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COMPENDIAL STANDARDS FOR PHARMACEUTICAL EXCIPIENTS

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While standards for drugs have in the past usually taken precedence over standards for excipients, history has provided numerous unfortunate lessons which have demonstrated the fallacy of this approach. Fortunately, with the separation of excipient standards into their own compendium, the National Formulary, and the long awaited publication of the Handbook of Pharmaceutical Excipients, excipient standardization and characterization has come of age.

The object of this paper is to explain the past role of the compendia in the process of excipient standardization and to present thoughts as to the major problems which must be addressed now and in the future relative to standard setting.

The United States Pharmacopeia and the National Formulary, both before and after their merger, have contained standards for pharmaceutical excipients. These standards, in line with the long tradition of the USP and NF, have been focused on identity, quality and purity as well as packaging and labeling.

Since the inception of the USP in 1820 and the NF in 1888 and up through the major changes in the character of drug standards which occurred during the 1950-1960 decade, standards have been set for excipients on the basis of their use in one or more of the formulas which existed in the compendia. Many of these excipients were substances commonly found in vehicles for extemporaneously compounded prescriptions. Many were of botanical origin including numerous flavors and volatile oils. However, excipient chemicals used primarily in large scale manufacture of pharmaceuticals were mostly overlooked.

In the past 25 years, this policy has changed dramatically. The need for standards for excipients utilized by the pharmaceutical industry was first recognized by the NF in the early 1960's, but soon also became of concern to the USP. This concern has developed into a major thrust since the merger of the USP and NF in 1975.

Upon merger of the two organizations, a decision was made to separate the monographs for excipient

TABLE I

HISTORY OF COMPENDIA STANDARDS

U.S.P. (1810)	N.F. (1888)
Drugs	Drugs
Excipients	Excipients
U.S.P./N.F. (1980)	
U.S.P.	N.F.
Drugs	Excipients

materials and list them under the heading NF (National Formulary). Thus for the first time in 1980, drug substances became USP monographs and excipient substances became NF monographs (Table I). One problem with this separation arose in regards to the listing of substances which were used both as drugs and excipients such as mannitol, methyl cellulose, lanolin, etc. A decision was made to list these items in the USP with a cross reference in the National Formulary. Relocation of some of these items has continued up through the present revision cycle. For instance, lactose was moved from the USP to the NF in 1985, because there is no therapeutic use for this historically important chemical.

A summary of the numerical count of excipients dating back to the 1948-50 revision of the USP and NF

TABLE II

EXCIPIENT MONOGRAPHS

Revision	N.F.	U.S.P.	Total
1950	79	144	223
1975	119	117	236
1980		MERGER	
1985	223	75	328

can be found in Table II. These figures may vary slightly because of the difficulty in differentiating between drugs and excipients in the earlier compendia. As you can see the number stayed somewhat constant in the 25 year period from 1950 to 1975. However, the nature of the excipients changed as many botanical materials were dropped and synthetic or processed chemicals added. Since the merger of the NF and USP the number of new excipients for which monographs have become official is truly remarkable. In spite of some common misconceptions, the new USP XXI-NF XVI contains 328 monographs for substances which are excipients and over 20 have since been added by supplement. In fact today there are no significant excipient substances which are not covered by compendial monographs. In addition, many monographs have been updated and improved including the addition of microbial limits.

There are three questions which one might ask. How are substances selected for Pharmacopeial monographs? Who writes the monographs? What are their strengths and deficiencies?

Suggestions of substances for monographs can come from many sources:

1. Survey of the Pharmaceutical Industry
2. Recommendations by pharmaceutical companies or by suppliers
3. Review of List of Excipients found in NDA's and ANDA's submitted to the Food and Drug Administration
4. Recommendation of USP/NF Revision Committee members

An extensive survey of pharmaceutical manufacturers was conducted in the 1970-75 revision period of the USP and this was followed by additional questionnaires in 1980. These efforts represented the most comprehensive survey of excipient substances which were either widely used or uniquely significant.

Another source of information has been the list of excipients which appear in New Drug Applications or Abbreviated New Drug Applications approved since 1964 by the FDA. A list of some of the most often named substances is found in the Table III. These individual counts are obtained from a total of approximately 7,400 applications approved up through June 1984.

TABLE III

SUBSTANCES APPEARING IN MORE THAN 400 NDA'S AND ANDA'S SINCE 1964

	Count		Count
Acacia	464	Propyl Paraben	456
Benzyl Alcohol	462	Silicon Dixoide	513
Dicalcium Phosphate	439	Sodium Chloride	634
Cellulose, Microcrystalline	1050	Sodium Hydroxide	739
		Starch	2339
Elatin	468	Stearic Acid	996
HCl	536	Sucrose	889
Lactose	2021	Talc	758
Magnesium Stearate	2414	Water	2513
Methyparaben	620		

In spite of the efforts of the past decade, there are still many chemicals used as excipients for which official standards do not exist. However, the extent of use of these is very limited as is illustrated in Tables IV and V.

Who sets priorities for monograph writing? Recommendations for priority in writing standards is made by a Subcommittee of the Revision Committee PH1, Pharmaceutical Ingredients. This committee is composed primarily of pharmaceutical scientists from both academia and industry who are elected every five years. The committee presently includes George Zografi (University of Wisconsin), Zak Chowan (Syntex), Gil Banker (University of Minnesota), Garnet Peck (Purdue Universi-

TABLE IV

NON-COMPENDIA EXCIPIENTS FOUND IN NDA'S/ANDA'S
(1964-1984)

INCIDENCE - >100

Denatured Alcohol
Lakes and Dyes (9)

INCIDENCE - 50-100

Non-Pareil Spheres*
Lakes and Spheres (4)

INCIDENCE - 25-50

Edible Black Ink
Flavors (Many)
Opalux/Opaspray

*Added by Supplement

TABLE V

NON-COMPENDIAL EXCIPIENTS FOUND IN NDA'S/ANDA'S
(1964-1984)

INCIDENCE - 10-25

Calcium Acetate*
Invert Sugar
Potassium Metabisulfite
Flour
Plasticized Hydrocarbon Gel
Trichloroethane
Zein*
Dyes/Lakes

*Added by Supplement

ty), John Fletcher (Union Carbide) and Ralph Shangraw (University of Maryland) as Chairman.

Once identified as a priority, excipients are assigned to one of the committeemen, but the primary responsibility for collecting the information and drafting initial monographs has been assumed by the Committee's Staff Liasion, Mr. Edgar Theimer, who is a Senior Scientific Associate at USP/NF. It is mainly through his efforts that over 100 monographs have been added to the NF since 1980. The primary source of information for the initial draft of a monograph is provided by the supplier or the users of the excipients whom are contacted by the USP staff for input.

During drafting, the Subcommitteeman responsible assists in identifying important issues and comments on draft standards. Efforts are made to settle conflicts between suppliers of the same excipient. Major suppliers are requested to comment on a final draft. After approval by the responsible committeeman, the draft monograph is published in Pharmacopeial Forum.

Finally, after all comments are received, final details are ironed out, the entire committee is required to vote on admission to the Compendia. A favorable vote of two-thirds of the members of the Subcommittee results in a recommendation for official publication, a decision which is ratified by the entire Commitee of Revision.

In most cases, this process goes very smoothly. Occassionally disagreements arise requiring compromise on the part of both suppliers and the committee. Two recent monographs which have given rise to differences in opinion are sugar spheres and zein, but monographs have now been published.

The major issues relative to compendial standards which must be faced in the next decade are listed below:

1. Improvement of standards
2. Addition of functionality standards
3. Mandatory standards for all excipients
4. Standards for
   - flavors
   - fragrances
   - lakes and dyes
5. Standards for components of drug delivery systems
6. Mandatory listing of excipients on drug products

The remaining portion of this paper will deal with these issues.

1. <u>Improved Standards</u>

Although the revision process in the USP/NF is ongoing, there is a need to intensively review a number of major monographs in light of modern technology and

the diversification of materials which sometimes at present fall under a single monograph heading. For instance, the monograph for lactose N.F. covers hydrous, anhydrous, compressible, noncompressible, free flowing and nonflowing forms.

During the past few years, a thorough review of existing monographs has sometimes suffered because:

A. Emphasis was placed on expanding the number of new monographs rather than rewriting old ones

B. Anticipation of publication of the Handbook and a hesitancy to duplicate efforts

These justifications are now behind us and work has started on monograph updates for both lactose and magnesium stearate.

2. Functionality or Performance Standards

Since 1975, the Subcommittee on excipients has wrestled with the question of whether or not functionality and performance standards should be included in N.F. monographs and if so which ones and how. Performance standards include such properties as fluidity, compressibility, lubricability, disintegration properties, viscosity, etc. It is obvious that when many persons speak of lack of compendial standards, they are in fact referring to these types of tests.

The Handbook of Pharmaceutical Excipients has provided some directions for such tests. However, it would not be wise to take all the tests and characterizations in the Handbook and try to make them official. Indeed contributors to the Handbook expressly cautioned about the use of such information. It must also be remembered that all USP specifications must have an appropriate and reproducible test. One can imagine the difficulty in devising such tests for compactability. One of the factors which has limited the development of such compendial performance tests in the past has been the need to set a specific limit or limits. When it comes to performance this in fact may not be wise because there is a wide variability in desirable performance levels within a single chemical substance. A direction which the USP/NF is exploring and which would make more sense is a combination of labeling specification and performance tests. A supplier would have to label, according to monograph requirements, a substance with a specific value for viscosity, moisture, compactability, particle size, etc. and the resulting values for that material would have to fall within a given per cent of the labeled value when this specific compendial test was applied. Such an approach would overcome a major stumbling block which has existed in the past.

As one of the first steps in establishing more relative standards, a Panel has been established to review the area of moisture which includes methods of testing and specifications and monograph-to-monograph uniformity. Another group will be studying particle size and surface area measurements. These groups will need the assistance of the pharmaceutical industry, chemical suppliers and academia if they are to be successful.

3. Compendial Standards for all Excipients

There certainly are many reasons why it would be beneficial to have compendial standards for all excipients. What sense does it make to have standards for identity, purity and quality of drug substances when in fact in preparing dosage forms these substances can be combined with one or more excipients for which no compendial standards exist?

Setting standards for excipients is often a more difficult task than setting standards for drug substances. Excipient materials are usually not developed solely for use in pharmaceuticals. They are often used principally in foods, cosmetics or other industrial products. In many cases their pharmaceutical use provides such a low percentage of their total use volume that there is a resistance to setting the tighter specifications which may be necessary in drug product manufacture.

In addition, excipients are sometimes mixtures of substances obtained by proprietary processes, and their composition may be purposely ill-defined. In many cases, functionality is a result of physical form rather than chemical composition and in other cases, impurities improve functionality.

One of the problems in requiring standards for all excipient substances is the possible detrimental influence on the research and development of new excipient materials. In the case of drug substances, the innovator is motivated to develop standards in order to assure the identity, quality and purity of the drug to be marketed. The same company that initially makes the drug product often also manufactures the drug substance. On the other hand, the developers of excipient materials do not control the use of their products but depend upon the pharmaceutical manufacturer to include them in finished dosage forms. The traditional system wherein the user and not the supplier of excipients often develop the body of knowledge to prove pharmaceutical utility would no longer be practical if standards were required for all excipients before they were marketed. The manufacturer would not use excipients for which there were no standards and there would be no reason to set standards for excipients that were not being used. The establishment of any requirement for standards for all

excipient materials would thus have to allow for an interim period of acceptability for new excipient materials. In addition, the development of standards for excipient materials should probably be synchronized with the submission of a master file to the FDA.

Standardization and characterization of all components in drug products would certainly be an advantage to the public and to the medical and pharmaceutical professions. The pharmaceutical industry would benefit from having at least some specifications on which to base their purchases and to make comparisons between multi-source substances. Finally, legitimate suppliers dedicated to producing high quality pharmaceutical excipients would be assured that less committed companies were not supplying questionable products and thus providing unfair economic competition.

However, compendial standards for all excipients are still a long time away. Resources for standard settings are limited. Drugs will continue to take priority over excipients. Thus it is more likely that a continuing period of voluntary standard setting with clear encouragement to both users and suppliers to assist in the standard setting process. The policy of the Subcommittee PH1 has been to move ahead as rapidly as possible concentrating first on the development of

standards for all excipients used in oral and parenteral products.

4. Standards for Flavors, Perfumes and Colors

One of the ever-changing areas in pharmaceutical excipients is that of flavors, perfumes and colors. As many pharmaceutical products contain one or more of these agents, any decision to set standards for all excipients would obviously have to take into consideration what to do about these classes of materials.

For the most part, inclusion of flavors and fragrances has been a result of tradition. Classically, both the USP and the NF contained many formulations. As it was a requirement that any ingredient in a formulation to have standards, it was necessary to include monographs for many old flavoring agents or perfumes such as anethole, glycyrrhiza, lavendar oil, nutmeg oil, etc. A total of 46 monographs for these materials can be found in NF XVI. In line with present USP/NF policy, almost all formulations have been deleted from the Compendia and recommendations have been made for the deletion of most flavors and fragrances. The justification for this policy is that it is inconsistent to have monographs for a few old flavors and fragrances when there are literally hundreds of others in use today for which no compendial standards exist. To undertake, the development of standards for all flavors and fragrances would be

an impossible task. It seems more logical to leave standard settings in these areas to either the Food Chemical Codex or to the Cosmetic, Toiletries and Fragrances Association. Suitable recognition of such standards could be referenced in the USP/NF.

The question of colors raises a somewhat different issue as the authority for setting standards for these substances has been specifically assigned to the Food and Drug Administration by law. The FDA thus has the responsibility not only for developing standards but in fact for determining what colors can actually be used in food and/or drug products. However, because there are a limited number of these colors which are specifically approved for drug use, it is logical that standards for these materials be recognized at least by a monograph title in the NF. Reference to the availability of the actual tests and specifications in the regulations of the Food and Drug Administration could be handled in the same manner as was the case with antibiotic standards up to recently.

The elimination of monographs for all perfumes and flavors, while at the same time including standards for all FDC and non-certifiable colors not only makes sense but would bring uniformity to a situation which has been inconsistent for over a century.

5. Standards for Components of Drug Delivery Systems

An even greater challenge for the Compendia in the last decade of the 20th century is the establishment of standards for components of drug delivery systems. This includes the polymers used for membranes, platforms, coatings, carriers, etc. If indeed these systems become the dosage forms of tomorrow, then it is essential that the Compendia lead the way in assuring standards of identity, quality and purity. Who is ready to argue that it is less important to have standards for ethylene/vinyl acetate copolymer than it is to have standards for tragancanth? This task is a most formidable one and will require a major commitment of resources and the time of volunteers with expertise that has not been utilized up to this time.

6. Listing of Inactive Ingredients on Drug Product Labels

In the November-December 1986 issue of Pharmacopeial Forum, a recommendation was made to include in the General Notices and Requirements Section of the USP/NF, the following paragraph: "All dosage forms other than parenteral and topical preparations" (labeling of inactive ingredients is already required for these dosage forms).."shall be labeled to state, in alphabetic order by name in a list distinguished

from that of active ingredient(s), the identity of all added substances (inactive ingredients) present therein, including colors, except that flavors or fragrances may be listed by the general term "flavor" or "fragrance". In addition, it is proposed that a section be included in the General Information chapter of the USP/NF which would list the guidelines for voluntary labeling programs proposed by the Proprietary Association and The Pharmaceutical Manufacturer's Association.

Although this proposal seems logical and one whose time has come, the pharmaceutical industry and their professional associations have been uniformly and adamently opposed. It is difficult to understand why in this age of consumers rights, the industry is so shortsighted. Their arguments in general are feeble, self-serving and lack consistency, in light of the fact that parenteral and topical preparations already have such requirements. The U.S.P. has agreed to defer further action until the voluntary programs have been evaluated.

In conclusion, it is fair to say that while much has been done in the last decade to improve compendial standards for pharmaceutical excipients, much still remains to be accomplished. The separation of excipients into a separate compendia - the National Formulary, allows a unique opportunity for the United

States to lead the way in becoming recognized as the world leader in excipient standards, just as the United States Pharmacopeia is recognized internationally as the leader in drug standards.