Pharmacopeial Standards and Specifications for Bulk Drugs and Solid Oral Dosage Forms

Similarities and Differences

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Tests for tablet weight variation, drug content, and disintegration time described in the "United States Pharmacopeia," "The National Formulary," the "British Pharmacopoeia," the "Pharmacopée Française," the "State Pharmacopoeia of the U.S.S.R.," and the "Nordic Pharmacopoea" are compared with regard to methodology, apparatus, scope, and compliance. Similarities and differences characterizing these standards are discussed. Comparable appraisals are made of assays for bulk drugs and compressed tablets included in the United States Pharmacopeia, the National Formulary, the British Pharmacopoeia, and the State Pharmacopoeia of the U.S.S.R. Discrepancies of sufficient magnitude exist between these tests and specifications to warrant closer cooperation among pharmacopeial agencies. Such cooperation should ensure greater uniformity of drug testing, encourage wider drug trade, and promote better public health throughout the world. These objectives are actively pursued by the World Health Organization.

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Received May 15, 1967, from the Research Laboratories, Food and Drug Directorate, Department of National Health and Welfare, Ottawa, Ontario, Canada.
Accepted for publication September 1, 1967.
The authors express their appreciation to Dr. Lloyd C. Miller, the United States Pharmacopeia; Dr. Edward G. Feldmann, the National Formulary, Dr. T. C. Denston, British Pharmacopoeia Commission; Professor M. D. Mashkovsky, Ministry of Health, U.S.S.R., and Dr. Kjeld

PHARMACOPEIAL STANDARDS have been developed in many countries. Realizing their value as mutually acceptable criteria of pharmaceutical quality control and their commercial importance, some countries have come to agree on common standards and specifications. The Nordic Pharmacopoea, official in Denmark, Finland, Iceland, Norway, and Sweden, may be cited as an example, and the European Pharmacopoeia—aiming to encourage and facilitate drug trade between countries of the European Common Market—likewise reflects this trend. Yet a great deal of work remains to be done to establish truly international standards as reference criteria, *i.e.*, standards that can be used conveniently anywhere and mean the same thing to analysts working in their national laboratories throughout different parts of the world.

It is the purpose of this paper to point out

TABLE I—WEIGHT VARIATION TOLERANCES[a]
(USP XVII, NF XII, B.P. 1963)

Av. Wt. of Tablet (mg.) from 20 Determinations			Not More Than Two Tablets Differ from Av. Wt. by More Than	No Tablet Differs from Av. Wt. by More Than
USP XVII	NF XII	B.P. 1963		
	<13[b]		±15%[b]	±30%[b]
<130	13–130	<120	±10%	±20%
130–324	130–324	120–300	±7.5%	±15%
>324	>324	>300	±5%	±10%

[a] Not applicable to sugar-coated, compression-coated, or enteric-coated tablets. [b] Deleted in Second Supplement to NF XII.

TABLE II—WEIGHT VARIATION TOLERANCES[a]
(PHARMACOPÉE FRANÇAISE VIII)

Theoret. Wt. of Tablet, mg.	Tolerance, %
<150	±7.5
>150	±5

[a] Not applicable to coated tablets.

TABLE III—WEIGHT VARIATION TOLERANCES[a]
(STATE PHARMACOPOEIA U.S.S.R. IX)

Av. Wt. of Tablet, mg.	Tolerance from Av. Wt., %
<120	±10
>120	±5

[a] Not applicable to coated tablets.

tablet preparations, and to emphasize the need for greater interpharmacopeial uniformity.

GENERAL STANDARDS APPLICABLE TO SOLID ORAL DOSAGE FORMS

Weight Variation

Pharmacopeial standards and specifications have been established to provide limits for permissible variations in the weights of individual dosage forms, expressed in terms of the allowable deviation from the average weight of a representative sample. Separate procedures and limits are described in most reference compendia for uncoated tablets, capsules, and sterile solids.

United States Pharmacopeia, National Formulary, and British Pharmacopoeia—USP XVII (1), NF XII (2), and B.P. 1963 (3) specify that 20 whole tablets be weighed individually, the average weight calculated, and the variations compared with specifications. Samples meet requirements if weight variations observed are not greater than those shown in Table I.

The British Pharmacopoeia allows performance of this test on 10 tablets also, specifying that in this case not more than *one* tablet may deviate from the average weight by a percentage greater than that shown in the table, and none of the tablets differ from the average by more than double that percentage.

Pharmacopée Française VIII (Codex Médicamentarius Gallicus) (4)—This compendium specifies with specifications. Samples meet the requirements if weight variations observed are not greater than those shown in Table II.

State Pharmacopoeia U.S.S.R. IX (5)—This compendium specifies that 10 tablets be weighed collectively and the average weight calculated. Another 10 tablets are to be weighed individually (each to within 10 mg.) and the variations compared with specifications. Samples meet requirements if weight variations observed are not greater than those shown in Table III.

Pharmacopoea Nordica III (6)—This compendium requires that 100 tablets[1] be weighed collectively (to within 1 mg. if the tablet is lighter than 80 mg. and to within 10 mg. if the tablet is heavier than 80 mg.) and the average weight calculated (to within 0.1 mg. if the tablet is lighter than 80 mg. and to within 1 mg. if the tablet is heavier than 80 mg.). Thirty tablets are selected at random from this sample and weighed individually (to within 0.2 mg. if the tablet is lighter than 80 mg. and to within 1 mg. if the tablet is heavier than 80 mg.). Requirements are met if weight variations determined are in accord with specifications shown in Table IV.

Similarities and Differences—Although the tests described are simple, easily carried out, and serve the same purpose—namely, the establishment of the weight uniformity of uncoated, compressed tablets from a given lot—they differ markedly in both methodology and requirements for compliance.

Methodology—The USP and NF tests are based on the use of a representative sample of 20 tablets weighed collectively and individually. Results based on similar examination of only 10 tablets are accepted by the B.P. The French pharmacopeia also specifies that 10 tablets be taken for the test, while the Russian pharmacopeia requires that 10 tablets be weighed collectively to assess the average weight and another 10 be weighed individually to appraise variations from the average weight. The Nordic pharmacopeia generally calls for the weighing of 100 tablets to compute their average weight and the examination of 30 of these tablets to determine individual variations from the average weight.

Compliance—Tolerances are generally a function of average tablet weight. The greater the average tablet weight, the smaller are the weight variations permitted. Yet, the trend lacks uniformity. While the NF recognized four ranges (one range deleted, see *Footnote b*, Table I) of average tablet weights and specified corresponding tolerances, it

as well as the B.P. and USP, now cover three such classifications. The French and Russian pharmacopeias both designate relevant parameters for only two categories—limiting tablet weights being 150 mg. and 120 mg., respectively. For uncoated compressed tablets weighing 80 mg. or more, the Nordic pharmacopeia, unlike other compendia, avoids step-wise changes in variability with respect to permitted tablet weight by using the formula: $y = 4 + 0.05x$, where y is the tolerance allowed in mg. (90% of sample), and x is the average weight in mg. In general, therefore, different tolerances are assigned to categories which cannot be readily compared, and products meeting the requirements of one national compendium need not necessarily meet those of another.

Scope—Although many products have been tested in the laboratories of the Food and Drug Directorate following the USP, NF, and B.P. procedure, few ever failed to comply. Pharmacopeial tolerances appear generally to be too wide and unappreciative of advances made during recent years in pharmaceutical manufacturing technology. Solid dosage forms of considerably smaller weight variations than those specified as pharmacopeial standards are produced with modern tableting machines.

Consider, for example, a batch of digoxin tablets, (USP requirements: assay ±8%; assay for content uniformity ±15%) formulated to weigh 100 mg. and contain 0.25 mg. of digoxin each, which had been prepared from a perfectly homogeneous and accurately dosed granulation but, manufactured under adverse conditions of compression, just met USP specifications for weight variation. A cardiac patient, maintained at a 0.25-mg. daily dose of the drug and dispensed 20 such tablets, could conceivably receive only four-fifths of the potent medication one day, and 1.5 times as much the following day (0.2 mg. and 0.3 mg., respectively).

It has been argued that weight variation is not an essential criterion of product quality—what is important is drug content. Little if any significance need be attached to differences in weight between tablets from a given batch or even from batch to batch as long as there is present in each the required amount of active ingredient.[2] Admittedly, the drug content of a tablet cannot be deduced from the weight variation test. It can only be derived from quantitative analyses of individual dosage forms. Such assays have already found recognition as pharmacopeial standards, and as their usefulness through application in pharmaceutical quality control is becoming more apparent, the need for retaining official weight variation tolerances much longer has been questioned.

As a pharmacopeial standard the test has, however, many virtues. Weight variation is easily determined. Requiring only a balance, the test provides a reliable means of gauging tablet uniformity in terms of tablet weight within a given batch as well as from batch to batch. Applied readily to all tablets, large and small, with practically the same degree of accuracy and precision, it is a dependable indicator of good pharmaceutical manufacturing practices and production technology. Uniform specifications of methodology and compliance and more realistic tolerances reflecting the precision with which tablet weight can be controlled by means of modern tableting equipment would greatly enhance its universal value in pharmaceutical quality control.

[2] It has so far not yet been established whether the physiological availability of a medication from a tablet is totally

TABLE IV—WEIGHT VARIATION TOLERANCES[a] (PHARMACOPOEA NORDICA III)

Av. Tablet Wt., mg.	Tolerances Based on 30 Determinations
<80	27 tablets (90% of sample) may differ from av. wt. by ±10% and 3 tablets (10% of sample) may differ from av. wt. by ±20%[b]
>80	27 tablets (90% of sample) may differ from av. wt. by ± (4 mg. +5% of av. wt.) and 3 tablets (10% of sample) may differ from av. wt. by ± (8 mg. +10% of av. wt.)

[a] Applicable to compressed, uncoated tablets. [b] Tolerance also applicable to coated and uncoated tablets not prepared by compression, regardless of weight.

Drug Content

As a rule, pharmacopeial assays for active ingredients are based on analyses of aliquots obtained from a given number of tablets reduced to a fine powder.

USP XVII and NF XII—*Methods*—(*a*) *Composite Assays*—Ten or, in most instances, 20 tablets are required for physicochemical assays of drug content. They are finely powdered and aliquots of the triturate examined in accordance with the method of analysis specified in the corresponding monograph.

(*b*) *Single Dosage Assays* (*Content Uniformity*)—A representative sample consisting of 30 tablets is obtained from a given lot, and 10 of these are analyzed individually by the method of assay specified in the relevant monograph. At the analyst's discretion the degree of dilution of solutions and/or the volume of aliquots used may be adjusted so that the concentration of the drug in the final solution will be comparable to that obtained for the assay described in the corresponding monograph.

Compliance—(*a*) *Composite Assays*—Experimental results, indicative of the drug content of an aliquot from a number of tablets, are expressed in terms of the percent of labeled amount of drug claimed to be present in a single tablet. Tolerances are specified in individual monographs and vary depending on the nature of the product examined and the analytical method applied. (See under *Assays of Bulk Drugs and Compressed Tablets.*)

(*b*) *Single Dosage Assays*—Requirements which must be met are shown in Table V.

B.P. 1963—*Method*—It is essentially that adopted for composite assays by the United States Pharmacopeia, with tolerances "framed to allow for all

TABLE V—SINGLE DOSAGE ASSAYS FOR CONTENT UNIFORMITY OF TABLETS (USP XVII, NF XII)

No. of Tablets Analyzed (Out of 30)	Requirements I	Requirements II
10	All results must be within 85–115% of av. of tolerances specified in official monograph	If one result exceeds limits specified under I, each of remaining 20 tablets must be within limits specified under I[a]

[a] A rare "flyer" will thus not cause rejection of an entire batch.

Compliance—Experimental results are expressed as previously defined. In circumstances where the required number of tablets cannot be obtained, a smaller number, but not less than five, may be assayed by the official method. To allow for sampling errors in such instances tolerances are widened progressively, as shown in Table VI.

The corrections are to be applied to tablets for which tolerances ranging from 90–110% have been specified. For limits exceeding these values, proportionately larger allowances are to be made. Reasons for extending consistently upper limits more than the corresponding lower ones are not stated.

Pharmacopée Française VIII—Monographs for tablets have not been included in this edition and generally applicable specifications for drug content and content uniformity are not described.

State Pharmacopoeia U.S.S.R. IX—Specimens are prepared by grinding one or more tablets to a fine powder. The amount of sample required for analysis, the assay procedure to be followed, and tolerances permitted are specified in official monographs. Tablets for which such monographs are not given must meet the requirements shown in Table VII.

Pharmacopoea Nordica—The examination of a specified aliquot obtained as a rule from the trituration of at least 10 tablets is required. In general, drug content may vary by not more than ±10% from label claims. The tolerances are considered to take into account variations arising from manufacture and storage as well as analytical methodology.

Canadian Food and Drugs Act and Regulations (7)—*Method*—Schedule B of the Canadian Food and Drugs Act and Regulations lists seven pharmacopeial compendia officially recognized by the Food and Drug Directorate. They include, at present, the Pharmacopoea Internationalis, the British Pharmacopoeia, the United States Pharmacopeia, the Codex Français, the Canadian Formulary, the British Pharmaceutical Codex, and the National Formulary. Methods specified in these reference texts are endorsed by the Food and Drug Directorate as valid standards of pharmaceutical quality control, unless an "official method," *i.e.*, a method of analysis or examination designated as such by the Director-General for use in the administration of the Act, is the method to be applied.

TABLE VII—DRUG CONTENT OF TABLETS (STATE PHARMACOPOEIA U.S.S.R. IX)

Active Ingredient Per Tablet, mg.	Tolerance, %
>100	±5
<100	±10

Compliance—Tolerances set forth in any of the pharmaceutical compendia cited above are accepted for products thus identified. For nonofficial drugs "put up in tablet or any other individual dosage or dispensing form other than in ampoules or vials, variations within the limits stated in the following table as determined by an acceptable method" are permitted (Table VIII).

TABLE VIII—LIMITS OF VARIABILITY FOR NONOFFICIAL SOLID ORAL DOSAGE FORMS (CANADIAN FOOD AND DRUGS ACT AND REGULATIONS)

Amt. of Drug Per Tablet gr.	Amt. of Drug Per Tablet mg.[a]	Limits, %
>5	>324	94–106
0.5–5	32.4–324	93–107
0.02–0.5	3.24–32.4	92–108
0.01–0.02	0.65–3.24	91–109
<0.01	<0.65	90–110

[a] Equivalents not given in original table.

Two exceptions are made: (*a*) "glyceryl trinitrate shall contain not less than 85% and not more than 115% of the labelled amount," and (*b*) "if the drug consists of several ingredients, the amount of each ingredient so dispensed shall be not less than 90% and not more than 110% of the amount calculated from the label description."

Similarities and Differences—Tablet drug content and content uniformity depend on a number of processes associated with tablet manufacture, *e.g.*, compounding, mixing, drying, slugging, dispersion, compression, *etc.* Pharmacopeial standards have been established to control these processes, permit

TABLE VI—ASSAY TOLERANCES FOR TABLETS INCLUDED IN B.P. 1963 BASED ON ANALYSIS OF LESS THAN 20 SPECIMENS

Wt. of Drug in Tablet, mg.	Tablets Used for Analysis, No. 15 — Extend Limits Specified in Monographs by Following Percentages: Lower	15: Upper	10: Lower	10: Upper	5: Lower	5: Upper

determination of the amount of active ingredient present in a given product, and gauge the uniformity with which the drug is incorporated into individual dosage units.

Methodology—The USP and NF require the examination of a specified aliquot obtained as a rule from the trituration of 20 tablets. The B.P. accepts assay values derived from the analysis of aliquots from a smaller number of tablets as well, and endorses results obtained with as few as 5 tablets if only that many are available. The French pharmacopeia does not include monographs for solid dosage forms, and guidelines concerning general techniques and methodologies are, likewise, not described.

Assays given in the Russian pharmacopeia are not based on the examination of an aliquot from a definite number of tablets, but on direct analysis of a specified amount of sample material representing a fraction of one or several tablets. The Pharmacopoea Nordica, in general, requires the use of at least 10 tablets. The Canadian Food and Drugs Act and Regulations endorse any acceptable method, *i.e.*, any method of analysis or examination sanctioned by the Director-General for use in the administration of the Act.

It should be emphasized in this connection that different methods of analysis displaying different degrees of selectivity and sensitivity may be specified for the same preparation in different pharmacopeias. Single dosage assays have so far been adopted only by the United States Pharmacopeia[3] and the National Formulary.[4]

Compliance—Tolerances are stated in official monographs and marked variations exist between different pharmacopeial standards (see under *Assays of Bulk Drugs and Compressed Tablets*). Limits are generally a function of the weight of active ingredient claimed to be present in a single dosage unit. The greater the amount of active ingredient per tablet, the smaller the variation permitted. Unlike any other pharmacopeia, the B.P. allows for a further extension of tolerances if assays are based on less than 20 tablets. No reference is made in the USP, B.P., or NF to tolerances for products for which official monographs have not been described. The Russian pharmacopeia, on the other hand, specifies tolerances for such preparations as well. Products containing more than 100 mg. of active ingredient may vary by ±5% and those containing less than this amount by ±10% from label claims. The Canadian Food and Drugs Act and Regulations also cover nonofficial products, specifying five concentration ranges and corresponding tolerances. The classification is an unrealistic one in the light of modern technology, and efforts to revise it are now being made.

Scope—It is generally recognized that tablet weight variation does not necessarily reflect drug content variation. While tablets satisfying pharmacopeial specifications for weight variation are readily made by means of modern machines, it is most difficult to produce truly homogeneous tablet granulations and to feed solid blends continuously into the tableting machine for compaction into truly uniform dosage forms. The smaller the concentration of the active ingredient present, the more difficult it becomes to attain product uniformity. Tablets containing potent drugs, *i.e.*, tablets whose safety and efficacy demand careful control, are, therefore, particularly prone to compositional variations.

Several studies relating tablet weight and drug content have been published during recent years. They covered both practical and theoretical aspects associated with the production of solid dosage forms (8, 10), principles of mixing solids and their application to pharmacopeial standards for content uniformity in the absence of single dosage assays (11, 12), the effect of sampling and bulk mix heterogeneity on tablet variation (13), reproducibilities of assay and drug recovery from dosage forms (14), the nature and scope of sampling techniques (15), the application of automated equipment to single-tablet assays (16), and the effect of tableting technology on the relationship between tablet weight variation and percent composition (17, 18).

Relevant investigation on commercial products were carried out in the laboratories of the Canadian Food and Drug Directorate (19) and are continuing (20, 21). The following experiments may serve to illustrate some of the problems encountered during the course of these studies.

Ten tablets of hydrocortisone (5 mg.)[5] were taken at random from a bottle of 100 and analyzed in accordance with the USP procedure (tolerances allowed 90–110%). They were found to be below labeled strength (87.3%). Another analyst repeated the assay using a second lot of 10 tablets selected, likewise, at random from the same container. His results showed that the product complied (91.8%). Concerned about the discrepancy, a third analyst decided to assay 10 tablets individually. He obtained an average assay value of 100.8% on the basis of results varying from 68.4% to 151.2%. In each case, the 10 tablets used for analysis met perfectly the requirements of the weight variation test.

Because they are based on the examination of sample composites obtained from randomly selected tablets, pharmacopeial assays cannot be relied upon to provide infallible criteria for uniformity of tablet drug content. The weakness inherent in these methods is their inconsistency in relating experimental design to data utilization. They express product dosage on an individual tablet basis but are, themselves, based on sample composites of many tablets. Such analyses may not only average out minor compositional variations between tablets, as originally believed, but also mask major deviations reflecting substandard "pharmaceutical workmanship." The greater the number of tablets used for such analyses, the greater the possibility of masking variation in active ingredient due to imperfections in mixing all components during formulation, which process is considered a most critical one (9, 11, 12). On statistical grounds, the variation in drug content of an indi-

[3] Applicable to tablets of chlorpromazine hydrochloride, digoxin, ergonovine maleate, hydrocortisone, methylergonovine maleate, metyrapone, phenobarbital, prednisolone,

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