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"INERT" COMPONENTS OF PHARMACEUTICAL PREPARATIONS*+

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Abstract

A discussion of the role of excipients in pharmaceutical formulation including an analysis of regulatory requirements in the United States and other countries as well as a description of recent efforts to develop concise, accurate and practical compilations of technical information of these substances.

Are the inactive components of dosage forms really inert, either inherently as a consequence of thermodynamic paralysis or on the basis of insignificant effects upon the properties of the dosage form before or after administration to the patient? A variety of interactions can be theorized and a great many have

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been reported. These can occur through chemical or physical interaction with the drug substance or through the creation by one or more inactive substances of a physical, chemical or microbiological environment affecting the stability, safety, or efficacy of the dosage form itself. Examination of this problem is rendered extraordinarily complex by the variety of dosage forms used in modern therapy and by the physiological constraints imposed by the various routes of administration. Additional factors that require consideration include a manufacturing technology that is increasingly controlled by good manufacturing practices regulations and the wide range of physical and chemical properties of the many hundreds of inactive substances currently used in the formulation of pharmaceutical products.

In order to avoid taking sides in a wordy argument on pharmaceutical semantics, I have chosen to go along with Lachman, Lin & Senkowski (1) and accept their convenient definition of an excipient as "any component of a finished dosage form other than the claimed therapeutic ingredient or ingredients". The British Medical Dictionary (2) appears to be romantically old-fashioned when it defines an excipient as "a binding agent enabling powdered drugs to be made into pills". And The Random House Dictionary of the English Language (3) is only slightly less old-fashioned when it defines an excipient as "a pharmacologically inert, adhesive substance, as honey, syrup, or gum arabic used to bind the contents of a pill or a tablet".

In describing excipients collectively by what they are not, that is, active therapeutic agents, we are then in a position to group them according to the function or functions for which they are intended. This structural arrangment sets the stage for supporting the inclusion of a particular excipient in a formulation and stimulates strong interest in the development and application of methods capable of quantitatively measuring functional performance. The possibility of introducing undesirable characteristics into a multicomponent drug delivery system along with

the achievement of one or more desirable objectives is considerable, and prevention demands a high priority on the part of scientists involved in dosage form design.

It is important to remember that scientific formulation requires critical consideration of all the elements that enter into the development of a safe and effective pharmaceutical preparation. The historical record indicates that in spite of an enormous volume of published work, the implication of "inertness" as a dependable characteristic of excipients has relegated the scientific investigation of these essential materials to a secondary level of importance in pharmaceutical research and development. The potential of excipients to affect the biological behavior of dosage forms has finally gained a measure of recognition. Rather general statements warning about the possible effects of excipients on the bioavailability or therapeutic efficacy of dosage forms can be found in the United States Pharmacopeia (USP) (4), National Formulary (NF) (5), British Pharmacopeia (BP) (6) and in the Bioavailability and Bioequivalence Requirements of the US Food and Drug Administration (FDA) (7).

The overall question of appropriate, reasonable regulatory standards and useful, accurate nonofficial compilations of technical data on excipients has not yet become a matter of widespread scientific analysis and debate. However, the subject is showing signs of attracting greater interest, and in this limited review, I will focus on recent efforts in this direction.

Regulatory Requirements for Excipients in the US

A few years ago, the Congress of the United States received a report on Drug Bioequivalence from the Office of Technology Assessment (OTA) (8) which was strongly critical of the excipient standards in the compendia, particularly with respect to nonspecificity of test methods, potential influence on bioavailability, and the absence of many important excipients from the official

requirements. The General Notices of USP XIX and NF XIV contain broad, restrictive statements that require all excipients to be harmless in the amounts used, not to exceed the minimal amounts needed to provide their intended effect, not to impair the bioavailability or therapeutic efficacy of the dosage form, nor to interfere with any of the assays or tests prescribed for determining compliance with compendial standards. However, there are a few more specific limitations elsewhere in the compendia regarding the use of colors or the concentrations of named excipients in certain dosage forms.

A broad spectrum of specific standards can be isolated from the 223 excipients in various sections of the compendia where they are identified as "pharmaceutic ingredients" or "pharmaceutic aids". An additional 37 substances, intended for use in the preparation of individual dosage forms with a stated therapeutic category, are considered to be "pharmaceutic necessities" and are therefore not included as general excipients in this review of compendial standards. In order to obtain the broadest possible view of the scientific basis for these standards, in terms of the selected test methods and overall consistency, the contents of every excipient monograph have been tabulated and characterized in accordance with the tests used to establish conformance with the standards (Table 1). As can be seen from the data in subsequent tables, such an exercise turns out to be as confusing as it is revealing due to the absence of available explanations for choices and variations.

A. Identification tests

Under the heading "Identification", compendial tests are provided to help in verifying the identity of substances taken from a labeled container. The compendia emphasize that, however specific, these tests do not necessarily establish proof of identity, an interpretation of the meaning of "specific" which might

TABLE 1

Characterization of 223 USP and NF Excipients[a]

Test	Number of excipients subject to test	Number of table giving examples
Test for identity	122	2,3
Assay	104	4
Biological and microbiological tests		
aqueous vehicles	6	5
excipients	12	6
Limit tests		
water content	29	7
loss on drying	49	8
chloride		
numerical value specified	19	9
qualitative test	9	9
sulfate		
numerical value specified	15	9
qualitative test	15	9
arsenic	53	10
heavy metals		
numerical value specified	93	9
qualitative test	11	9
ash	13	11
residue on ignition	77	12
non-volatile residue	17	12
solubility and insolubility	23	13
specific impurities not listed above		
numerical value specified	34	14
qualitative test	66	14
non-specific impurities not listed above		
numerical value specified	22	14
qualitative test	10	14
Specified physico-chemical properties	24	15
Tests for characterization of fats, oils and waxes	36	16

[a] includes 121 liquids and gases

puzzle the most liberal of lexicographers. However, all confidence need not vanish since, according to a statement in the General Notices of the USP, other tests and specifications in the monographs often contribute to establishing or confirming identity. A number of critics, including some officials of the FDA, have been unhappy with this philosophy of imprecision and have suggested that the application of newer analytical techniques would contribute much greater assurance of identity than is currently provided by the identification tests for drugs or excipients in the compendia.

From zero to four separate tests may be listed under the "Identification" caption in the monographs for excipients in the compendia. According to the World Health Organization (WHO/PHARM/76.489) (9), the hallmark of reliable tests for identity is specificity, of which ultraviolet and infrared spectrophotometry, thin-layer chromatography, specific color reaction, identification of degradative products and melting point are typical examples. Table 2 shows that the methods used in most of the 224 separate tests applied to 122 excipients for the purpose of identifying them are nonspecific and about 45 percent of the total number of excipients carry no identification requirement as such.

The General Identification Tests are intended to identify only the anionic or cationic portion of a molecule and attempt to do so mostly by the use of a visual endpoint. Just which of the other tests in the monographs represent supportive proof of identity is not made clear, but Table 3 lists a number of tests that might meet this or other objectives.

Earlier criticism of deficiencies in the identification tests for drug substances resulted in a rapid increase in the number of infrared spectroscopic test requirements in the drug monographs in the compendia. Should this analytical technique be adopted for excipients on a larger scale than at present, there would have to be a corresponding increase in the availability of official reference substances for testing excipients.

Table 2

Tests for Identity

Test	Numbers of separate tests (total=224)
Color development or discharge	46
Precipitate formation	45
Odor	10
Infrared	10
Gel formation	9
Botanical	7
Histological	7
Fluorescence	5
Gravimetric	
Twenty other methods applicable to less than 5 excipients	35
General identification tests: sodium[a](12), calcium[b](3), potassium (4) magnesium[d](2), barium (1), acetate[c] (4), chloride[d](4), phosphate[e](1), carbonate (1), salicylate (1), tartrate (1), nitrate (1)	45

[a] precipitate

[b] precipitate and color

[c] color

[d] precipitate and liberation of chlorine

[e] odor

B. Assay methods

The assay or strength of drugs and excipients is usually expressed quantitatively in terms of permissible percentage range, i.e., the content of the sample must be not less than x percent or more than y percent of the theoretically pure substances. The

Table 3

Other Tests for Identity, Purity of Properties

Test	Number of excipients subject to test
Specific (6) or angular (18) rotation	24
Solidification range of fatty acids	6
Infrared spectroscopy	3
Photometric	4
Weight of residue	1
X-ray diffraction	1
Refractive index	15
Temperature: melting (24), congealing (19), distilling (12) and boiling (1)	56
Specific gravity	60
Viscosity	17
Acid base: pH(32), acidity (20), alkalinity (15), reaction (9) and neutrality (1)	77

OTA Report states that reliance on simple approaches to specifications of materials and control of quality persists to this day. The view is expressed that in comparison to modern sources of analytical information, many of the methods used by the compendia for the assay of drug substances and dosage forms are relatively insensitive, inaccurate and nondiscriminating.

In spite of the inclusion of a general discussion of some of the newer techniques in the compendia, KumKumian (10) of the FDA has pointed out that a considerable number of monographs involve the application of such nonspecific assays as titrimetric or gravimetric procedures. If this is the case with drugs, the situation

can hardly be expected to be better with excipients. Table 4 shows the types of analytical methods used for the assay of 104 excipients while the other 119 excipients have no assay requirement.

C. Biological & microbiological tests

The pyrogen test in the monographs for Bacteriostatic Solution of Sodium Chloride and the four types of Water for Injection or Irrigation is the only biological test applied to excipients in the compendia. Table 5 shows which excipients are required to meet microbiological tests for Sterility, Effectiveness of Antimicrobial Preservatives, and Bacteriological Purity.

Of particular and growing importance are the microbiological tests for microorganisms present in excipients. The 12 monographs with such requirements are listed in Table 6.

A critical analysis and discussion of existing and proposed standards for the microbiological purity of oral solid dosage forms by Wallhauser (11) includes data on microbial contamination

Table 4

Assay Methods

Titrimetric	79
Gas chromatography	7
Volumetric	6
Gravimetric	5
Specific rotation	2
Photometric:	
infrared	2
atomic absorption	1
Column chromatography plus gravimetric analysis	1
Gas absorption	1

Table 5

Biological and Microbiological Tests on Waters and Saline Solution

	Pyrogens	Sterility	Antimicrobial effectiveness	Bacteriological purity
Sodium Chloride Injection, Bacteriostatic	+	+	+	—
Water for Injection	+	—	—	—
Water, Sterile, for Injection	+	+	—	—
Water, Sterile, for Irrigation	+	+	—	—
Water, Bacteriostatic, for Injection	+	+	+	—
Water, Purified	—	—	—	+

Table 6

Microbiological Tests on Excipients

Excipient	E. Coli	Salmonellae	Total bacteria: not more than
Acacia	—	+	—
Agar	—	+	—
Alginic Acid	+	+	100/gram
Charcoal, Activated	+	+	—
Cocoa	+	—	5000/gram
Gelatin	+	+	—
Lactose	+	+	100/gram
Pectin	—	+	—
Sodium Alginate	+	+	100/gram
Starch	+	+	—
Starch, Pregelatinized	+	+	—
Sugar, Compressed	+	+	—
Sugar, Confectioner's	+	+	—

levels in tablet excipients and a review of current efforts to establish reasonable and meaningful limits.

D. Limit tests

The inclusion of limit tests in compendial monographs is intended to assure a high level of purity of a drug or excipient and to establish maximum content levels of specific toxic contaminants in some of these materials. Depending upon how precisely the contaminant can be defined, the tolerance is expressed either numerically or as a particular response when tested under specified conditions. The stated tolerances apply only under conditions in which the drug or excipient is customarily employed. However, while it may be possible to roughly estimate such conditions for drugs, an excipient is often used in drug preparations administered in regimens that differ greatly. Confirmation that absolute assurance of purity can not be guaranteed is made clear in the General Notices of the USP that "it is manifestly impossible to include in each monograph a test for every impurity or adulterant that may present". The suggestion is made that suitable additional tests be employed when the source of a material or the process used to manufacture it has been changed. Unfortunately, suppliers of excipients do not always inform pharmaceutical manufacturers of such changes so that additional testing is not undertaken.

The so-called inert excipients are available as gases, liquids and solids which are representative of a wide variety of products or synthetic compounds, and frequently as polymers. The US compendia contain over 220 monographs for excipients that require innumerable tests for impurities of one kind or another. These tests can be separated into those in which a limit is set upon a specific substance or those in which the limit is set upon a composite of nonspecific components. In addition, they can be separated into those with a specified limit stated as a numerical value and those without a stated numerical value. The endpoint of a latter group of tests usually depends upon visual observation of a

physical change such as color, odor, turbidity, effervescence, etc., or the absence of these changes. The precise basis upon which the establishment of a limit is decided is not defined, but it may very well represent a level of impurity that is not generally exceeded in manufacturing the excipient. In principle, the rationale for specifications of known toxic contaminants should be based upon concentration-related experimental or clinical evidence of toxicological effects. Admittedly, such evidence may not always be adequate, but in the absence of reliable data, establishing a wide range of limits for a toxic contaminant without regard for the total amount administered, frequency and duration of administration, rate of accumulation in body organs or tissues, average contaminant level in the food consumption chain, and other factors may provide either a false sense of security or an unnecessary purity requirement. An overall review of limit tests tends to reinforce the impression that modernization of the standard is overdue. However, it is not certain as yet whether modernization of purity tests on "inert" components of pharmaceutical preparations will be considered to be sufficiently important to warrant the necessary investment in time and money.

The following series of tables provide an overall perspective of limit tests which in whole or in part, are an attempt to assure the purity and safety of excipients, the frequency with which such tests are applied, and the range of the limits whithin which compliance is required. Some of the tables are abbreviated because of their length, but the total number of excipients and impurities tested is noted in Table 1.

Table 7: Water content
Table 8: Loss on drying
Table 9: Chloride, sulfate and metals
Table 10: Arsenic
Table 11: Ash
Table 12: Residue on ignition & nonvolatile residue

Table 7

Examples of Limits for Water Content

Substance	Limit water content (%)
Dichlorodifluoromethane	0.001
Acacia	15.0
Lactose[a]	
Anhydrous	1.0
Hydrous	5.5
Hydrates[b]	
Disodium Edetate, Dihydrate	11.7
Cetylpyridinium Chloride, Monohydrate	4.5-5.5[c]

[a]Three excipients resemble lactose in having dual limits

[b]Three excipients are present as hydrates

[c]Range

Table 8

Limit Test for Loss on Drying

Limit (%)	Number of excipients
0.1	1
3.3	1
0.5	6
1.0	8
1.5	1
2.0	3
2.5	1
3.0	1
4.0	3
5.0	8
7.0	1
8.0	1
10.0	2
14.0	2
15.0	5
Range (%)	
0.35 - 1.0	1
5.0 - 8.0	1
11.0 -16.0	1
12.0 -19.0	1
19.0 -23.0	1 (Dihydrate)

Table 9

Limit Tests for Chloride, Sulphate and Metals.[a] The number of excipients for which the test is specified is shown in parentheses.

CHLORIDE	SULPHATE	HEAVY METALS	IRON
Limit in %	Limit in %	Limit in %	Limit in %
0.00005(1)	0.0001(1)	0.0001(1)	0.00002(1)
0.001(1)	0.002(1)	0.0005(11)	0.002(1)
0.0035(1)	0.005(2)	0.001(37)	0.001(1)
0.005(2)	0.006(3)	0.002(12)	0.002(2)
0.007(1)	0.01(3)	0.003(6)	0.005(3)
0.014(3)	0.015(1)	0.004(18)	0.01(1)
0.035(4)	0.2(1)	0.005(8)	0.05(1)
0.05(1)	0.05(1)	No numerical	
0.07(1)	No numerical	limit[b](11)	LEAD
0.1(1)	limit (15)		Limit in %
0.2(2)			0.0005(4)
0.25(1)			0.001(9)
No numerical			SELENIUM
limit(9)			Limit in %
			0.003

[a] See Table 10 for arsenic limit test
[b] Color test

Table 10

Limit Tests for Arsenic

Limit in %	Number of excipients subject to limit	Examples
0.000001	1	Nitric acid
0.00003	1	Cherry Juice
0.00006	1	Dilute Hydrochloric Acid
0.00008	1	Gelatin
0.0001	3	Polysorbate 80
0.00015	5	Providone
0.00025	1	Sorbitol Solution
0.0003	34	Dioctyl Sodium Succinate
0.0004	1	Aluminum Monostearate
0.0008	5	Colloidal Silicon Dioxide
(Range = 800x)		

Table 11

Example of Limits Tests for Ash

Excipient	Total ash	Acid-insoluble ash
Acacia	4.0	0.5
Alginic Acid	4.0	—
Cocoa	—	0.4
Guar Gum	1.5	—
Sodium Alginate	18.0-24.0	—

Table 12

Limit Tests for Residue on Ignition and Nonvolatile Residues. The number of excipients for which the limit is specified is shown in parentheses.

RESIDUE ON IGNITION Limit in %	NONVOLATILE RESIDUES[a] Limit in %
0.0005(1)	0.001(1)
0.002(1)	0.002(2)
0.005(3)	0.0025(3)
0.008(2)	0.004(1)
0.01(5)	0.005(2)
0.05(10)	0.008(1)
0.07(1)	0.015(1)
0.08(1)	0.02(2)
0.1(3)	0.05(2)
0.15(1)	1.7 or 2.0(1)
0.2(5)	9.5(1)
0.25(1)	
0.3(1)	
1.5(2)	
2.0(3)	
3.0(1)	
4.0(1)	
5.0(1)	
Range in %	
0.35-0.55(1)	
15.50-16.20(1)	

[a]Specified for 17 of the 121 USP and NF excipients that are liquids or gases.

Table 13: Solubility & insolubility

Table 14: Specific & non-specific impurities not shown in other tables

E. Properties of excipients

In addition to the more frequently tested properties of excipients shown in Table 3, a number of excipients possess special properties for which tests and specifications are provided. These are shown in Table 15.

The frequency with which certain properties of fats, oils and waxes are tested in order to determine compliance with a standard can be seen in Table 16.

The primary approach to compendial standards for excipients has been, and continues to be, directed towards assurance of identity, purity and strength. Criticism has been directed at test methods, specifications, and even at the unnecessary presence of so many tests for extraneous impurities, which are not easily removed once they are included in a monograph.

Undoubtedly, there is considerable room for improvement in all of these areas, but the main thrust for the immediate future appears to lie in expanding the total number of monographs for excipients to include all those in current use. How else is one to interpret the recent announcement of a plan by the USP to develop monographs for all ingredients that may be incorporated in pharmacopeial dosage forms? The implication made clear in this announcement is that a dosage form will fail to meet USP requirements if it is prepared with any excipient that is not defined in a USP monograph. In formulating such standards, the Revision Committee will have to lean heavily upon the willingness of pharmaceutical manufacturers to release confidential information on their in-house specifications for nonofficial excipients. To be useful, industry standards are necessarily based upon the specific dosage form or forms in which the excipient is required, the drug subs-

Table 13

Examples of Limits Tests Based on Solubility and Insolubility

Impurity	Times specified	Examples of excipients for which the limit is specified[a]
Water soluble substances	2	Cellulose, Powdered (1.5%)
Water soluble acids and alkalies	2	Lanolin (visual)
Water soluble oxidizable substances	1	Lanolin, Anhydrous (color)
Acid-soluble soluble substances	3	Talc (2.0%)
Ether-soluble substances	1	Thimerosal (0.8%)
Alcohol-soluble residue	1	Lactose (0.4%)
Water-insoluble substances	5	Polyvinyl Alcohol (0.1%)
Water-insoluble matter	1	Benzalkonium Chloride (visual)
Insoluble substances	2	Potassium Phosphate Monobasic (0.2%)
Insoluble matter	1	Sodium Acetate (0.05%)
Foreign insoluble matter	1	Agar (1.0%)
Insoluble residue	1	Acacia (1.0%)
Acid-insoluble matter	1	Guar Gum (7.0%)
Alcohol-insoluble matter	1	Sodium Stearate (visual)

[a]Limit in per cent or qualitative test shown in parentheses.

Table 14

Examples of Tests for Specific and Non-specific Impurities not shown in Other Tables

Impurity	Excipient	Detection	
		Limit in %	Qualitative
Specific Impurities			
Fluoride	Calcium Phosphate Dibasic	0.005	
Nitrilotriacetic acid	Edetic Acid	0.3	
Chlorinated compounds	Glycerin	0.003	
Calcium oxide	Mognesium Oxide	1.5	
Acetone and aldehydes	Methyl Alcohol	0.003	
Toluenesulphonamides	Saccharin	0.05	
Thiosulphate	Sodium Metabisulphite	0.05	
Formaldehyde	Tyloxapol	0.0075	
Foreign amines	Benzalkonium Chloride		Odor
Ammonia	Lanolin		Litmus
Barium	Calcium Phosphate Dibasic		Turbidity
Bicarbonate	Sodium Borate		Effervescence
Calcium	Disodium Edetate		Precipitation

Non-specific Impurities			
High-boiling residues	Dichlorodifluoromethane	0.01	
Foreign organic matter	Agar	1.0	
Loss on heating	Simethicone	18.0	
Loss on ignition	Magnesium Oxide	10.0	
Residue on evaporation	Rose Water, Stronger	0.015	
Total solids	Water for Injection	0.001	
UV absorbance	Cetylpyridinium Chloride	3.0	
Organic Impurities	Siliceous Earth, Purified		Color
Oxidizable substances	Water for Injection		Color
Oxidizing substances	Starch		Color
Foreign odor	Chloroform		Odor
Purity test	Caramel		Precipitate
Uncarbonized constituent	Charcoal, Activated		Color

Table 15

Specified Physico-chemical Properties of Excipients

Property	Excipient	Number of excipients subjects to tests
Adsorptive power	Charcoal,Activated	1
Antimicrobial agents	Bacteriostatic Water for Injection	1
Average molecular weight	PEG 300	7
CO_2 absorbency	Soda Lime	2
Cloud point	Tyloxapol	2
Color	Petrolatum	2
Completeness of suspension	Starch,Pregelatinized	1
Consistency	Petrolatum	2
Defoaming activity	Simethicone	1
	Bentonite	1
Gel formation	Bentonite	1
Gel strength	Gelatin	1
Hardness	Soda Lime	2
Moisture absorption	Soda Lime	1
Odor	Nitrogen	2
Rancidity	Peanut Oil	1
Saponification cloud test	White wax	2
Size of granules	Soda Lime	2
Swelling power	Bentonite	1
Water absorption	Agar	1

Table 16

Properties of Fats, Oil and Waxes

Type of Test	Number of Excipients Subject to test
Acid value	16
Acid value of fatty acids	1
Iodine value	23
Iodine value of fatty acids	1
Hydroxyl value	10
Saponification value	21
Ester value	2

tance(s) in the preparation, and the particular process technology used in manufacturing operations. While this pharmacopeial strategy might indeed represent a response to one of the criticisms in the OTA Report, a more critical analysis would certainly reveal a potential for undesirable consequences. Although the step taken by the USP may be in the wrong direction, the positive aspect is that attention is finally being directed towards the correction of long-existing deficiencies associated with standards for the "inert" components of pharmaceutical preparations.

F. The FDA position on excipients in drug products

The FDA position regarding the inclusion of an excipient in a prescription formulation is similar to the notice in the section on Added Substances of the General Notices which states that it is the legal responsibility of the manufacturer to adhere to the requirements of excipient as well as drug monographs. Except in the case of those excipients that are identified as "pharmaceutical necessities", the manufacturer selects the excipients and therefore bears the responsibility for any adverse effects upon the safety or efficacy of the product. For all official drugs and

excipients, relevant, if not totally satisfactory, standards exist and compliance can be determined. For those that are not official, the information submitted in a manufacturer's New Drug Application (NDA) provides an opportunity for the appropriate scientists within the FDA to exercise their judgement concerning the adequacy of the data. Essentially the same criteria have recently been proposed for nonprescription or over-the-counter (OTC) products by the FDA (12). For those excipients that are not listed as pharmaceutic aids in the compendia, the unofficial excipient must be described as performing one or more physical or technical functions from those presented in a descriptive table of 24 such functions. However, before taking any definitive steps, the FDA will await the completion of most of the on-going OTC Drug Review Panel reports, which may possibly include recommendations concerning the safety of any excipient in products reviewed by the panels. Should the overall evidence point to the need for more definitive measures for assuring the suitability and safety of excipients, the FDA might take one of the following steps:

1. Establish a list of safe and suitable excipients that can be used in OTC drug products.
2. Amend OTC drug product monographs to specify the acceptable excipients, or
3. Require the submission of product formulations by manufacturers in advance of marketing so that the FDA can determine if the product complies with the OTC drug product monograph and if it includes only safe and suitable excipients.

Obviously, the exact nature of excipient control measures will remain uncertain until the FDA is ready to move in one of these three possible directions. As long as a period of of uncertainty continues, the potential for distressing symptoms of hyperperistalsis among those responsible for the formulation of OTC products will persist.

Regulatory Requirements for Excipient in the United Kingdom

For multinational pharmaceutical companies, the problem of selecting excipients for products that will be marketed in many countries is compounded by variations in regulatory requirements. The basic concern with safety does not preclude differences of opinion concerning the approval of specific excipients or the standards that must be met as part of a quality control system. The ultimate objective of the European Economic Community is to unify the requirements among the member states. A Council Directive (13) on the testing of proprietary medicinal products states that excipients shall be subject "at least to characterization tests", an obligatory upper limit test for excipients that are subject to rules relating to toxic substances or function as preservatives, and an obligatory assay for those excipients liable to affect physiological functions. "Characterization" and "liable" are weak reeds on which to build clear-cut standards, but there is nothing weak about an additional statement in the Directive to the effect that "any excipient which has not previously been used in the pharmaceutical field shall be treated as an active ingredient". The mere economics of studying a potential excipient in the same manner as is required of a drug should effectively reduce the introduction of new excipients to a crawl. It should be noted that the Directive does not appear to excempt substances used in foodstuffs that have not as yet found applications in orally administered pharmaceuticals.

In the current revisions of the BP and the British Pharmaceutical Codex (BPC) (14), reference is made to applicable standards in monographs of the European Pharmacopeia (15) for some of the official excipients. The definitions of "added substances" in the BP and BPC are similar to those in the USP and NF, except for the application of the words "innocuous" and "inert" to the influence of added substances upon the therapeutic efficacy of preparations into which they are incorporated. The addition of

coloring and flavoring agents is not permitted unless specifically indicated.

Many of the monographs in the BP list excipients (appropriate pharmaceutical adjuvants) only as ingredients of stated dosage forms without identifying a function for the excipient. More precisely then, these substances belong in the category of pharmaceutical necessities that are essential for the formulation of listed preparations and therefore they should not be considered to be officially approved for use as general excipients. These same excipients, and many others, are described in much greater detail in the BPC, together with the functions that they are intended to perform. In analyzing the current status and standards for excipients in the UK, both volumes must therefore be considered.

In discussing the influence of ingredients, other than drugs, that are presumed to be pharmacologically inactive, the BPC lists such effects as the enhancement or retardation of the rate of dissolution of a drug by certain fillers in tablets; the direct alteration of the rate of absorption of a drug by a surface-active agent, and the modification of the rate of release of a drug from a preparation applied to the skin. Not only must the formulator stand watch over the behavior of excipients, but he is also warned that manufacturing processes are capable of exerting important and not necessarily beneficial effects upon the properties of formulated products.

By including only those added substances for which a function is stated in the BP or BPC, approximately 130 monographs can be identified as general excipients. Almost two-thirds of these are also officially recognized by the US compendia. As is the case in the US volumes, the analytical methods used for determining the identity of excipients in the British compendia are primarily the simple, visual observation methods, while assay methods, when stated as such, are almost exclusively titrimetric.

Comparison of permissible limits of foreign substances in the two countries provides an interesting measure of the judgement exercised in the establishment of specifications for toxic substances. In 29 of the excipient monographs, the British compendia set a limit on arsenic ranging from 0.0001 to 0.0005 percent. Sixteen monographs for the same excipients are official in the US compendia, and Table 17 shows the differences in the permissible limit for arsenic. An additional number of excipients in the British compendia are not required to meet an arsenic limit test, whereas the same substances in the US compendia must do so.

Almost half of the monographs for excipients in the US compendia include a limit test for heavy metals, a test which is not applied to excipients in the British compendia. However, about 20 percent of the monographs for excipients in the BP and BPC and 7 percent of those in the USP and NF include a limit test

Table 17

Arsenic limit tests: comparison of British and US specifications

Excipient	BP/BPC Limit in %	USP/NF Limit in %
Methylcellulose (4 types)	0.0001	0.0003
Cellulose, Microcrystalline	0.0002	No limit test
Charcoal	0.0002	No limit test
Povidone	0.0002	0.00015
Sorbic Acid	0.0002	No limit test
Gelatin	0.0002	0.00008
Glycerol	0.0002	0.00015
Saccharin	0.0002	No limit test
Alginic Acid	0.0003	0.0003
Polysorbate 80	0.0003	0.0001
Sodium Alginate	0.0003	0.00015
Sorbitan Monooleate	0.0003	No limit test
Caramel	0.0005	No limit test

for lead. For the four excipients in which the test is a requirement in both countries, the limits are identical.

Regulatory Requirements for Excipients in Other Countries

A comparison of regulatory requirements for excipients in several other countries may be useful in providing a broader perspective of the problems involved in establishing consistent and meaningful standards for these essential components of pharmaceutical preparations. The following brief summaries are intended only for this limited purpose and should not be considered to be complete or definitive:

A. Switzerland

The current revision of the Swiss Pharmacopeia (16) contains about 130 monographs for excipients as well as advisory information on appropriate concentrations of antioxidants and antimicrobial preservatives. For oral preparations, substances described in the Swiss Manual of Foodstuffs would generally be acceptable. The Intercantonal Control Office in Bern may also grant approval for other excipients upon the submission of adequate supporting data.

B. Sweden

There are no lists of approved pharmaceutical excipients in Sweden, but common food additives and excipients with monographs in major pharmacopeias are generally acceptable. Information concerning specific aspects of safety and full descriptions of quality standards for new excipients must be submitted for review and subsequent approval. In submitting new drug applications, quality control specifications for all ingredients are an essential part of the application.

C. Japan

The Japanese Ministry of Health and Welfare exerts a rather firm control over the use of excipients in pharmaceutical prepara-

tions. Only those excipients that are listed in the current revision of the Japanese Pharmacopeia (17) are acceptable, provided of course that they are used in appropriate dosage forms. Aside from certain restricted items requiring special approval, excipients listed in the Japanese Food Additives Codex (18) are acceptable for orally administered pharmaceuticals while those included in the Japanese Standards of Cosmetic Ingredients are acceptable for use in dermatological preparations. In all cases, what is "acceptable" to the Ministry are the standards; i.e., test methods and specifications described in the above compendia, and therefore do not have to be included in the applications submitted for approval. There are over 160 monographs for excipients in the Japanese Pharmacopeia, the majority of which are also described as monographs in the US compendia.

Of unique interest in connection with nonprescription products is a list of excipients for anticold preparations issued on October 2, 1970 by the Ministry of Health and Welfare in connection with approval procedures for the licensing of such medications. The function of each excipient is stated and monographs for almost 80 percent of the 94 excipients can be found in the revisions of the Japanese Pharmacopeia and Food Additives Codex official at that time.

The Japanese regulations require that new excipients be treated in the same manner as new drugs, so that data must be submitted on the origin, physical and chemical properties, stability, acute and chronic toxicity in animals, etc. However, once an application for a new excipient has been approved by the Ministry, other manufacturers may use the same material for drugs intended for administration by the same route.

Although the licensing requirements of the Ministry provide a mechanism for the regulatory control of excipients, variations in standards and acceptability between countries represent a barrier to a freer movement of pharmaceutical preparations across

national boundaries. In that respect, international standards would represent a step forward, without however eliminating the problems involved in the possibilities for interactions between excipients and specific drug substances.

D. Australia

In August 1973 and September 1975, the National Biological Standards Laboratory in Canberra released lists of excipients approved for use as coloring agents, as solvents or additives for use in parenteral products, and as additives in oral preparations. I have been informed that these lists identified as Proposed Standards, have been withdrawn since they could be construed as automatically implying the permission to use these excipients in the stated dosage forms. The BP and BPC are recognized as official books of standards in Australia and where specific references to the European Pharmacopeia are made in the BP, such standards are also obligatory. For those excipients not so standardized, complete control procedures to be implemented by the pharmaceutical manufacturer must be described in the registration documents of new products.

E. Belgium

The Belgian Pharmacopeia (19) lists approximately 90 substances which fit a broad definition of excipients; i.e., raw materials included in formulations of pharmaceutical preparations which are not generally used as therapeutic agents. Most of the listed excipients are also official in the US compendia and represent a large number of essential oils, antimicrobial agents, antioxidants, and pharmaceutic aids of importance in the processing of tablets and semisolid preparations. Monographs in the Belgian Pharmacopeia do not distinguish between excipients and active drug substances.

A legal requirement for excipients which are not included as monographs in the Belgian Pharmacopeia is that their use in phar-

maceutical preparations is permitted provided that they meet the standards of monographs in a sequential list of other national or international pharmacopeias. In case an excipient is not described in any of the named pharmacopeias, the manufacturer must prepare and submit a monograph to the registration authorities and wait for approval before marketing the product. When a newly developed and marketed excipient is used, the submission of data on safety must be included with the registration documents for review by the "Commission des Medicaments".

F. France

The French Pharmacopeia IX (20) does not distinguish between active ingredients and excipients. The only statement concerning the latter appears in the Preface in the form of a requirement that pharmaceutical manufacturers must comply with all the standards in every monograph. Approximately 100 of the substances in these monographs can be considered to be excipients with almost 90 also official in the current revisions of the US compendia. Seven other monographs describe substances which can be treated as excipients or active ingredients depending upon specific use and concentration.

Since the 9th Edition was published in loose-leaf form and is not represented as complete, all monographs appearing in previous editions of the French Pharmacopeia retain their official character. A total of 14 excipients in the French Pharmacopeia VIII (1965) do not appear in the current revision and should therefore be added to the official list. In the light of present knowledge of drug activity, distinguishing between excipients and active ingredients in the French Pharmacopeia VII (1949) is more difficult, especially with respect to the large number of natural products in various forms. Nevertheless, until the 9th Edition is formally declared to be complete, compliance with the monographs in the previous editions is compulsory.

For all excipients which are not described in monographs in the French Pharmacopeia, an AnalyticalDossier must be established

by an official expert (Expert agrée) who has been instructed to use monographs for such substances in foreign pharmacopeias as a basis for judgement in addition to any additional data obtained from manufacturers of excipients. Also available to formulators of pharmaceutical preparations are lists of colorants, preservatives, flavors and sweeteners. These materials tend to be those acceptable to the European Economic Community (EEC) and are understandably in a state of flux at the moment. In France, there does not appear to be an equivalent to the GRAS (Generally Regarded as Safe) list used in the USA.

G. Italy

There is no complete list of approved excipients in Italy, but, with certain exceptions, substances which are nontoxic and do not alter the pharmacological properties of the drug substance qualify as excipients. However, in the absence of official monographs in the Italian Pharmacopeia (21) or in the current volumes of the European Pharmacopeia, the results of chronic toxicity studies carried out on three animal species must be submitted to the Ministry of Health.

Certain restrictions are imposed upon the use of specific excipients based upon their intended function in a pharmaceutical preparation. Permissible concentration ranges for antioxidants in hydrophilic or hydrophobic products include such excipients as ascobic acid, ascorbic acid esters, sodium bisulfite, gallic acid esters, and tocopherols. Antimicrobial agents, e.g., benzalkonium chloride, chlorobutanol, benzyl alcohol, etc., carry similar concentration restrictions or are limited in use to particular dosage forms. Other specific limitations prohibit the use of ethyl urethane as a solubilizing agent; of hexachlorophene in pediatric preparations, or of boric acid and its salts in topical preparations which are applied to inflammatory or traumatized skin or to any mucous membranes. These restrictions tend to emphasize the

necessity for a more critical approach to the use of excipients with respect to acceptable concentration levels and route of administration.

The Swiss Excipient Catalog (22)

Pharmacopeial monographs for excipients primarily describe tests and specifications for identity, purity and assay. With few exceptions they are generally lacking in tests for many physical properties of considerable importance to dosage form process technology and in tests for functional efficiency; for example, particle size distribution, density, flow rate, lubricity, sorption or adsorption. Advances in the technical design of tablet presses resulting in significant increases in production rate and the rapid development of direct compression formulations have led to the introduction of new excipients, many of which are not as yet official in pharmacopeias.

Almost 15 years ago, a suggestion was made by a Swiss pharmaceutical educator that a Codex of Auxiliary Substances not described in pharmacopeias would be of great value. In conservative Switzerland, ideas bear fruit slowly, but by 1972 the major Swiss pharmaceutical companies, as part of their Interpharma arrangement, were ready to initiate a collaborative project leading to the publication two years later of an excipient catalog, the Katalog Pharmazeutische Hilfsstoffe, (Catalog of Pharmaceutical Additives). This loose-leaf book contains monographs for 96 excipients or suitable groups of excipients with general descriptive information, names of suppliers, technical data for various properties obtained from the literature or measured in the laboratories of the collaborating companies, and the intended functional role and average concentration of each of the excipients in pharmaceutical dosage forms.

The selection of the excipients for the Swiss catalog and some of the information included in the monographs was to a large extent

based upon the needs of these large, international, collaborating companies and the documentation available from suppliers. Well over half of the monographs are for excipients official in the U.S. or British compendia. Detailed descriptions of the methods used by the laboratories for the determination of density (solids), poured and consolidated bulk volume, particle size distribution, moisture sorption isotherms, and moisture content are included, as are 57 electron-scanning photomicrographs of 26 excipients taken at different magnifications. A comparison of the type of information in the monographs for povidone in the USP and the Swiss Excipient Catalog is shown in Table 18.

Table 18

Monographs on Povidone (PVP): Comparison of USP and Swiss Excipient Catalogue

Specified Information	USP	Swiss Excipient Catalogue
Category (function)	+	+
Description	+	+
Solubility	+	+
Preparation or composition	+	+
Packaging and storage	+	—
Identification	+	—
pH	+	+
Water content	+	+
Residue on ignition	+	—
Limit tests:		
arsenic	+	—
lead	+	—
aldehydes	+	—
vinylpyrrolidone	+	—
Suppliers	—	+
Density	—	+

(continued...)

For some time now, experienced formulators have recognized the important relationship between the properties of excipients and the quality of dosage forms. The more highly developed preformulation programs in industrial pharmacy research include experimental studies intended to clarify the effect of excipients on stability, process technology, and bioavailability. The diffuse

Table 18 (continued)

Specified Information	USP	Swiss Excipient Catalogue
Pour volume	—	+
Tap volume	—	+
Viscosity of different molecular weights in water and ethanol	—	+
Hygroscopicity	—	+
Sorption isotherm	—	+
Softening point	—	+
K-value (average molecular weight)	—	+
Incompatibilities	—	+
Stability	—	+
Standards in pharmacopeias	—	+
Technological application: granulating direct compression coating liquid and semisolid preparations sterile preparations cosmetics	—	+
Comments: standardization of solutions timed release preparations disintegrant properties of crosslinked PVP	—	+

[a] + means information specified.

—means information not specified.

nature of public information on excipients and the variability and inadequacy of a large portion of the technical data provided by suppliers has always been and remains a problem to those industrial and academic pharmaceutical scientists concerned with the attainment of the highest level of dosage form quality. The collaborative efforts of a relatively small group of individuals in the successful preparation and publication of the Swiss excipient catalog deserves commendation and we hope we will serve as a precedent for similar projects that are beneficial to the advancement of the pharmaceutical sciences.

The USA/UK Excipient Project

In consideration of the possibility of publishing a similar type of compilation in English, contact was established with British academic and industrial pharmacists and it was agreed that in addition to satisfying the formulation requirements and practices existing in the United States and the United Kingdom, the proposed text must also reflect the views and needs of a very large, broad-based pharmaceutical industry and the educational and research programs of about 80 schools of pharmacy in both countries.

In April 1976 the US Academy of Pharmaceutical Sciences established a program tentatively designated as the Codex of Pharmaceutical Excipients Project and assigned the organization and implementation to its Industrial Pharmaceutical Technology Section. Shortly thereafter, the Council of the Pharmaceutical Society of Great Britain approved the request of its Industrial Practices Sub-Committee to collaborate with the Academy in the preparation of the codex.

In recognition of the complexity of this project, strong efforts were made to assemble a committee composed of pharmaceutical scientists with extensive experience in basic pharmaceutics, process technology and quality control. Scientific direction of the project in the US is the responsibility of an 18-member commit-

tee representing five schools of pharmacy and nine pharmaceutical companies. Additional specialized technical support is available from 12 Corresponding Members based in three schools of pharmacy in Australia, Belgium and Switzerland, eight pharmaceutical companies in England, Italy, Japan, France, Sweden, Pakistan and Switzerland, and one governmental agency in Canada.

Next, the monograph committee was organized and given the responsibility for the acquisition of all available technical information on excipients, a task requiring a vast amount of documentary research and compilation. The preparation of monographs in accordance with a specified format has been assigned to members on an individual basis. There are now 91 pharmaceutical scientists with a wealth of experience in all areas of pharmacy research and development, analytical and physical chemistry, production technology, and quality control, who serve as members of the monograph committee. Eighteen schools of pharmacy are represented by 26 members, 37 pharmaceutical companies by 62 members and governmental research by 2 members. An additional scientist represents a Canadian pharmaceutical company as a corresponding member.

The distribution of an initial list of excipients for development into monograph form by members of the Monograph Committee has been completed. The basis for inclusion on this list was either the relative frequency of use of particular excipients, with due consideration for the diversity of dosage forms, or the possession by an excipient of a property of special significance to the processing or final quality of a dosage form. In addition to opinion surveys of committee members, the availability of an FDA computer print-out covering the frequency of use of all excipients, exclusive of colors, flavors, and perfumes, in about 6,600 marketed drug products in 160 dosage forms proved to be most helpful. Analysis of the information obtained from all sources led to the initial selection of 88 excipients, or, where applicable, groups of excipients suitable for combining into a single monograph.

Omitted from the list, at least for the time being, are colors, flavors, pharmaceutical necessities: that is, substances specifically required for the preparation of formulations official in the compendia, complete formulations listed as Pharmaceutic Aids in the compendia, and well-defined chemicals used only in solution form. A special effort was made to include excipients whose physical properties when used in dosage forms are of particular importance to processing technology or to the quality of the finished product.

The majority of the members of the Steering Committee preferred to omit monographs for individual colors or flavors, primarily because of the certification requirements for colors and the complexity of many flavor compositions, which is further complicated by master file arrangements. However, an attempt will be made to prepare concise, informative sections on colors and flavors with emphasis upon the effects of these materials on the quality of dosage forms or upon the technology involved in their preparation.

The formal organization of the UK group is continuing under the direction of Robert F. Weir, Chairman of the Pharmaceutical Excipients Project; John E. Rees, scientific coordinator; and John H. Bell, administrative coordinator. In June 1977, an initial meeting on the topic in London included a series of brief presentations on specific excipients, as well as a review and discussion of the project objectives and plans. A survey of excipients in current use in the United Kingdom and opinion surveys similar to those conducted in the US will provide a basis for supplementing the initial list of excipients proposed for development into monographs.

Conclusion

The administration of drug substances without the simultaneous presence of one or more excipients is extremely rare, with the average number of excipients present in a dosage form reflecting the physiological requirements of the route of administration

and the technological necessities of the manufacturing process. When excipients are considered with reference to dosage forms as solids, semisolids, or liquids, or even as injections, solutions or suspensions, oversimplification can be dangerous. The FDA computer print-out of excipients lists 30 single or multiple routes of administration under the dosage form heading, "Injections". The risk involved in a poor choice of excipient for an intrathecal injection can be serious, but the chemical, physical, and microbiological properties of excipients selected for ophthalmic, nasal or otic drops are also of concern to the formulator. Even in the testing of new drugs in animals, experience has shown that good experimental design must take into consideration the possible effects of excipients as components of the administered dose.

Although the tendency to consider excipients as inert is slowly diminishing, efforts to formalize the role of these important constituents of pharmaceutical preparations could founder in a swamp of oversimplification. Recent evidence tends to indicate an effort to clarify the functional role or roles of an excipient and to require clear-cut definitions of such roles in the submission of documents to government agencies. The current revisions of the US compendia use 55 words or phrases to define the functions of official excipients. By combining some functions into compatible groups, the FDA arrived at 24 functional categories of inactive ingredients. To achieve greater specificity, an increase in the number of functional categories would result and may actually prove to be a superior alternative.

Up to the present time, efforts by the compendia to establish tests and specifications for functionality in areas where they would be most useful have been unsuccessful. Not only do some excipients have multiple listed functions, but the same excipients can be used in several types of dosage forms in which the effect of a particular property can be favorable or unfavorable, irrespective of the function of the excipient. The inclusion of a monograph for an excipient in a pharmacopeia does not assure its

functional suitability in formulations containing different drug substances or other excipients that vary from product to product. My own analysis of the present standards for excipients in the compendia clearly demonstrates that almost exclusive consideration is given to identity, purity, and strength. Although there is considerable room for improvement along these lines, such standards continue to be of vital importance and expansion of the number of excipients with monographs in the compendia would be a constructive step. The projected Codex of Pharmaceutical Excipients, free from the legalistic constraints imposed upon a pharmacopeia, would appear to be a more appropriate vehicle for technical information covering a wide variety of other properties and experiences with excipients.

The Codex project is unique for several reasons. First, it is an open project with clearly stated objectives, depending upon the cooperation of a large number of volunteers who are convinced that its publication will be of great practical value to formulators, technologists, analysts, and educators. Offers of cooperation have been received from the USP, FDA, United States Adopted Names Council, and other organizations directly or peripherally interested. Second, the scope of the project is broader than just nationwide and has already enlisted the cooperation of eminent scientists from a number of countries not officially involved in its implementation. Third, the collective focus on excipients by almost 200 pharmaceutical scientists is bound to improve the working relationship between the suppliers and users of these materials through a better understanding of their mutual responsibility to the public health. Finally, the Codex will have no legal status and the choice of any listed excipient with respect to the safety, efficiency and stability of a drug product in which it is included would remain the complete responsibility of the formulator and his scientific colleagues. This combination of freedom from traditional or formal constraints and proper recognition of responsibility in a complex, multidisciplinary area of the pharmaceutical

sciences is unusual enough for a cautious optimist to anticipate a reasonably successful outcome.

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