PROBLEMS AND SOLUTIONS RELATING TO THE REGULATORY USE OF AUTOMATED EQUIPMENT[1]

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The previous days discussions have touched on the importance of drug quality control especially in relation to the more powerful drug entities and smaller dosage units. The need for more rigid quality control specifications has prompted the officials of the United States Pharmacopeia (USP) and the National Formulary (NF) to include content uniformity in many monographs of the new revisions of the compendia.

The Food and Drug Administration, having responsibility for quality of the drugs on the market today, and viewing the increased incidence of recalls in recent years as an indication of the need for a new approach to the control of drugs in the United States, instituted the National Center for Drug Analysis. The Center was initiated as a pilot program on February 20, 1967 and received official status on July 1, 1967 as a field installation of the Division of Pharmaceutical Sciences in the Bureau of Science. The principal responsibility of the National Center is to test the most important groups of drugs in large volumes according to a program design capable of yielding statistically reliable data. Many samples of the same type of drug are collected throughout the United States to be assayed for potency, content uniformity and identity. The program is written to cover samples of certain types of drugs which we designate as studies (e.g. adrenocorticosteroids).

It seemed logical to develop an automated facility which could expeditiously examine huge numbers of samples. We began the program with teams of analysts using batch procedures while we instituted a study of the various automated systems on the market. We selected what we considered the most suitable equipment to meet our needs for automating all or part of our analyses. Emphasis was placed on versatility since we were scheduled to examine all kinds of drugs involving a variety of chemical reactions with different modes of detection.

Many of the pharmaceutical houses are using similar automated procedures for quality control on individual tablet requirements. The exchange of information and methodology with some has been extremely helpful.

The NF XIII in their preface under Automated Analysis, page xxvi, reflects their awareness of this problem. It is so pertinent to our topic today that I would like to quote from it:
"A growing awareness has developed that drug quality control testing by manufacturers, and drug quality enforcement testing by government agencies, must be increased even further to provide better assurance of a safe and effective drug supply. This view also is shared by the NF Board and is reflected in many of the new tests and specifications. A particular case in point is

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the content uniformity test, since this specification is directed at determining uniformity ’within a given batch or lot, rather than simply uniformity between lots.

However, one major complaint has been raised concerning the greatly increased analytical load caused by the new test. Even though in certain instances a more simplified test procedure can be utilized in place of the monograph assay, nevertheless, the requirement that at least ten and as many as 30 separate individual replicates be performed, is obviously burdensome and constitutes a greatly increased demand on facilities and personnel for the parties involved - whether in the laboratory of the manufacturer or in some enforcement agency such as the Food and Drug Administration.

As an unrelated but nonetheless parallel development, an entirely new dimension has been added to pharmaceutical analysis within the last five years. We have witnessed the successful application of the technology of automation to drug analysis. Automated analytical equipment presents a means of saving both time and personnel and ultimately equipment and costs. Unfortunately, the application of automated analysis to official compendium procedures is not without some difficulties.

The first problem encountered is the prohibition - under Section 501(b) of the Federal Food, Drug and Cosmetic Act - against the use of an analytical method different from that appearing in the NF. The second problem is that of prohibition against alternative methods. This policy recognizes that the NF test and assay procedures must be the common ground between plaintiff and defendant - between enforcement agency and manufacturer. If compliance or lack of compliance could be shown by different method, this would either place an undue burden of proof on the government or place the manufacturer in double jeopardy. The third problem pertains to the obligation that NF procedures be general in nature, indicating that it wouId not be reasonable to require that everyone perform a particular procedure, such as the content Uniformity test$_y$ using automated equipment.

In the face of these considerations, the NF Board gave the matter deep study with the hope of formulating a, policy end interpretation which ,would at the same time fulfill pragmatic and practical aspects while still satisfying the legal obligations and responsibilities of the NF as an enforcement device. ’The Board concluded that: (a) the NF only intends to state what shall be done and is silent on who or what shall perform the actions; (b) the NF only intends to recommend equipment which would be suitable (see initial paragraph under Apparatus, page 8); and (c) the NF does require that in order to demonstrate compliance, or lack of compliance - the exact chain of chemical and physical steps must be conducted. This says that the integrity of the official procedure must be maintained in that a different analytical procedure cannot be used nor can significant steps be eliminated. There is no flexibility in this latter area.

"To clarify beyond any doubt the Board’s position in this regard, the General Notices have now been revised accordingly (see initial paragraph under procedures, page 9)."

Under the section for Tests and Assays of the National Formulary (page 9) they describe the following:

"Automated procedures employing the same basic chemistry as those procedures given in the monographs are also recognized as being suitable for determining compliance. Compliance also may be shown by use of alternative methods (including automated procedures), chosen for convenience under special circumstances, provided the results thereby obtained are of equivalent accuracy. However, in the event of doubt or dispute, only the result obtained by the procedure given in this National Formulary is authoritative."

In order to assure reliability of analytical results obtained with automated equipment, we at the National Center for Drug Analysis have devised what we term our "Quality Assurance Program. This program begins with an attempt by the Research Section to automate the official procedure. If this procedure does not lend itself to automation we attempt to automate some other previously published method or attempt to devise a new method.

When we are satisfied that our automated procedure is applicable we analyze the pure standard materiel several times to determine the accuracy and precision of the method. We then formulate a test sample from the standard material and inert ingredients as closely representative of a commercial product as we can possibly make it. We again determine the accuracy and precision of this known formulation on our automated equipment.

A quantity of a commercial product is then purchased and a large composite is made of the product. This composite is assayed a sufficient number of times by both the automated method and the official procedure to permit us to calculate standard deviations of results obtained by both procedures. It also allows a comparison to determine any bias between the two methods. We attempt to obtain comparable or lower standard deviations by the automated procedure as compared to the official procedure. When satisfactory results are obtained, the method and our quality assurance sample is delivered to the Analytical Section for use in the initiated study. The quality assurance sample is assayed periodically throughout the life of the study to assure us that the automated method is performing properly.

To initiate these studies, information concerning the number of batches of the particular drugs involved in the study, over a given period of time, is collected. The program then issues to collect six samples at random from each batch available that has been released by the manufacturer's quality control department. These samples are collected from the manufacturer or from his first line of distribution point. The samples are then forwarded to the National Center for Drug Analysis for examination.

Five individual tablets are assayed from each sample, preferably by the automated procedure, for a total of 30 individual tablets from each batch. If any deviation from compendial limits is noted an additional five tablets from each sample are assayed.

Based on the results of the 60 assays, additional determinations may be made to ascertain whether the product meets or fails compendial limits.

Since the compendium states, "However, in the event of doubt or dispute, only the result obtained by the procedure given in this National Formulary is authoritative," we therefore check analyze those samples which we have found to fall outside of the compendial limits. This check

analysis is by the official procedure. This involves a great deal of time consuming "manual analysis" on out-of-limits samples but fortunately these samples comprise a small percentage of the total number of samples received. By following this program we have complete confidence in reliability of results obtained at the Center.