May 13, 1973

THE NCDA BRIEF

The National Center for Drug Analysis (NCDA) is a division of the Office of Pharmaceutical Research and Testing, Bureau of Drugs, U.S. Food and Drug Administration. The Center was established in St. Louis in 1967 by the Secretary of the Department of Health, Education and Welfare to design, develop and utilize the best, and most efficient high production techniques for the chemical analysis of drug products in order to guarantee that the highest quality drugs are available to the American Consumer. The NCDA has followed this mandate by continuously searching for ways to improve the efficiency, reliability, and effectiveness of the laboratory and its procedures.

Prior to 1967, the FDA had 18 district offices whose territories jointly covered the entire United States. The drug manufacturers located within the various districts are visited periodically by trained FDA inspectors who check each phase of the manufacturing process, review the quality control procedures of the firms and collect samples for analysis by FDA laboratories. During fiscal year 1967, an increasing number of drug recalls and other problems related to quality control indicated that a more comprehensive program for statistical sampling and monitoring of drug production was needed.

The 18 district laboratories completed 37,000 drug assays in the fiscal year 1967. At that time, FDA felt that 150,000 to 300,000 lots should be sampled and examined each year to keep abreast with the rapidly changing drug industry. In addition, the United States Pharmacopeia (USP) XVIII and National Formulary (NF) XIII were extending the requirements for content uniformity testing of tablets and capsules to well over 200 specific drugs. The need for additional analytical testing was clear.

The Administration wanted to expand its capability, utilizing its human and physical resources more efficiently. A new concept in regulatory drug analysis emerged which required the establishment of a centralized laboratory that would focus its efforts exclusively on drug analysis and drug quality. The probability of success for such a project depended significantly on the personnel. The increase in efficiency through automation placed new demands on the manpower in that the workload of the chemists shifted from primarily routine analysis to the non-routine. This shift required the staff to be flexible and to possess a willingness and dedication to continuous education in order to cope with the challenge of the increased complexity of the operation and the increased production volume.

The St. Louis District was selected for the pilot study primarily because the responsibilities of the St. Louis District could readily be assigned to other nearby districts. In addition, the St. Louis District Laboratory was centrally located which facilitated shipment of samples from all Districts. The chemists in the laboratory already had considerable training and experience in modern drug analytical methods. Also, the metropolitan area had educational facilities readily available for continued education in analytical chemistry, computer technology, and advanced managerial training.

Thus in February 1967, the St. Louis District was abolished, the existing district boundaries were dissolved, and inspection areas and inspectors were reassigned to the adjacent districts. The St. Louis laboratory facilities were rearranged and slightly expanded to meet the needs of the anticipated workload. Additional equipment - spectrophotometers, spectrophotofluorometers, an automated electrobalance, and two complete Technicon AutoAnalyzer Systems were added to existing laboratory capability. The laboratory staff began attending specialized training sessions, primarily in pharmaceutical analysis.

The centralized approach to drug analysis was formally begun in February 1967. Anticoagulants and minor tranquilizers were selected for the first two drug categories, and were sampled under the "Pharmacy Program." This program statistically sampled drug products from retail and hospital pharmacies located in the various districts. Most of these samples were composites involving single assays per sample and were analyzed by teams of chemists using manual methods. The concept proved sound and efficient. Additional analytical systems were acquired and semiautomated methods utilizing them were developed for subsequent studies. The output of batches analyzed, and the number of individual analyses per batch increased, but the time required to perform each determination greatly decreased.

In late 1969, the Pharmacy Program was dropped in favor of a new sampling plan, the Formulator-Oriented Rx Drug Study (FORDS) Program. The FORDS program centered on a specific category of drugs, as did the Pharmacy Program, but drastically shifted the point of sampling much closer to the Manufacturer's Production Plant. This sampling plan caused individual tablet assays to be carried out on all samples. The FORDS approach to sampling ensured coverage of all manufacturers of a category of drugs, whereas, the Pharmacy Program more closely modeled the marked place.

The National Center for Drug Analysis has accomplished several objectives during its 5 year history. (1) It has automated analytical procedures and achieved the ability to make large numbers of assays at less cost in manpower and resources than was previously possible in the district laboratories; (2) It has uncovered problems in the drug industry not previously defined; and (3) It has published papers, articles and methods that have had acceptance in the scientific community, and has assisted quality control in industry.

The drug classes (called drug studies) analyzed by the Center since its inception are outlined in Table I. This is a list only of those studies that have been completed by the Center, and does not include the 10 drug classes currently being examined. Table I shows that while most drug classes had low defect rates, a few of the classes had rather high defect rates. The defect rate is found by dividing the number of samples analyzed by the number found defective. It is interesting to note the change in the defect rate when these drug classes were re-examined. For example, Reserpine was originally examined in 1967 (Study X07) and found to have a defect rate of 9.4%. Re-examination

in 1969 (Study 799) yielded a defect rate of 3.6%. The Center is examining Reserpine tablets for a third time (not shown in the tables), and analyses are being made on individual tablets, which was not done previously.

The cardiac glycosides were studied in 1968 under the Pharmacy based studies and found to have a relatively low defect rate of 1.4% based on composite assay. However, restudy in 1970 showed a defect rate of 25.9%. This increase resulted from in-depth individual tablet testing, coupled with the new FORDS program. The therapeutic significance of these products and the high defect rate resulted in a special monitoring program for Digoxin and Digitoxin tablets. The FDA, moving quickly, requested certain manufacturers to submit to a extralegal certification program. Under this program, those manufacturers whose products had been found defective would consent to sampling and analysis of each batch of product by NCDA before releasing them for sale. Manufacturers were released from this program only when they had proven they could manufacture a series of batches that met the requirements.

The National Center for Drug Analysis continues to re-examine classes of drugs that were found to have high defect rates in past studies as well as instituting studies on new classes of drugs. A comment should be made about the amount of testing that was performed on each sample. During the late 1960's, the compendia usually required that one composite of tablets or capsules (usually 20 in number) be made for each sample, and this composite was analyzed to determine compliance with the compendial limits. Usually one assay was made on each sample. This type of testing was used in the Pharmacy based studies. It became apparent, however, that more testing was needed on each sample to insure the safety of the National drug supply. Logically, the consumer ingests a single unit such as a tablet or capsule rather than an average of 20 units. The compendia published in 1970 recognized this fact by extending content uniformity coverage, generally requiring individual unit assays for tablets and capsules containing less than 50 mg per unit dose. The National Center for Drug Analysis routinely began testing individual units for all drug samples with the Formulator-Oriented Rx Drug Studies (FORDS). This policy resulted in increased testing for each drug sample. Where previously one assay per sample was conducted, now each batch routinely required 60 assays and could require many more assays if the batch did not comply with the compendial requirements.

The policy of analyzing individual units presented NCDA with its greatest challenge. Compendial methods were found to be too slow and too laborious to permit analyzing the large volume of units the Center planned to examine. At NCDA's inception, published methodology existed for the analysis of some drugs using automated methods. These publications, however, were generally concerned with one manufacturer's product, and many of the methods exhibited marginal accuracy and precision. Thus, in most cases, it was necessary for the Center to develop methodology to permit analysis of the number of individual units from many companies production, as required by the new policy.

In response to this challenge, the Center continues to devise new and more efficient methodology. This is demonstrated by the number of publications credited to NCDA Staff. For example:

(1) The Center began compilation of the FDA Drug Autoanalysis Manual, for rapid dissemination of automated procedures. Although the manual includes contributions from outside sources, about three-fourths of the methods in it were developed at NCDA.

(2) Since the establishment of the Center, over 85 separate papers, reports, and publications have been issued.

(3) Eighteen publications have been contributed to professional journals by Staff Personnel of NCDA. These publications are listed in Table II.

This methodology is available to FDA District Laboratories as well as other government agencies and private industry. It represents an extremely valuable, though hard to quantitate, contribution to improved Quality Control in the drug industry.

To show the National Center for Drug Analysis to be more efficient, one would have to demonstrate that it can process increasing numbers of samples with fewer people. Table III is an organizational chart for NCDA in 1967 and in the present. This chart indicates the number of chemists employed in the respective periods. In 1967, there were 5 chemists assigned to the Research Section and 20 chemists assigned to sample analysis. In 1973, there are 13 chemists and 2 technicians assigned primarily to sample analysis. The Center has been able to reduce the number of analysts assigned to sample assay work by 25%. These people were reassigned within the organization to other important functions. Research Section Staff was increased by two chemists and a Computer Group, made up of three chemists, was created as an extension of the Drug Monitoring Branch, NCDA continually strives to find new and better ways of doing its job and increase its analytical output.

A 25% reduction in personnel assigned to sample analysis is not the entire story. In 1967, all analysts at NCDA were professional chemists. The journeyman level for chemists is usually GS-11 (General Salary Schedule). Increased emphasis on automation, high speed data processing equipment, and refined management and control techniques permitted NCDA to operate with a lower ratio of chemists to para-professionals.

In 1971, three chemists technicians were hired to fill vacancies of professional chemists. This arrangement has worked so well that staff replacements have since been made with para-professionals. Liberal use has also been made of FDA's Student Co-op program, in which college chemistry students are hired for on-the-job training and experience. Consequently, NCDA has been able to reduce both the number and average grade level of the staff performing sample analysis.

One might expect that a reduction in analytical personnel would result in a reduction of samples analyzed. The opposite has occured, Table IV lists the number of samples analyzed by fiscal year. From fiscal year 1968 until the middle of fiscal year 1970 NCDA operated under the Pharmacy Based sampling plan. In each of these years, the number of analyzed samples increased. In fiscal year 1970, the Center changed to the FORDS sampling plan with a corresponding drop in the number of samples. However, FORDS levied the requirement of individual unit assay. The more meaningful number then became total assays. Whereas one sample formerly required one assay, now one batch requires at least 60 assays and if the sample appears to be out of limits (compendial limits), as many as 180 assays can be required. The consequences was a tremendous increase in the total number of assays after fiscal year 1970.

The automation of sample analyses also generated a tremendous increase in the volume of computations, sample writeup and data processing. To accomplish this, an increased personnel and capital resources were committed to developing automated data processing capability.

Even considering this good record of sample production, NCDA could have been more productive. Automated analysis, to be efficient, requires an adequate and continuous flow of samples with similar chemical characteristics. The more samples that can be analyzed, without equipment reconfiguration, the more efficient the system becomes. There have been periods when an adequate flow of samples necessary to maintain maximum efficiency was not available. Increased emphasis on activation, prompt and complete sampling of each drug class being studied, and attention to the expected number of samples available have helped to increase efficiency.

The National Center for Drug Analysis is presently quartered in laboratory facilities on the 10th floor of the U.S. Court House and Custom House building in downtown St. Louis. The laboratory facilities are adequate, but not spacious. Architectural plans have been completed for construction of larger facilities on the grounds of the Jefferson Barracks Veterans Hospital in St. Louis. The planned facilities would be suitable for a 150-man operation with an estimated 100 laboratory or laboratory related assignments. The planned facility, utilizing the experience and talent of our present personnel as a nucleus, would provide an estimated ten fold increase in drug surveillance capability, thus improving the consumer's protection and confidence in the drug market.

TABLE 1

SUMMARY OF RETAIL BASED STUDIES

STUDY	IDENTIFICATION	SAMPLES ANALYZED	DEFECTIVE SAMPLES	%
001	ANTICOAGULANTS	1454	57	3.9
002	TRANQUILIZERS	1411	5	0.4
003	ADRENOCORTICOSTEROIDS	2009	41	2.0
X07	RESERPINE	245	23	9.4
004	HYPOGLYCEMICS	997	1	0.1
005	CARDIAC GLYCOSIDES	1677	23	1.4
006	SULFONAMIDES	1146	14	1.2
007	AMPHETAMINES	1030	14	1.4
008	BARBITURATES	1192	7	0.6
009	ANTIHISTAMINES	926	4	0.4
010	NITROGLYCERIN	1343	45	3.4
799	RESERPINE	968	35	3.6
013	OXYTOCICS	188	11	5.9
014	NONSTEROID ESTROGENS	1024	8	0.8
015	THIAZIDE DIURETICS	1161	14	1.2
016	ANTICONVULSANTS	1087	6	0.5
017	CARDIAC ANTIARRHYTHMICS	973	3	0.3
018	SKELETAL MUSCLE RELAXANTS	845	6	0.7
019	SKELETAL MUSCLE RELAXANTS	816	3	0.4
020	TUBERCULOSTATICS	582	2	0.3
021	ANTICOAGULANTS	62	0	0.0

SUMMARY OF FORMULATOR-ORIENTED RX DRUG STUDIES (FORDS)

STUDY	IDENTIFICATION	SAMPLES ANALYZED	DEFECTIVE SAMPLES	%
222	ADRENOCORTICOSTEROIDS	348	18	5.2
223	OXYTOCIC AGENTS	17	0	0.0
224	ADRENERGIC AGENTS	142	3	2.1
225	MAJOR TRANQUILIZERS	24	0	0.0
226	MAJOR TRANQUILIZERS	25	1	4.0
227	URINARY ANTIBACTERIAL	42	1	2.4
228	ANDROGENIC HORMONE	133	7	5.3
229	DIURETICS	39	0	0.0
230	CENTRAL NERVOUS SYSTEM DEPRESSANTS	45	1	2.2
231	ANTITHYROID	31	0	0.0
232	CARDIAC GLYCOSIDES	193	50	25.9
233	CORONARY VASODILATOR	93	2	2.2
234	ANTICOAGULANTS	43	0	0.0
235	ANTIMALARIALS	92	4	4.3
236	LOCAL ANESTHETICS	188	6	3.2
238	LOCAL ANESTHETICS	23	0	0.0
241	ANTIEMETICS	33	0	0.0
242	ORAL CONTRACEPTIVES	158	1	0.6
243	STEROID ESTROGENS	15	4	26.7
245	PROGESTINS	79	8	10.1
250	ADRENOCORTICOSTEROIDS	626	48	7.7
251	PSYCHOSTIMULANTS	42	0	0.0
253	CENTRAL NERVOUS SYSTEM STIMULANTS	52	2	3.8
259	ETHINYL ESTRADIOL	8	1	12.5
260	PROGESTINS	51	3	5.5

TABLE II

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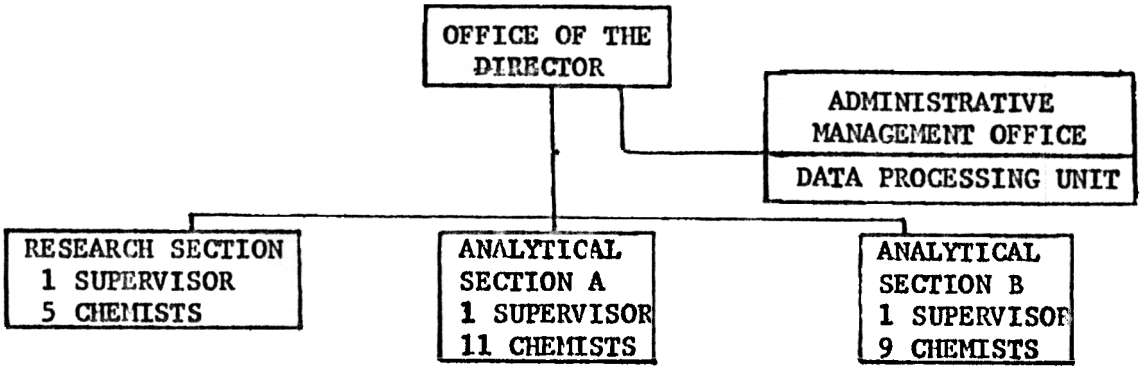
TABLE III

1967



1973

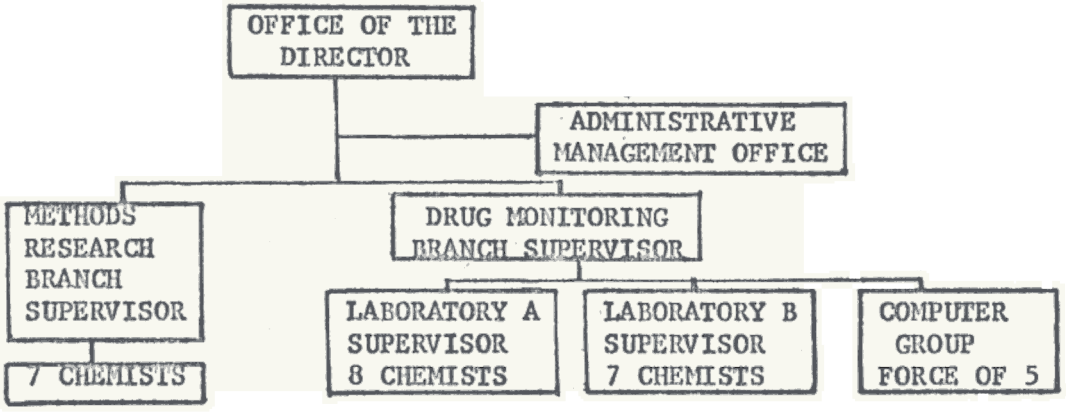


TABLE IV

Fiscal Year	Samples	Total Assays
1968	7849	9419*
1969	9616	11539*
1970	9426	11311*
1971	5833	54130
1972	7834	54426
1973 (6 months)	4632	46992**

*Estimated total assays based on 1.2 assays per sample. This is considered an appropriate estimate in that about 20% of the samples would probably require additional assays.

**If batches are received during the second half of FY 73 at the same rate as during the first half, NCDA would expect to complete over 90,000 total assays during FY 73.

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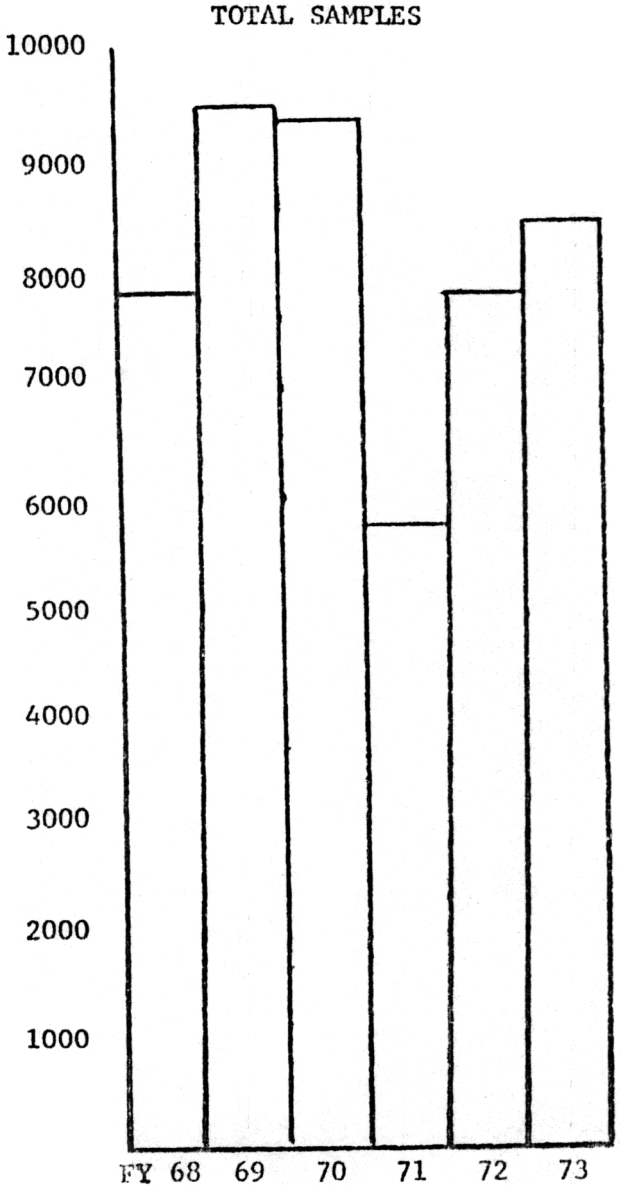
FISCAL YEAR	SAMPLES	TOTAL ASSAYS
1968	7849	9419*
1969	9616	11539*
1970	9426	11311*
1971	5833	54130
1972	7834	54426
1973	8551	89033

*Estimated total assays based on 1.2 assays per sample. This is considered an appropriate estimate in that about 20% of the samples would probably require additional assays.

GRAPH I
TOTAL SAMPLES



GRAPH II
TOTAL ASSAYS