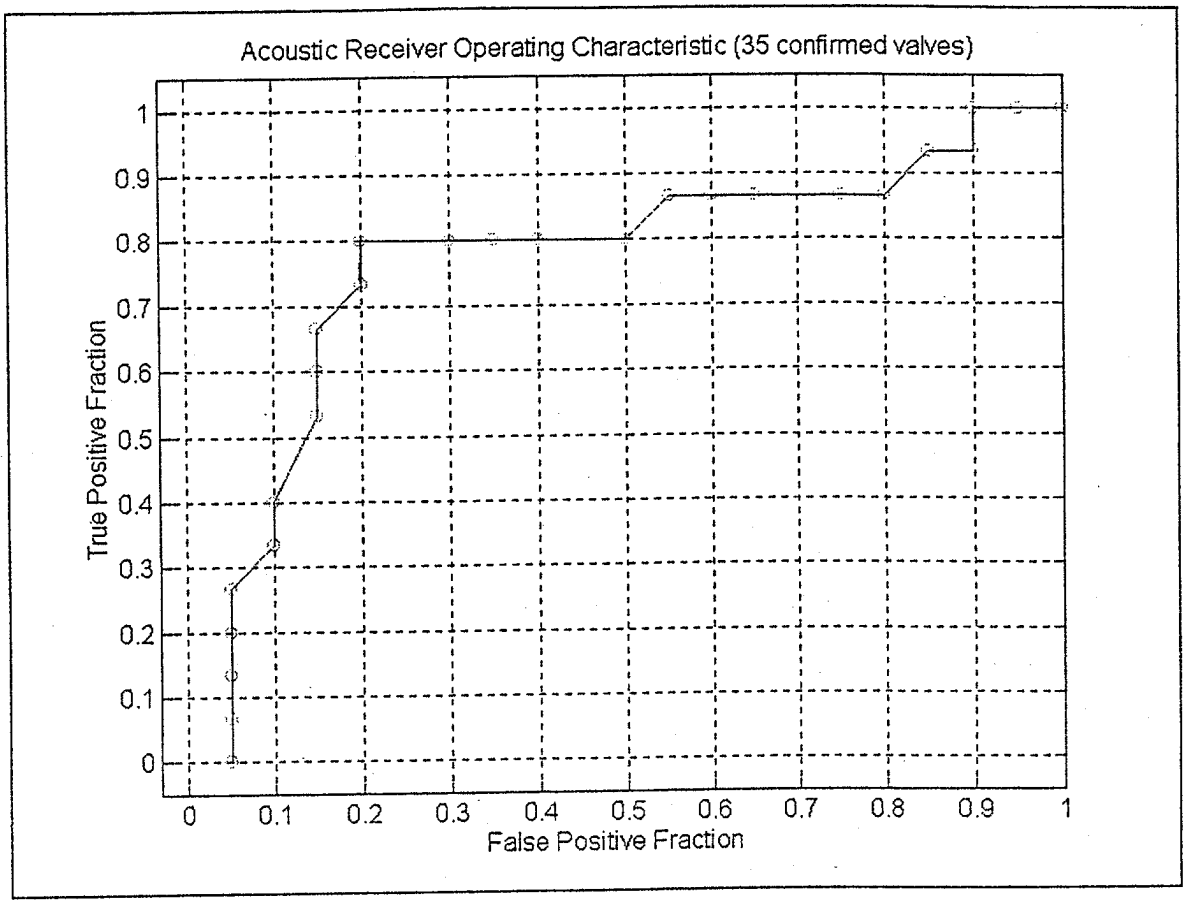
ROC curve for 50 data sets of 1996 blinded data.



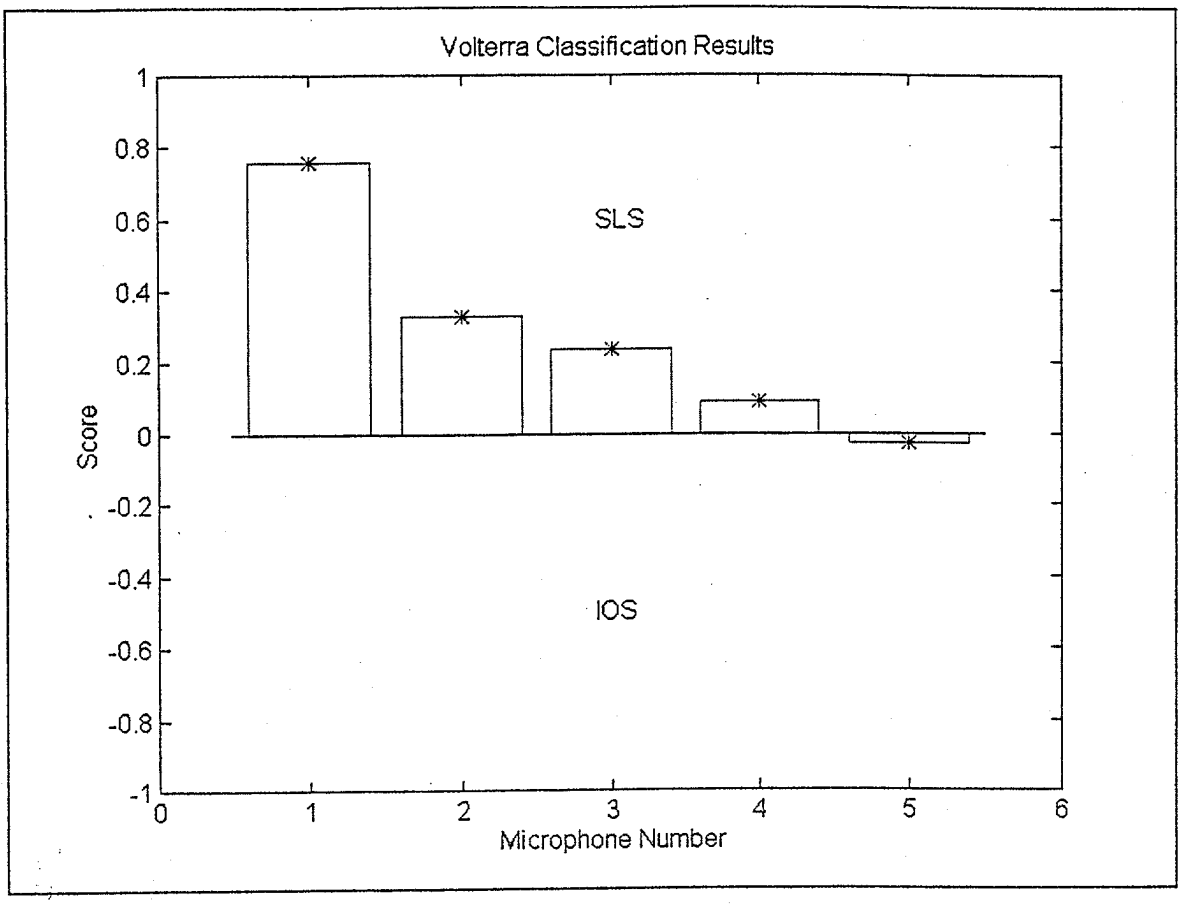
Separation of the 35 valves of 1996 blinded data.



Threshold effect on the 35 valves of 1996 blinded data.



ROC curve for 35 valves of 1996 blinded data.



Classification results of a single SLS valve for data acquired at five microphone positions.

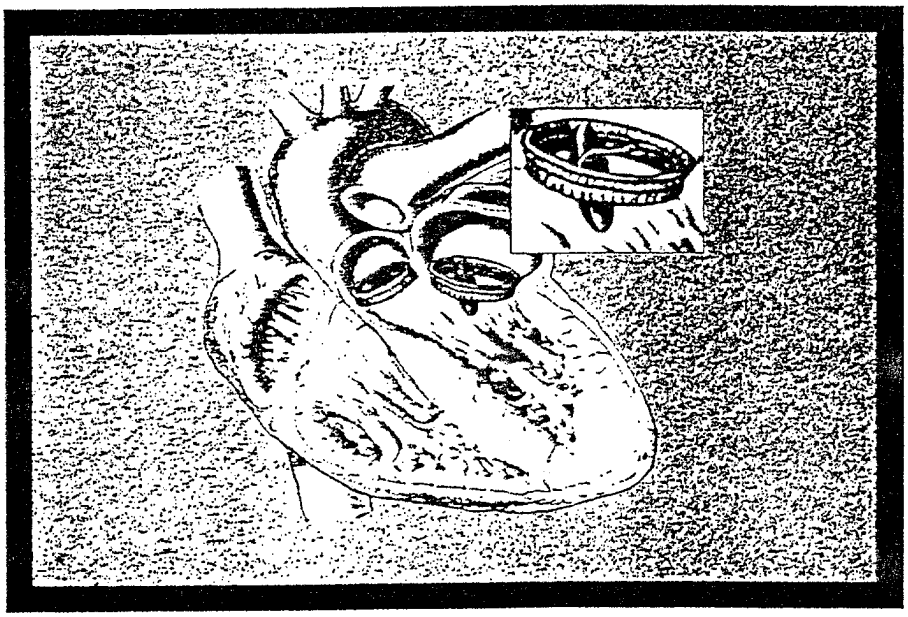
APPENDIX B

Imaging and Detection Program
Lawrence Livermore National Laboratory
An equal opportunity employer

LLNL HEART VALVE CONDITION CLASSIFICATION PROJECT

BLIND STUDY RESULTS

FINAL REPORT
to the
BOWLING-PFIZER SUPERVISORY PANEL



James V. Candy
Principal Investigator

November 27, 1996

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ABSTRACT

This final report contains the Blind Test results for the Bowling-Pfizer Heart Valve Supervisory Panel (BPHVSP) in accordance with the Department of Energy Work for Others (WFO) Contract commencing on July 7, 1996. The report satisfies the requirements for Task I of said contract and describes the results of designing the LLNL Heart Valve Condition Classifier (LLNL-HVCC) on training data received from the BPHVSP and the subsequent application of this Classifier to fifty (50) blind acoustic recordings provided by the Panel for testing its performance. Here we briefly outline the approach in order to explain the resulting figures and tables which detail the performance of the LLNL-HVCC.

BACKGROUND

The structure of the LLNL-HVCC is shown in Figure 1 where the approach is to extract the heart valve sounds both closing and openings from the measured acoustic recordings. We concentrate our discussion on the opening sounds, which are understood to possess the direct outlet strut fracture (vibrational) information, and perform the necessary signal processing to extract pertinent features which are used to distinguish between two (2) prescribed conditions: *intact* (INT) outlet strut or *single leg separated* (SLS) outlet strut. We, therefore, classify the condition of the valve under test as INT or SLS. From the figure, once the features are selected, they are used to calculate the required decision metric which is compared to a prescribed threshold to classify the condition of the heart valve under test. Once the required quality control of the raw data (outlier rejection, etc.) and signal processing have been accomplished, there are three critical aspects to the design of the classifier: (1) the *type* of feature used to characterize the valve; (2) the *selection* of the most sensitive features to classify the heart valve condition (INT or SLS); and (3) the determination of the *threshold* value used to make the decision.

Our choice of the feature type for this study is based on the underlying vibrational response of the heart valve characterized by spectral bands of acoustic energy, that is, the valve sounds are transformed to the Fourier domain and decomposed into spectral frequency bands (or bins) which are then automatically sorted by the computer and ranked from the most important (sensitive) to the least. This procedure is the feature selection operation (shown in Figure 1). Based on the number of training valves available, we use the first three (3)* most sensitive bands to construct the classifier.

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* In this problem due to the limited number of valves available for training (23), we are limited (by choice) to only 3 features. This choice is based on a well-known, tried-and-proven rule in classification theory that determines the number of features based on the number of known training samples available.

Prior to application of the classifier to the blind data set, it is "trained" using known valves (ground truth) for each class--this is called *supervised* learning, where the classifier is taught the training set. In this study we had a total of 23 valves (13 INT,10 SLS) which represent the training set used to design (train) the classifier. After carefully pre-processing each beat or opening sound for a given training valve, those beats qualifying as statistically acceptable are extracted and incorporated into the training set for supervised classification. It is important to understand that supervised classifiers can only perform as good as the training set data input during the supervised training requiring this data to be a valid representation of the valves to be classified. That is, *good* training data will lead to *good* classifier performance and visa versa. Therefore, it must be stressed that our procedures (beat selection, outlier rejection, signal processing, etc.) are all aimed at extracting only the best beats to represent each valve and therefore represent each class. Much care and diligence must be exercised in processing data prior to acceptance into the training set. Here the old axiom, "one rotten apple spoils the barrel," applies. Once the training set has been extracted and processed, a "self-consistency" check is performed on this set called *cross-validation* or more colloquially *hold-one-out*. This calculation involves: (1) removing each valve in the training set--one at a time (hold-one-out); and (2) classifying the (already known) condition of the valve held out to assure it is still represented by the remaining valves. Theoretically, the classifier should be able to classify each valve in the training set correctly validating its performance.

Finally, once the training set (of valves) is constructed, the performance of the classifier can be characterized by its operating characteristic or equivalently receiver operating characteristic (ROC) curve, which is a measure of sensitivity (probability of detection) versus (1-specificity) or probability of false alarm. The ROC can *only* be obtained from the "training set" data, since the condition of the valves must be known a priori to construct the curve. Once the ROC is determined, *an operating point* (for the classifier) must be selected from the curve based on the desired sensitivity/specificity. A *threshold value* corresponding to this operating point is then used for the blind set classification.

TRAINING (Openings)

With this information in mind, next let us investigate the performance (and design) of the LLNL-HVCC based on the available training data. As mentioned after careful pre-processing, our training set consisted of 23 total valves: 13 INT and 10 SLS. Note that even though we had multiple sessions of each valve (55 sessions to be precise), we decided to use only the "last session" *before* explant to eliminate any question of ground truth (e.g. possible valve condition change from recording of INT to SLS) or biasing of the feature selection towards valves with multiple sessions. The three

spectral bands automatically chosen by the feature selector were (center frequency, bandwidth): (13.6 kHz,469 Hz), (16.7 kHz,469 Hz), and (20 kHz,94 Hz).

We can succinctly summarize our classifier performance in a so-called confusion matrix (or contingency table) shown in Figure 2. The 2-row, 2-column matrix whose entries on the diagonals represent the sensitivity, that is, the probability that the valve classified as SLS given it is SLS (*Prob(SLS/SLS)*) and corresponding specificity, *Prob(INT/INT)*. The off-diagonals represent the different error types: *miss* or probability that the valve is classified INT given that it is SLS (*Prob(INT/SLS)*) or corresponding false alarm, *Prob(SLS/INT)*. For our training set using the "hold-one-out" check, the LLNL-HVCC performed perfectly: *Prob(SLS/SLS)=1.0; Prob(INT/INT)=1.0; Prob(INT/SLS)=0.0;* and *Prob(SLS/INT)=0.0* as shown in the table. The ROC is shown in Figure 3 along with the operating point and threshold shown on the two posterior probabilities used to calculate the ROC. The operating point on the curve was selected corresponding to a (sensitivity, specificity) of (1.0,1.0) giving a threshold of 0.5. The LLNL-HVCC classifies a valve by processing one beat at a time calculating its posterior probabilities (*Prob(SLS),Prob(INT)*) and averaging all of these beat posterior probabilities to obtain the final decision metric (overall "valve" posterior probability). For each valve in the training set (openings), the average posterior probability is shown in Figure 4. Since we are estimating the "average" using sample statistics, we can also estimate a "confidence interval" or bound around each posterior probability estimate to indicate "how good the estimate is." This bound (line ending in a bar) surrounds the estimate and gives us a method of determining the quality of our posterior estimate, that is, a small bound or interval surrounding the estimate implies that the "true value" is close to the estimated value. Therefore, a large interval implying a "bad" estimate would lead us to discount the estimated posterior probability. We use this approach to "tag" questionable classifications, that is, if the confidence interval crosses the decision threshold, we tag the valve and prefer to place it in a "no-call" region not specifying its class. In clinical practice, this would lead us to "take more data," while the patient is still available. From the figure, we see that the results of our training were excellent as predicted simply by the confusion matrix (Figure 2) or in detail from the posterior probability plots (Figure 4). We see that not only were the valves classified correctly (lying above or below the 0.5 threshold), but almost all beats were perfectly classified giving posterior probability that were *Prob(SLS/SLS)=1.0* and *Prob(INT/SLS)=0.0* with extremely high confidence in the posterior probability estimates (negligible intervals) except for INT valves No. 4 and No. 12. A more detailed summary of the training is shown in Table 1. From the table we see the details of each valve, its total number of beats extracted, the classification of each beat along with the % of beats classified as SLS and the corresponding posterior probability and along with confidence intervals plotted in Figure 4.

We summarize the performance of the LLNL-HVCC during training as:

LLNL-HVCC TRAINING (Openings) SUMMARY

No. of Valves:	23 (13 INT, 10 SLS)
Correct Classification (x 100):	100 %
Sensitivity (x 100):	100 %
Specificity (x 100):	100 %
Operating Pt (Sens.,Spec.)@Thresh.:	(1,1)@0.5
Spectral Features (center freq., bw):	(13.6 kHz,469 Hz) (16.7 kHz,469 Hz) (20 kHz,94 Hz)

BLIND TEST (Openings)

Next we applied the classifier to the blind data set supplied by the BPHVSP. After again carefully processing the data, the blind test opening beats were extracted and classified, first beat-by-beat and then overall using the spectral features and the corresponding threshold selected during training from the ROC curve. The results are summarized in Table 2. Here we again see the number of beats and % SLS beats estimated by the LLNL-HVCC. Each valve classified (posterior probability) is shown in Figure 5 along with its corresponding confidence interval. After the classification was performed, we obtained the true valve class (ground truth) and annotated each correctly classified valve by a "diamond" and each misclassified valve by a "circle" on the plot along with the predicted confidence interval and threshold. For this table those valve tagged as questionable or uncertain (large confidence interval) are highlighted. Again the predicted estimates cross the 0.5 decision threshold defined as the "no-call" region. With the ground truth made available (post-blind test), we are able to calculate the confusion matrix shown in Figure 6. For the blind test on *openings*, we are able to achieve a sensitivity of *80%* and specificity of *66%*. A more meaningful overall measure is the probability of correct classification (x 100) which is *72%*. It is also interesting to note that if we exclude the tagged values or no-calls due to high uncertainty in the posterior probability estimate, then we eliminate 15 sessions (highlighted in Table 2) and our probability of correct classification increased to *85.7%* with a corresponding sensitivity of *87.5%* and specificity of *84.2%*. We summarize our opening blind test results for these two cases as:

LLNL-HVCC BLIND (Openings) SUMMARY:

No. of Valves:	50 (30 INT, 20 SLS)
Correct Classification (x 100):	72 %
Sensitivity (x 100):	80 %
Specificity (x 100):	66 %
Operating Pt (Sens.,Spec.)@Thresh.:	(1,1)@0.5

REMOVE NO-CALLS:

No. of Valves:	50 (19 INT, 16 SLS)
Correct Classification (x 100):	85.7 %
Sensitivity (x 100):	87.5 %
Specificity (x 100):	84.2 %
Operating Pt (Sens.,Spec.)@Thresh.:	(1,1)@0.5

Thus, summarize the performance of the LLNL-HVCC on the blind opening beats, we have that:

- our raw results for the openings are: 36 sessions representing 36 different valves correctly classified out of 50 blind sessions for a total correct classification of *72%* with a sensitivity of *80%* and specificity of *66%*.
- removing the no-calls indicated by the LLNL-HVCC, then of the 35 sessions classified, a total correct classification of *85,7%* with a sensitivity of *87.5%* and specificity of *84.2%* resulted.
- since our training ROC indicate we could select a threshold between 0.2-0.8 to achieve 100% correct classification, then if we move the threshold to 0.66 corresponding to the a priori knowledge of the ratio of known SLS/INT in the blind set, then a total correct classification of *78%* with a sensitivity of *75%* and specificity of *80%*.

After the ground truth was disclosed for the valves, we included a subset of the previous 50 blind valves choosing 30 valves discarding misclassified and no-call valves to create a new 53 valve training set. We then performed a post-blind test hold-one-out. The resulting run is shown in Figure 7 with the

corresponding confusion matrix in Figure 8. Here we see that of the 53 available valves all were classified correctly during cross-validation except one, which curiously was previously classified correctly (no explanation at this time). A total correct classification of *98%* with a sensitivity of *100%* and specificity of *97%*. These results for the opening sounds are quite encouraging.

TRAINING & BLIND TEST (Closings)

We applied the LLNL-HVCC approach to the closing sounds as prescribed in Task 1B&C of our WFO contract. We used the same classification scheme; however, with the feature types (spectral bands) selected automatically from the closing spectra. We found out a most disturbing fact. Besides the closing sounds not having direct isolated contact with the outlet strut as in the opening sounds, various modes are excited during each closing event rendering the spectra nonstationary (non-repeatable) and either requiring a time-frequency spectrogram approach as used in the SAI closings classifier or just extracting the "tail" of the closing sound as used in the TRACOR classifier. This information coincides with the "non-repeatable" spectra (due to this nonstationarity in closings) we found when processing the closing sounds using our spectral estimator and severely limiting the number of repeatable beats (stationary) we could extract for each valve. The spectral features chosen automatically by the feature selector for the closings were: (center frequency, bandwidth): (8.3 kHz,469 Hz), (14.1 kHz,469 Hz), and (19.8 kHz,94 Hz).

The training phase of the classifier resulted in a probability (x 100) of correct classification of *86.2%* with an *80%* sensitivity and *92.3%* specificity. The results are shown in Table 3.

We summarize the performance of the LLNL-HVCC during training as:

LLNL-HVCC TRAINING (Closings) SUMMARY

No. of Valves:	23 (13 INT, 10 SLS)
Correct Classification (x 100):	86.2 %
Sensitivity (x 100):	80 %
Specificity (x 100):	92.3 %
Operating Pt (Sens.,Spec.)@Thresh.:	(1,1)@0.5
Spectral Features (center freq., bw):	(8.3 kHz,469 Hz) (14.1 kHz,469 Hz) (19.8 kHz,94 Hz)

The classifier was then run on the blind data and the final results were disastrous owing directly to our lack of experience with closings. The results are shown in Table 4 with the corresponding final posterior probabilities shown in Figure 9 for completeness. We decided to concentrate our remaining efforts (after discussing the results with J. L. Hirsch of RMG) on analyzing the opening sounds rather than attempting to improve the performance of the closing classification scheme.

SUMMARY & LESSONS LEARNED

Our classification results based on the openings is much better than the closings for the reasons discussed above. It is clear that more work would have to be accomplished on the closing algorithm to compensate for the nonstationarity of the closing valve spectra.

The following list summarizes our experiences in processing and classifying the training and blind data sets for OPENING sounds exclusively <possible solutions>:

- the training data are not representative of the blind data, in fact, we found out post-blind that of the 14 sessions we missed 9 of them came from facilities where we had no training data
- the sample size (no. of valves) is small <obtain more data using sheep or opportunistic recordings>
- there are no adequate models capable of predicting the vibrational response of the BSCC heart valve <anechoic and duplicator studies>
- there are variations within each class (beat-to-beat, valve-to-valve, session-to-session, site-to-site) <better data acquisition, multiple sensors, anechoic and duplicator work to estimate better signal models>
- lack of prior probabilities and losses to aid in setting decision thresholds <incorporate more priors>
- find more robust feature sets for classification <8kHz spectral band, peak frequency histogram, model coefficients, fusion, etc.>
- find more robust classifiers <transform data to gaussian and use linear classifier, parametric or nonparametric schemes, etc.>
- optimal feature selection <branch and bound method, robust covariance estimation>
- fuse various feature sets <beat level, data level, feature level, decision level>
- unknown data statistics <statistical analysis and modeling, transformations>

- data acquisition problems (auto gain, filters)<develop new acquisition system based on anechoic design, use anechoic and duplicator spectral information to improve the preprocessing of already collected data base>
- data extraction inefficient <develop and easy-to-use data base and devoted computer system (with passwords) to enable researchers in acoustics/biomedical etc. access to the data base as well as processing techniques>

This completes our final report and summary.

FIGURE 1. LLNL Heart Valve Condition Classifier (LLNL-HVCC)

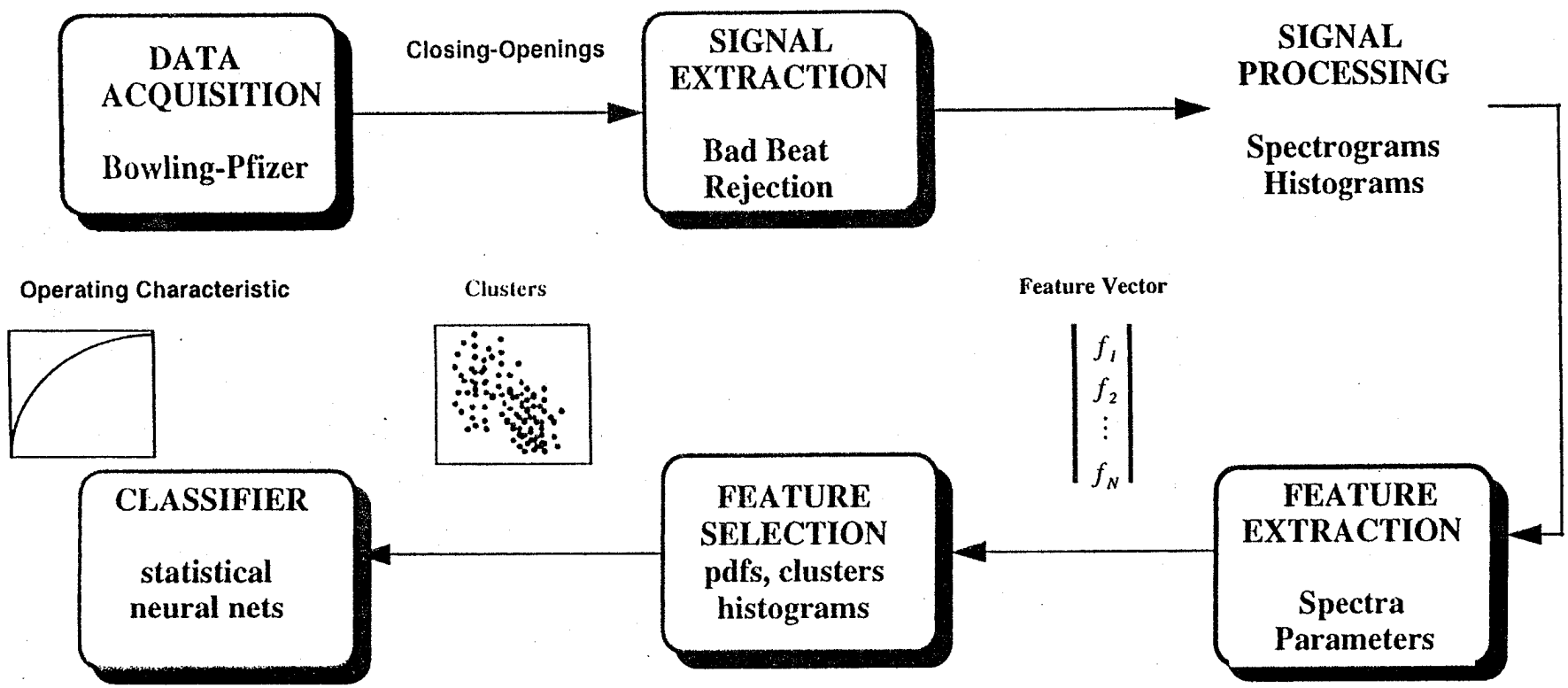


FIGURE 2. The confusion matrix specifies the performance achieved during training (Openings)

- We use the "Hold-one-out" method of training
- **The training data set** (Number of valves = 23)
  - Number of Intact valves = 13
  - Number of SLS valves = 10

Truth / Decision	SLS	INT
SLS	**P(SLS | SLS) = P(Detection)** = 10/10 = 1.0	**P(SLS | INT) = P(False Alarm)** = 0/13 = 0.0
INT	**P(INT | SLS) = P(Miss)** = 0/10 = 0.0	**P(INT | INT) = P(Specificity)** =13/13 = 1.0

Note: P(SLS | SLS) + P(INT | SLS) = 1 and P(SLS | INT) + P(INT |INT) = 1

P(Correct Classification) = .5 [P(SLS |SLS) + P(INT | INT)] = .5 (1.0 + 1.0) = 1.0

FIGURE 3. ROC Curve: Training Results (Openings)

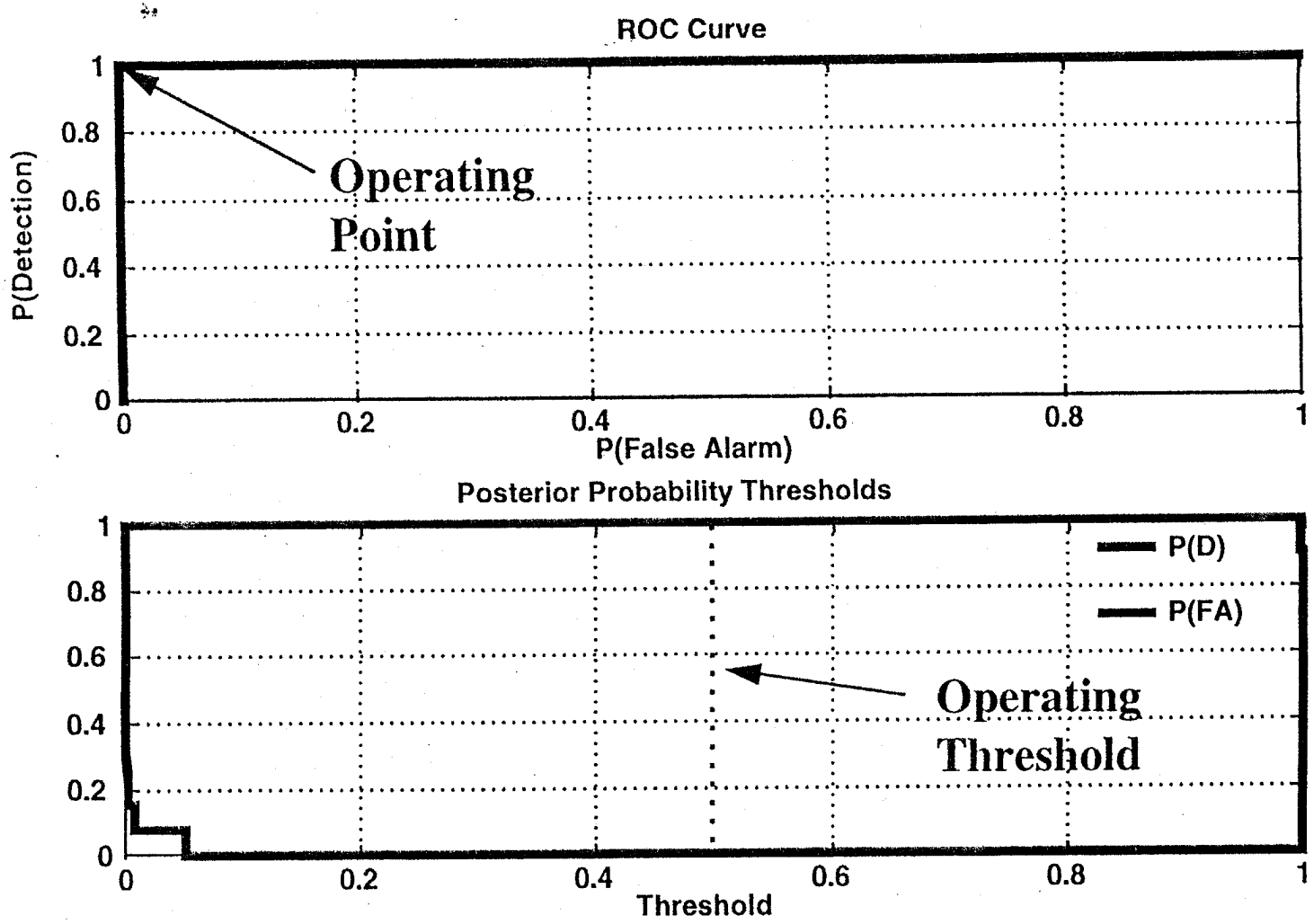


FIGURE 4. Training Performance (Openings)

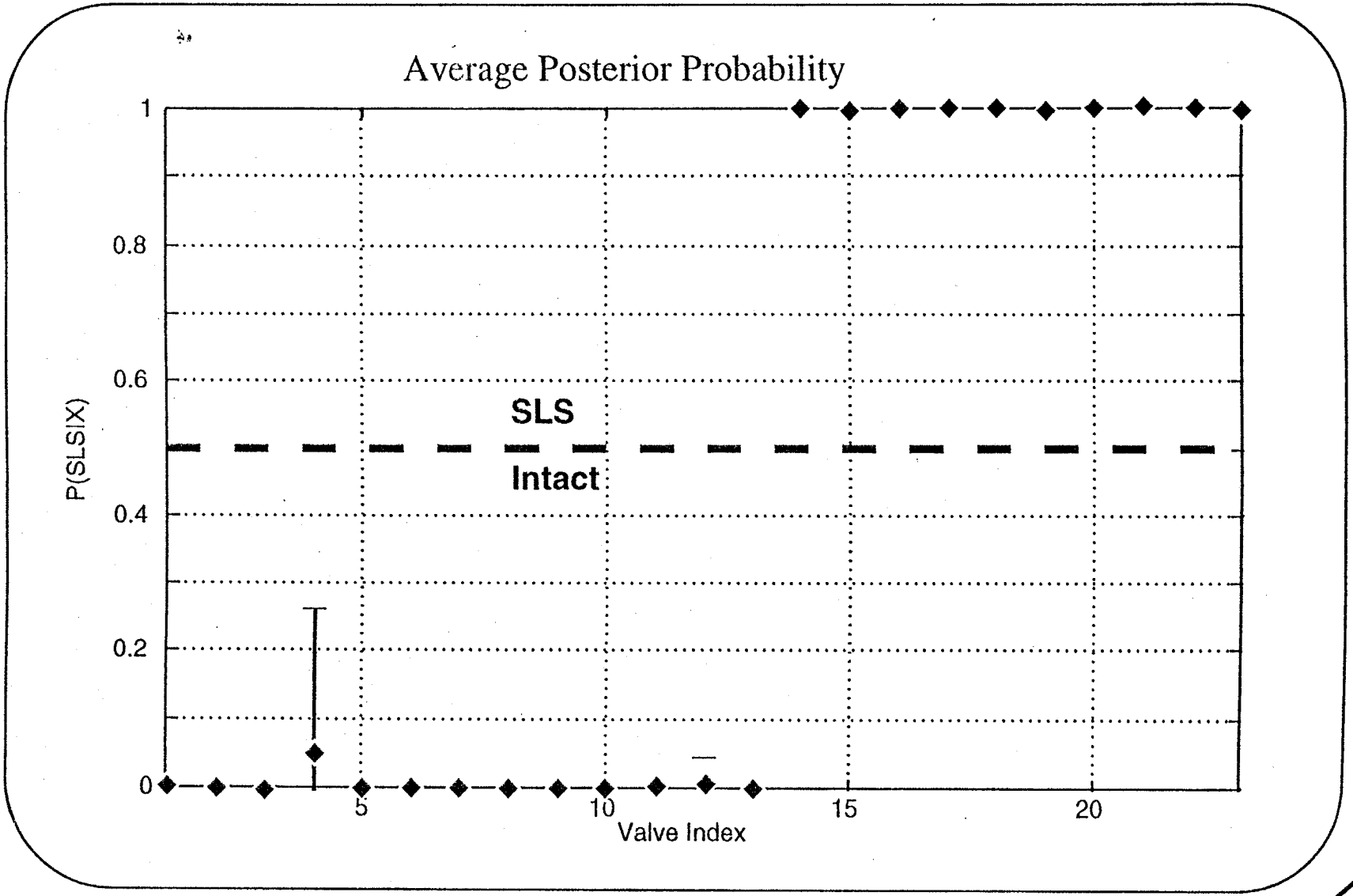


FIGURE 5. Opening Blind Test Results (30 INT, 20 SLS)

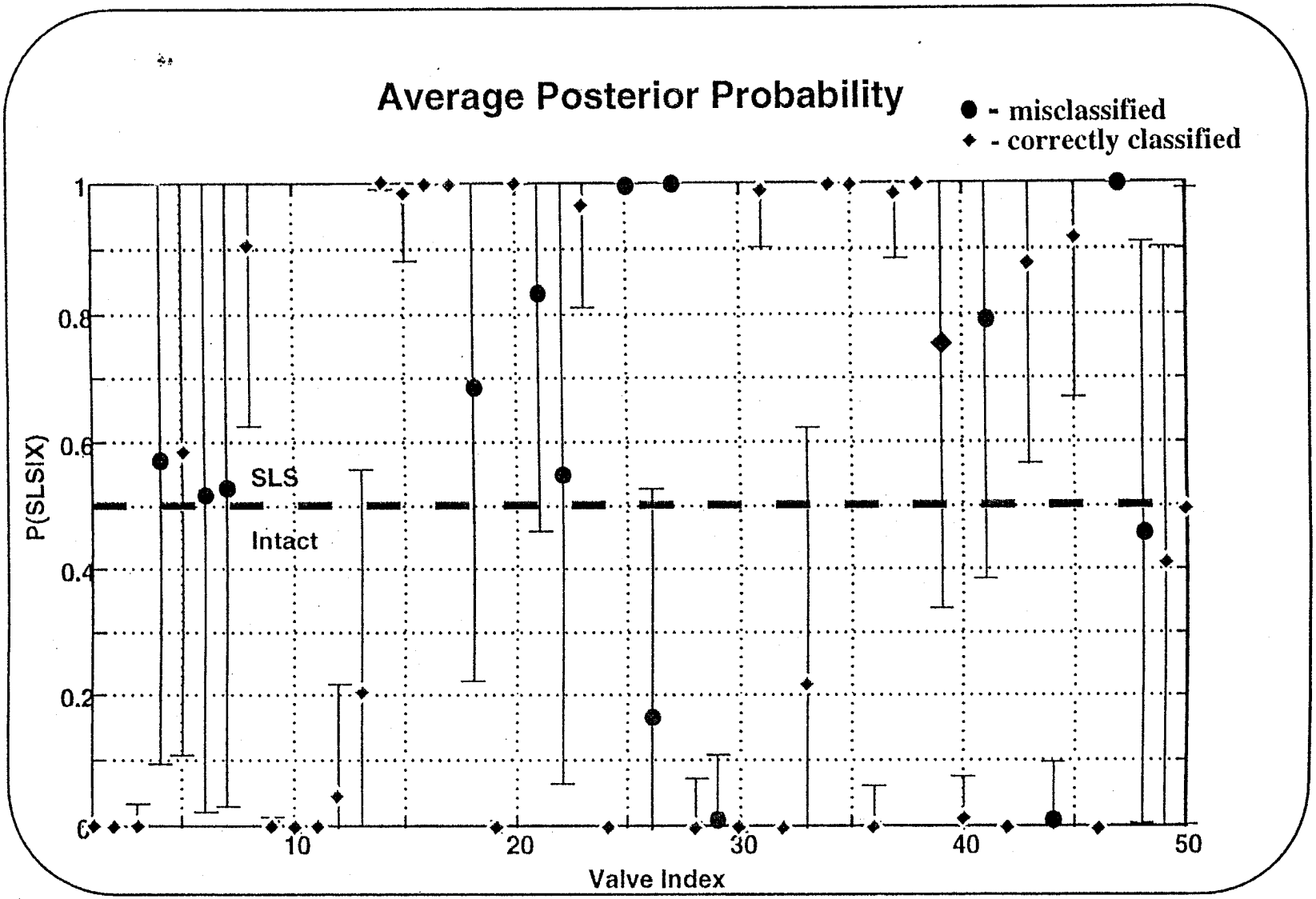


TABLE 1. Training Results (Openings)

	Session			$\Delta = \lvert\Theta - K\rvert$		Class	Truth
# 1	v110a	84	0	50	0.001	INTACT	INTACT
# 2	v120a	120	0	50	0	INTACT	INTACT
# 3	v170b	102	0	50	0	INTACT	INTACT
# 4	v210b	122	5	45.082	0.05	INTACT	INTACT
# 5	v250a	74	0	50	0	INTACT	INTACT
# 6	v310a	54	0	50	0	INTACT	INTACT
# 7	v320a	95	0	50	0	INTACT	INTACT
# 8	v330a	69	0	50	0	INTACT	INTACT
# 9	v400b	83	0	50	0	INTACT	INTACT
#10	v420a	71	0	50	0	INTACT	INTACT
#11	v430b	57	0	50	0.002	INTACT	INTACT
#12	v470a	35	0	50	0.007	INTACT	INTACT
#13	v480a	51	0	50	0	INTACT	INTACT
#14	v140b	75	100	50	1	SLS	SLS
#15	v150b	52	100	50	1	SLS	SLS
#16	v160f	86	100	50	1	SLS	SLS
#17	v190a	61	100	50	1	SLS	SLS
#18	v240a	72	100	50	1	SLS	SLS
#19	v290a	57	100	50	1	SLS	SLS
#20	v300b	52	100	50	1	SLS	SLS
#21	v380a	75	100	50	1	SLS	SLS
#22	v440b	59	100	50	1	SLS	SLS
#23	v460a	81	100	50	0.997	SLS	SLS

Table 2. **LLNL Classification Results**

Openings

	Session	# Beats	% SLS Beats	Class	Truth	Source
#1	b017	106	0	INTACT	INTACT	WIG
#2	b025	75	0	INTACT	INTACT	WBH
#3	b029	107	0	INTACT	INTACT	WBH
#4	b055	103	57	SLS	INTACT	WBH
#5	b065	157	58	SLS	SLS	WIG
#6	b083	35	51	SLS	INTACT	WBH
#7	b087	60	53	SLS	INTACT	SUMC
#8	b089	148	91	SLS	SLS	SUMC
#9	b094	83	0	INTACT	INTACT	WBH
#10	b118	44	0	INTACT	INTACT	WIG
#11	b125	94	0	INTACT	INTACT	WBH
#12	b133	76	4	INTACT	INTACT	WBH
#13	b153	101	21	INTACT	INTACT	LEIDEN
#14	b154	137	100	SLS	SLS	WIG
#15	b169	106	99	SLS	SLS	SUMC
#16	b170	103	100	SLS	SLS	SUMC
#17	b176	278	100	SLS	SLS	SUMC
#18	b179	164	69	SLS	INTACT	SUMC
#19	b309	116	0	INTACT	INTACT	WIG
#20	b313	274	100	SLS	SLS	SUMC
#21	b372	107	83	SLS	INTACT	LEUVEN
#22	b399	138	54	SLS	INTACT	SUMC
#23	b410	114	97	SLS	SLS	WIG
#24	b454	130	0	INTACT	INTACT	LEIDEN
#25	b488	41	100	SLS	INTACT	WBH
#26	b489	198	17	INTACT	SLS	SUMC
#27	b500	175	100	SLS	INTACT	SUMC
#28	b535	209	0	INTACT	INTACT	WIG
#29	b578	98	1	INTACT	SLS	WIG
#30	b585	143	0	INTACT	INTACT	WBH
#31	b606	119	99	SLS	SLS	WIG
#32	b613	112	0	INTACT	INTACT	SUMC
#33	b616	109	22	INTACT	INTACT	WBH
#34	b642	133	100	SLS	SLS	SUMC
#35	b678	23	100	SLS	SLS	WIG
#36	b751	159	1	INTACT	INTACT	WBH
#37	b755	106	99	SLS	SLS	SUMC
#38	b761	105	100	SLS	SLS	SUMC
#39	b770	25	76	SLS	SLS	WIG
#40	b777	281	0	INTACT	INTACT	WBH
#41	b791	71	79	SLS	INTACT	WBH
#42	b818	92	0	INTACT	INTACT	WBH
#43	b822	125	88	SLS	SLS	WIG
#44	b826	78	1	INTACT	SLS	WIG
#45	b851	145	92	SLS	SLS	SUMC
#46	b901	87	0	INTACT	INTACT	WBH
#47	b935	139	100	SLS	INTACT	WBH
#48	b945	147	46	INTACT	SLS	BARCELONA
#49	b977	85	42	INTACT	INTACT	WBH
#50	b995	223	49	INTACT	INTACT	WBH

Note: Shaded entries represent questionable data.
Decision Threshold for **% SLS Beats** is set at 50%

FIGURE 6. The confusion matrix specifies the performance achieved for the Blind Test (OPENINGS)

- Ground truth is known after the blind test
- **The Blind data set** (Number of sessions = 50)
  - Number of Intact sessions = 30
  - Number of SLS sessions = 20

Decision \ Truth	SLS	INT
SLS	**P(SLS | SLS) = P(Detection)** = 16/20 = .80	**P(SLS | INT) = P(False Alarm)** = 10/30 = 0.33
INT	**P(INT | SLS) = P(Miss)** = 4/20 = 0.20	**P(INT | INT) = P(Specificity)** = 20/30 = 0.66

Note: P(SLS | SLS) + P(INT | SLS) = 1 and P(SLS | INT) + P(INT |INT) = 1

P(Correct Classification) = .5 [P(SLS |SLS) + P(INT | INT)] = .5 (.80+.66) = .73

FIGURE 7. Post-Blind Hold-One-Out (OPENINGS)

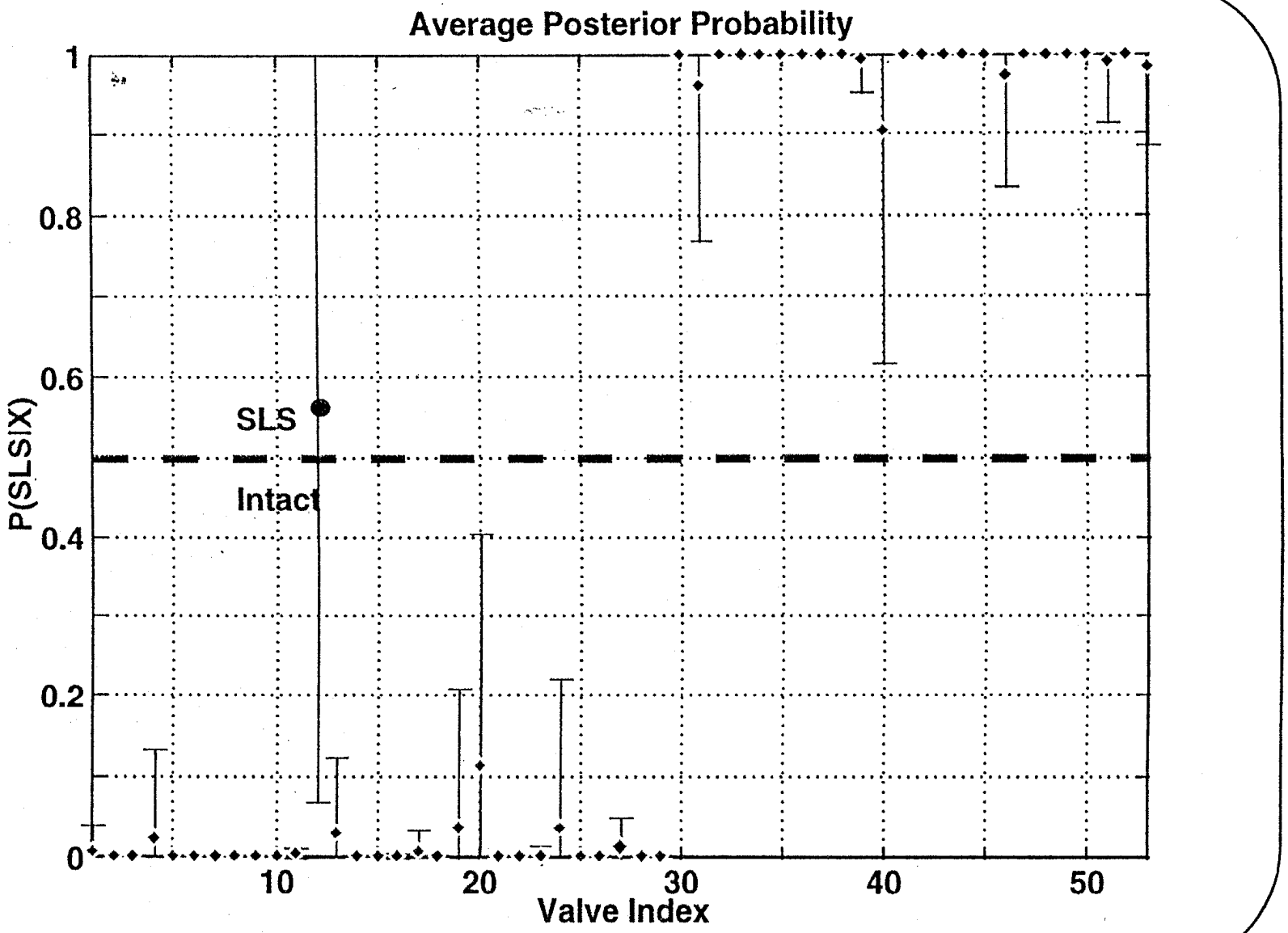


FIGURE 8. The confusion matrix for the POST Blind Test (OPENINGS)

- Ground truth is known after the blind test
- **The Blind data set** (Number of Valves = 53)
  - Number of Intact valves = 29
  - Number of SLS valves = 24

Truth / Decision	SLS	INT
SLS	**P(SLS | SLS) = P(Sensitivity)** = 24/24 = 1.0	**P(SLS | INT) = P(False Alarm)** = 1/29 = 0.035
INT	**P(INT | SLS) = P(Miss)** = 0/24 = 0.0	**P(INT | INT) = P(Specificity)** = 28/29 = 0.97

Note: P(SLS | SLS) + P(INT | SLS) = 1 and P(SLS | INT) + P(INT |INT) = 1

P(Correct Classification) = .5 [P(SLS |SLS) + P(INT | INT)] = .5 (1.0+.97) = .98

TABLE 3. Training Results (Closings)

CLOSINGS: TRAINING				Average P(SLS|X)	Class	Truth
# 1	30	13		0.128	INTACT	INTACT
# 2	52	13.5		0.1831	INTACT	INTACT
# 3	41	4.9		0.315	INTACT	INTACT
# 4	69	10.1		0.265	INTACT	INTACT
# 5	68	0		0.013	INTACT	INTACT
# 6	82	0		0.034	INTACT	INTACT
# 7	83	0		0.021	INTACT	INTACT
# 8	100	5		0.304	INTACT	INTACT
# 9	38	7.9		0.074	INTACT	INTACT
# 10	64	0		0.09	INTACT	INTACT
# 11	27	18.5		0.297	INTACT	INTACT
# 12	62	90.3		0.913	SLS	INTACT
# 13	72	9.7		0.26	INTACT	INTACT
# 14	41	95.1		0.867	SLS	SLS
# 15	51	78.4		0.725	SLS	SLS
# 16	89	86.5		0.832	SLS	SLS
# 17	21	81		0.72	SLS	SLS
# 18	57	100		1	SLS	SLS
# 19	78	56.4		0.563	SLS	SLS
# 20	63	98.4		0.923	SLS	SLS
# 21	25	4		0.175	INT	SLS
# 22	34	94.1		0.9	SLS	SLS
# 23	65	7.7		0.234	INT	SLS

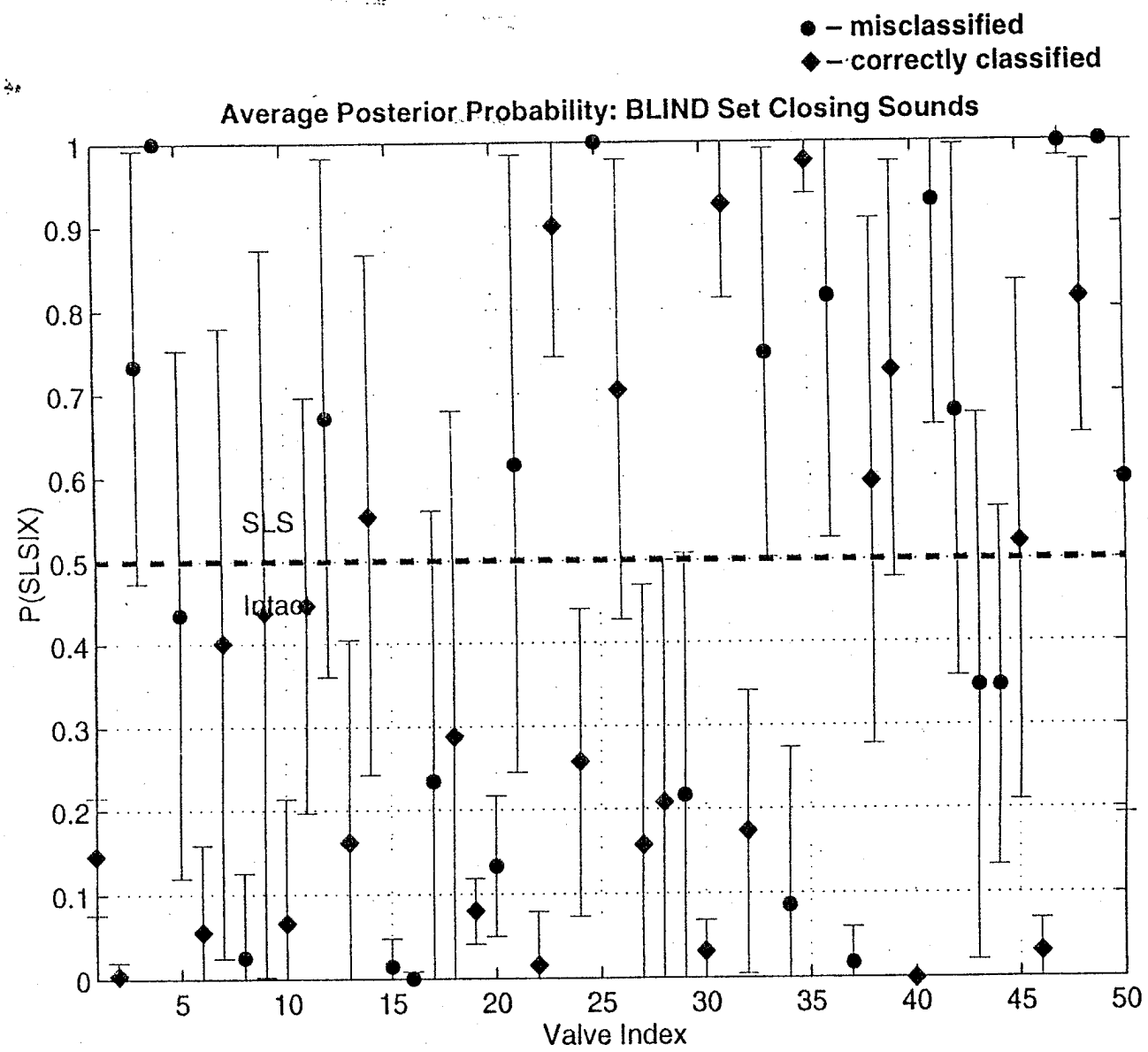
Table 4. **LLNL Classification Results**

Closings

	Session	# Beats	% SLS Beats	Class	Truth	Source
#1	b017	97	0	INTACT	INTACT	WIG
#2	b025	74	0	INTACT	INTACT	WBH
#3	b029	18	78	SLS	INTACT	WBH
#4	b055	17	100	SLS	INTACT	WBH
#5	b065	66	44	INTACT	SLS	WIG
#6	b083	120	1	INTACT	INTACT	WBH
#7	b087	21	38	INTACT	INTACT	SUMC
#8	b089	362	1	INTACT	SLS	SUMC
#9	b094	37	43	INTACT	INTACT	WBH
#10	b118	30	3	INTACT	INTACT	WIG
#11	b125	144	42	INTACT	INTACT	WBH
#12	b133	43	72	SLS	INTACT	WBH
#13	b153	52	10	INTACT	INTACT	LEIDEN
#14	b154	76	53	SLS	SLS	WIG
#15	b169	262	0	INTACT	SLS	SUMC
#16	b170	119	0	INTACT	SLS	SUMC
#17	b176	51	22	INTACT	SLS	SUMC
#18	b179	92	30	INTACT	INTACT	SUMC
#19	b309	103	0	INTACT	INTACT	WIG
#20	b313	76	0	INTACT	SLS	SUMC
#21	b372	91	66	SLS	INTACT	LEUVEN
#22	b399	100	0	INTACT	INTACT	SUMC
#23	b410	47	96	SLS	SLS	WIG
#24	b454	32	9	INTACT	INTACT	LEIDEN
#25	b488	15	100	SLS	INTACT	WBH
#26	b489	90	80	SLS	SLS	SUMC
#27	b500	49	18	INTACT	INTACT	SUMC
#28	b535	36	25	INTACT	INTACT	WIG
#29	b578	34	15	INTACT	SLS	WIG
#30	b585	157	0	INTACT	INTACT	WBH
#31	b606	57	100	SLS	SLS	WIG
#32	b613	27	4	INTACT	INTACT	SUMC
#33	b616	132	83	SLS	INTACT	WBH
#34	b642	98	5	INTACT	SLS	SUMC
#35	b678	87	100	SLS	SLS	WIG
#36	b751	26	85	SLS	INTACT	WBH
#37	b755	260	0	INTACT	SLS	SUMC
#38	b761	220	66	SLS	SLS	SUMC
#39	b770	58	78	SLS	SLS	WIG
#40	b777	63	0	INTACT	INTACT	WBH
#41	b791	14	93	SLS	INTACT	WBH
#42	b818	32	75	SLS	INTACT	WBH
#43	b822	160	29	INTACT	SLS	WIG
#44	b826	26	23	INTACT	SLS	WIG
#45	b851	81	60	SLS	SLS	SUMC
#46	b901	37	0	INTACT	INTACT	WBH
#47	b935	96	100	SLS	INTACT	WBH
#48	b945	43	95	SLS	SLS	BARCELONA
#49	b977	50	100	SLS	INTACT	WBH
#50	b995	111	64	SLS	INTACT	WBH

Note: Shaded entries represent questionable data.
Decision Threshold for % SLS Beats is set at 50%

FIGURE 9.


● – misclassified
◆ – correctly classified
Average Posterior Probability: BLIND Set Closing Sounds
P(SLS|X)
SLS
Iotac
Valve Index
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
5
10
15
20
25
30
35
40
45
50

Appendix C1

PARTICIPANTS IN ACOUSTICS REVIEW

	Name	Representing/Role
1.	Abbie Warrick	LLNL/Classification
2.	Graham Thomas	LLNL/Classification, anechoic
3.	Michael Axelrod	LLNL/Statistics
4.	Allen Eberhardt	SAI/Mechanics, accoustics
5.	Gregory A. Clark	LLNL/Classification
6.	David Scott	LLNL/Classification
7.	Charles Chasszing	SAI/Classification
8.	James V. Candy	LLNL/PI
9.	Ned Weyman	Massachusetts General Hospital
10.	Donald C. Harrison	University of Cincinnati

APPENDIX C2

Subcommittee of the Bowling-Pfizer Supervisory Panel
November 24-25, 1996
Livermore, California

AGENDA

Sunday, November 24

4:00-4:15 p.m.	Introduction and Review of the Purposes for the Meeting
4:15-4:45 p.m.	SAI presents results of "blind analysis" and discussion
4:45-5:15 p.m.	LLNL presents results of "blind analysis" and discussion
5:15-6:15 p.m.	General discussion and correlation of the results from SAI and LLNL
7:00 p.m.	Dinner - site to be determined

Monday, November 25

8:30 a.m.	Badging and entrance at West gate to Livermore
8:45 a.m.	Welcome
9:00-12:00 p.m.	1. Lessons learned 2. Proposed changes in acoustical a. recording equipment b. analysis algorithms c. clinical application 3. Do acoustical studies have a future in BSCC valve patients
12:00-1:00 p.m.	Lunch
1:00-2:30 p.m.	Classification demonstrations, anecholic study status
2:30 p.m.	Wrap-up and future direction
3:00 p.m.	Adjourn

VANDERBILT UNIVERSITY
NASHVILLE, TENNESSEE 37235

APPENDIX D

Department of Physics & Astronomy • Box 1807 Station B • Direct phone (615) 322-2828

Living State Physics Group

November 11, 1996

Dr. Don Harrison
Senior Vice President and Provost for Health Affairs
University of Cincinatti
250 Health Professions Building
P.O. Box 670663
Cincinatti, OH 45267-0663

Dear Don,

I enclose my review of the Quantum Magnetics proposal to the Bowling-Pfizer Supervisory Panel. I recommend that Tasks 1-4 should be funded, at a much reduced budget and with the stipulation that they pay appropriate attention to the issues raised in this review.

In the event that this or other non-invasive approach is moderately successful in detecting SLS, it would be prudent to develop a secondary technique to confirm the diagnosis before replacement surgery is conducted. In light of the differential risk of mortality from open-heart valve replacement and a cardiac catheterization, it would seem prudent to develop a catheter-based system to be used to confirm the non-invasive diagnosis prior to surgery. Catheter-based direct measurement of the inductance by means of a coil placed in the outlet port is promising and very simple. Phase angle differences of about 0.25° were observed in the QM tests. Such a device would be easy to construct - simply a catheter with a small coil wound on it, and a commercial impedance analyzer. Possibly the *in vivo* valves and an *in vitro* reference valve could be observed simultaneously in a bridge configuration, so that the effects of heart valve size and the angle of the valve relative to the coil in the catheter could be examined in the cath lab - the two valves would be measured simultaneously and during x-ray visualization of the implanted valve. For the same reason, it may also be useful to develop a catheter microphone. There is a possibility that esophageal inductance probes or microphones could serve as an intermediate step.

Please let me know if you need any further information or more detailed comments. I have spent six (6) hours reviewing this proposal and discussing it with you and John Newell. My social security number is 224-64-5499. If you need an invoice or bill, please let me know what it should contain.

I find this a fascinating problem, and would enjoy being kept up to date with the overall project.

Sincerely,

John P. Wikswo
A.B. Learned Professor of Living State Physics
Professor of Physics

cc: John Newell

Review of "Non-Invasive Assessment of Artificial Heart Valves," Yacine Dalicaouch, P.I., Quantum Magnetics, Inc.

This proposal is for a Phase II effort to develop an electromagnetic system for the non-invasive detection of single leg separation (SLS) in the Bjork-Shiley heart valve. Failure of these valves is an important clinical problem and electromagnetic techniques may offer promise for the non-invasive detection of SLS.

In Phase I, the investigators conducted preliminary studies with two small coils and a commercial impedance bridge. Reasonably large signals were obtained with a small coil placed within the outlet strut structure. The induction coil placed immediately outside the coil (page 11) presented results that were less clear. Because the coupling of the coil to the outlet port is reduced and that to the flange and inlet port was increased, the changes in phase angle are smaller - on the order of 0.07°, or twice that if the peak-to-peak signal with valve rotation is utilized. That would suggest that the phase angle difference will have to be measured to 0.02%. or 2 parts in 10,000. It is obvious that rotating the valve affected the signal, and the damaged valve produced a larger $\Delta\theta$ signal than did a pair of intact valves. There were possibly other sources of uncertainty in the measurement or the data. The $\Delta\theta$ versus ϕ plots show that while the θ_2 - θ_1 and the θ_2 - θ_3 curves are not as sinusoidal as that for θ_1 - θ_4, the peak-to-peak amplitudes of these curves differ by only a factor of 6. The investigators then used a new sample holder and a vibration generator to optimize the signal. The use of a vibration generator to modulate the SLS increased the signal strength. This section presents a number of questions, including an apparent problem in rationalizing the data in Fig. 6 with those in Fig. 7. Figure 6 showed a $\Delta\theta$ of 0.05° at an orientation of 40° and a frequency of 100 kHz, while the data in Fig. 7 show a 0.01° phase difference at 100 kHz. Figure 7 doesn't show a 0.04° phase shift until 600 kHz. On page 13, line 6 and line 8, is it 0.04% or 0.14%? Is there an inconsistency between the text and the graphs regarding percent change and angle changes in degrees?

In Phase I, the investigators proposed theoretical studies, *in vitro* tests, and tests on live sheep. On page 15, it was stated that the change in the research plan was made in consultation with the NIH Contract Office Technical Representative. The specific aims were revised to 1) the development of a numerical model for the inductance of a normal and SLS valve; 2) tests of detection on real heart valves; and 3) evaluation of sensor types.

Under Experimental Design and Methods, the investigators propose 12 tasks for Phase II. In year one, they will 1) Characterize the electromagnetic response in *in vivo* conditions; 2) Investigate non-contact SLS modulation techniques; 3) Design and fabricate the source coil; 4) Design and fabricate a single-channel magnetometer for *in vitro* tests; 5) Design and fabricate two 3-axis magnetometers; 6) Design and fabricate custom electronics; 7) Develop preliminary software algorithms for use with the 6-element array; and 8) Integrate the system and begin preliminary measurements. In year two, they will test the integrated system; 9) Complete software routines for data analysis; 10) Make final adjustments of hardware; 11) Test prototype instrument on live sheep with implanted BSCC heart valves; and 12) Design clinical magnetometer system for commercialization in Phase III.

In discussing the steps in the proposed research, the investigators indicated that they detected a 1.3% change in the dipole moment when the SLS opened and closed. This was for a dry

valve, and not one with saline or blood in the crack, nor with blood and tissue surrounding the metal. There may be shunting by blood and connective tissue and muscle in and around the valve, and by fluids and other materials in the crack of the SLS. Later, under the first proposed task, the investigators indicate that shunting by saline should not be a problem.

Because of manufacturing variations, the absolute dipole moment of the valve is not sufficient constant from valve to valve for the dipole moment alone to provide adequate discrimination. Hence the modulation is necessary, but the extent of the modulation that is achieved *in vivo* is not known. The proposal could be strengthened by answering a number of questions. Are comparison valves available for every size/batch of valve that was made? What is the statistical variation in the signals between valves; so far, the investigators have examined very few valves.

It should be possible to measure this modulation directly with wires attached to a valve with SLS implanted in sheep or mounted in a pulse duplicator. It may also be possible to conduct these tests with a small coil around the flange of the valve, implanted at the same time as the valve. Other investigators were able to measure the contact loads reproducibly (page 17), so it should be possible to measure the electrical modulation at the desired frequency, either directly or inductively before proceeding to construct a prototype instrument.

In Section 4.3 (Magnetic Imaging of the Heart Valve), the investigators propose to examine magnetic imaging of the valve to detect the SLS if cardiac modulation of the SLS does not prove sufficient to produce the desired discrimination between normal and SLS valves. They provide little specific information about the approach they will take, other than to use a finite element program to generate two- and three-dimensional magnetic field images that will be compared with measured fields. There are a number of issues regarding the non-uniqueness of the magnetic inverse problem that may affect the feasibility of this approach. The investigators provide insufficient technical detail to justify funding this task at this time.

In Section 4.4 (Cyclical Motion of the Valve Implanted in the Heart), the investigators note that if the sensor and the valve are separated by 15 cm, and the valve moves 1 mm during the cardiac cycle, then the magnetic signal from the heart valve will change by approximately 2 percent, *i.e.* twice the differential signal of interest. The investigators are expecting "the heart valve to move in some reasonably continuous manner throughout the heart cycle." They then expect that the magnetic signature from the electrical closure of the SLS will be an abrupt signal superimposed upon this modulation (Figure 9). Before this approach is deemed feasible, ultrasound, X-ray, or MRI imaging should be used to determine the actual trajectory of the valve in a human subject. The valve motion will be complex, with both translation and rotation, and with an amplitude sufficient to mask the SLS modulation signal.

If motion artifact proves to be a problem, the investigators propose to use position-insensitive coil arrays, such as a Helmholtz pair, to detect the signal. There may be significant practical limitations to this approach, including avoidance of microphonics and the need to maintain both instrument balance and rejection of directly-coupled signals under a variety of conditions. Calculations would be necessary to determine whether the requisite sensitivity can be achieved, and if so, how the gradiometers will be configured for noise rejection. On page 21, the investigators seem to recognize this problem, and do not seem to have any confidence in this approach.

In section 4.5.1 (Numerical Inversion Approach), the dipole inversion approach is interesting, but a quantitative analysis of the signal-to-noise ratio required to obtain a one-percent or better measurement of the magnetic dipole moment and a corresponding separation of the moment and position contributions to the signal. In Figure 10, the investigators show that this might be done with a pair of vector coils (without crediting Malmivuo, from whose papers or book the torso appears to have been copied). While only six numbers are required, when accurate dipole fits are required, few investigators would use only six coils, but would use many more and make a least-squares fit.

More thought is needed regarding the relationship between field direction, valve orientation, dipole moment, and detected field. The orientation of the dipole moment is determined solely by the orientation of the plane of the valve flange. The current induced in the valve structure is determined by the valve orientation relative to the applied field. The detected field is determined by the relative orientation of the valve and the sensor. Thus if the valve tilts, then the amplitude of the dipole moment is reduced, but the amplitude of the detected signal may increase. From the point of view of SLS detection, it will then be necessary to determine the angle of the flange relative to the local magnetic field. The preliminary studies used the same coil for excitation and detection (by means of the impedance bridge), but the proposed method utilizes independent excitation and detection coils. These need not be either coaxial or coplanar. Unless the excitation coil is coaxial with the valve, the divergent excitation field may have an angular variation that confounds interpretation of the data. The analysis on page 23 assumes that the dipole strength is constant during a 5° rotation, producing a 0.4% signal. However, if the dipole moment changes, the effect could be twice that size, or zero, depending upon the relative orientation of the excitation and pick-up coils. No data are presented to justify the 5° rotation.

The investigators indicate that they can use the Frahm-Wynn-type algorithms for determining dipole strength and location. It is important to note that these algorithms require the measurement of the five independent gradients and the field magnitude at a single point, which is easy to achieve when using a flux-gate magnetometer or a SQUID to track a truck-sized target, but is harder to implement when trying to locate a heart valve that is smaller than one of the six magnetometers. From this perspective, the effects of finite coil size and gradiometer baseline on the accuracy of this approach would need to be determined, and may not be trivial. The errors that would be introduced into the Frahm-Wynn approach by these factors may be significant, particularly since localization accuracies of one millimeter or better will be required. It may be that a least-squares approach will be more practical, but typically in this type of localization procedure, the accuracy of the determination of each of the six parameters depends strongly upon the location of the detectors relative to the source.

The investigators indicate (page 24) that they will be able to use the Frahm-Wynn techniques to remove the background signal due to the motion of the heart valve. They are making a number of rather important assumptions, including that the signal from the motion of the valve will be a smooth curve and that the opening and closing will produce a distinctive step change in the signal. Due to the absence of realistic numbers on the actual motion of the heart valve, the strength of the open signal in the presence of saline, the undocumented accuracy of the Frahm-Wynn algorithm in the near field region, and the effects of the substantial noise on the inverse procedure, it remains uncertain whether this approach will work. It is not sufficient to simply state that "if the implanted valve is intact, we we [sic] should see a relatively flat m(t) pattern

whereas in the presence of an SLS we expect to see a flat background containing small δ peaks or spikes occurring at a frequency of about 1 Hz, the heart beat frequency."

The investigators do not address the problems of motion of the sensors relative to the excitation coil. The instrument that they are describing may have some interesting microphonics.

On page 26, the authors initially approximate the body as a homogeneous volume of saline with a conductivity of 1 $(\Omega\ m)^{-1}$. They estimate the eddy-current attenuation factor to be 0.85 at 300 kHz. While the authors are correct in recognizing that the 15% attenuation will not seriously compromise the detection of the signal, they have overlooked what is probably the key difficulty with this approach: redistribution of mass due to cardiac motion. The fact that the conductivity of the body is sufficiently high to allow the induction of eddy currents means that the time-varying conductivity inhomogeneities will produce measurable magnetic signals. The thorax is not a homogenous conductor: the heart is a conductor whose location and volume is changing within the thoracic cavity, with a total stroke volume both ventricles of about 150 cm^3 and a displacement of the cardiac center of mass by several millimeters. The heart is surrounded by the lungs, whose conductivity is one-fifth to one fifteenth of that of blood. In addition, the chest wall moves with an amplitude of a fraction of a millimeter that varies in both amplitude and phase over the chest. The investigators are urged to study in detail the experiments by Tarjan and McFee (Ann NY Acad Sci, 170(2) 462-475 (1970) and IEEE Trans BME 15(4) 266-278 (1968), and references therein), in which a 100 kHz inductive impedance bridge was used to measure cardiac volume changes, and the articles by Fenton and Vas (Med Biol Eng, Sept 1973, pp. 552-559) and Vas *et al.* (Cardiovasc Res, 8 811-815 (1974) where a similar instrument was used to measure cardiac displacements. The rather large signals detected by these investigators will in fact serve as noise in the proposed instrument. A determination of the magnitude of these signals for the proposed instrument and the techniques required to eliminate them are of the greatest importance before proceeding with the development of the proposed prototype instrument.

The investigators correctly state that inductive sensors should be adequate for the proposed measurements at 300 kHz. The noise analysis presented for the induction coil is not terribly sophisticated. Issues of resonances, capacitive coupling, the distributed capacitance of the windings, and the ability to match coils to form a gradiometer will eventually need to be addressed. The impedance of the coil is not given; if a transformer is required to match the coil and preamplifier impedances, there will be a further loss of signal energy.

At the frequencies proposed, it is unclear whether it would ever be advantageous to use a SQUID. At such high frequencies, typical SQUIDs will not be as sensitive as room-temperature induction coils, particularly where the size of the coil is of little concern. The wide bandwidth of the IBM SQUIDs is important to allow the SQUIDs to detect low-frequency signals without being adversely affected by high-frequency interference. The proposed measurements will require a restricted bandwidth and hence are not subject to the same constraints that motivated the development of the IBM system. The investigators should note, however, that the detect of the sharp step in the signal from the opening of the SLS may require a bandwidth of 100 Hz or greater, whereas the investigators suggest that bandwidths as low as 10 Hz may be adequate. Whether or not the bandwidth can be reduced will also be of concern in the possible use of

magnetoresistive sensors. Without actual data regarding the modulation of the SLS signal both in saline and *in vivo*, it is difficult determine the required sensor parameters.

In the analysis of environmental noise and its remediation, much of the discussion seems to be based upon the investigators familiarity with instrumentation and measurement techniques for biomagnetic measurements at frequencies between dc and 1 kHz; the problems at 100-300 kHz will be quite different. The conventional RF shielded rooms used in many hospital neurology suites for recording electrical signals from nerves, muscles, and the brain may be quite sufficient.

A further review of the proposed project tasks follows.

1) Characterize the electromagnetic response of heart valves in in vivo-like conditions. The investigators' calculations indicate that the presence of heart electrolytes does not short out the resistance associated with the SLS. The investigators propose to use a modified version of the Phase I apparatus to test this. The effects of connective tissue or other materials in the gap should be examined, or at least the condition of the SLS fracture surfaces determined by microscopic evaluation of recently-explanted valves. This is an important measurement that would have been reasonable to do in Phase I and should be pursued immediately.

2) Investigate various non-contact SLS modulation techniques and their safety factors. The investigators propose to use either a pulse-duplicator or the Shiley heart phantom to determine whether the cardiac cycle produces sufficient modulation of the SLS for detection. Either or both of these measurements should be pursued immediately. The authors indicate that if the natural modulation is insufficient, they will examine "the possibility of using an acoustic pressure transducer to modulate the SLS without risk to the patient." Insufficient details are provided to justify funding such an approach at the present time.

3) Design and fabricate a source coil and *4) Design and fabricate a single-channel magnetometer using an induction coil sensor for in vitro tests.* So far, the investigators have used an inductance bridge and a single coil that is either inside of or surrounding the valve. They propose to design and construct a coil system suitable for inducing currents in the valve and detecting the SLS modulation signal at a distance of 15 cm. This will be the next logical step, but only if the results of Tasks 1 and 2 are encouraging. This instrument should then be used to determine the relative magnitude of the SLS signal and those from changes in cardiac volume and location and cardiac-induced chest-wall motion. A shielded room could be used to obtain adequate noise rejection with the single-channel instrument. Studies from normal human volunteers could provide important data about non-SLS signals resulting from cardiac mechanical activity.

5) Design and fabricate 3-axis magnetometers from inductive sensors, 6) Design and fabricate custom electronics, 7) Develop preliminary software algorithms for use with the 6-element array, 8) Integrate the system and begin preliminary measurements. In year 2 (as stated on page 15), the tasks will include *9) Complete the software routines for analysis of the data obtained with the magnetometer array, 10) Final design adjustments of hardware, 11) test prototype instrument on live sheep, and 12) Design final clinical magnetometer system for commercialization in Phase*

III. Sections 5 through 12 of the proposal are not well developed. The one-channel system developed under Tasks 3 and 4 could be used for both *in vitro* and *in vivo* studies to determine whether the approach is feasible prior to the development of the six-channel instrument. Under the proposed task list, the first *in vivo* studies are not considered until the next to the last task. Given the possible problems with signals from the heart and chest wall, many more preliminary experiments would be justified prior to embarking on Tasks 5-10 and 12. Until tasks 1 through 4 are completed successfully, it would be premature to consider funding the development of a more complicated instrument.

The investigators should be funded for the studies in Tasks 1-4, with appropriate attention paid to the issues raised in this review.

The investigators have a technical background that is well-suited for the proposed research. The expertise and facilities at Quantum Magnetics are outstanding. Quantum Magnetics is a highly reputable firm with a number of impressive accomplishments.

TRUSTEES FOR THE BOWLING-PFIZER HEART VALVE SETTLEMENT FUNDS

BALANCE SHEET

AS OF OCTOBER 31, 1996

UNAUDITED

ASSETS

CASH:	
Consultation Fund	$ 594,965
Patient Benefit Fund	104,359
U.S. TREASURY BILLS:	
Consultation Fund (Par Value $46,350,000)	45,813,243
Patient Benefit Fund (Par Value $9,967,000)	9,865,640
OFFICE FURNITURE AND EQUIPMENT - NET:	
Research Management Group	24,422
Administrative Office	13,195
OTHER ASSETS	43,762
	$ 56,459,586

LIABILITIES AND FUNDS BALANCE

ACCOUNTS PAYABLE AND ACCRUED EXPENSES	$ 515,607
FEDERAL TAXES PAYABLE	165,000
Total Liabilities	680,607
FUNDS BALANCE	55,778,979
	$ 56,459,586

TRUSTEES FOR THE BOWLING-PFIZER HEART VALVE SETTLEMENT FUNDS

STATEMENT OF INCOME, BENEFIT PAYMENTS AND FUNDS BALANCE

FOR THE TEN MONTHS ENDED OCTOBER 31, 1996

UNAUDITED

	BUDGET 1/1/96-12/31/96	ACTUAL 1/1/96-10/31/96
INTEREST INCOME:		
Consultation Fund		$ 2,493,448
Patient Benefit Fund		331,505
Total		2,824,953
BENEFIT PAYMENTS:		
Consultation Fund:		
Implantees		10,951,500
Spouses		1,363,250
Total		12,314,750
Patient Benefit Fund:		
Valve Replacement Surgery		639,882
Total		12,954,632
RESEARCH PROGRAMS	$6,976,000	3,659,634
LITIGATION ATTORNEYS-FEES & EXPENSES		11,073,946
EXPENSES:		
Supervisory Panel (1)	2,075,000	1,115,105
Trustees' fees and expenses	350,000	139,436
Professional fees	170,000	58,474
Research Management Group (1)	517,000	311,974
Administrative Office (1)	592,000	411,875
Notification expense	200,000	119,760
Total	$3,904,000	2,156,624
PROVISION FOR FEDERAL TAXES		265,000
CONTRIBUTION BY SHILEY INCORPORATED		6,250,000
NET CHANGE IN FUNDS BALANCE		(21,034,883)
FUNDS BALANCE, DECEMBER 31, 1995		76,813,862
FUNDS BALANCE, OCTOBER 31, 1996		$ 55,778,979

(1) - See Schedule 1 herewith.

Schedule 1

TRUSTEES FOR THE BOWLING-PFIZER HEART VALVE SETTLEMENT FUNDS

SCHEDULE OF EXPENSES
UNAUDITED

	BUDGET 1/1/96-12/31/96	ACTUAL 1/1/96-10/31/96
SUPERVISORY PANEL:		
Panel members' compensation	$1,000,000	$ 675,662
Guidelines Committee compensation	240,000	37,250
Consultants' compensation	410,000	249,845
Travel and other expenses	425,000	152,348
Total	$2,075,000	$ 1,115,105
RESEARCH MANAGEMENT GROUP:		
Rents	$ 62,000	$ 42,913
Office payroll	200,000	135,826
Payroll taxes	21,000	12,858
Employee benefits	63,000	32,814
Outside services	12,000	3,741
Computer and telephone support	51,000	12,523
Travel	60,000	12,691
Printing and postage	24,000	27,886
General insurance	3,000	1,125
Telephone	6,000	12,909
Research supplies	3,000	
Office supplies and expense	9,000	7,681
Depreciation		4,300
Miscellaneous	3,000	4,707
Total	$ 517,000	$ 311,974
ADMINISTRATIVE OFFICE:		
Rents	$ 48,000	$ 40,782
Office payroll	290,000	193,444
Payroll taxes	30,000	15,088
Employee benefits	20,000	17,757
Outside services	96,000	72,716
Printing and postage	54,000	37,507
General insurance	6,000	970
Telephone	24,000	19,569
Office supplies and expense	12,000	7,672
Depreciation		819
Miscellaneous	12,000	5,551
Total	$ 592,000	$ 411,875

Deloitte & Touche LLP

BOWLING-PFIZER HEART VALVE LITIGATION SETTLEMENT FUND

Statements of Assets, Liabilities and Fund Balance - Modified Cash Basis as of December 31, 1995 and 1994 and Statements of Income and Settlement Payments in Excess of Expenses and Benefit Payments and Change in Fund Balance - Modified Cash Basis for the Years Ended December 31, 1995 and 1994 and Independent Auditor's Report

Deloitte & Touche LLP

250 East Fifth Street
P.O. Box 5340
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INDEPENDENT AUDITORS' REPORT

Bowling - Pfizer Heart Valve Litigation Settlement Fund
525 Vine Street, Suite 1300
Cincinnati, Ohio 45202

We have audited the accompanying statements of assets, liabilities and fund balance - modified cash basis of the Bowling - Pfizer Heart Valve Litigation Settlement Fund (the "Fund") as of December 31, 1995, and 1994 and the related statements of income and settlement payments in excess of expenses and benefit payments and change in fund balance - modified cash basis for the years then ended. These financial statements are the responsibility of the Fund's management. Our responsibility is to express an opinion on these financial statements based on our audits.

We conducted our audits in accordance with generally accepted auditing standards. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. An audit includes examining, on a test basis, evidence supporting amounts and disclosures in the financial statements. An audit also includes assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

As described in Note 2 to the financial statements, these financial statements were prepared on the modified cash basis of accounting, which is a comprehensive basis of accounting other than generally accepted accounting principles.

In our opinion, such financial statements present fairly, in all material respects, the assets, liabilities and fund balance of the Fund as of December 31, 1995, and 1994 and its income and settlement payments in excess of expenses and benefit payments and changes in fund balance for the years then ended on the basis of accounting described in Note 2.

Deloitte & Touche LLP

November 1, 1996

BOWLING-PFIZER HEART VALVE LITIGATION SETTLEMENT FUND

STATEMENTS OF ASSETS, LIABILITIES AND FUND BALANCE - MODIFIED CASH BASIS AS OF DECEMBER 31, 1995 AND 1994

	1995	1994
ASSETS		
CASH	$ 528,682	$ 268,530
INVESTMENTS (Note 3):		
Consultation Fund	66,408,269	92,159,249
Patient Benefit Fund	10,861,909	12,105,478
Total Investments	77,270,178	104,264,727
TAX REFUND RECEIVABLE (Notes 2,6)	100,000	108,280
OTHER ASSETS (Note 2)	92,476	46,177
TOTAL ASSETS	$ 77,991,336	$104,687,714
LIABILITIES AND FUND BALANCE		
ACCOUNTS PAYABLE AND ACCRUED EXPENSES (Note 2)	$ 1,177,474	$ 311,313
Total Liabilities	1,177,474	311,313
FUND BALANCE (Note 1):		
Consultation Fund	66,956,949	92,345,628
Patient Benefit Fund	9,856,913	12,030,773
Total Fund Balance	76,813,862	104,376,401
TOTAL LIABILITIES AND FUND BALANCE	$ 77,991,336	$104,687,714

See notes to financial statements.

BOWLING-PFIZER HEART VALVE LITIGATION SETTLEMENT FUND

STATEMENTS OF INCOME AND SETTLEMENT PAYMENTS IN EXCESS OF EXPENSES AND BENEFIT PAYMENTS AND CHANGE IN FUND BALANCE - MODIFIED CASH BASIS FOR THE YEARS ENDED DECEMBER 31, 1995 AND 1994

	1995	1994
INCOME:		
Settlement payments by Pfizer/Shiley (Note 1)	$ -	$ 22,500,000
Net investment income	5,253,426	3,670,661
Total Income	5,253,426	26,170,661
EXPENSES AND BENEFIT PAYMENTS:		
Benefit payments - Consultation Fund (Note 2)	28,319,250	2,406,500
Benefit payments - valve replacement surgery	116,534	-
Research programs	479,471	-
Supervisory panel expenses (Note 1)	1,707,538	571,593
Trustees' fees and expenses	313,532	93,428
Special master - SLF fees and expenses	20,367	-
Professional fees (Note 5)	156,284	44,954
Research Management Group	351,861	-
Other administrative expenses	441,128	99,241
Notification expense	10,000	407,606
Provision for income taxes (Note 6)	900,000	971,720
Total expenses and benefit payments	32,815,965	4,595,042
INCREASE (DECREASE) IN FUND BALANCE	(27,562,539)	21,575,619
FUND BALANCE, BEGINNNG OF YEAR	104,376,401	82,800,782
FUND BALANCE, END OF YEAR	$ 76,813,862	$ 104,376,401

See notes to financial statements.

BOWLING-PFIZER HEART VALVE LITIGATION SETTLEMENT FUND

NOTES TO MODIFIED CASH BASIS FINANCIAL STATEMENTS

1. ORGANIZATION AND GENERAL INFORMATION

The Bowling-Pfizer Heart Valve Litigation Settlement Fund (the Fund) is the result of a settlement between Pfizer Inc. (Pfizer) and its wholly-owned subsidiary Shiley Incorporated (Shiley) and a class of plaintiffs (Plaintiffs) consisting of all persons who were alive on January 23, 1992 with a Bjork-Shiley convexo-concave (C/C) heart valve still implanted, and their spouses on that date, except those persons who filed valid and timely requests for exclusion from the class.

The Settlement requires that Pfizer/Shiley pay a minimum of $165 million to the Fund to settle the claims of the Plaintiffs. Certain provisions exist whereby Pfizer may be required to pay additional amounts to the Fund based on certain criteria as defined in the Settlement. The minimum Settlement is allocated between the "Patient Benefit Fund" ($75 million) and the "Consultation Fund" ($90 million).

The Patient Benefit Fund is to be used for: research and development of diagnostic techniques to identify implantees who may have a significant risk of strut fracture and to make such diagnostic techniques available to plaintiff implantees; research concerning the characterization and/or reduction of the risks of valve replacement surgery; and payment of covered expenses for qualifying surgery to explant, due to the risk of strut fracture, a Plaintiff implantee's C/C heart valve and replace it with another prosthetic valve.

The Consultation Fund, initially $80,000,000 for Plaintiff implantees, is intended to provide Plaintiff implantees with funds to obtain medical and psychological consultation as they deem best. It is to be divided equally among Plaintiff implantees after paying or providing for fees and expenses to be paid out of the implantee portion of the Fund. In addition, $10,000,000 was paid into the Fund which is to be paid, after fees and expenses, equally to all Plaintiff spouses.

The terms of the Settlement required Pfizer/Shiley to initially deposit $12,500,000 into the Patient Benefit Fund. Additionally, beginning on the second anniversary of the final approval of the Settlement, Pfizer/Shiley is required to make annual deposits into the Patient Benefit Fund of not less than $6,250,000 until a total of $75,000,000 has been paid.

Pfizer/Shiley paid $80,000,000 to the Consultation Fund in 1992 and paid $10,000,000 to the Consultation Fund in 1994. In addition, in 1994 Pfizer/Shiley also paid $12,500,000 to the Patient Benefit Fund. Pfizer/Shiley also paid $6,250,000 in October, 1996 to the Patient Benefit Fund.

As of November 1, 1996 the Fund had received Consultation Fund proof of claim forms from 15,865 potential claimants. Of this number, 15,505 claims had been processed and 13,128 had been approved as valid claims under the Settlement Agreement.

The research activities of the Patient Benefit Fund are supervised by a Supervisory Panel (Panel). The Panel, subject to Court approval, shall adopt guidelines for the use of diagnostic testing techniques and for valve replacement surgery. Also, the Panel will create a publicly accessible repository of information concerning the status of the research and the risks of valve fracture and of valve

replacement. The Panel is made up of six members who are recognized scientific or medical experts and one member who is not a scientist or physician.

2. SIGNIFICANT ACCOUNTING POLICIES

Basis of Accounting - The Fund prepares its financial statements on the modified cash basis of accounting. Therefore, it records interest receivable for interest earned not yet received, taxes receivable (payable) and accounts payable for expenses when incurred rather than when paid (modified cash basis). Under this basis all settlement payments by Pfizer/Shiley are recognized when received and all benefit payments and Plaintiffs' counsel fees and expenses are recognized when paid rather than when incurred. Additionally, the "Amounts due to Pfizer/Shiley" will be recognized when paid rather than when incurred.

Settlement Payments - All Consultation Fund claims submitted by each claimant are reviewed for qualification by the Fund and payments of qualified claims are approved by the Court. The Fund paid initial distribution payments to qualified Consultation Fund claimants in 1994 and 1995. The total number of eligible claimants has not yet been determined.

Amounts due to Pfizer/Shiley - The Fund has agreed to reimburse Pfizer/Shiley for certain medical expense payments made for qualifying valve replacement surgeries. These medical expense payments were made by Pfizer/Shiley for qualifying surgeries that occurred after January 23, 1992 and before the Fund commenced processing valve replacement surgery claims. The Fund has agreed to contract for, and continue certain research programs that were initiated by Shiley Incorporated. In addition, the Fund has agreed to reimburse Pfizer/Shiley for the reasonable costs of maintaining these research programs from the date of the appointment of the Supervisory Panel until the dates that the research programs come under the control of the Supervisory Panel. These amounts will be paid to Pfizer/Shiley after review by the Fund and approval by the Court. These amounts will be reported as a distribution when paid by the Fund. Management has estimated the total amount due to Pfizer/Shiley to be approximately $3,400,000 and $1,700,000 as of December 31, 1995 and 1994 for these two categories of costs to the Patient Benefit Fund.

Other Assets - Other Assets represents prepaid expenses, office furniture and computer equipment used by the Fund.

Estimates - The preparation of financial statements requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities, disclosures of contingent assets and liabilities at the date of the financial statements and the reported amounts of revenues and expenses during the reporting period.

3. INVESTMENTS

Investments at December 31, 1995 and 1994 consist of U.S. Treasury Bills and are carried at cost plus accrued interest. The market value of such investments was approximately $77,316,000 and $104,284,000, at December 31, 1995 and 1994, respectively.

4. OPERATING LEASES

The Fund subleases its office facilities under an agreement classified as an operating lease from an unrelated litigation settlement fund. Effective July 1, 1994 the original lease was amended and assigned to the Fund for the period April 1, 1996 through March 31, 1999. Total future minimum lease and sublease payments due are as follows:

1996	$ 39,803
1997	53,071
1998	53,071
1999	13,268
Total	$ 159,213

5. RELATED PARTY TRANSACTIONS

One trustee of the Fund is a partner of the law firm that provides miscellaneous services to the Fund. Payments of professional fees to this firm, approved by the Court, amounted to $34,064 and $18,818 in 1995 and 1994.

6. TAX STATUS

For Federal income tax purposes, the Fund is treated as a taxable complex trust, a "Designated Settlement Fund" under Section 468(B) of the Internal Revenue Code. The Fund is required to pay taxes on the excess of interest income earned over expenses incurred for the administration of the Fund. The settlement payments by Pfizer/Shiley, benefit payments and payment of Plaintiffs' counsel fees and expenses are not taxable transactions.

In March 1996, the Fund requested a ruling from the Internal Revenue Service, regarding the taxability of the Fund and the deductibility of certain disbursements from the Fund. No amounts have been recorded in the accompanying financial statements for a potential unfavorable ruling.

7. LEGAL ISSUES

There are appeals pending in the Court of Appeals for the Sixth Circuit that could impact the Fund. No amounts have been recorded in the accompanying financial statements for any potential liabilities that may result from these appeals.

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