"Biobanking: How the Lack of a Coherent Policy Allowed the Veterans Administration to Destroy an Irreplacable Collection of *Legionella* Samples"
Subcommittee on Investigations and Oversight
House Committee on Science and Technology
September 9, 2008

Testimony of Victor L Yu, M.D.

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Introduction

My name is Dr. Victor Yu. I am a Professor of Medicine in the Division of Infectious Diseases at the University of Pittsburgh. I have been a University Professor since 1978 and most of that time was also Chief of the Infectious Disease section at the VA Medical Center, an affiliated teaching hospital of the University of Pittsburgh.

I have published widely on Legionnaires' disease, pneumonia, bloodborne pathogens, MRSA (Methicillin resistant *Staph. aureus)*, antibiotic resistance, and medical informatics. I have a background in mathematics and computer science so I have devised an idea of accumulating clinical information about patients, their laboratory values, their underlying diseases, the antibiotics that they received, and their outcome. I realized that having a computer database for thousands of patients would enable us to make statistical correlations about epidemiology and therapy In the era of antibiotic resistance and new emerging pathogens, such a database has been invaluable .

Using this approach, over 100 articles in different areas of infectious diseases have been published and led to therapeutic advances. I organized large international collaborative groups of physicians and scientists who have contributed patient information into the computer database as well as microbial pathogens that caused these infections. This treasure trove of computerized data plus a collection of human pathogens has led to many advances in management and diagnosis of very difficult infectious diseases.

Encounter with Legionnaires' Disease

After the American Legion outbreak in Philadelphia in 1976, it was soon discovered that other cases of Legionnaires' disease were occurring. As a junior assistant professor in 1979, I came across the first cases of hospital-acquired or nosocomial Legionnaires' disease. It had caused a serious problem at three VA Medical Centers: Wadsworth VA Medical Center in Los Angeles, the Pittsburgh VA Medical Center, and the Togus, Maine, VA Medical Center. It was a shock to find out that it was being contracted by patients in the hospital.

Dr. Janet E. Stout, Ph.D. would soon make the startling discovery that the *legionella* bacteria, the causative agent of Legionnaires' disease was in the drinking water supply of the hospital. The prevailing theory at that time was that it was in cooling towers and air conditioners. Even today, many physicians are not aware that drinking water is the major source.

Because of this occurrence, we were given funding by VA Central Office to add a special microbiologist to the Infectious Disease staff to assist us. *Legionella* is a fastidious organism that requires expertise and special techniques to isolate. Dr. Susan Mather in VA Central Office (enclosed letter) oversaw the investigation into Legionnaires' disease.

One of the reasons we were given extra funding and assistance is that outbreaks were being described all over the world besides the VA Hospital, and we had formulated a culture media that microbiologists could identify *Legionella* by the coloration on the culture plates. This technical advance accelerated the ability to diagnose *Legionella* from patients and from the environment. Over the next many years, we would accomplish a number of things with respect to *Legionella*, microbiology and public health.

Dr. Stout has listed the advances made by the VA Special Pathogens Lab in her testimony which includes evaluating all the commercially available tests for Legionnaires' disease, evaluating all commercially available antibiotics for therapy of Legionnaires' disease, describing the clinical manifestations of Legionnaires' disease, and formulating the disinfection method of eradicating *Legionella* from drinking water.

HISTORY OF THE SPECIAL PATHOGENS LABORATORY

The Special Pathogens Lab was established in about 1980. Because of the large number of outbreaks that were occurring in Veterans Affairs Medical Centers, VA Central Office awarded 2 full-time employee slots to Pittsburgh to respond. During those early years, we pioneered the use of various tests and most importantly, formulated the culture media in which *Legionella* could be identified by color, thus allowing the microbiologists to get preliminary identification of the *Legionella* by looking at a culture plate; a microscope was not needed. In the next several years, we became quite prolific in advances in Legionnaires' disease.

About 1984, we received our first VA Merit Review Grant dealing with Legionnaires' disease. About three years later, Martin Sax, then Chief of the Research and Development Committee, approached us and suggested that we become active members of the Veterans Research Foundation. Given our reputation, we could solicit funds from industry and other sources to supplement the funds coming into the Veterans Research Foundation. He offered us lab space as cuts in the VA budget were forcing many VA researchers to discontinue their studies. We agreed. We subsequently were able to bring in funds from foundations and industry for work on disinfection modalities, and antibiotic studies of a whole host of pathogens, including *Staphylococcus aureus* (MRSA), *Streptococcus pneumoniae, Enterococcus, Pseudomonas aeruginosa, Enterobacter, Stenotrophomonas maltophilia, Bacteroides,* and fungi *(Candida, Cryptococcus, Aspergillus).*

However, in subsequent years we branched out into pathogens of community-acquired pneumonia , urinary tract infections, abdominal abscesses, and endocarditis. We acquired expertise in antimicrobial resistance and published about 100 articles in this area. We were able to bring in hundreds of thousands of dollars into the Veterans Research Foundation which allowed them to gain critical mass and justify laboratory space.

In 1994, as the VA budget was being cut, VA Central Office sent out a solicitation to academic researchers about the possibility of using their capabilities to

initiate laboratories for profit. This was based on a 1994 Special Clinical Resource Center memorandum. In 1996, the Director of the VA and Chief of Pathology agreed that designating the Special Pathogens Laboratory as Special Clinical Resource Center was feasible. And, in 1996, the Special Pathogens Lab went national.

Over the next many years our laboratory and clinical work continued. Funds were brought into the Veterans Research Foundation under grants I wrote as Professor of Medicine at the University of Pittsburgh. Five University employees including a CDC-trained microbiologist were brought in to handle the growing amount of research activity. New instrumentation, equipment and supplies awarded to the University of Pittsburgh was brought into the Special Pathogens Lab. All this equipment was tagged as University of Pittsburgh equipment.

In those early years, the VA budget was very thin and most VA laboratories were not only understaffed but their equipment was outdated. Since we were using microbiology equipment for research which also could be used to handle the clinical load, we outfitted the VA Clinical Microbiology Laboratory with modern equipment and furniture. This made our laboratory one of the best equipped laboratories in Pennsylvania, and both the research and patient care benefitted.

Graduate students, infectious disease fellows, and visiting professors came to the Special Pathogens Lab to our laboratory to learn new techniques and assist with clinical studies. Their participation led to many breakthroughs in infectious diseases over the next 12 years.

In 2006, inexplicably, the Special Pathogens Lab was shut down by Mr. Moreland, Director of the Pittsburgh VA. The specific reasons were never given to us as noted in my letter of July 12, 2006 (Appendix). We were given only 48 hours notice and the entire Lab was to be shut down. All the Lab personnel were fired, and the Lab was to be padlocked. Mr. Moreland had been in his position as Director of the Hospital for only a few years and some of the laboratory personnel had been there for more than 10 years and their livelihood and occupation was shattered with one 48-hour notice. It should be noted that this violated the provisions of the Special Clinical Resource Center memorandum which had guidelines to insure that patient care and other aspects would not suffer from abrupt lab closure.

However, Mr. Moreland overlooked the fact that we were processing specimens for the Pittsburgh VA Medical Center patients as well and reluctantly agreed to a two-week moratorium. During that time specimens from all over the country continued to come into the Special Pathogens Laboratory as usual.

We were ordered to notify all of our clients that the lab was being closed, but since we had 600 different clients including health departments and hospitals, faxing to 600 clients was impossible. Moreover we had two weeks to complete a huge workload . During this time, the laboratory personnel were harassed by security guards and administrators. Microscopes were removed. When the laboratory technician left the

laboratory for breaks or lunch, the security guards refused to unlock the doors such that the personnel in the lab had to come out an open the doors for them. It was a Gestapo like atmosphere and caused tremendous stress among the laboratory personnel. Yet, they accelerated their efforts in trying to process all the samples that were coming in.

Because the results were so important to the hospitals and health departments, we no longer had the time necessary to enter them into the computer, send out invoices, and so forth. Moreover, Mr. Moreland stopped the supplies from entering into our laboratory so that supplies which had been purchased were not allowed to be used and delivered to the personnel. Moreover, he refused to allow us to purchase materials for the specimens which included Pittsburgh VA patients to be processed. The laboratory personnel pooled their own funds to buy these supplies.

They were true heroes working for the VA patients and the US community. In the last two weeks, Mr Moreland ordered me to stop accepting specimens from outside the University of Pittsburgh. I wrote to him that this was a Hobson's choice: Obey an administrative order from the Director or follow my conscience as a physician researcher and process specimens from patients, hospitals, and public health agencies. I decided to process these specimens and informed Mr. Moreland the reasons for doing so. One set of samples came from the Phoenix VA Medical Center. 65% of the hospital drinking water specimens yielded *legionella* and uncovered an endemic outbreak of Legionnaires' disease. This outbreak and the source would not have been identified if I had not continued to process the incoming water specimens.

During this time, the Lab personnel were not only harassed, but each was asked to give sworn testimony at an investigative hearing. This was done during their work hours and added to their stress.

The saga of what happened to the last 15 clients' specimens that were processed is a matter of record (See www.legionella.org/vaspl.asp). On the day of closure where the lab was to be padlocked, culture specimens from 15 clients remained to be read. They included hospitals, a government building, and samples from a patient's home. The lab successfully processed all these samples, but since they required 48 to 72 hours of incubation, they could not be read. The security guards would not allow staff into the laboratory. We made a plea to Mr. Moreland to allow the culture plates to be read. He refused. We made a plea to VA Central Office; they never replied. However, Senator Arlen Specter wrote a letter to Mr. Moreland on our behalf requesting that the final 15 culture samples be processed. He ignored that request. We offered to transport the VA cultures to another laboratory. Mr. Moreland refused. Those culture specimens dried out in the laboratory, were left unread, and ultimately trashed. The only thing that was needed to be done was to interpret the culture plates.

Ironically, in the 10 days after the closure, the Pittsburgh Tribune Review ran a front-page story of accomplishments of the Pittsburgh VA with the discovery of Legionnaires' disease. Because of the National Legion Convention was held in

Pittsburgh that week , Congressmen from Pennsylvania attended . The American Legion knowing of our contacted Congressman Mike Doyle and Senator Arlen Specter , both of whom wrote letters of support. These letters were ignored by Mr. Moreland and VA Central Office.

The reasons they gave to the Congressmen and to the lay media are a matter of record. For example, Mr. Cowgill alleged we were not processing VA specimens but instead processing specimens from other countries. In letters from VA Central Office, William Feeley, Underscretary, claimed we were not doing any research and that commercial labs could do the same work. These were outrageous exaggerations and untruths

We have already furnished documentation showing errors and the difficulty of doing *Legionella* laboratory work. Experience, training and special equipment is necessary. We had become the premier reference laboratory for Legionella for the United States. Not only were visiting professors and scientists coming to the lab, but commercial laboratories sent their technicians to our laboratory to learn the correct technique as mandated by the American Society of Microbiology Manual of Clinical Microbiology written by Janet Stout and John D. Rihs... We did not charge for this teaching.

Response to VA Audit

In response to the outcry generated by the destruction of the scientific collection, the VA claimed that I had conducted non-approved research studies. The conducted an audit which was never shown or discussed with me. I obtained a copy of this audit from congressional investigators. In this biased audit of 39 articles and 11 projects, not a single study was found to be non-approved. The audit by the Pittsburgh VA administrators showed numerous errors that were obvious and blatant. Some examples:

Seven articles were cited as having no documentation for VA approval involved no VA patients and were not performed at the VA. (one of these studies involved no patients whatsoever and would not be covered by human subject review)

Six articles were cited as having no documentation . Yet Appendix B contained the documentation for all of these articles.

Ten articles were cited as having no documentation were observational studies that did not fall under human subject research as defined by federal code. So no approvals were required

Two articles were cited as having no documentation . However, the articles did not involve any patient contact or physician intervention, and therefore would not require human rights approval.

Three articles involved clinical trials and intervention which would require IRB and R&D approval. The audit showed that all three were approved.

Articles by Dr Yu that were funded via VA Merit Review and would , of course, be approved by the VA R&D committee were not included in the audit.

In Appendix B, 11 Projects were reviewed. All 11 Projects were approved by R&D and/or IRB. Missing forms were cited, although it was clear that the studies were approved by R&D and IRB. Since approval was given, these forms were either lost by the R&D Committee or overlooked by the auditor.

For full details, see Appendix. Response to VA Publication Audit by Victor L Yu.

The sheer number and the blatancy of these errors are consistent with a witch hunt conducted by a biased VA administration.

Klebsiella and Levofloxacin studies were cited inaccurately as unapproved. Details of the the studies are summarized below

Klebsiella - a virulent Klebsiella discovered by us in an international antibiotic resistance study was found in Taiwan but not elsewhere. In the past 5 years, patients who are Asian have been found to have a similar disease in US. 2 critically-ill patients were referred to us who were non-Asians and had not traveled outside of US. Examination of the molecular type of these Klebsiella showed that were identical to the Taiwan Klebsiella. This Klebsiella is now in the US. Our entire collection of Klebsiella collected in 2 large-scale studies in the US and all 6 inhabitable continents was destroyed . We lost the ability to compare the molecular characteristics of the Klebsiella in our collection with those of newly-infected patients. Study of our original collection and new Klebsiella would allow us to develop antibiotics and vaccines
(See Appendix – Approval from Request to Review Research Proposal for "Pathogenicity of Klebsiella")

Levofloxacin: Janet Stout found a new compound from OrthoMcNeil to be highly effective in the lab against Legionella. This compound was brought to clinical use and in the first trial of pneumonia, the compound cured an amazing 100% of patients with LD. This experience was reported and the compound was released as levofloxacin. 4 years later, levofloxacin was used in a huge outbreak of LD in Spain. 100% cure. All of our Legionella isolates were destroyed.
(See Appendix – Response to publication audit . Project 9. Documentation of approval of "Levaquin Community-Acquired Pneumonia")

In summary, this massive collection of more than 8000 microbes (5000 Legionella, 300 species of other bacteria and fungi), 3000 patient sera, and 200 patient specimens (urine, respiratory tract) was destroyed without warning . The VA administration never even confirmed that this collection had been destroyed despite

repeated requests. The collection was unique in that the microbes and specimens were linked to the clinical histories of the patients who were infected by these microbes.

Testimony of Victor L. Yu, M.D.

Appendix

I. Response to Publication Audit by Pittsburgh VA

> Conclusion: For the 39 articles reviewed, not a single example of human subject research without appropriate approval was found

II. Research and development Approval Form for Legionella Studies

III. Research Project Approval for Klebsiella Study

IV. Memo from Victor L. Yu to M. Moreland requesting written justification for closure –July 12, 2006

V. Letter to Drs Jain, Graham, DeRubertis protesting the destruction of the scientific collection – January 17, 2007

VI. Phoenix VA letter of support for assistance in Legionella cultures

Response to Publication Audit
VA Pittsburgh Healthcare System
September 5, 2006
Victor L. Yu, M.D.

The document from the Pittsburgh VA concluded that the audit "suggests a strong likelihood that Dr. Yu was engaged in human subject research at the VAPHS without the appropriate committee approvals."

A close reading of this audit shows numerous errors were made in the audit of the 39 articles published: some were minor, but many errors were so obvious as to bring in the issue of bias. Using the language of the audit, I conclude that this audit "suggests a strong likelihood" that numerous errors found in the VA Pittsburgh Healthcare audit were due to the bias of the Pittsburgh VA Medical Center administration. The Pittsburgh VA needed to rationalize the illegal and unjustified closure of the Pittsburgh Special Pathogens Laboratory and the willful destruction of a scientific collection. So, they produced a misleading and erroneous audit. The magnitude and obviousness of some of the errors is striking.

1. **Multiple Counting**
9 articles emanating from a single study were counted to inflate the total number of articles purported to be in question
Articles 1, 9, 15; Articles 7, 11, 16, 29; Articles 12, 13

Audit Error: Article 1. This article is derived from Article 9 and 15 which has IRB and R&D approval. None of the patients discussed were at the Pittsburgh VA.

2. **Audit Error:** NonVA studies.
7 studies covered in the audit involved no patients at the Pittsburgh VA; the studies were conducted elsewhere.
Articles 1, 5, 8, 10, 14, 17, 34

3. **Audit Error:** 6 studies in which it was claimed in *VAPHS IRB and R&D records contain no documentation for this study*" had documented IRB approval which were in the files of the VA Research and Development office. The projects containing the documentation are in Appendix B.
Articles 1 (Project 1), 8 (Project 9), 6, 19, 27, 29 (all 4 are under Project 7)

4. **Audit Error:** 10 studies did not meet the definition of human subject research according to the federal code. This code is cited explicitly on page 17 of the audit. Thus, IRB approval was not required.

These studies were "observational" in the "no intervention nor interaction with the individual patient "occurred" and "no identifiable private information" was involved. In each of the articles a statement in the Methods noted that "the study was observational in that administration of antimicrobial agents and other management was controlled by the patient's physician, not the investigator." This audit error is inexplicable since the title of some articles and the methods classified the study as observational was so obvious.

Moreover, HIPAA regulations known as the Privacy Rule was not mandated until 2003 prior to the approval of these proposals. So, at the time of these studies, formal approval was not mandated.
Articles 4, 7, 11, 12, 13, 16, 20, 22, 24, 30

5. Only three studies of the 39 articles reviewed involved interventional studies involving VA patients. These 3 studies clearly fulfilled the definition of human subject research. For these studies, both IRB and Human Subjects approval were obtained and approved by the R & D Committee. Informed consent was obtained on all patients and copies were given to patients and placed in the patient chart. In two studies, the audit states "VAPHS IRB records contain some documentation for the study". In one study (Article 21), approval was listed under the PI, who was not Dr. Yu.
Articles 18, 21, 23

Audit Error: Article 25. In this study, nasal swabs for *S. aureus* were obtained as part of Infection Control policy and patient care. Nasal swabs are routinely used in the Pittsburgh VA for surveillance. Moreover, the article was published in 1999 prior to HIPAA Guidelines.

6. **Audit error.** 2 studies reviewed did not involve any patient contact and intervention and involved isolates not specifically linked to individual patients.
Articles 36, 39

7. **Audit Error:** One article fulfills the OHRP Guidelines discussed on page 18, paragraph 3. In these studies, the specimens were saved and "not collected specifically for the proposed research project" and "the investigator cannot ascertain the identity of the individual to which specimens pertain".
Article 39

8. Seven articles reviewed had IRB approval by the PI (who was not Dr. Yu). This is discussed on page 18, paragraph 1.

9. Six articles were not cited and had full documentation.
Articles 15, 26, 28, 32, 33, 35

Note that several articles listed above as "Audit Error" fulfilled different criteria.

In summary, for all 39 studies reviewed, not a single example of human subject research without appropriate approval was found.

Appendix B – Record Review
IRB and R&D

11 projects were reviewed by the Pittsburgh VA auditor.

Many reviews by the auditor noted the following: Lack of "*Request for continuing review*" and Lack of "*R&D approval of the study closure*"; or Lack of "*Request for study closure*". The implication is that these were unapproved studies.

In fact, all of the projects were approved. All of the citations noted by the auditor were technicalities noted after the projects were approved. The technicalities were not related to research merit or human rights issues. However, it is important to note that the validity of appropriateness of the projects from a research and human rights perspective can be confirmed in the audit document itself.

In the 20 plus years that I have performed over 100 studies, I have never been informed of any delinquency in this area by either the IRB or R&D Committee. I saw the results of this misleading and flawed audit only after the Congressional Investigational Oversight Subcommittee showed it to me.

The chairman of the VA Research Committee introduced a policy for all VA investigators that submission of an abstract or publication of the article would be sufficient as documentation for IRB continuing approval or study closure. Every year, our research group and other VA researchers submitted all abstracts and publications for the year to the Committee. The Research Foundation also used these documents to demonstrate the research productivity of the Pittsburgh VA Medical Center. Thus, the fact that this audit was based on a review of our published articles immediately validates that the "*R&D for study closure*" was fulfilled. This is pertinent to Projects 1 and 6.

Comments on each specific Project:

Project 1 Prospective Observational Study on Pneumococcal Bacteremia
Citation: Request for continuing review
Request for study closure

Note that this approved project was concluded and an article published. The article was awarded the Wolinsky Prize for the best clinical infectious disease article for 2003. The fact that the article was published fulfills the criteria for study closure.

Project 2 Retrospective surplus sample collection for B
Citation: Request for continuing review 02/2003

This project was never initiated. This is confirmed by R&D approval of study closure on 03/05/2003.

Project 3: Prospective observational study in pneumococcal meningitis

Citation: Request for continuing review

This approved project has been completed and an abstract presented. No VA patients participated in this study. We were the repository for the pneumococcal isolate collection.

Project 4: Azithromycin vs. erythromycin
Citation: IRB continuing review – 01/1993
R&D final approval – 01/1992

This approved study was completed and published.
Note that IRB approval of study closure was given on 07/03/1997 and R & D approval of continuing review was on 05/13/1994. So, the IRB continuing review in 01/1993 and R&D final approval on 01/1992 must have been lost by the R&D Committee or overlooked by the auditor.

Project 5: Topical antibiotic prophylaxis
Citation: Final R & D approval

Note that IRB approval of study closure was 08/02/1996. So, the study was formally closed on 08/02/1996. The R&D approval was either lost by the R&D Committee or the auditor overlooked it.

Project 6: Efficacy of topical antibiotics
Citation: Request continuing review
Request for study closure
Final R&D approval

This study was never initiated.

Project 7: Various studies examining treatment, prevalence, and eradication of Legionella
Citation: Original submission to R&D
Final R&D approval
R&D continuing review request
Request for study closure

This is an important document which confirms that all of the *Legionella* studies conducted were approved by the R&D Committee.

The dates show that *R& D approval of continuing review* was performed. So, the original documents must have been lost by the R&D Committee or overlooked by the auditor. I have in my possession the form that documents that the initial R&D approval was performed on 10/01/1998 and that it did not expire until 12/11/2006. The Special Pathogens Laboratory was terminated in July, 2006.

This project was also cited for lack of "*Request for study closure*". It seems a gross injustice to cite Lack of *Request for study closure* after the Pittsburgh VA terminated the Pittsburgh VA Special Pathogens Laboratory. The VA closed the study when I was terminated.

Project 8: Randomized trial of fluconazole
No Citation

Project 9: Levaquin (levofloxacin) Community-Acquired pneumonia
No Citation
Note: It was the basis for Article 8 which the auditor claimed had no documentation.

Project 10: Preemptive prophylaxis
No Citation

Project 11: University of Pittsburgh
The study was concluded by 2004 so we did not request renewal.

One reasonable conclusion from review of Projects 1, 2, 3, 4, 5, 6, 7, 11 in Appendix B was that this was a targeted witch hunt attempting to cast aspersion on Dr. Yu's reputation as a clinical investigator. These minor technicalities were never pointed out to Dr. Yu during his 25 years as the most productive researcher in the Pittsburgh VA as judged by publication numbers. None of the technicalities dealt with project approval. It is ironic that that information provided in the audit itself confirmed that all the projects were approved. Documents lost by the Research Office or overlooked by the auditor were then used to impugn Dr. Yu and imply that improprieties occurred.

Victor L. Yu, M.D.
Professor of Medicine
University of Pittsburgh
Date: September 5, 2008

Animal Studies Subcommittee (IACUC)
VA Pittsburgh Healthcare System #646
University Drive • Pittsburgh, PA 15240

CONTINUING REVIEW SUBMISSION FORM

Date: October 24, 2003
Investigator: **Victor L. Yu, M.D.**
Protocol: Pathogenicity of Klebsiella Pneumoniae Isolated from Different Geographical Locations and Disease Presentations
ID: 02096 Prom#: N/A Protocol#: N/A

Initial AnSS Approval Date: 03/20/2003
Previous Continuing Reviews: N/A
Approval Expiration: 03/19/2004

Submission Form Due Date: 03/04/2004
Continuing Review Date: 03/18/2004

This form is used for the first and second renewal of an approved animal protocol. NOTE: Prior to the third anniversary, the IACUC must conduct a re-review of the entire protocol.

Request to Review Research Proposal/Project

646 Pittsburgh, (UD), PA

1. **Principal Investigator/Program Director:** Yu (Last) Victor (First) L. (MI) _____ (Degree)

2. **SSN:** 476 - 46-9721 3. **Telephone:** 412/688-6179 **Ext.:** _____ 4. **Mail Code:** _____

5. **VA Appointment:** (Check one) [xx] Full-Time [ ] Part-Time [ ] WOC [ ] Consultant [ ] Contract

6. **Status of PI in Proposal:** 01 (Enter Code) *(01 = Awardee or Initiator 02 = Not Awardee; i.e., Participant in VA Co-Op Study)*

7. **Type of Submission:** (Check one) [x] New [ ] Renewal of Active Project

If Renewal, complete a and b: a) Enter 4-digit number of active project_____ *b)* Has title changed? [ ] Yes [ ] No

8. **Project Title:** (142 characters maximum) Pathogenicity of Klebsiella Pneumoniae isolated from different geographical locations and disease presentations.

9. **Co-Principal Investigators:** *(Enter only if study is funded. Must have a VA appointment and must be designated a Co-PI in application.)*

_____ (Last name, first name, mi, degree) _____ (Social Security Number) [ ] Check if at another VAMC

_____ (Last name, first name, mi, degree) _____ (Social Security Number) [ ] Check if at another VAMC

10. **Anticipated Starting Date:** 04 / 01/ 99 *(mm/dd/yy)*

11. **Funding Source and Fund Administration:** *(Codes are on back of instruction sheet)*

Source Code (4-digits)	Name if Source Code ends in "99"	Admin Code (2-digits)	Name if Admin Code is "08"
0000		01	

If Source Code is 9007, 9022, or 9024, enter VACO Project Number: _____

12. **Project Uses:** *(Mark each item and submit completed forms. If Animal Subjects is Yes, Complete Item 15.)*

Human Subjects	[ ] Yes [x] No	Invest Drugs	[ ] Yes [x] No	Radioisotopes	[ ] Yes [x] No
Animal Subjects	[x] Yes [ ] No	Invest Devices	[ ] Yes [x] No	Biohazards	[ ] Yes [x] No

13. **Project Focus:** *(Mark each item.)*

Agent Orange	[ ] Yes [x] No	Females	[ ] Yes [x] No	Prisoners of War	[ ] Yes [x] No

14. **Keywords:** *(Minimum 3, maximum 6. Use MeSH terms only. Enter one term per line.)*

1) Klebsiella
2) Pneumonia
3) Animal
4) _____
5) _____
6) _____

15. **Animal Subjects:** *(Species and, if applicable, strain. Enter one species per line.)*

1) Mouse C57BL/6J
2) _____
3) _____
4) _____
5) _____
6) _____
7) _____
8) _____

16. **Abstract:** *(Submit on separate sheet or on floppy disk; see instructions)*

17. **Institutional Support:** *(Mark each item. *If Yes, a letter of support/collaboration must be attached to this form.)*

Laboratory*	☐ Yes ☒ No	Medicine*	☐ Yes ☒ No	Pharmacy*	☐ Yes ☒ No
Radiology*	☐ Yes ☒ No	Nuclear Medicine*	☐ Yes ☒ No	Nursing*	☐ Yes ☒ No
Psychiatry*	☐ Yes ☒ No	Outpatient*	☐ Yes ☒ No	Surgery*	☐ Yes ☒ No

Other* ☐ Yes ☒ No > If Yes, Specify _____

Lab Space ☒ Yes ☐ No > If Yes, Bldg and Room Animal Facility, Building 6

Budget Page ☐ Yes ☒ No > Must be included with all submissions (except Funding Source Code 0000)

18. **Institutional Approvals:** *(Signatures as appropriate)*

Section Chief _____ Date 3/19/99

Service Chief _____ Date 3/19/99

19. **Comments:** _____

Principal Investigator See above (Dr Yu) _____
Signature Date

Note: If this is your First Research Proposal submitted at this Medical Center, please also submit an Investigator Data Sheet (Page 18) and a Personal Data Form. The same applies to co-principal investigators who have not submitted these forms.

Research Office use only:

Date Received: _____

Item check: 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 VAF 10-5368

Date Returned: _____ *Reason:* _____

Date Entered: _____

Research & Development Committee
VA Pittsburgh Healthcare System #646
7180 Highland Drive • Pittsburgh, PA 15206

CONTINUING REVIEW SUBMISSION FORM

Date: July 10, 2006
Investigator: **Victor L. Yu, M.D.**
Protocol: Various Studies Examining Treatment, Prevalence and Eradication of Legionella
ID: 00137 Prom#: 0010 Protocol#: N/A

Initial R&D Approval Date: 10/01/1998
Previous Continuing Reviews: 01/25/2006
Approval Expiration: 12/11/2006

Submission Form Due Date: 10/04/2006
Continuing Review Date: 10/25/2006

Regulations specify that Continuing Review is required for all approved research studies. Failure to comply will result in suspension or termination.

Please provide the following:
1) An Abstract (Guidelines Attached)
2) Research Staff Form
3) A NEW VA Conflict of Interest Form for the PI and each Investigator, Co-investigator, or Collaborator devoting 5% or more effort to the project.
4) Any manuscripts that have been submitted for publication or peer reviewed abstracts of work that have been presented during the past year.

Have there been any changes, since the last report, with respect to:
1. Your role at the VA? ☐Yes ☐No
2. The programmatic relationship to VAPHS R&D activity? ☐Yes ☐No

If you answered yes to any of the above questions, attach documentation explaining the change.

3. Has the study terminated? ☐Yes ☐No If yes, provide a final report.

If you have any questions, please contact the Research Office at 412-688-6104.

Signature: _____ Date: _____
(ONLY THE PRINCIPAL INVESTIGATOR IS AUTHORIZED TO SIGN)

APPROVED/DISAPPROVED

Signature: _____ Date: _____
Chairperson, Research & Development Committee

Department of Veterans Affairs

REPORT OF SUBCOMMITTEE ON HUMAN STUDIES

MIRB# 00253

Project/Program Title: Exposure Assessment for Community Acquired Legionnaire's Disease

Principal Investigator: Janet E. Stout, PhD

VAMC: Pittsburgh, (UD), PA Review Date: 12/14/2001

COMMITTEE FINDINGS

1. The information given in the Informed Consent under the Description of Research by Investigator is complete, accurate, and understandable to a research subject or surrogate who possesses standard reading and comprehension skills.	[X] YES [ ] NO
2. The informed consent is obtained by the principal investigator or a trained and supervised designate under suitable circumstances.	[X] YES [ ] NO
3. Every effort has been made to decrease risk to subject(s)?	[X] YES [ ] NO
4. The potential research benefits justify the risk to subject(s)?	[X] YES [ ] NO
5. If subject is incompetent and surrogate consent is obtained, have all of the following conditions been met: a) the research can't be done on competent subjects; b) there is no risk to the subject, or if risk exists the direct benefit to subject is substantially greater; c) if an incompetent subject resist, he/she will not have to participate; d) If there exists any question about the subject's competency, the basis for decision on competency has been fully described.	[X] YES [ ] NO
6. If the subject is paid, the payment is reasonable and commensurate with the subject's contribution.	[ ] YES [ ] NO [X] NA
7. Members of minority groups and women have been included in the study population whenever possible and scientifically desirable.	[X] YES [ ] NO

8. Comments: (Indicate if Expedited Review) This study is approved for the period of 1/17/02 to 12/13/02. Extension beyond 12/13/02 requires reapproval of the SHS. Any adverse effects must be reported to the SHS and the Research Office.

RECOMMENDATION: [X] APPROVED [ ] DISAPPROVE/REVISE

SIGNATURE OF CHAIRMAN: Ali E. Sonel, M.D. DATE: 1/17/02

VA FORM OCT 1995 10-1223

EXISTING STOCK OF VAF 10-1223 JAN 1950 WILL NOT BE USED

Department of Veterans Affairs

REPORT OF SUBCOMMITTEE ON HUMAN STUDIES

Project/Program Title: Legionella Colonization of Health Facility Water Systems

Principal Investigator: Robert R. Muder, MD and Janet E. Stout, PhD

VAMC: Pittsburgh, (UD), PA Review Date: 9/25/98

COMMITTEE FINDINGS

1. The information given in the Informed Consent under the Description of Research by Investigator is complete, accurate, and understandable to a research subject or surrogate who possesses standard reading and comprehension skills.	[X]	YES
	[ ]	NO
2. The informed consent is obtained by the principal investigator or a trained and supervised designate under suitable circumstances.	[X]	YES
	[ ]	NO
3. Every effort has been made to decrease risk to subject(s)?	[X]	YES
	[ ]	NO
4. The potential research benefits justify the risk to subject(s)?	[X]	YES
	[ ]	NO
5. If subject is incompetent and surrogate consent is obtained, have all of the following conditions been met: a) the research can't be done on competent subjects; b) there is no risk to the subject, or if risk exists the direct benefit to subject is substantially greater; c) if an incompetent subject resist, he/she will not have to participate; d) if there exists any question about the subject's competency, the basis for decision on competency has been fully described.	[X]	YES
	[ ]	NO
6. If the subject is paid, the payment is reasonable and commensurate with the subject's contribution.	[ ]	YES
	[ ]	NO
	[X]	NA
7. Members of minority groups and women have been included in the study population whenever possible and scientifically desirable.	[X]	YES
	[ ]	NO

8. Comments: (Indicate if Expedited Review) This study is approved for the period of 10/29/98 to 9/25/99. Extension beyond 9/25/99 requires reapproval of the SHS. Any adverse effects must be reported to the SHS and the Research Office.

RECOMMENDATION: [X] APPROVED [ ] DISAPPROVE/REVISE

SIGNATURE OF CHAIRMAN: Albert Bjorn DATE: 10/29/98

cc: Mona F. Melhem, M.D.

Department of Veterans Affairs

Memorandum

Date: July 12, 2006

From: Victor L. Yu, M.D

Subj: Written justification for closure requested

To: Michael Moreland, Director,

Thru: Frederick DeRubertis, Vice President, Medical Specialty Service Line
Thru: Rajiv Jain, Chief of Staff

I am responding to the memo signed by Dr. Jain on 7/5/06 and the verbal comments by Dr. Jain at the meeting between myself and Frederick DeRubertis on July 5, 2006. I was stunned by the decisions in the memo of 7/5/06. At the meeting, no clearcut justification for closure of the Special Pathogens Laboratory was given only - vague generalities that bordered on innuendo.

"The Special Pathogens Lab is a commercial lab that does not perform research." "The Special Pathogens Lab is a commercial lab that furnishes funds for your research." "Your research activities are not IRB-approved." All of the above statements are absurd and demonstrably false. If they are indeed the reasons, please place them in writing so that I can respond to them.

After I objected to this drastic action, Dr. Jain informed me I could appeal to Mr. Moreland. Two days later on 7/07/06, Nicholas Squeglia, Administrative Officer, informed me by telephone that the Special Pathogens Laboratory had been terminated, the 5 scientific personnel were to be fired that day, and Dr. Janet Stout had been demoted to a bench technician in the hospital microbiology laboratory.

My loyalty and commitment to the VA has been shattered in a very disheartening manner. The Special Pathogens Laboratory has existed for 25 years and is one of the great reference laboratories in the U.S. Documentation of the publications reporting on the patient lives in the VA that have been saved, and the discoveries that have affected management of patients in the VA and worldwide have already been given to you.

Given the abruptness and severity of the decision to close down the Special Pathogens Laboratory and terminate the employment of the individuals working in this laboratory with only 24 hour notice, detailed justification for this action should have been made in the memo of 7/5/06. In this memo, no justification whatsoever was given. I request the reasons for such a punitive decision in writing, so that we can adequately respond. Fairness in dealing with such a situation is a reflection of the integrity of the institution.

VICTOR L. YU, M.D.
Chief, Infectious Disease Section

Moreland SpecialPathogensLab
Yu/memo

VA FORM MAR 1989 2105

www.Legionella.org
The Legionella experts
Home Page

www.legionella.org-
the most complete Legionella website on the Internet
Selected on the basis of their scientific content and adherence to standards of Internet publishing by Clinical Infectious Diseases - the official journal of the Infectious Disease Society of America (IDSA).

University of Pittsburgh
School of Medicine
Department of Medicine

January 17, 2007

Dr. Rajiv Jain
Dr. Steven Graham
Dr. Frederick DeRubertis
VA Medical Center
University Drive C
Pittsburgh, PA 15240

Dear Drs. Jain, Graham and DeRubertis:

We are writing this letter to protest and express our outrage and sorrow over the destruction of valuable and irreplaceable research material that is critical to future research efforts. This includes developing new laboratory tests for atypical pathogens, new media for identification of *Legionella*, assessment of new antibiotics for Legionnaires' disease and correlation of virulent isolates with proposed models of pathogenesis. Before release to physicians and microbiology labs worldwide, all FDA-approved lab tests and antibiotics used for diagnoses and therapy for Legionnaires' disease were tested in the Special Pathogens Laboratory using these materials

Consequences of the Action

This treasure trove of research material includes the most comprehensive set of *Legionella* isolates worldwide, including rare species isolated from fewer than 10 patients. The pathogenesis of *Legionella* is now being elucidated using new molecular methods. Our collaboration with basic scientists has been predicated on the use of isolates from this collection that are known to be virulent to patients and from environmental isolates that are not linked to disease.

Moreover, the collection included environmental isolates from the Pittsburgh VAMC and other VAMCs nationwide. It included isolates collected from patient homes in ongoing studies supported by the American Legion, Environmental Protection Agency, and 5 US state departments of health. Retrieval of these isolates allowed assessment of the success
of disinfection measures over time. It also allowed identification of the environmental source using molecular methods if patients contracted Legionnaires' disease in the future. The greatest harm from this action will be to patients from our VAMC and other VAMC's as *Legionella* outbreaks continue to affect VA patients because they have the highest risk factors for the disease -smoking, alcohol use, and age.

How Could This Have Happened?

Dear Drs. Jain, Graham and DeRubertis:

We have received no reply to our email of January 17, 2007.

We still need to verify the status of the collection of non-Legionella isolates. These isolates were accumulated from multiple observational studies and were the property of over 40 international collaborators.

We need an immediate answer to whether you have destroyed the entire collection for the following reason: A virulent Klebsiella has been seen in Taiwan that causes an invasive syndrome of liver abscess and endopthalmitis with high mortality rate. We were the first to demonstrate that it was a Taiwan phemenonon not seen in Europe, North America, South America, or Australia. At least 11 suspected cases have now been reported in the US, but confirmation is lacking. Klebsiella isolates from California, New York, and Barcelona from bacteremic patients with liver abscesses have been sent to us for storage and safekeeping. We injected these isolates in a mouse model of Klebsiella in a VA IRB-approved protocol, These 3 Klebsiella isolates killed mice similar to the Taiwan isolates in storage, and, in contrast, to Klebsiella from other continents which were avirulent in mice. Our collaborators from Taiwan have recently developed new methods of subtyping based on capsular serotype and presence of virulent factors. They have requested our 3 isolates to confirm the fact that the virulent Klebsiella has now reached Spain and the US. If we were able to confirm that the Taiwan isolates have indeed made it to the US, it would have immediate public health implications. Were over 400 Klebsiella isolates from 6 continents and the 3 Klebsiella isolates from US and Spain destroyed as were the legionella isolates?

If not, then it is imperative that the entire collection of microorganisms including the Klebsiella isolates should now be transferred to the University of Pittsburgh as planned months ago.

If Drs Sonel and Melhem indeed destroyed the entire collection, it becomes your responsibility to uncover the truth of why this despicable action could have occurred. On the other hand, if you stonewall or attempt to whitewash our inquiry, this irresponsible action would be consistent with your vindictive and unethical response to our attempts to save the Special Pathogens Lab. Eventually the truth would be revealed and besmirch all of you. As of now, your silence adds to the complicity of the entire Pittsburgh VA administration.

Victor L. Yu , MD and Janet E Stout, PhD

Phoenix VA (Peterson) -Letter of support for VA Lab

Victor Yu victorlyu@gmail.com

On 9/1/06, Peterson, Rick C <Rick.PetersonCQ2@va.gov>wrote:

Dr. Yu,

I would like to thank you for processing the Legionella water samples from the Phoenix VAMC in
July, 2006. I know that pressure existed to not process these environmental samples. And, I
understand that the dedicated staff of the Special Pathogens Laboratory worked without pay on
these specimens to fulfill their public health mission.

Fortunately you were able to get them done. The results we received were important for the
healthcare of our veteran patients. 65% of our water samples were positive. These results have
confirmed that the recent addition of copper/silver ionization to our domestic water system was the right thing to do. The staff of the Pittsburgh VA Special Pathogens Lab has worked with us every step of the way in our fight to rid our water system of Legionella. Not only with lab analysis but with development of a treatment strategy. Your Lab has brought deserved prestige to the OVA Healthcare System and improved our care of the veteran patients at the Phoenix VAMC.

With the help of you and Dr. Stout, our facility is on the way to significantly reducing the odds of
an outbreak of Legionnaire's Disease.

Thanks to you and your group.

Rick Peterson
Plumbing and Mechanical Supervisor
Phoenix VA Medical Center
(602) 277-5551 ext 7122

Testimony of Victor L. Yu, M.D.

Appendix

I. Response to Publication Audit by Pittsburgh VA

> Conclusion: For the 39 articles reviewed, not a single example of human subject research without appropriate approval was found

II. Research and development Approval Form for Legionella Studies

III. Research Project Approval for Klebsiella Study

IV. Memo from Victor L. Yu to M. Moreland requesting written justification for closure –July 12, 2006

V. Letter to Drs Jain, Graham, DeRubertis protesting the destruction of the scientific collection – January 17, 2007

VI. Phoenix VA letter of support for assistance in Legionella cultures