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EXCIPIENT STANDARDIZATION: USER'S VIEWPOINT*

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ABSTRACT

Reproducibility of excipients from lot to lot and vendor to vendor is a necessity for the production of finished product batches having consistent quality. Many excipients have been subjects of pharmacopeial monographs for many years while others have received more recent recognition. The use of such standardized raw materials in drug products aids in their acceptance by regulatory authorities and leads to a universal acceptance of the excipient by the pharmaceutical community. This is of importance to the company that is multi-national.

The single source specialty excipient supplier who has achieved compendial status for his product communicates his

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commitment to that product. The user can have confidence in continuity of supply as well as access to specifications/test methods that have been reviewed/accepted by supplier and customer alike.

However, excipient specifications must have meaning. They must often go beyond mere characterizations of purity to include standards of performance. There are examples of materials meeting compendial specifications but performing differently depending upon lot or source.

The incorporation of such standards in pharmacopeias probably has not been accomplished partly because of their orientation toward purity and identity and partly because of a lack of agreement on performance standards. With the consolidation of excipient monographs in the NF it may now be appropriate to consider establishment of performance standards in it particularly with the emerging recognition of the Pharmacopeial Forum. Another possibility is the establishment of an extra-pharmacopeial certification mechanism. All means of obtaining and guaranteeing appropriate excipient performance standards need to be explored.

DISCUSSION

"Excipient specifications are developed to control the properties of excipients." That statement, as obvious as it is, is meant to reflect the fact that there are intrinsic properties

that can be measured directly as, for example, particle size, and that there are properties that must be measured indirectly. An example of the latter might be powder flow which can be a function of particle shape, cohesiveness and density as well as particle size. Both kinds of properties, directly and indirectly determined need to be controlled for excipients to be used. Without specifications to control excipient properties, our products and our manufacturing operations would be uncontrolled.

Taken in that context, the next considerations which should follow should be those of what we need to control, the kinds of specifications that will control, how we set them, and how we test for compliance. These considerations are, in my opinion, the cornerstone of the entire question of where we go from here and a theme that will no doubt be of interest and concern for some time to come.

It would not be necessary to institute these control concepts if there were not variations in excipient materials. Sources of these variations which have been taken from Chambliss (1) are as follows.

Upper-most in the minds of many when presented with a new excipient is, "will it be the 'same' from batch to batch?" This is of importance to those in product development for it will help in designing a marketable dosage form. It is also of importance to manufacturing units for it affects the manufacturing process in regard to accomodations that must be made because of excipient

variation. It is of importance to quality control where the charge rests after the product development phase testing for "sameness". "Sameness" must reflect chemical composition but in the case of excipients, functionality as well must be a part of that definition.

The nature of free enterprise being what it is, it is inevitable that sooner or later there will be multiple suppliers of the "same" material. How can it be known for certain before use that multiple sources are, in fact, producing material that is the same? Consider, for example, Tricalcium Phosphate, NF. There are marketed in this country two direct compression grades which conform to NF specifications. However, one is said to differ from the other in color and compressibility. In addition, Tricalcium Phosphate, NF can be purchased as a non-flowable powder not intended for direct compression. None of these can be distinguished by present NF specifications.

Two other sources of variation - variation within a batch and variation with time - are usually less troublesome but have caused some problems in the past.

None would dispute the observation that without excipients drug substances would remain just substances and there would be no products to administer. At least there would be no products convenient for self-administration by a patient or products possessing characteristics necessary for the treatment of many diseases. Since they are so important, first, in making a

product possible and, second, in defining the characteristics of that product, it is axiomatic that control of the reproducibility of excipients from lot to lot and from vendor to vendor is a necessity for the production of finished product batches having consistent quality.

It is not necessary to dwell at length on the past history of pharmaceutical excipient specifications. Suffice it to say that others have noted there was criticism that many commonly used excipients were not even included in the compendia (2,3). Individual manufacturers set specifications on these materials for their own use. Recently there has been a much welcomed movement to stimulate the inclusion of all excipients in the NF, although as recently as a year ago it was estimated that there were still more than 200 which remained unofficial (4). It should be noted that NF XVI contains 253 monographs for "inactive agents".

There are three very practical reasons for users to support this compendial excipient standards setting movement. First, formulations containing excipients all of which are official in United States compendia are much more likely to be accepted in a shorter time frame by foreign regulatory authorities than those which do not. This may be because specifications applied to them and the test methods used to evaluate them have been reviewed by a body which has no stake in the commercial success of that product. This may even be due directly to the fact that USP/NF

is the last of the world's official drug standards setting compendia to remain out of government hands. Whatever the reason, this observation is of much interest to the company that is multi-national in scope. In fact, the first preference when formulating a product for world-wide use is to include USP/NF excipients, although it is recognized that this is not always possible. Also, as a practical matter, simple referral in a filing to a compendial monograph should reduce the volume of material which a reviewer must digest. That is applicable to United States filings as well.

In regard to USP/NF being the last of the non-government controlled compendia, James Dickinson likened this situation to being the last of the dinosaurs and warned that we all know what happened to them (5).

Second, a basic purpose of a pharmacopeia is to provide standards so that any article bearing the official name and conforming to the standards set forth can be expected to give predictable and consistent performance (6). USP/NF standards carry the force of law. Therefore, one can assume that an excipient so included will be of consistent, known quality and the user then has an option of utilizing that material without further testing if he so chooses. This is not to say that any of the unofficial excipients are being produced in a manner that is less conscientious and that they, too, could not be used without prior testing. (While such may have been done in the

past, it should be noted that the draft guideline issued in April, 1985, by the FDA for submitting documentation for the manufacture of finished dosage forms requires that excipients be tested prior to use for conformance with appropriate specifications.)

Third, under the present system, the user can have confidence in the continuity of supply of an excipient for which a manufacturer has applied for and received compendial status. I cannot recall a compendial excipient withdrawn from commerce, although several that were not come to mind. Of course, an obvious reason for this is that part of the requirement for USP/NF inclusion is wide-spread use which in itself guarantees the supplier's commitment to future production. One can also have confidence in the specifications and test methods for compendial excipients. They have been agreed upon by supplier and customer alike. While the necessity for future revision can never be totally eliminated, the user can be assured that everyone is using the same product within the limitations of the specifications and the test methods.

Shangraw put forth a proposal that finished products which have compendial status should contain excipients also having compendial status (4). As he pointed out, in the era when formulations themselves were included in USP/NF it was a requirement that all ingredients in the formulation have compendial standards. Even now the active drug substances in

officially recognized products are always officially recognized. It would seem to follow, then, that all ingredients in that product ought to be recognized also.

He asked the question whether colorants, flavors and fragrances should not also be included in the NF and concluded that the latter should not (4). One could take the view that an excipient is an excipient no matter what it is or its function. The situation with regard to colors is in chaos around the world today. There is none that is accepted in every country. For flavors and fragrances a similar problem exists. It is not likely that any improvement will be noted by the inclusion of any of these in USP/NF. Coupling this with the fact that flavors and fragrances are so individualized for particular products, there seems to be little justification to require their inclusion. Colors, on the other hand, are another matter. It has always been puzzling to me why they are not presently included.

The mandatory use of USP/NF excipients in USP/NF products gives some cause for concern. It may not be true, but it seems to infringe somewhat on the formulator's freedom of excipient choice. When developing a new drug product he would be forced to choose among only the excipients that are in USP/NF since eventually he would want his product to receive USP/NF status. If he did not use such excipients and in the time between new product development and submission to the USP/NF of that new product, the excipients used were not accepted by USP/NF, then his product could not be accepted either.

It is true also that most formulators will only use excipients which are "FDA approved". The additional requirement that they be "NF approved" seems to add little difficulty. The problem would seem to be that one of the present prerequisites for compendial inclusion is wide-spread use and that wide-spread use cannot be achieved without first having attained compendial status. I will leave the resolution of these contrasting conditions for future discussion and say again only that the formulator's choice of excipients must not be limited by this proposal.

The establishment of excipient specifications and their inclusion in a compendium, as worthwhile a goal as it is, is only the first consideration. We must also consider the kinds of specifications we are going to apply to them.

When the USP first made its appearance in 1820 its purposes were to provide standards for drugs and medicines of therapeutic usefulness or pharmaceutic necessity sufficiently used in medical practice throughout the United States and its possessions; to lay down tests for the identity, quality and purity of these; and to insure as far as possible, uniformity in physical properties and active constituents (7).

Pharmacopeial specifications have always been basically chemical purity specifications. In view of the conditions which prevailed, such a development was necessary and logical. A notable exception to the exclusive application of purity and

identity standards was the establishing of dissolution specifications for tablets and capsules. These can be defined as performance characteristics. It has been said, however, that most of the tests described in pharmacopeias in general are of limited value in characterizing materials for pharmaceutical applications (1). The reason for such a statement is that, for the most part, efforts by the compendia to establish tests and specifications for functionality have been unsuccessful (2). One can find support within the industrial community for such view.

Cooper has presented some opinions as to why this is such a difficult problem (2). First, some excipients have multiple functions. An example might be a binder-disintegrant in tablet formulations. For a binder an important property is the ability to "carry" other poorly compressible materials and some measure of that property is needed. For a disintegrant a determination of the relationship of amount present as a function of disintegration time as well as influence of other ingredients, whether soluble or insoluble, and compaction pressure is required. Second, the same excipient can be used in several types of dosage forms in which the effect of a particular property can be favorable or unfavorable. An example is the comparison of a disintegrant's behavior in a loosely packed capsule with that in a tablet.

Adding to the difficulty of setting functional standards is the fact that sometimes one doesn't know an excipient can exhibit different behavior depending on lot or source.

Sorbitol is made by different processes and it is difficult to subtitute sorbitol from one supplier directly for that from another in direct compression formulations. DuRoss noted that changes in various commercial crystalline sorbitol products were found which altered the characteristics of tablet products (8). In several instances even the sorbitol manufacturers and the tablet manufacturers were unaware that any changes had occurred.

The variations in magnesium stearate are well known. Probably what most people have suspected, if not examined in their own laboratories, was published by Frattini and Simioni (9). These investigators used three batches of magnesium stearate differing in morphology, particle size, bulk density and specific surface area in preparing direct compression tablets. When the lubricant lots were used in the same amount by weight, the resulting tablets differed in hardness, disintegration time and dissolution. When they were used by equivalent areas, the final characteristics of the tablets were almost identical.

Equally well known are the differences in lactose. Some accomodations in labeling have been made for these differences in the present NF as well as previous issues of USP as to process origin and whether hydrous or anhydrous, while differences in compressibility, color stability, flow, etc. are documented only in the literature (10,11).

Bowen and Vadino reported that differences in the degree of hydration were found in Pregelatinized Starch, NF depending on

vendor (12). They suggested that the observed differences in physical properties of each pregelatinized starch may represent functional variables which could only be evaluated in an actual formulation or manufacturing process.

An example of an excipient in which a functional difference was found and as a result a controlling specification included in USP XXI is Povidone. Povidone was used as a binder in lithium carbonate tablets (13). An incident occurred where the drug dissolution was greatly reduced following tablet storage. Certain lots of Povidone K-30, including the one used in the tablets exhibiting poor dissolution, were found to cross-link under alkaline conditions and heat. This cross-linking resulted in the production of a gelled, insoluble material. A viscosity test was developed to evaluate and screen lots for cross-linking and this test was incorporated into the USP XXI monograph.

In the case of titanium dioxide, however, an experience which led to the investigation of polymorphic modifications has not yet been translated into pharmacopeial specifications. Tablets coated with a commercial film coating suspension were found to contain black specks of iron on the surface and the coating pan itself was scratched, indicating the source of the particles (14). The abrasion of the pan was related to the batch of coating suspension used and further traced to the lot of titanium dioxide which it contained. In the batch of suspension which caused abrasion, the titanium dioxide contained about 40%

of a polymorph which was harder than the pan surface. The percentage of this polymorph in the titanium dioxide in the suspension lots which were used without causing abrasion was only about 10%.

There are, no doubt, other examples of functional differences in excipients which can be cited, depending on the particular materials and circumstances encountered. It would not be an overstatement to say that control of functionality is as important as more conventional control for identity and purity.

That is, however, more simply said than done. For the effective establishment of performance criteria several considerations are necessary. First, one must recognize that a problem exists. From the examples given above, some problems are well known and widely recognized while others are not. In fact, in some cases specifications are needed and in some cases they are not. Second, there must be a direct or indirect property we can measure that will allow us to set a specification. With increasing analytical sophistication this ought not to be the problem it was in the past. An example of such sophistication is the use of instrumented tablet presses compared to single tablet compression using a Carver laboratory press.

Third, the test method must be available to those who will use it on a general basis. It would seem to be of little value to have a test method so sophisticated or so specfic that only one or two laboratories can use it. Consider again the

comparison of a Carver press with an instrumented tablet machine. Carver presses are reasonably standard devices which are widely available. Compressing a given weight tablet in a certain size die with a given pressure is a simple procedure. Instrumented equipment has also become widely available but caution must be exercised that the variety of measuring devices available actually measure the same parameter. Even given the fact that a tablet has been produced at a given compaction pressure, different types of hardness testers give different readings of tablet hardness. Thus, the problem of assurance that everyone is conducting all phases of testing exactly alike is extremely important.

Fourth, there must be a communication of the test specification and method to potential users. This must include a mechanism for revision when necessary. Recognition of excipient problems and how to measure them are intuitive to pharmaceutical scientists as illustrated by the examples given above and by the initiation of the Handbook of Pharmaceutical Excipients project. This project correctly recognized the need for expanding pharmaceutical excipient specifications beyond the traditional concerns for identity and purity. Without establishing a communication base, no amount of performance specification setting will accomplish the universal acceptance and application of those specifications.

There are two publications now available dealing with excipient specifications. These, of course, are the Handbook of Pharmaceutical Excipients and the USP/NF. The purpose of the Handbook at the time it was conceived was not and still is not to be a specifications manual. Rather, it is informational in nature - a vehicle for technical information covering a wide variety of properties and experiences with excipients (2). While the NF at one time appeared destined for oblivion it has become an excipient compendia. There are good reasons for it to continue as such. The Pharmacopeial Forum is an excellent place to publish proposed specifications, thoughts and ideas for comment. Supplements and revisions provide a mechanism for updating between USP/NF editions.

For some it may be that the legal status of the NF is a problem. It has been expressed that performance specifications need not be legal requirements. Magnesium stearate conforming to surface area requirements may be useful but in some applications quite unnecessary. Pregelatinized starch may have different sedimentation volumes when obtained from different manufacturers but is a legal limit on such a property reasonable? However, who has not had experience with a material which was represented to meet legal standards of identity and purity (and, in fact, did) and some non-legal standard of performance (and, in fact, did not)? In other words, the product that is NF in quality (as in identity and purity) and is supposed to perform as the NF product

upon which experience has been built, turns out to perform poorly or not at all in your formulation or manufacturing process. Control of performance by surface area or sedimentation volume is just as important and valid a measure of the quality of an excipient as is control of purity and identity.

Having established that excipients can vary in performance, that performance criteria are needed and that the NF is at this time the only, put by no means poor, choice as the repository of these specifications, how are we to select the specifications that we will apply and their test methods and who will make these choices?

At the risk of making the same suggestion that always seems to be made in situations like this, I will suggest the formation of a committee whose task it would be to develop specifications and test methods. Robinson has called for a working Compendial/ Regulatory Advisory Committee to supplement the present USP system of article admissions with representatives from the USP, FDA, PDA, PMA and the Academy of Pharmaceutical Scientists (15). Perhaps a similar group with a variety of disciplines and organizations represented could be commissioned to undertake this assignment.

An alternate to the NF as a performance specification compendia might be a publication in some sort of combination NF/ Handbook format. Perhaps a group or committee serving under sponsorship of the Academy or one of its sections could, through

such a non-legal publication, certify the performance characteristics of excipients contained therein. The need for providing potential excipient users with test methods so that everyone could conduct their own testing was noted earlier. Such an approach is traditional and often desirable but may not be practical in performance testing of excipients. It may be that we will need to be content with some kind of extra-pharmacopeial certification mechanism. I am not proposing that each batch of excipient be certified as to performance, only each product from a specific vendor. When batches fail to perform as expected in the field, they would be considered on an individual basis.

The topic of listing excipients on product labels deserves mention. When you come down to basics, the most compelling reason to include excipients on labels is the issue of consumer protection, specifically with regard to hypersensitivity reactions. Foods carry ingredient listings. It seems no more than reasonable to require the same for the nation's drugs. I can find no reasons to the contrary but would raise the question for discussion as to the seriousness of the oral administration of quantities of excipients likely to be encountered in pharmaceuticals. Further, in the case of prescription items, it is not clear how this information will be made available to the patient. I am sure that others have considered these points and

I raise them as items for discussion and not as objections to ingredient labeling.

The question remains of where do we go from here. The wizards of prose and poetry have the ability to see into the future and to conjure up great and wonderful things. In our world it is not as easy. Accomplishments do not occur as a result of magic words but as a result of hard work. Unfortunately, going on from here will require plenty of that.

In an edition of Instruments and Control Systems, editor Jack Hickey commented that it is no longer possible, for a variety of reasons, to run a plant by guess-work (16). Tools are available that are within the means of everyone to use to gather useful information that will allow higher quality and more economical plant processses and products. The same can be said for pharmaceutical excipients. We cannot be content to guess at their performance. We must apply those means which are today at our disposal to assure ourselves that the excipients we use are unchanging and of the highest quality. We must not be constrained by what was or what is but we must plan for what must be.

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