This paper was presented by Mr. Ross D. Kirchhoefer in 1979 at the “ASQC Technical Conference” in Houston, Texas

QUALITY ASSURANCE IN AN FDA LABORATORY

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ABSTRACT

The National Center for Drug Analysis has implemented a Quality Assurance Program based on the proposed Good Laboratory Practice (GLP) regulations published in the Federal Register **41**, 51205-51230, 1976. The proposed GLPs highlight areas of operation that needed to be strengthened. The final GLP regulations have been published in Federal Register **43**, 59986-60020, 1978, and become effective June 20, 1979. A Protocol was written covering the Quality Assurance Program for Selected Marketed Drugs (QASMD), a primary function of the Center's operation.

My presentation will show how we accomplished this in a laboratory with diverse functions. In addition, the paper will acquaint conferees with the National Center and show specifics of how the Protocol affects the laboratory operation.

TEXT

In the Federal Register of November 19, 1976, the Food and Drug Administration presented their "Proposed Regulations for Good Laboratory Practice for Nonclinical Laboratories Studies."

To quote from the preamble of these proposed regulations: "The Commissioner fully appreciates that the agency's establishment of regulations governing the conduct of nonclinical laboratory studies represents a major new initiative for FDA that will have significant impact on the private testing community. He is convinced, as is the Congress of the United States, that deficiencies discovered in the current conduct of such testing, both in the private sector and in government, require this initiative to be pursued vigorously. Decisions about the safety of consumer products that are based, wholly or in part, on data derived from such testing are too important for the agency to accept anything less than the best scientific data that can be obtained. At the same time the Commissioner wants the final good laboratory practice regulations to be both sound scientifically and realistic."

The purpose of these GLPs is clearly to ensure that the scientific data on which the safety of consumer products is based is of the highest quality.

Every successful organization incorporates maximum production of the highest quality in its goals. The impact of the proposed GLPs will vary depending on the controls one already has established to ensure quality.

The National Center for Drug Analysis (NCDA), a nonclinical laboratory of FDA, has expanded its quality-control program and implemented a Quality-Assurance Protocol based on the Federal Register requirements for GLPs.

Before we discuss the sections in the GLPs that pertain to our laboratory, let's look at how NCDA is set up and how it functions. This overview will help the reader tie the Center and the Protocol together.

There are two basic functions at NCDA:

- Drug Monitoring/Quality Control and
- Research.

The Center is assigned the responsibility through the Quality Assurance for Selected Marketed Drugs (QASMD) program to analyze samples of finished-dosage pharmaceuticals of the same group or type of drug or of the same therapeutic value, e.g., Cardiac Glycosides (Digoxin and Digitoxin), Antihistamines (Chlorpheniramine Maleate), Analgesics (Aspirin), etc. Samples are then collected under an assigned program number; e.g., for Aspirin it is QASMD #78-14. Inspectors from the FDA field offices across the country will then collect samples of these products currently being manufactured by firms in their area. This sample collection usually takes 1 to 2 months. Each sample is analyzed for compliance with the legal standard. This includes content uniformity, strength, identification, disintegration, and dissolution. Since NCDA specializes in high-speed computer- assisted analyses, the initial analysis is usually automated. Any sample which fails any specification is checked by another chemist using official methods. The responsibility for this work falls to the Drug Monitoring Branch.

The Methods Research Branch is engaged in long-range research for the purpose of increasing analysis speed and other related long-term projects.

From this brief description of the Center, it is obvious that at least two protocols needed to be written, one covering research, the other covering drug monitoring. The first protocol we wrote, called the "QASMD Protocol," covers the QASMD program as implemented by the Drug Monitoring Branch.

Twelve items are identified as being pertinent to the protocol under the GLPs. They are:

1. Title and purpose of each QASMD survey
2. Sponsor and testing facility
3. Start and completion of QASMD survey
4. Personnel involved with QASMD survey
5. Standard operating procedures (SOPs) for running the QASMD survey
6. Identification of samples and drug standards
7. The methods used and the frequency of testing
8. The stability of samples and drug standards
9. Maintenance of records
10. Final reports
11. Personnel health and safety
12. Change or revision to any portion of protocol

Items 1, 2, 3, 4, and 12 are straightforward and simply require filling in the appropriate information. As an example, Aspirin QASMD 78-14:

1. Aspirin QASMD 78-14. To survey the marketplace for the quality of aspirin formulations regarding strength, content uniformity, dissolution characteristics, and purity.

2. The National Center for Drug Analysis, in St. Louis, MO, is the testing facility sponsored by the FDA's Bureau of Drugs.

3. QASMD 78-14 samples will be collected over a one-month period starting in April 1978. The estimated date of completion of testing is December 1978.

4. The names of the personnel involved with the survey, including the laboratory supervisor, are filled in.

12. Any change to any portion of the protocol must be documented, signed by the survey director (supervisor), dated, and maintained with the records.

Of the remaining protocol items, it was necessary to find out what documents controlling the laboratory operation were on hand and what documents needed to be written. These are items 5, 6, 7, 8, 9, 10, and 11. They are the heart of the protocol and required developing the SOPs. These items control the operation of the laboratory, from receiving the sample at the Center through sample analysis, report writing, and record keeping.

There were three existing FDA documents that already controlled parts of our operation such as identification and numbering of samples by field inspectors, logging samples into and out of the Center's storeroom, what kind of records to keep, etc. These documents are called the Regulatory Procedures Manual, the FDA Compliance Program Guidance Manual, November 1976, and the Sampling Schedule for QASMD. The Sampling Schedule for QASMD is received with each separate survey.

The problem then centered on writing SOPs governing everything else the laboratory does that is related to the analysis and reporting of the samples. These SOPs had to contain such things as validation of automated methods, modification of methods, data acquisition, either manually or by computer tracking, data handling, reagents, equipment (calibration and maintenance), drug standards, controlled substances (drugs of abuse), safety, reports, notebooks, quality-control samples, in-house forms to record specific information, and many other separate but related functions of the Center.

Five separate SOPs had to be written to cover the above items. They were combined with three existing NCDA SOPs in order to finalize the "QASMD Protocol." This task took approximately one year, and only six of the total of eight are completed. The following SOPs are used in the "QASMD Protocol."

a) Laboratory Quality-Control Program, June 1976
b) Analytical Protocol, October 1976

c) Pure-Drug Protocol
d) Analytical Guidelines for Conducting a QASMD Survey
e) Safety at NCDA
f) Testing and Stability of Standards and Standard Solutions
g) Maintenance and Calibration of Equipment (partially complete)
h) Computer Maintenance and Calibration (partially complete)

Without going into detail about each SOP, let's look at one of them for some specifics and to see how the protocol affects the laboratory operation: Testing and Stability of Standards and Standard Solutions. A standard solution that is used routinely with an automated method shall be treated as follows: A "stock standard solution" is a solution that results from quantitatively dissolving and diluting to volume a fresh weight of dry standard material. A "working standard solution" is a solution that results from a quantitative dilution of a “stock standard solution.” A “working standard solution” shall not be used for more than one week after its preparation. A “stock standard solution” shall not be used for more than one month after its preparation. These instructions leave no doubt as to what one is to do.

The other SOPs contain other specific instructions for laboratory personnel to follow. Some examples are: if a modification is made to an existing method, it is documented in writing by the chemist in charge and given to the supervisor for approval. Spectrophotometers and other equipment used in automated procedures are overhauled, calibrated, etc., before use. A form declaring that the piece of equipment is satisfactory is taped to the equipment. Persons using the equipment remove the form and file the form with their survey protocol.

To summarize, then, the laboratory personnel are now required to keep better records concerning everything they do. We feel the small amount of extra time this will take is justified. In addition, the Center's Quality Assurance Officer makes periodic inspections of ongoing surveys for compliance with the protocol. These reviews and checks are a necessary part of any well-functioning system and provide an important evaluative mechanism to measure the quality of all operative processes.

At present the Center complies with about 90% of the requirements, and by the end of the calendar year 1979 we should be in full compliance.