Several current and former FDA St. Louis laboratory staff members asked me to draft a brief overview of the times we shared in the development of the great pharmaceutical testing laboratory that evolved from the FDA St. Louis District laboratory. I was recruited in 1967 to join the FDA St. Louis District as a Science Advisor (consultant) while a Professor of Analytical Chemistry at St. Louis University. Although my involvement in the evolution of the laboratory initially was somewhat peripheral,[1] it was exhilarating to share in the dynamics at the laboratory. Because my role as Science Advisor had been so rewarding, I in 1976 joined the FDA full-time as the laboratory director; both the Director, Dr. Arthur Steers and Deputy Director, Mr. Richard Heuermann previously had retired. During my FDA service Dr. William Furman directed the laboratory automation and method development efforts,[2] and for most of my service Dr. Lawrence Jones[3] had primary responsibility for managing the analytical operations and information systems. Because of our long tenure together at the laboratory I enlisted their assistance to help prepare this document. We feel it can serve as an overview and introduction to the Executive Summaries of Accomplishments, which are also on this page. Many of our colleagues and friends made noteworthy contributions to the laboratory work and we apologize for not including everyone in this brief overview. It is difficult to compress over 20 years of development, and work with hundreds of colleagues into these few pages. We have concluded this history at 1994 because that is the last Executive Summary available to us.

[1] As a Science Advisor (consultant) I spent between one-half and one day per week at the laboratory working initially with Heuermann and then later with both Steers and Heuermann.

[2] Bill Furman s literature compilations and research in this area provided part of the basis for his Ph.D. Dissertation in Analytical Chemistry and the basis for his book titled Continuous Flow Analysis, Theory and Practice which was published by Marcel Dekker.

[3] Jones had begun his FDA career as a chemist in the Cincinnati District and transferred to the St. Louis District just prior to the reorganization. His interests in management lead him to continue his education to receive a Ph.D. in Quantitative Management.

A Brief History of the Great FDA St. Louis Pharmaceutical Testing Laboratory
1967-1994
Thomas Layloff and Lawrence Jones

The FDA laboratory activities in St. Louis began in 1909 just three years after the establishment of the FDA. In 1966 the FDA developed a model structure that would align its Field operation borders along the Federal Judicial lines to facilitate legal actions. At that time the St. Louis District Office territory was bounded by Tennessee on the Southeast, the southern half of Illinois on the Northeast, Nebraska on the Northwest and Arkansas on the Southwest. This territory spanned several Judicial Districts and in the realignment it was proposed to disband the District, reassign the inspectional responsibilities to the Kansas City and Chicago Districts, and downgrade the St. Louis operations to a Station without laboratories. [4] When this proposal was presented to U.S. Congresswoman Leonor K. Sullivan from St. Louis, she informed the FDA staffers that if there was a single FDA job lost in her District she personally would fight to take it out of FDA s budget-hide.[5] Congresswoman Sullivan was very powerful and the FDA attempted to comply with her request by proceeding with the reorganization while retaining the FDA St. Louis personnel ceiling level. The former District laboratory and administrative staff, and equipment were offered to other FDA units and the great visionary, Dr. Daniel Banes rose to the task. Dr. Banes had come through the FDA ranks beginning his career in the testing laboratories and it was his opinion that the generalist field laboratories were inefficient because of their diverse program requirements. He felt that significant economies of scale could be effected in a highly controlled surveillance laboratory operation which focused only on pharmaceutical quality assessments. This defining moment was his. The St. Louis District was abolished and the laboratory and administrative units (staff, equipment, space, etc.) were assigned to Dr. Banes Office of Pharmaceutical Research and Testing (OPRT)[6] in the Bureau of Drugs for a two-month pilot study to test his hypothesis. No new analysts or staff members were added for the pilot study so the Banes' hypothesis would have to be verified with the existing staff members. There were concerns about the possible success of the pilot because the district laboratory staff had been involved primarily with food analysis. As soon as the reassignment was made a training program in pharmaceutical analysis was undertaken to retrain the staff. At the time of the transfer Mr. Richard F. Heuermann, St. Louis District Chief Chemist, was named Acting Director with Mason Goldman and Lawrence Jones continuing to serve as Lab Supervisors responsible for the laboratory operations. Heuermann also had begun his FDA career in the laboratory testing ranks of the FDA, and his drive and determination along with the good will of the staff made the pilot effort a resounding success. Sodium Warfarin was the first drug survey conducted during the pilot program. In one sample individual tablet analysis showed a range of 30% which could pose a health threat. This survey resulted in a product recall and revisions in the USP monographs. With the success of the pilot program the FDA formally established the laboratory as a part of OPRT and it was named the National Drug Testing

[4] Prior to the reorganization the District Chief Chemist, Richard Heuermann, had recruited me in 1967 to serve the lab as a Science Advisor.
[5] I personally heard Ms. Sullivan make that remark at a St. Louis Section American Chemical Society Meeting where she had been invited to discuss the FDA reorganization and the formation of the new laboratory function. This was the first defining moment for the new laboratory.
[6] At the time of the transfer the OPRT included the Division of Drug Biology (DDB), Division of Drug Chemistry (DDC), and the National Center for Antibiotic Analysis (NCAA).

Center; [7] the name was changed very shortly thereafter to the National Center for Drug Analysis (NCDA). [8]

Dr. Arthur Steers transferred from the Seattle District Office to become the first Director of the lab and Heuermann was named the Deputy Director. William Furman[9] transferred to NCDA shortly after its founding to establish a method development branch. While Furman headed up the development activities, Jones spearheaded the surveillance program operations. The success of the pilot program was due to the economies of scale that came about through testing many samples of the same drug type. However, the laboratory continued to increase in productivity in large part due to the hard driving efforts of Heuermann who directed the staff to develop automated analysis systems. Although Technicon AutoAnalyzer (TAA) equipment was first introduced to FDA at the National Center for Antibiotic Analysis, its use there never blossomed, whereas NCDA rapidly adopted the technology and quickly moved to the forefront of TAA pharmaceutical analysis applications. In the early 1970s NCDA began publishing a compilation of validated continuous flow methods titled "Drug AutoAnalysis Manual" (DAM). Although validated methods were solicited from all sources, the majority of those published were developed at NCDA. The DAM was widely distributed through the industry and FDA. During this era representatives from many firms visited NCDA and a number of them adopted the automation technologies.

At the time NCDA was established there was in the FDA a strong commitment to method and data validity, which was based on concepts established by the then Association of Official Analytical Chemists.[10] As noted previously the increasing TAA-based automation imposed significant validation requirements on the operations and Furman spearheaded the NCDA development of AOAC concept-based quality control program manuals to orchestrate these efforts. These manuals documented the automated method validation, system suitability, and quality control test procedures required to ensure that the analytical results conformed to those obtained through the application of the legal reference methods.[11] These manuals were in continuous revision and expansion to govern the quality systems of the lab and were published as our "Quality Control Program" (QCP). NCDA and the Technicon Corporation distributed many copies of the QCP.

Because the TAA systems were so precise, it was possible to develop repeatable analytical procedures for individual tablet analysis of Digoxin and Digitoxin. These content uniformity

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[7] This title was very short lived because it could be construed to include animal testing.

[8] The name of the laboratory was changed over the period 1967-1994 from the National Center for Drug Analysis (NCDA) to the Center for Drug Analysis (CDA) to the Division of Drug Analysis (DDA). The location, staff levels, and functions were not effected by these organizational changes.

[9] Furman began his career as a chemist in the Detroit District later moving to the Division of Drug Chemistry in Washington before coming to NCDA.

[10] The FDA heavily supported the Association of Official Analytical Chemists, now the AOAC International, until 1977 when the secretariat functions were removed from FDA and assigned to a not-for-profit association. Prior to 1977 all FDA staff members were considered members of AOAC and the AOAC method development and validation protocols, which had evolved under the FDA and the former Bureau of Standards, provided the quality training and credentialing for FDA laboratory staff members. When AOAC was removed from FDA in response to a contractor recommendation, the FDA quality training programs also de facto were removed.

[11] In these validation efforts many of the legal reference methods were found to be deficient and corrections were instituted.

tests for cardiac glycosides uncovered a major health problem in that many of the marketed products were so non-uniform as to pose a hazard to health.[12] Later and again with more sensitive methods of analysis, it was found that cardiac glycoside products from different manufacturers did not dissolve to the same extent when tested by the USP procedure. These dissolution differences also posed a threat to health of heart disease patients who used these products. These observed content uniformity and dissolution problems lead the FDA to supersede through a Federal Register announcement the USP quality standards for these products because they were deemed unsuitable to assure the quality of the marketed products.[13] In addition, the FDA instituted a voluntary certification program at NCDA so each manufacturer's products could be shown to be suitable before they could be marketed. Later a less dramatic content uniformity and dissolution testing certification program for all manufacturers of Prednisone tablets was instituted at NCDA to assure their quality.

It became apparent early after the implementation of the TAA equipment that information management would be a major problem. Heuermann, who always added daring and vision to the automation and productivity increases, directed in the late 1960s efforts to automate the data handling of the TAA systems. These early and successful computational efforts provided the justification for the acquisition of a Hewlett-Packard (HP) 2116 minicomputer in 1970.[14] Direct data capture and processing from the TAA systems was implemented along with sample accountability systems. These ongoing development and automation efforts provided large leverages on productivity and the lab began to outrun both the Bureau of Drugs surveillance program planning and the FDA field organization collection processes.[15] Through extensive training programs in pharmaceutical chemistry and instrumental analysis, and constant oversight on exploiting economies of scale and automation, NCDA became the FDA's premier pharmaceutical surveillance unit. NCDA productivity eventually grew to the point where the lab was performing over one-half of the analyses of pharmaceutical samples collected by FDA investigators. This testing capacity along with strong information support systems allowed the implementation of an innovative voluntary mail-in sampling program instituted jointly with the American Society of Hospital Pharmacists[16] (ASHP) through their members. This program showed that products in the distribution system exhibited quality levels consistent with sampling programs at the manufacturer level. The results of these surveys were published in the ASHP journal.

Also in 1976 FDA published the Good Laboratory Practices (GLP) Regulations in the Federal Register. Although these regulations did not strictly apply to our type of laboratory operation our analysts reviewed them and felt that they addressed important quality areas beyond those

[12] I recall reviewing Digoxin tablet content uniformity data that ranged from ca. 50-300% from the same bottle.
[13] The Digoxin product standards are published in 21 CFR 310.500. It is of interest to note that the dissolution apparatus described therein was never used to obtain data on a regulatory sample; it was obsolete by the time the surveillance and certification programs began.
[14] The first computer system acquired in 1970 was a Hewlett Packard 2116c that came with 4k of ram and was expandable in 4k increments to a maximum of 16k. Needless to say there was almost a standing order for more memory.
[15] The FDA Field operations sample collection processes were designed to support legal actions that required extensive documentation of interstate commerce along with the establishment of a chain-of-custody. This approach is very valid when the legal action rate is high but in high volume surveillance activities where the legal actions rates are low it is very burdensome.
[16] This organization has been renamed the American Society of Health-System Pharmacists.

addressed in our QCP. As a result of that observation our staff prepared the NCDA GLP Manual, [17] which was an expansion based on the concepts and procedures in our previously developed "Quality Control Program." The NCDA GLP Manual was first described publicly at an American Society for Quality Control meeting. The presentation was reported extensively in the "Gold Sheet,"[18] and NCDA received requests for and distributed over 100 copies of the GLP Manual before transferring distribution to the FDA Freedom of Information Office. That office responded to hundreds of additional requests and soon transferred the distribution to the U.S. Government Services Administration s National Technical Information Service (NTIS). That distribution of hundreds of copies of the manual was a major impetus for the development and implementation of current good manufacturing and laboratory practices worldwide.

In the mid-1970s FDA and industrial laboratories encountered repeatability/reproducibility problems with drug dissolution testing procedures. NCDA analysts addressed these issues and as part of that effort focused on evolving the "Poole paddle method" to make it more easily used and robust. In concert with the USP Revision Committees and the Pharmaceutical Manufacturers Association (PMA)[19] the modified Poole paddle method was adopted as the USP Method II.[20] Furman s Branch spearheaded the standardization of dissolution testing methodology and USP Method 2 (paddle method). NCDA scientists published a series of papers that addressed problems which could significantly improve the reproducibility.[21] The culmination of this development effort was a successful 11 FDA-laboratory collaborative study, which demonstrated that the dissolution procedures were reproducible if the critical variables were properly controlled.[22] In addition, to further facilitate the assimilation of these technologies into the regulated industry, NCDA analysts, under Furman s tutelage, developed training materials and publications along with a 35mm slide/audiotape training program on the proper performance of USP Dissolution Test Methods 1 and 2. The 35mm slide/audiotape presentation along with some training materials was distributed in the FDA and in the industry through the GSA National Audiovisual Center. In addition to providing training materials, NCDA analysts conducted workshops in New York, St. Louis, and Los Angeles primarily for industrial employees to further speed the dissemination and adoption of these methods and techniques to assure that solid dosage forms dissolved properly.

Jones and Donald Page, Chief of the Drug Monitoring Branch, continued to keep the critical surveillance activities in control and productive and spearheaded the development of the computer-based Laboratory Information Management systems (LIMS).[23] The initial laboratory LIMS were established on the laboratory's first computer, the Hewlett-Packard 2116 system (see

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[17] The manual was titled the NCDA Good Laboratory Practices Manual although the laboratory operations did not involve the animal studies, which were the target of the Good Laboratory Practices Regulations.
[18] F-D-C Reports, Inc., 5550 Friendship Blvd., Suite One, Chevy Chase, Maryland 20815-7278.
[19] The PMA is now known as the Pharmaceutical Research and Manufacturers Association (PhRMA).
[20] The initial paper in this effort was: Kirchhoefer, R. D., "Use of a Round-bottom Resin Kettle for In Vitro Dissolution Testing," J. Assoc. Off. Anal. Chem., 1976, 59, 367.
[21] This effort was summarized in a paper: Layloff, T., "Studies in the Development of USP Dissolution Test Method Number 2," Pharmacopeial Forum, 1983, 9, 3752-3757.
[22] Cox, D.C. and Furman, W. B., "Collaborative Study of the USP Dissolution Test for Prednisone Tablets with Apparatus 2," J. Pharm. Sci., 1984, _73,
670-676.
[23] The LIMS development and implementation was conducted by the Computer Group which was one of the operating unites of the Drug Monitoring Branch.

footnote 12). Validation of automated laboratory testing equipment data acquisition, calculation algorithms, tracking of interspersed quality assurance samples, maintenance of unassigned and in-process sample inventories, and maintenance of historical files were initially developed on that HP system. In the mid-1970s an HP System 1000 laboratory computer replaced the HP 2116 computer, and the increased capacity of this machine resulted in an expansion of our ADP applications. NCDA staff programmed this system to acquire and process data from 16 TAA systems simultaneously and to write laboratory reports of results; in addition all sample control information was maintained on this system. The HP 2116 and System 1000 computers were used to acquire analytical data for all surveillance samples analyzed by our laboratories from the summer of 1971 to 1991; these data arrays containing over one million analytical results on a wide array of different products.

Throughout these developments there was an ongoing stream of reports, both peer-reviewed and general interest, from the laboratory staff in addition to maintaining high productivity in sample analysis. Over the period from 1967-1985 the quality of marketed pharmaceutical products markedly improved in large part due to the surveillance activities at NCDA.[24] In the spring of 1985 the laboratory was assigned responsibility to test Active Pharmaceutical Ingredients (APIs) submitted to the Office of Generic Drugs (OGD) as a part of the Abbreviated New Drug Application (ANDA) approval process. The Hatch-Waxman legislation opened the Agency to a landslide of ANDA applications and this support testing was essential in the OGD approval process. Although many of the USP monographs for the analysis of APIs at that time did not require the use of chromatographic techniques, the Division instituted a comprehensive program of analyzing all submitted bulk drug samples by HPLC methods to obtain impurity profiles. During the course of analyzing these submitted materials, an import bulk sample was found to meet all of the requirements of the USP but contained over 1% of an unidentified impurity, which was not present in the innovator product used in the U.S.A. Although the impurity was shown to be an isomer/metabolite of the drug substance, the product was declared unacceptable based on that impurity. Subsequent negotiations and investigations led to the adoption by the USP of the general quality standard requirements for bulk drug substances of no impurity greater than 1% and the sum of all impurities less than 2%. The Division database, which contained HPLC test results on over 3,000 bulk drug submissions, was essential to show that these general quality standards would not disrupt the U.S. market place, i.e., the overwhelming majority of products met these specifications.

In the fall of 1985 the Division was assigned the New Drug Application methods validation and proposed USP Reference Standards testing programs, which had been conducted by the Division of Drug Chemistry. That Division was abolished and it s chemistry staff was reassigned to serve as Review Chemists in the New Drug Application (NDA) reviewing process to help reduce the NDA approval backlogs. The NDA backlogs had become a significant issue in the Agency and this drastic action was taken with much reticence. As a result of those two actions the functions of the Division essentially were abolished, e.g., none of the work activities underway in January 1985 were underway in January 1986. The Division managed to keep these new work

[24] A number of reports were prepared which showed that the number of defective products declined on repeat surveys over the years. There was however a market cost; the number of Digoxin manufacturers markedly declined when the certification program was instituted.

assignments current but that currency came at the expense of the surveillance activities, which were essentially eliminated to carry out the new assignments.

In 1989, upon the discovery of fraudulent bioequivalence submissions through the ANDA process, over 1,500 paired applicant/innovator bioequivalence samples were collected at commercial laboratories and submitted to Division to determine if there had been fraudulent testing involved. It immediately became apparent that there is no formulation enforcement strategy associated with the FDA approval process, i.e., there are no legal reference methods of analysis available to determine if a product was produced the way it was approved to be produced. For example, almost all legal reference methods test for the API or its synthetic precursors and/or degradation products only. The excipient materials are not addressed in the test methods. Because of this deficiency, Division staff members focused on developing physical/chemical methods, and related information management technologies, to determine if products were different from each other by sameness comparisons. This database approach was called "fingerprinting" because the characterizations are based on arrays of information which cannot be readily assigned to a given chemical entity, i.e., the data sets may arise from unresolved mixtures of substances, such as would occur in an intact tablet or the contents of a capsule.[25] This "fingerprinting" approach currently is being used in some parts of the pharmaceutical industry to characterize incoming materials, monitor in-process procedures, characterize final products, and detect counterfeit products. When differences in the "fingerprints" occur, the systems are not at the same level of control; i.e., the sameness is not there.

In the early 1980s the foreign supplier of thalidomide, which is the drug of choice to treat one stage of Hansen's Disease, refused to ship the product to the PHS Center in Carville, Louisiana unless the U.S. Government provided a liability waiver to the firm for the use of the product. [26] The government refused to provide the waiver and the firm stopped supplying the material. A request was initiated by the Hansen's Disease Center through the Assistant Secretary for Health to the Commissioner of FDA to direct the Division to develop a synthesis procedure and control methods for the production of thalidomide for submission to the FDA New Drug Evaluation for approval. After the approval was obtained, the Division manufactured the bulk drug material on a kilogram scale to supply for clinical use at the Hansen's Disease Center.[27] Hansen s Disease Center subsequently was able to obtain contractors and other suppliers for thalidomide and portions of those materials were submitted to the Division, which in concert with the FDA New Orleans District tested them to assure their quality before they were released for use at the Hansen s Disease Center. The Division also supplied copies of the synthesis procedure and analytical methods for thalidomide, and reference standard quantities of racemic thalidomide in addition to each of the optical isomers.

[25] An overview of this effort was presented as: Layloff, T., "Scientific Fingerprinting: A Pharmaceutical Regulatory Tool," Pharm. Technol., 1991, 15, 146-148, and Kirchhoefer, R. D., "An FDA Laboratory Approach to Uncovering Potential Fraud in the Generic Drug Industry," J. AOAC Int., 1992, 75, 577-580.

[26] Thalidomide was implicated *in* birth defects *in* the 1960s and was not approved for distribution in the U.S.A. The use of the drug at the Hansen's Disease Center was under a PHS initiated Investigational New Drug.

[27] DIVISION scientists D.C. Cox and J.C. Reepmeyer received in 1987 the FDA Award of Merit for this effort.

Later assignments included supporting Commissioner David Kessler s extensive tobacco testing initiatives. These activities and many others are documented in the Executive Summaries which are included on the website.

The dedicated and talented staff members of the St. Louis laboratory had built the finest pharmaceutical regulatory laboratory in the world, which, de facto, was the US National Drug Control Laboratory. Dr. Daniel Banes vision was vindicated again and again over that almost thirty-year history.