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OVERVIEW OF COMPENDIAL STANDARDS FOR SOLID ORAL DOSAGE FORMS

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ABSTRACT

Compendial standards define acceptable articles at the time of use, in contrast to process control and product release strategies. The establishment of drug names and the setting of requirements for identity, strength, quality, purity, packaging, storage, and labeling are addressed by compendial standards. Because the solid oral dosage forms of drugs are used most frequently in drug therapy, it is crucial to examine how the attributes of these forms affect the development of quality standards. Compendial selections of tests for identity, dose uniformity, dissolution/disintegration, and limits and of assays to confirm content are surveyed in this article. Also discussed are the packaging and storage standards established by the compendia and the relationships between drug names and labeling requirements.

INTRODUCTION

Pharmacopeias arose out of physician-pharmacist-patient interfaces and strove to define identity, strength, quality, and purity, as well as packaging and labeling standards for drugs. When medicinal materials are described accurately, all participants benefit. To achieve its goals, a pharmacopeia must address many different issues of drug product quality that can impact on the efficient use of drugs.

It is the dosage form of a drug that is prescribed, dispensed, and taken. A pharmacopeia must develop tests and specifications for substances in dosage forms that will be meaningful to pharmacists and physicians and appropriate for the realities of drug product manufacture, storage, and distribution. Most drug therapy uses solid oral dosage forms because of their convenience, portability, stability, elegance, and patient acceptability. This article examines the attributes of solid oral dosage forms that are important from a compendial point of view and discusses the aims and means of standards for these attributes.

COMPENDIAL STANDARDS

Names and Labeling

A principal of compendial thought is that the same thing should have the same name everywhere and that different things have different names. Articles that are not interchangeable in patient therapy are thus different and require different names. Thus, the United States Pharmacopeia recognizes separate

articles for Aspirin, Aspirin Capsules, Aspirin Tablets, Aspirin Delayed-release Tablets (Enteric-coated), and Aspirin Extended-release Tablets, even though laboratory testing procedures may be the same for most quality attributes. Other examples of dosage-form names selected to emphasize the non-interchangeability of closely related articles are Extended Phenytoin Sodium Capsules and Prompt Phenytoin Sodium Capsules. Moreover, the USP requires the label on the "Prompt" capsules to state "Not for once-a-day dosing" because of the potential hazard of toxic serum concentration of phenytoin.

Recognition of separable dosage forms, however, does not extend to soft-gelatin as against hard-gelatin capsules. Some experts believe that earlier distinctions are no longer valid because both kinds of capsules are filled with either liquid or solid contents and both can be made sufficiently tamper resistant. The USP lists "Capsules" as a single item, with further differentiation limited to drug release patterns.

Early in 1988, the USP Subcommittee on Biopharmaceutics proposed labeling requirements to meet the complex challenges presented by Theophylline Extended-release Tablets, Phenylpropanolamine Hydrochloride Extended-release Capsules and Tablets, Co-triamterzide in varying combinations, and Nitroglycerin Transdermal System. Graphic or tabular representation of plasma-level profile and drug-release characteristics would appear in the labeling of these articles. These proposals corresponded to the Case Three drug-release policy that was adopted in our previous revision cycle but was resisted early on. The soundness of this approach is now more

widely evident. Case Three is a reasonable response wherever multiple formulation concepts have been brought to bear on any one problem in drug administration. In this way, diverse but, for practical purposes, interchangeable (or partially so) articles can bear a single compendial name. This is an important feature relative to cost reimbursement by U.S. third-party payers or by cost-conscious consumers.

Identity

Monographs for oral solids always have identity test requirements to establish that the active ingredient, or active moiety, claimed on the label is indeed present.

Most of these monographs refer back to the identifications under the drug substance monographs. Seldom is there a planned identification of inactive counterions for dosage forms in contrast to drug substance testing.

The objective of compendial identity testing is not to assert that one molecule out of all ever published is present, much less to produce a proof of structure. Only one burden must be met: confirmation of the presence of an already claimed component. It is not surprising, therefore, that infrared spectrophotometry is the main testing approach, often coupled with chromatography for added assurance among related drugs having the same functional groups. Optical rotations, arguably either identity or quality tests, are not repeated in dosage-form monographs except in rare circumstances (for example, Epinephrine Injection). Some color tests for

identity remain but usually are dropped at times of other monograph revisions.

Colors, sizes, and shapes of solid forms have obvious recognition values. Manufacturers strive to present elegant, distinctive products. Pharmacopeias differ in approaching these issues. USP believes these are not issues in drug product performance and, therefore, does not promulgate standards for color, shape, and size. However, in 1988 USP's sister-publication, USP DI, published a "Medicine Chart" of approximately 800 color photographs of the most widely used drugs in capsule and tablet forms (in Drug Information for the Health Care Professional, Vol. IB, and Advice for the Patient, Vol. II).

Dose Uniformity

Pharmacopeial standards for more than a generation have included limits on the weight variation allowed among solid oral dosage forms. In 1970 USP began requiring, with a few drugs, the chemical determination of individual dosage unit content because it was discovered that blending did not always achieve homogeneous dispersion of drugs among excipients, particularly where the ratio of drug to excipient was low. The determination of dosage-form uniformity by assay of individual units is preferred by USP and is now widespread. Determination of dosage-form uniformity by weight variation is applied only for qualified preparations, e.g., liquid-filled soft capsules and solids prepared from true solutions and freeze-dried. Preference is given to analytical methods that can be automated

because of the large testing loads arising from these requirements. Specificity is of no interest here.

As a result of the decision rules adopted by USP, between-unit variation must decrease to pass a test as the average lot assay departs from 100%. This is exactly the intent of USP--maintaining standards for uniformity of dosage units ensures that a patient has a low probability of receiving a dosage unit that varies by as much as 25% from the labeled article strength. To accomplish this, a statistically informed plan called "narrow gauging" is used to reach conclusions on a manageable number of individual chemical determinations. In addition, a "variance attribute" feature is used along with narrow gauging to produce the desired results.

Nonconformance to dose uniformity standards continues to result in occasional recalls of drug products. Thus it is obvious why these standards have long been recognized as important to process control and validation.

Dissolution/Disintegration

Solid oral dosage forms offer convenience, portability, coverage of bad tastes, stability associated with dryness, and precision of dosage relative to dose-response curves. But these advantages come at a price. The steps taken to achieve product elegance and low friability act against prompt release of active ingredients after a patient swallows a drug.

Coatings, whether for elegance or enhanced stability, consistently prevent reliable drug release. Shellac is the single worst coating from

this perspective and is used in hundreds of "sugar-coated" tablets. Such tablets have been prominent among the relatively few clinically significant problems in bioavailability or bioinequivalence.

Low aqueous solubility of an active ingredient is the most obvious parameter likely to eventuate in slow drug release and is well documented in studies in the literature. Yet, there have been many successful formulations of these drugs through careful reduction and control of particle size, or by including wetting agents in the units or by adding carrier excipients to facilitate dispersion.

Magnesium Stearate is the most common lubricant for both tablets and capsules. Both low- and high-speed tableting or capsuling operations use lubricants. Only small amounts ($\leq$0.5% for tablets) are needed. Also, long blending times increase the preparation of coverage of powders or granulations. No single ingredient is responsible for as much of the bioinequivalence literature, that is, of actual rather than virtual (political and economic-motivated) problems. Failure to formulate an efficient disintegration property into products is also a problem of solid oral dosage forms worldwide.

One cuts through the fog surrounding bioavailability/bioinequivalence by looking at cause-and-effect relationships. The factors discussed above account for almost all of the documented cases of clinically significant problems for tablets and capsules. Each of those causes is demonstrated reliably by low-agitation dissolution tests in water. As an aside, testing the

disintegration rate of tablets and capsules within 10 minutes without using disks to pound away at the product mass usually suffices in most cases and may be considered in Third World countries where dissolution testing is not practical on a routine basis.

So USP now (1988) includes 466 dissolution requirements and 132 disintegration requirements for 615 monographs on ordinary tablets and capsules. Dissolution has become a regular feature of compendial monographs. This is not to say that problems do not exist. International commerce and local manufacture in some nations have not gotten on top of this aspect of drug product quality.

"Delayed-release" is a separate, valid formulation objective. New polymeric coatings can give highly reliable delayed release, most significantly as enteric coatings that take advantage of pH profile for dissolution. USP now has separate monographs for four such articles.

Polymer science largely underlies the resurgence of technical interest in extended-release oral solids. A minority of drugs have characteristics suitable for such formulations (i.e., not long biological lives, not metabolized to inactive forms by intestine or liver, not too large a dose, etc.), but formulations from the technical side have been successful. Problems of food interaction, intestinal transit times, and pH dependencies confound the clinical value of these otherwise admirable formulations. USP has adopted 18 such monographs to date, with more under study. As discussed under the "Names and Labeling" section, a three-pronged policy allows the construction of monographs for

multiple-source (multiple-formulation) articles as well as for the straightforward single-source items.

Packaging and Storage

Packaging and storage standards established by the compendia apply throughout the shelf life of recognized articles. Almost no solid oral dosage form is impervious to environmental stress. Chemical decomposition by hydrolytic mechanisms is the usual first effect to be generally recognized. Less well appreciated is the severe loss in the dissolution-deaggregation-disintegration aspect that has been documented to be clearly significant. The problem is a mismatch of formulation with the moisture-barrier qualities of packaging material, which affects safe drug storage even in temperate climates.

All advanced countries have stability/expiry requirements that relate to the dosage form in the original, unopened manufacturer's package. But many drugs in both developed and developing nations are repackaged. Further effort on the part of all pharmacopeias to set standards for repackaging will immediately benefit drug-consuming populaces worldwide. USP has standards to prescription containers and hospital unit-dose strips and blisters, but does not contemplate widespread distribution or lengthy storage of repackaged pharmaceuticals. My experience is that the importance of this issue is consistently underrated at scientific meetings where drug product quality is discussed. This is nowhere more evident than at biopharmaceutics meetings.

COMPENDIAL ASSAYS AND TESTS

Assay of Content and Rubric

A compendial dosage-form monograph specifies the active ingredient used to prepare the final form plus the molecular formula (salt counterion also defined) for added precision of definition. The assay results are calculated in terms of this molecular formula. Allowances must be made for assay variability, both within and between laboratories---between laboratory bias and procedural peculiarities are forestalled by the liberal use of USP Reference Standards in assays. Allowances also should be made for normal variation in manufacture and, in one direction, loss of content during the expiry period. (Note that USP requires the label content as the manufacturing target.) All of these allowances are subsumed into a single assay range of ±10% of the value definition. Because the content of the entire article (i.e., batch rather than individual) is at issue, the compendia instruct that the assays be performed on a composite specimen of several dosage units to exclude dose variation--a separate subject.

Present-day pharmaceutical analysis leans heavily on instrumental methods. The ability of chromatography simultaneously to separate and measure meets the 19th-century structure: to make measurements on purified specimens. So the compendial need to measure drug content separate from excipients and decomposition products is answered by chromatography in most new monographs and, by revision, in many older monographs. USP presently has hundreds of such uses of liquid chromatography

and of gas chromatography. Our policy is that the monograph as a whole is stability-indicating. Many ultraviolet or colorimetric determinations of excipient-free extracts also meet this need.

Compendial selection of analysis methods must keep an eye open to compliance testing so that only those methods are admitted for which reagents, instruments, and materials are widely available and where laboratories may reasonably be expected to know or to learn the methods. Older monographs are a problem because their described methods, albeit chemically correct, are no longer au courant in pharmaceutical analysis centers. The primary barrier to modernizing older monographs some years ago was the unavailability of reference standards that would update methods and terminology. USP saw and removed that barrier to analytical practice in equilibrium with our industry.

Limit Tests

Controversy exists on the issue of repetition of analyses performed on active ingredients or excipients that determine components not likely to increase during manufacture or storage of the final dosage forms. For example, USP's 90 new "Ordinary Impurities" tests, $\leq$2%, for drug substances are not repeated in dosage-form monographs. USP policy is not to do so in recognition of the required retention of samples of all batches of ingredients. Some older monographs retain such limit tests as a result, not of a prior policy, but the lack of one. Where a decomposition product is of significance on the shelf, say salicylic acid in aspirin or open-ring

compounds in thiazides, then a compendial limit is to be expected.

A new type of limit test on total organic volatile impurities has been proposed in USP's bimonthly journal Pharmacopeial Forum. These impurities are measured by headspace gas chromatography, including mass spectrometry as the detection-measurement in one format. The underlying policy is noteworthy. The total of any volatile impurity is what the patient receives, no matter which ingredients or coating processes introduce the impurity. Thus, the limits are expressed as integral values, and corrections are made to maximum labeled dosage. Constraints are proposed for the number of volatiles in any one article. USP has proposed daily limits for the following impurities: ethylene oxide, benzene, methylene chloride, 1,4 dioxane, trichloroethylene, chloroform, and tetrahydrofuran. The analytical system will allow assignment of limits for as many as 20 individual volatile organic impurities. It is the responsibility and prerogative of the manufacture/quality assurance function to examine ingredients and processes so that batches of finished goods need not be rejected because of one separately identifiable and controllable source. In practice, a manufacturer may be able to control a single incoming excipient to ensure final conformance. Alternatively, specific measure of a single coating solvent may be all that is necessary.

As noted under the "Assay" section, the power of chromatography to separate and quantitate bespeaks extensive use in monitoring low levels of non-volatile organic impurities. Several hundred such applications are now official in USP.

Microbial Limits Tests

Microbiological problems are not frequent among tablets and capsules since the ingredients are usually synthetic chemicals or highly refined natural products such as starch and lactose. Also, these dosage forms are dry, which is an unattractive environment for microbial survival or growth. Nevertheless, a number of naturally derived drug substances, because of their source and/or constraints on processing, can carry a microbial load forward into the solid oral dosage form. USP sets microbial limits on tablets and capsules prepared from these drugs: Dehydrocholic Acid, Digitalis, Pancreatin, Pancrelipase, Psyllium Husk, Rauwolfia, Thyroglobulin, and Thyroid. Each of these has a *Salmonella* limit and some also limit *Escherichia coli*. Magaldrate Tablets limit *E. coli*.

Moisture Tests

Many antibiotic solid oral dosage forms have limits on water content in recognition of the hygroscopic character and source of these drugs and their frequent hydrolytic sensitivity.