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AS THE PHARMACEUTICAL WORLD TURNS

(A SCIENTIST'S VIEW ON USP AFFAIRS)

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ABSTRACT

The following issues are discussed:

(1) The dynamics of specifications. The impossibility of any published public document providing the last word in total specifications of a drug substance and its dosage form.

(2) The compendium and the compendium process and its weaknesses. The fact that it is still a viable system and that alternatives such as those suggested by the OTA Panel bring with them many, many more inherent weaknesses with no guarantee that there would be an improvement in drug quality and specifications.

(3) Suggestions to strengthen the compendium process.

"As the World Turns" is a very popular daily TV soap opera. Like most soap operas, it depicts the problems of its leading characters and the efforts that are made to solve their problems and arrive at their utopia. Thus I thought it most appropriate to entitle this presentation "As the Pharmaceutical World Turns" for we here are trying to solve our problems and arrive at our utopia. As the Pharmaceutical World Turns, specifications, the "Guiding Light" of the world must change. In our quest for a completely safe and effective drug supply, "Our Search for Tomorrow" is deeply involved with the adequacy of our drug specifications.

DYNAMICS OF SPECIFICATIONS

I mean to drive home at least one most important point which I feel is very relevant to the whole question of compendia specifications, in-house specifications, government monographs, and the like. I feel this point is not often emphasized and yet it is most important. The point is that specifications are dynamic. They are not static. They are continually evolving. Because they are dynamic, it is almost impossible in my way of thinking, to consider that the last word in specifications on drug products would be a published public document. As pharmaceutical science advances, becomes more complex, more sophisticated, this idea of a public document being the final word in product control even becomes more impossible. Clearly the word for effective specifications is dynamic, dynamic, dynamic!

How dynamic? Well, at Wyeth we publish an average of one original specification or specification revision per day. Now Wyeth is not the largest pharmaceutical company, although it is of good size, nor does it have the most diverse product line, although it has considerable diversity, yet we publish one specification change per day. Is there any way that a government or other public organization could keep pace with this kind of change? Consider the number of pharmaceutical companies and the number of changes which would have to go into the hopper on a daily basis. What are these changes? Some are quite complex, whereas others are simple and relatively routine. But all require data collection, study and the necessary paper transactions to inform all necessary parties of the change.

As an example let us consider the action necessary for qualifying a particular supplier of a drug substance or of a pharmaceutical excipient for use in a specific dosage form. Many questions must be answered such as: can the material be processed; does it have some peculiar impurity which is not present in the currently used material, and what effect does this impurity have on the toxicity of the material and the stability of the dosage form; does it require some special testing; does it change the dissolution of the dosage form and thereby affect bioavailability? It would be impossible

for any public organization, government or otherwise, to handle and keep up to date just this one aspect of specifications for every drug manufactured by every pharmaceutical company in the country. Presumably, however, each individual quality and morally conscious company, with the available expertise, is performing this kind of action for all of its own products.

Because of differences in formulations and processing equipment even requirements for the physical characteristics of any one active drug are different from company to company. For example, it is not unusual for company A to have a bulk density or particle size need for an active drug quite different from company B even though they are both manufacturing the same active in a tablet formulation. One can see that it would be necessary for a public body to catalogue for each product, all the different requirements for all the various companies, and keep up to date the changes in these requirements as they occur. If that were not feasible, then the public body would have to assume the responsibility for dictating the formulation that should be used for a particular drug substance and the type of equipment that a company must have in order to manufacture such a drug. I cannot believe that any knowledgeable person could be in favor of the establishment of some Gargantuan public or government organization to administer such a specification and control program.

A couple of man-days per day is spent at Wyeth just keeping our specifications up to date, to assure a certain level of quality in our products and in a continuing effort for further quality improvement. A great deal of time is expended in the study and establishment of an original specification for a drug substance and its dosage form. This time is spent on such things as, the development of a stability indicating method, that is a method which will measure an intact drug in the presence of its degradation products; the development of identification procedures which will clearly distinguish this product from all other products made by Wyeth; the development of adequate dissolution tests and the collecting of the necessary correlatable data to support the appropriateness of the test; the development of methods which will control the levels of impurities present in the drug substance, and the collection of stability data and the subsequent study of the data to set limits on the product.

Then, once having established specifications for a product, we are involved in a continuous process of examination of the specifications and the performance of the product to determine whether revision of the test limits may be warranted. That is, for example, if originally based on the experience we had to date, we set in-house potency specifications on a product at 93-107% of labelled claim but examination of the data clearly

shows that more restrictive limits, such as 95-105% of labelled claim could be met, then we would certainly change the specifications to the more restrictive limits. The philosophy here is that if we can make a product meet a particular criteria over a reasonable length of time then we would most certainly want to restrict our production people to that kind of performance in the future. Any deviation from that kind of performance would clearly point to an unusual situation, not necessarily a hazardous one, but one which would deserve, and receive, further consideration. But note here again that I am talking about the dynamics of this specification situation.

Thus, my thesis is that the compendium organization or any other public official body cannot do the kind of job necessary in order to adequately provide a complete, up to date specification system for the drug manufacturers.

USP WEAKNESSES AND THE OTA REPORT[1]

Then are we saying that there should be no public specifications or that all should remain as is? Do we imply that the compendium system does not have deficiencies? By no means do I want to make that implication! As a daily user of the compendium and a member of the USP Committee of Revision and the NF Committee on Specifications, I must unfortunately agree that there are deficiencies in the compendia. But my view is not entirely in agreement with that expressed in conclusions number 5, 6, and in particular 10 of the OTA Panel report. As you will

remember, conclusion number 5 stated "present compendial standards and guidelines for Current Good Manufacturing Practice do not insure quality and uniform bioavailability for drug products. Not only may the products of different manufacturers vary, but the product of a single manufacturer may vary from batch to batch or may change during storage". Conclusion number 6 stated "New compendial standards for drug substances, excipients and finished drug products should be developed and revised on a continuing basis to reflect the best available technology to assure quality and uniform bioavailability. Appropriate statistical procedures should be specified to make certain that the purposes of the standards are objectively satisfied. The guidelines for Current Good Manufacturing Practice should be expanded to include specific descriptions of all significant aspects of manufacturing processes from the raw materials to the final product." Conclusion number 10 stated "A single organization capable of setting standards adequate to assure the quality and uniform bioavailability of drug products should be established to replace the present USP and NF as the official standard-setting organization of the Federal Government." Much of what the OTA Panel recommended be included in a compendium is, of course, incorporated in our in-house specifications and controls. Thus, there is really very little fault that I can find with the substance of the OTA Panels's recommendations.

Such recommendations would cause no difficulty for Wyeth or any other research and control oriented pharmaceutical company. But the point is clearly that the manner in which the OTA Panel recommends that we proceed is unrealistic. One gets the impression that the OTA Panel advocates operating under a system where a government body would dictate and control completely a company's operation. Thus a company would be told the kinds of equipment that must be used, the formulation of an active which will be allowed, the in-process controls that should be used, and so on. But, even such a drastic measure as this would not necessarily assure a totally effective drug supply and, of course, such a step would introduce all the weaknesses that we are all aware are present in large bureaucratic, non-competitive controlled operations. Such a step is not necessary.

Let us reconsider the compendium. What the compendium tries to achieve is control over the finished product because, after all, that is what reaches the patient. Thus, where I am in agreement with the OTA Panel is that the compendium monographs must be capable of specifying tests and limits which assure the patient that he is getting an effective quality drug. There are compendium monographs which do not give such assurance. There are compendium monographs for dosage forms for example which do not have present a stability indicating assay method. We suspect that the assay procedures in monographs for perphenazine, procainamide hydrochloride, lidocaine

hydrochloride, promazine hydrochloride, secobarbital, metaraminol bitartrate, hydroxyzine hydrochloride and dicycloamine hydrochloride are not totally stability indicating. This is a real weakness in these monographs. Further, there are drug substance monographs where there is no suitable measure of potency and no attempt made at controlling impurity levels. For example, in our compendium work we found that phytonadione did not have a potency test. In working with the two prime suppliers of this material, in an attempt to obtain an assay procedure for potency measure, it was discovered that this substance had some ten percent or more of another species present. This other species proved to be the cis-isomer of phytonadione. By additional study it was shown that the cis-isomer had been present in the product of commerce for a number of years and that it is a non-toxic species. Since the two isomers are extremely difficult to separate in the commercial synthesis, it was decided that it would be sufficient to control the level of the biologically inactive cis-isomer present in the biologically active trans-isomer. Thus, up until the XIX revision of the USP the phytonadione monograph did not have a potency test and it will not have a test to control the impurities until the First Supplement of the USP XIX.

More recently we uncovered a weakness in a drug substance monograph that we still have not had an opportunity to communi-

cate to the USP office, but we will certainly do so shortly. This drug substance is an acid salt and the testing methodology in the USP monograph is rather non-specific. We discovered that material synthesized by our developmental chemists met all the compendium monograph specifications but by our devised more specific methodology had 7% impurity.

THE SCIENTISTS' INVOLVEMENT

I could present additional specific monograph weaknesses but I believe the point has been made. I am aware of these difficulties. Yet, I do not believe that they can be eliminated by establishment of still another organization. The existing organization, that is the USP, is a good one. Its manner of operation may have to be modified, however. As you know, the organization consists of volunteers from academia and industry. All members of the USP Revision Committee for example, volunteered because they have a definite interest in the program and the necessary expertise to do a competent job. The problem is that there just is not sufficient time to do all the work we would like to accomplish. Thus, and I talk from personal experience, because of the multiplicity of monographs that the USP Revision Committeeman has assigned to him, he may only have the time to do an in-depth study on those monographs where it is clear to him that there are definite problems. He does not try to uncover problems which may be lurking below the surface. There is simply not sufficient time. This

then makes the improvement of the monographs a slow process since a monograph's deficiency must be brought out in the open before any action commences. In addition, the fact that a compendium monograph for a drug substance controls many different manufacturers' products, requires that all major manufacturers have an opportunity for input into the monograph and criticism from their point of view. This is the American way. It is a democratic process and therefore it is a slow process. However, like all democratic processes they can be improved and it is not necessary for us to sacrifice yet another freedom in order to accomplish an improvement in drug specifications.

In the OTA Panel report, there is a hint that industrial scientists should not be an influential part of the specification process because of their assumed proprietary interest. This is ridiculous. If there are weak monographs in the compendium it is not because industrial scientists are not capable of taking off their company hat and putting on their compendium hat. It is simply because they do not put on their compendium hat often enough because of time limitations. In fact, if the OTA Panel is serious about wanting to improve the monographs they are being totally unrealistic when they suggest that this could be done without the participation of industrial scientists as an influential part of the process.

The reason is that there are simply not sufficient numbers of people outside of industry with the expertise required for such an involvement. If anything, it is my feeling that in order to improve the compendium, there is a need for greater involvement from the industrial scientist, not less.

INDUSTRIAL SPECIFICATIONS VIS-A-VIS USP SPECIFICATIONS

I would like to make certain that my position is understood with regard to the compendium. That is that although I might agree that specific monographs are weak and that indeed the whole compendial process needs to be strengthened, I do not agree that there should be an extension of compendial involvement into matters where it was not intended to be. It need not concern itself for example with in-process controls and statistical sampling. The compendium is meant to control the quality of the final product and this is important because this is what the patient receives. The compendium demands that at any time in the lifetime of the product that all the monograph specifications be met. That is that no matter what particular bottle from a batch a patient's prescription is dispensed, the patient is assured that the bottle's contents will meet the requirements as set forth in the USP monograph. Thus it is necessary for a manufacturer to set his own specifications such that each and every unit that he manufactures is capable of meeting those monograph specifications throughout the lifetime of the product.

In terms of content uniformity the compendium demands that nine of ten tablets or capsules fall within limits of 85-115%

of the content specified. Just looking at the face value of this specification it appears to me that to desire to have nine out of ten or better yet ten out of ten tablets of a potent drug within 85-115% is a reasonable goal and from a patient's point of view, a goal which should be achieved. Consequently, we have devised specifications at Wyeth which include additional testing, incidentally by automated techniques, and a particular criteria based on a nomograph on which we plot mean assay value versus relative standard deviation, to give us assurance with a high probability that a patient will not receive a tablet outside the potency range of 85-115%.

Another simple example of the difference between compendium specifications and industrial in-house specifications can be found in considering potency limits. That a product should not be less than 90% or more than 110% of its declared amount is certainly a reasonable limit. But in order to achieve such a limit throughout the lifetime of the product, it may be necessary for a manufacturer at time of release to meet specifications of 95 to 105% or tighter, depending on the rate of degradation of the product and the variability of the assay procedure. These tighter specifications will then allow for the small amount of predicted degradation and any assay variability. Analysis of a product released within the tighter in-house specifications at time of manufacture will assay within the monograph specifications at any time during its lifetime.

I suspect that at one time there was a feeling that in-house specifications were something that, although not illegal, were not totally ethical. But it is clear that such a feeling was inappropriate because, not only are in-house specifications ethical, they are a representation that a manufacturer is attempting to do the best job possible. As a result of this new enlightened attitude, we feel that the new GMP regulations should give recognition to the existence of an in-house specification system which is more demanding than the compendium specifications in order to assure adherence to compendium specifications throughout the life of the product.

SUGGESTIONS FOR USP IMPROVEMENT

As I suggested earlier, the compendium process needs to be updated, revitalized. There are monographs which need to be improved. Left to its own devices, the system would eventually catch up and make the improvements. But this is obviously not good enough. The system must be changed so that the monograph weaknesses can be rapidly removed. There are a number of ways by which this might be accomplished. I would like to enumerate a few possibilities:

(1) The Revision Committee could be expanded from 60 members to some larger number, for example 120 members. That the USP Revision Committee must be enlarged goes without question. Now that the United States Pharmacopeial Convention has assumed responsibility for the National Formulary and its monographs, there will,

of course, have to be an increase in the number of Revision Committeemen to handle the monographs. With an enlarged Revision Committee, each committeeman would be given fewer monographs. This then could lead to a more complete and in-depth study of each monograph. However, to be certain that an in-depth study is made, it will be necessary for USP headquarters to provide a check list of items to be considered. Such a check list should then be returned with the completed monograph to the compendial office by the USP Revision Committeeman indicating that all pertinent matters had been considered.

As a corollary to the expansion of the Revision Committee we feel consideration should be given to a reorganization of this body. In such a reorganization a greater number of the committeemen should be assigned to the real work of the committee and that is monograph revisions. In the past, many Revision Committeemen were not pulling their weight of the load, since they were given assignments which were not actually involved in monograph revision work.

(2) I believe as an enticement to both industrial and academic scientists, the USP should join with the Journal of Pharmaceutical Sciences to once again institute a separate section in the Journal, that is separate from the existing section called Pharmaceutical

Analysis, in which would be published a critical study of individual monographs. This section which could be called, for example, "Drug Standards" would provide to the scientist a place to publish work on specification development. Such work most scientists feel does not qualify as original research yet is does increase the scientific storehouse of knowledge and as such deserves public exposure. Thus, anyone who had an interest to consider a drug or class of drugs could make a point by point study of the monographs covering these drugs and publish their findings. They could provide a critique of the present methodology and if found inadequate suggest alternative methodology. In providing alternative methodology, they would support any claims they made with the necessary data. In this way, it is hoped that we would bring into the compendium revision process many more contributors.

(3) The USP should insist that they receive certain information on drug substances and formulations from the prime manufacturers. Of course, all are aware that the pharmaceutical manufacturers are most cooperative with the compendium, but sometimes it is necessary to overcome the natural inertia which may be present for a variety of reasons. The USP should request that prime manufacturers supply a stability indicating method and the data to support such a method, a chromatographic

method of analysis for impurity content in drug substances, a dissolution test where it is felt such is needed, and so on.

(4) The USP should seek government funds for support of work done under contract to improve monographs by certain qualified laboratories. We feel this is a more viable approach than an attempt by the USP to build up the Drug Standards Laboratory to a size where it could handle the problems. Parenthetically we should state that we certainly support any move to improve the Drug Standards Laboratory but it is not practical to consider enlarging the laboratory to a point where it could handle the entire problem. First of all because there is not sufficient expertise available to permit a rapid buildup of the Drug Standards Laboratory. Further, it is felt that the need would only be of short duration. If contracts were given to an industrial or academic laboratory, where supervisory expertise and equipment already existed we feel the problems could be solved more rapidly. In operation then, an industrial or academic laboratory might be put under contract to improve the monographs of the phenothiazine drugs or the benzodiazepine drugs or any other group of drugs.

NOTE

This paper was presented at the 14th Annual International Industrial Pharmacy Conference in Austin, Texas on February 26, 1975.

FOOTNOTE

1. The OTA Report here refers to the report of the Drug Bioequivalency Study Panel to the Office of Technology Assessment, Congress of the United States. The ten member blue ribbon panel of medical and scientific educators was headed by Robert W. Berliner, M.D., Dean of the School of Medicine Yale University. The report was made to Congress in July 1974. Its substance was summarized in eleven conclusions and recommendations.