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 Pharmacopeia 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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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 certain differences and similarities which exist between pharmacopeial tests and specifications applied in the quality control of bulk drugs and

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

USP XVII	Av. Wt. of Tablet (mg.) from 20 Determinations NF XII	B.P. 1963	Not More Than Two Tablets Differ from Av. Wt. by More Than	No Tablet Differs from Av. Wt. by More Than
	<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 that 10 tablets be weighed individually from a batch of homogeneous manufacture, the average weight determined, and the variations compared

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,

[1] If it is not possible to use 100 tablets, weight determination may be made with a smaller number, but not less than 20,

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 prac-

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.

tically 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.

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 permissible variations including that of the active ingredient itself and that due to the process of manufacturing."

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[2] It has so far not yet been established whether the physiological availability of a medication from a tablet is totally independent of tablet weight for *any* type of formulation. Lozinski, for example, has shown that dicoumarol tablets of identical formulation and drug content, but larger size, displayed markedly reduced therapeutic efficacy. [*Can. Med. Assoc. J.*, **83**, 177(1960).]

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

No. of Tablets Analyzed (Out of 30)	Requirements	
	I	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

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

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

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.

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		Limits, %
gr.	mg.[a]	
>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

	Tablets Used for Analysis, No.					
	15		10		5	
Wt. of Drug in Tablet, mg.	Extend Limits Specified in Monographs by Following Percentages					
	Lower	Upper	Lower	Upper	Lower	Upper
<120	0.2	0.3	0.7	0.8	1.6	1.8
120–300	0.2	0.3	0.5	0.6	1.2	1.5
>300	0.1	0.2	0.2	0.4	0.8	1.0

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 individual tablet taken from a number of tablets may

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

[4] Applicable to tablets of amphetamine phosphate, amphetamine sulfate, betamethasone, cortisone acetate, dexamethasone, dextroamphetamine phosphate, methylprednisolone, methyltestosterone, and syrosingopine.

[5] Average weight of tablets 104.4 mg.; maximum deviation from mean 5.4 mg.

be as large as the square root of this number multiplied by the limit set for the composite assay. That is, an individual tablet taken at random from a group of 20 tablets for which drug content limits of 90–110%, *i.e.*, ±10% have been set, may deviate from the standard by as much as $\sqrt{20} \times 10 = 44.7\%$. Conversely, if all tablets should be within the range of 90–110%, *i.e.*, ±10% of label claim, the limit of variability for the composite assay based on 20 tablets should be no more than $10 \div \sqrt{20} = 2.25\%$.

Atropine sulfate tablets B.P., for example, may contain as little as 0.25 mg. of the potent anticholinergic and no less than 80 such tablets are required for the official assay. Yet, theoretically, a sample composite complying with the official B.P. standard of drug content (90–110%) may consist of individual tablets, some of which could contain as little as 10% or as much as 190% of the required amount. More pertinent information concerning the extent of tablet variation can be obtained by carrying out several composite assays and calculating standard deviations of individual tablets from the standard deviations of the composites. However, direct criteria of drug content uniformity are provided only by single-tablet assays, as described in the United States Pharmacopeia and the National Formulary, respectively (see Table V). Admittedly, such a scheme of quality control increases the time and cost of drug analysis, but it permits a more reliable appraisal of true product uniformity and its application to tablets containing potent chemotherapeutic agents should be of major concern to governmental and industrial laboratories alike.

The principle of pharmacopeial standards for monitoring intertablet dosage variation has been favorably received and accepted by the pharmaceutical industry in Canada and the United States.[6] At present, analytical methods for determining content uniformity involve spectrophotometric techniques only, and provided tablet formulations are amenable to such determinations, accurate measurements are readily made. Other equally sensitive methods are being developed in order to obtain single-tablet assays for as many products as possible. It should be in the pharmaceutical manufacturer's interest to produce only simple dosage forms which can readily be subjected to quantitative analysis.

Tablet Disintegration

Tests for gauging the disintegration of tablets under controlled conditions are described in most official compendia. Although not necessarily indicators of therapeutic efficacy, they are widely applied in pharmaceutical quality control.

Apparatus can be obtained commercially, and methodology is simple. Most pharmacopeias require that the tablet be placed in a tube (transparent plastic or glass) of precise dimensions fitted at its lower end with a wire gauze of specified mesh. The tube, suspended in a fluid kept at constant temperature, is raised and lowered at a uniform rate throughout a specified distance for a given period of time.

The tablet is considered disintegrated when, except for fragments of insoluble coating, only a soft mass having no palpable firm core remains above the gauze. The time required to reach this stage is called the disintegration time. Depending on the type of product and the pharmacopeial standard selected, a plastic disk of definite weight, shape, and size may be placed above the tablet in the tube either for the duration or throughout certain phases of the test.

Commercial units meeting official requirements are available and permit testing of as many as 6 tablets at a time.

USP XVII and NF XII—*Apparatus*—Vessel for basket rack assembly: a suitable vessel, preferably a 1-L. beaker. Temperature of medium: 37 ± 2°. Tube dimensions: length, 7.75 ± 0.25 cm.; inside diameter, 21.5 mm.; wall thickness, 2 mm. Wire mesh: nominal width of aperture 0.075 in. (1.90 mm.). Disk: material, transparent plastic, sp. gr. 1.18–1.20; thickness, 9.5 ± 0.15 mm.; diameter, 20.7 ± 0.15 mm.; perforations, five, each 2-mm. wide; notches, four having V-shaped planes. Movement: rate, 30 ± 2 c.p.m.; distance, 5–6 cm. Wire mesh position: high point, not less than 2.5 cm. below surface of fluid; low point, not less than 2.5 cm. from bottom of vessel.

Methodology and Compliance—These are summarized in Table IX.

B.P. 1963—*Apparatus*—Vessel: depth not less than 15 cm. Temperature of medium: 37 ± 2°. Tube dimensions: length, 8–10 cm.; inside diameter, 28 mm.; wall thickness, 2–3 mm.; volume, 200–250 ml. Wire mesh: nominal width of aperture 0.0661 in. (1.68 mm.). Disk: material, plastic; thickness, 2 mm.; diameter, 26 mm.; weight, 1.9–2.1 Gm. Guide ring: 27 mm. o.d. Movement: rate, 30 c.p.m. (by hand or mechanically); distance, 7.5 cm.; high point, wire gauze just breaks surface of medium; low point, upper rim of tube remains clear of medium.

Method—Five tablets are placed into the tube suspended in the required medium. The tube is raised and lowered repeatedly in a uniform manner, by hand or mechanically, through the specified distance and disintegration of the tablets observed continuously or at critical time intervals.

Compliance—(a) Tablets which are not enteric coated should disintegrate in water within 15 min. unless otherwise stated in the monograph.

(b) Tablets which are sugar coated should disintegrate in water within 1 hr.

If the tablets referred to under (a) or (b) fail to comply, the test is to be repeated on a further five tablets using the guided disk positioned directly above the tablets—and under these conditions they must meet requirements.

(c) Tablets which are enteric coated are tested in acid pepsin solution[7] for a period of 3 hr. (there should be no evidence of disintegration) washed rapidly by immersion in water, and thereafter placed in alkaline pancreatin solution[8] in which

TABLE IX—TABLET DISINTEGRATION (USP XVII, NF XII) METHODOLOGY AND COMPLIANCE

Pretreatment	Disks	Immersion Fluid and Test Conditions	Compliance[a]
		Uncoated (6 Tablets in Test)	
None	+	Water, unless otherwise specified in official monograph	At end of time limit specified in monograph all tablets should have disintegrated. If one or two have not disintegrated, test is to be repeated on 12 additional tablets. Not less than 16 of total of 18 tablets must disintegrate completely
		For example, if disintegration time specified in monograph is 15 min., the time limit is 15 min. in water.	
		Plain Coated[b] (6 Tablets in Test)	
If desired, immerse in water at room temperature for 5 min. to wash off soluble external coating	+	Simulated gastric fluid T.S.[c] for 30 min. If disintegration incomplete at that time, simulated intestinal fluid T.S.[d] for a total period of time, including exposure to water equal to the time specified in monograph plus 30 min.	If at end of test one or two tablets have not disintegrated, repeat on 12 additional samples. Not less than 16 of total of 18 tablets must disintegrate completely
		For example, if disintegration time specified in monograph is 15 min., the time limit is either (i) 30 min. in simulated gastric fluid plus 15 min. in simulated intestinal fluid, or (ii) 5 min. in water plus 30 min. in simulated gastric fluid plus 10 min. in simulated intestinal fluid.	
		Enteric-Coated (6 Tablets in Test)	
If desired, immerse in water at room temperature for 5 min. to wash off soluble, external coating	—	Simulated gastric fluid T.S. for 1 hr., followed by	No distinct evidence of dissolution or disintegration after gastric fluid treatment
	+	Simulated intestinal fluid T.S. for 2 hr. *plus* time limit specified in individual monograph, or where only an enteric-coated tablet is recognized for only the time limit specified in monograph	If at end of test one or two tablets fail to disintegrate, repeat on 12 additional samples. Not less than 16 of total of 18 tablets should disintegrate completely
		For example, if (i) 60 min. is the time specified in the monograph, the time limit is 60 min. in simulated gastric fluid plus 180 min. in simulated intestinal fluid; (ii) an enteric-coated tablet only is recognized, and a time of 120 min. is specified, the time limit is 60 min. in simulated gastric fluid plus 120 min. in simulated intestinal fluid	
		Buccal (6 Tablets in Test)	
None	—	Water, unless stated otherwise in monograph	All tablets should have disintegrated after 4 hr.
		Sublingual (6 Tablets in Test)	
None	—	Water, unless stated otherwise in monograph	All tablets must disintegrate within time limit specified in individual monograph[e]

[a] Tablets exempted from these requirements: those exceeding 15 mm. in diameter; those used as troches; those which are to be chewed; those designed to liberate drug content gradually over a period of time (prolonged action); those designed to release the drug over two or more separate periods with a distinct time interval between such release periods (repeat action). [b] Plain coated is any tablet having a nonenteric coating. [c] Composition: sodium chloride 2 Gm., pepsin 3.2 Gm., hydrochloric acid 7.0 ml., water *ad* 1,000 ml. The pH of this solution is approximately 1.2. [d] Composition: potassium phosphate (monobasic) 6.8 Gm. in 250 ml. water, sodium hydroxide (0.2 N) 190 ml., water 400 ml., pancreatin 10 Gm., sodium hydroxide (0.2 N) to adjust pH (7.5 ± 0.1), water *ad* 1,000 ml. [e] If one or two tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrate completely (First Supplement to USP XVII).

medium disintegration should be complete within 1 hr.

If the tablets fail to disintegrate in the alkaline pancreatin solution as required, the entire test must be repeated with a further five tablets using the guided disk during operation in the alkaline pancreatin solution. The tablets must then comply.

Canadian Food and Drugs Act and Regulations—Although apparatus, methods, and requirements for compliance are similar and in some respects even identical to those specified in the USP, there are some essential differences.

Apparatus—Its size differs considerably. The F.D.D. test is carried out in a vessel of approximately 3-L. capacity containing 2.5 L. of fluid. The USP test is carried out in a 1-L. vessel but does not specify the exact volume of fluid. A specific component of the F.D.D. apparatus is its plunger—a unit of precise dimensions consisting of a stainless steel rod separating two plastic disks. It is placed above the tablet or the slotted perforated disk riding atop the tablet in the tube.

Methodology and Compliance—These are summarized in Table X.

TABLE X—TABLET DISINTEGRATION
(CANADIAN FOOD AND DRUGS ACT AND REGULATIONS) METHODOLOGY AND COMPLIANCE (22)

Disk	Plunger	Immersion Fluid and Test Conditions		Compliance[a]
		Uncoated and Plain Coated (6 Tablets in Test)		
+	+	Simulated gastric juice[b] for 30 min. and, after gentle rinse with water, simulated intestinal juice[b] until disintegration is complete	Average disintegration time of tablets should be not more than 60 min. (30-min. testing in simulated gastric juice and remainder of time in simulated intestinal juice)	If 1 of 6 tablets disintegrates in more than 75 min. (30-min. exposure to gastric juice plus more than 45-min. exposure to intestinal juice) the test must be repeated with additional 12 tablets. Average disintegration time of 18 tablets must not be more than 60 min. and not more than one tablet shall disintegrate in more than 75 min. (total time)
		Enteric-Coated (6 Tablets in Test)		
−	+	Simulated gastric juice for 60 min.; there should be no distinct evidence of disintegration	Tablets should not disintegrate while tested for 60 min. in gastric juice but their average disintegration time should be not more than 60 min. during subsequent testing in simulated intestinal juice	If 1 of 6 tablets disintegrates in more than 75 min. the test must be repeated with additional 12 tablets. Average disintegration time of 18 tablets must not be more than 60 min. and not more than 1 tablet shall disintegrate in more than 75 min.
+	+	Simulated intestinal juice thereafter until disintegration is complete		
		Enteric-Coated Vitamins (6 Tablets in Test)		
Same as for enteric-coated tablets			Tablets should not disintegrate while tested for 60 min. in simulated gastric juice, but average disintegration time should be not more than 30 min. in simulated intestinal juice	If 1 of 6 tablets disintegrates in more than 40 min. the test must be repeated with additional 12 tablets. Average disintegration time of 18 tablets must not be more than 30 min. and not more than 1 tablet shall disintegrate in more than 40 min.

[a] All tablets intended to be swallowed whole are subject to these requirements except those which release their medicaments at time intervals (repeat action) or in sustaining quantities over a specified period of time (prolonged action). [b] Composition identical to that specified in USP XVII (1).

Pharmacopée Française VIII (Codex Médicamentarius Gallicus)—*Apparatus*—Vessel: glass jar (vol. ~400 ml.); i.d. 7.5 cm. Temperature of medium: 37 ± 2°. Petri dish: height, 3 cm.; i.d., 5 cm. Cylindrical screen: height, 9.5 cm.; i.d., 6.5 cm.; wire mesh, nominal width of aperture 0.0787 in. (2 mm.). Movement: rate, 30 c.p.m. for 30 sec. every 5 min.; distance, 5 cm.

Method—The cylindrical screen is placed upon the Petri dish in the vessel containing 350 ml. of water kept at 37 ± 2°. Five tablets are transferred onto the wire mesh of the cylindrical sieve which, after the elapse of 5 min., is moved up and down for 30 sec. completing one cycle each 2 sec. This mode of operation is maintained throughout the duration of the test.

Compliance—(a) Uncoated tablets must disintegrate in water within 45 min. (b) Coated tablets must disintegrate in water within 2 hr. (c) Enteric-coated tablets should not show any evidence of

disintegration in 0.6% (v/w) aqueous hydrochloric acid for 1 hr., but disintegrate within 2 hr.

Tablets exempt from these requirements include: (a) those intended to dissolve or disintegrate in the mouth; (b) those which are designed for implantation; (c) those not intended to dissolve in the stomach; (d) those designed for prolonged action; and (e) those designed to obtain a specific therapeutic action from the active ingredient.

State Pharmacopoeia U.S.S.R. IX—*Apparatus*—Special apparatus is not required.

Method—A tablet is placed into a 100-ml. flask, 50 ml. of water heated to 37° is added, and the flask is gently moved back and forth once or twice per second.

The tablet is considered disintegrated when it has dissolved or been reduced to a powder, small fragments, or loose mass. At least three such tests must be carried out.

Compliance—(a) Uncoated tablets must disinte-

grate within 10 min. (*b*) Coated tablets must disintegrate within 30 min. All tablets should be tested annually.

Pharmacopoea Nordica III—*Apparatus*—No special apparatus is required.

Method and Compliance—Three tablets are placed into a conical flask containing 30 ml. of distilled water warmed to 36–40°. The flask is shaken gently while the tablets are being observed for evidence of softening, dissolution, or disintegration. All three tablets must dissolve, become a soft, palpable mass, or disintegrate within 10 min. Coated tablets are subject to the same procedure, but their disintegration time may take 1 hr.

Enteric-coated tablets are tested in 30 ml. of a phosphate buffer solution (pH 7.4) instead of in 30 ml. of distilled water. They must disintegrate in less than 1 hr.

Glyceryl trinitrate tablets must disintegrate in less than 1 min.

Similarities and Differences—Comparison of apparatus, methodology, and tolerances embodied in pharmacopeial standards for the disintegration of tablets reveals that there exist far more differences than similarities. Experimental data obtained in accordance with specifications of one pharmacopeia do not, therefore, indicate compliance with specifications of some other pharmacopeia. The most common requirement is that tests be performed at 37 ± 2°.

A few obvious differences in experimental design and data interpretation may be cited to illustrate the extent of interpharmacopeial discordance. Such a critical parameter of disintegration as the width of the aperture of the wire mesh is specified to be 1.9 mm. in the USP, NF, and the Canadian Food and Drugs Act and Regulations, 2 mm. in the French pharmacopeia, and 1.68 mm. in the B.P. No screen is used in the apparatus specified by the Russian and Nordic pharmacopeias, respectively.

The tubes and tablets are raised and lowered at a rate of about 30 c.p.m. through a distance of 5–6 cm. in accordance with specifications of the USP NF, and the Canadian Food and Drugs Act and Regulations, throughout a distance of 7.5 cm. in accordance with specifications of the B.P. (either by hand or mechanically), and throughout a distance of 5 cm. in accordance with specifications of the French pharmacopeia. No such specifications are given in the Russian or Nordic pharmacopeias. Most compendia require that movement of the tubes be a continuous one—yet the French pharmacopeia specifies that it be a discontinuous operation.

The USP, NF, and the Canadian Food and Drugs Act and Regulations specify that six tablets be tested simultaneously, each in a separate tube, whereas the B.P. requires that five tablets be tested collectively in a single tube. The French pharmacopeia specifies that five tablets be tested together in a moving cylindrical screen, and the Russian pharmacopeia requires that three tablets be examined individually. The Pharmacopoea Nordica specifies that three tablets be tested collectively.

The test medium is, moreover, of variable composition. The British Pharmacopoeia uses water as the immersion fluid for tablets which are not enteric coated, and an acid pepsin plus alkaline pancreatin solution for tablets which are enteric

coated. The French pharmacopeia uses water as the immersion fluid for uncoated and plain coated tablets, but dilute hydrochloric acid as the immersion fluid for enteric-coated tablets. The Russian pharmacopeia uses water as the test medium for all types of tablets. Simulated gastric and/or intestinal fluid, different in composition from that specified in the B.P., is required for tests carried out in accordance with methodologies described in the USP, NF, and the Canadian Food and Drugs Act and Regulations. The volumes of the test media and the exposure times of different tablets to these media vary also appreciably.

Differences in apparatus and methodology are reflected in marked differences of compliance as well. The number of tablets required for examination varies considerably (from 3 to 18). The USP, NF, and the Canadian Food and Drugs Act and Regulations allow for distinct deviations of 1 or 2 tablets out of 18 from an average value, whereas the British, French, Nordic, and Russian pharmacopeias require that all tablets tested comply with specifications. Tolerances for buccal and sublingual tablets are given in the USP and NF; the Pharmacopoea Nordica indicates tolerances specifically for only glyceryl trinitrate tablets in this category. Limits, based on data of physiological availability, for the disintegration time of tablets containing vitamins are specified in the Canadian Food and Drugs Act and Regulations.

Scope—The test was developed to assess batch-to-batch disintegration reproducibility of tablet formulations made by definite processes from specific ingredients and subjected to appropriate in-process manufacturing controls. It was also considered to provide information concerning the relative ease with which tablet formulations break up under controlled experimental conditions simulating *in vivo* environment. For over a quarter of a century it has been recognized as a pharmacopeial standard (23).

Far less appreciated than its value in pharmaceutical quality control, however, remained its value in the assessment of drug response. Originally, a tablet disintegrating rapidly was thought to be clinically more effective than one disintegrating over a long period of time and the process of disintegration regarded not only as a tool for ensuring product compliance but also as a means of gauging the physiological availability of medicinal preparations. It is not intended to trace the historical development of the test or present a detailed account of its applications, for several excellent reviews have been written on this subject (24–31). The importance of the disintegration test cannot be denied. Specifying simple sets of conditions under which different types of tablets are examined, it represents a physical method of pharmaceutical quality control which allows a drug manufacturer or distributor to check his products for uniformity of performance from batch to batch without recourse to complex and expensive apparatus or personnel requiring advanced academic training. In this respect the test fulfills and will, no doubt, continue to fulfill a useful function.

As a pharmacopeial standard it postulates minimum and maximum allowable tolerances for tablet formulations most frequently used, but for a fuller appreciation of the significance of the data

it provides, other closely related and important criteria must, likewise, be taken into account. It has been pointed out that it would not be difficult to formulate a compressed tablet meeting pharmacopeial requirements for disintegration time from granules of cement passing through the gastrointestinal tract without change (25). Experiments conducted in these laboratories as well as elsewhere have shown that tablets claimed to contain potent chemotherapeutic agents do in fact so behave because of improper or faulty formulation (32). Such observations emphasize that tablet disintegration is indeed an important criterion of product quality, for no therapeutic effect can be expected from a tablet that fails to disintegrate.

The role of the disintegration test in the assessment of drug response cannot, however, be summarized that categorically. Original studies concerning this aspect of tablet disintegration were first carried out in the research laboratories of the Canadian Food and Drug Directorate under the direction of J. A. Campbell. They showed that tablet disintegration *in vitro* had to occur within a given period of time to ensure physiological availability of drugs administered as compressed or coated solid dosage forms. Data obtained from *in vitro* disintegration tests were correlated with results from *in vivo* measurements based on urinary excretion and/or blood level determinations and meaningful tolerances were thus established. Official specifications embodied in the Canadian Food and Drugs Act and Regulations—made mandatory in 1957—are largely based on this work (33-46). They motivated Canadian manufacturers to modify many of their tablet formulations for the purpose of producing pharmaceutical dosage forms displaying improved physiological availability and therapeutic efficacy.

Related studies published since are in accord with the findings that were made and confirm that results of *in vitro* disintegration tests can be considered as criteria of physiological availability only to the extent they correlate with quantitative *in vivo* data obtained on humans. *In vitro* results alone cannot be relied upon as indices of drug availability. Only through correlation with data reflecting *in vivo* response can they be utilized as parameters of biopharmaceutical quality control and monitors for product reproducibility. This shortcoming of the test is, unfortunately, not referred to in pharmacopeial texts.

What is to be more generally realized is that contrary to concepts originally conceived and accepted without question or scientific inquiry, tablets disintegrating quickly need not necessarily display enhanced clinical effectiveness and tablets disintegrating slowly need not necessarily display reduced therapeutic activity. Lack of knowledge of mechanisms underlying drug absorption and inability to duplicate precisely physiological conditions *in vitro* stand in the way of translating reliably data obtained *via* physical tests to drug response. It has been demonstrated, for instance, that agitation of a tablet during the USP disintegration test is far more intense (possibly more than three times as great) than during its residence time in the human stomach or during intestinal transit (29, 31). In this regard alone, most disintegration tests must be considered physiologically unrealistic.

Only through independent and objective appraisal of physiological availability can the therapeutic efficacy of tablet formulations be ascertained. This task should be a most important consideration of the pharmaceutical manufacturer in the development of new drug products.

Although some pharmacopeial commissions have made considerable revisions for tablet disintegration times and specified stricter limits for many dosage forms in succeeding editions of compendia (see Tables XI–XIII, summarizing data extracted from the United States Pharmacopeia and the National Formulary) these standards still provide liberal tolerances for tablet disintegration time, and at the present state of the art the production of solid oral dosage forms meeting official specifications is not likely to impose any hardships on the pharmaceutical industry.

The need to establish—in Canada—tolerances providing for disintegration times longer than those stated in the Food and Drugs Act and Regulations (7) has so far not been demonstrated. Nevertheless, the Food and Drug Directorate allows for the production and sale of compressed as well as enteric-coated tablets which fail to meet official specifications for disintegration time provided experimental evidence demonstrates that all therapeutically active ingredients are physiologically available as claimed. It should be in the manufacturer's interest to keep tablet composition and processing as simple as possible in order to avoid unpredictable effects not only in disintegration time but on the therapeutic efficacy of the product as well (47–52).

Difficulties in establishing accurate methods of analysis should always be regarded as early warning signals for a reassessment of biological response. Concerned about potential health hazards resulting from formulation changes, the Canadian Food and Drug Directorate requires that all manufacturers duly inform the Director-General of any modification in composition and/or processing for any medication accepted on the basis of a preclinical or new drug submission (7, 53, 54). In this connection, the World Health Organization recently drew to the attention of member states pertinent observations concerning the composition of a chloramphenicol palmitate formulation which had failed to produce satisfactory clinical response (55). Dissemination of such information under the auspices of WHO should be encouraged.

During the last few years the inherent weaknesses of the disintegration test have come to light and into sharper focus through the development of and correlation with a companion test appraising drug dissolution. Although a prerequisite to drug response, tablet disintegration is but one of a number of phenomena preceding drug absorption. The rate at which a drug diffuses from a tablet matrix into the surrounding fluids has been shown to represent an even more important process. Studies correlating disintegration time, dissolution rate, and physiological availability have supported this concept (29–31).

Recent investigations in the authors' laboratories have shown that wide variations in rate of drug dissolution may occur not only between products of different manufacturers (different brands containing the same active ingredient), but also between different lots of a given product supplied by the

TABLE XI—TABLET DISINTEGRATION TIMES SPECIFIED IN THE UNITED STATES PHARMACOPEIA

Tablet	USP XVI (1960)	USP XVII (1965)	Reduction, min.
Acetozolamide	30	30	...
Aminophylline	30	30	...
Aminosalicylic acid	30	30	...
Ammonium chloride (enteric-coated)	150	120	30
Amobarbital	30	30	...
Ascorbic acid	30	30	...
Aspirin (listed as acetylsalicylic acid USP XVI)	5	5	...
Atropine sulfate	30	30	...
Bethanechol chloride	30	30	...
Bishydroxycoumarin	15	15	...
Busulfan	30	30	...
Calcium gluconate	60	30	30
Calcium pantothenate	30	30	...
Carbarsone	30	30	...
Chlorambucil		30	...
Chlorcyclizine hydrochloride	30	30	...
Chloroquine phosphate	60	30	30
Chlorpheniramine maleate	30	30	...
Chlorpromazine hydrochloride	30	30	...
Chlorpropamide		30	...
Codeine phosphate	30	30	...
Colchicine	15	15	...
Cyclizine hydrochloride	10	10	...
Dapsone		30	...
Decavitamin	120	60	60
Desoxycorticosterone acetate (buccal)			
Dextroamphetamine sulfate	30	30	...
Dichlorphenamide		30	
Diethylcarbamazine citrate	30	30	...
Diethylstilbestrol	30	30	...
Digitalis	60	30	30
Digitoxin	30	30	...
Digoxin	30	30	...
Diiodohydroxyquin	60	60	...
Dimenhydrinate	30	15	15
Ergonovine maleate	30	30	...
Ergotamine tartrate	30	30	...
Erythromycin	60	60	...
Ethinyl estradiol	30	30	...
Ferrous fumarate		30	...
Ferrous sulfate	60	30	30
Folic acid	30	30	...
Griseofulvin		30	
Guanethidine sulfate		30	
Hydrochlorothiazide		30	
Hydrocortisone	30	30	
Hydroxychloroquine sulfate	60	30	30
Iopanoic acid	30	30	...
Isoniazid	30	30	...
Isoproterenol hydrochloride (sublingual)		3	
Lucanthone hydrochloride		30	
Magnesium trisilicate		30	
Mecamylamine hydrochloride	30	30	...
Meclizine hydrochloride	30	30	...
Medroxyprogesterone acetate		30	
Menadione	30	30	...
Mercaptopurine	30	30	...
Methadone hydrochloride	30	30	...
Methamphetamine hydrochloride[a]		30	
Methazolamide		30	
Methenamine mandelate	30	30	...
Methimazole	30	30	...
Methylergonovine maleate[a]		30	
Morphine sulfate	30	30	...
Neomycin sulfate	60	60	...
Neostigmine bromide	30	30	...
Niacinamide	30	30	...
Nitrofurantoin	30	30	...
Nitroglycerin (sublingual)		2	
Nystatin (oral)	120	120	...
Nystatin (intravaginal)	60	60	...
Phenacetin		30	
Phenobarbital	30	30	...
Phthalylsulfathiazole	30	30	...
Phytonadione	30	30	...
Piperazine citrate	30	30	...
Potassium chloride	30	30	...
Potassium penicillin G (gastric)		60	
Potassium permanganate			
Potassium phenoxymethyl penicillin (gastric)	60	60	...
Prednisolone	30	30	...
Prednisone	30	30	...
Primaquine phosphate	30	30	...
Primidone	30	30	...
Probenecid	30	60	...
Prochlorperazine maleate	30	30	...
Promethazine hydrochloride	30	30	...
Propantheline bromide	30	30	...
Propylthiouracil	30	30	...
Pyridostigmine bromide	30	30	...
Pyridoxine hydrochloride	30	30	...
Pyrimethamine	30	30	...
Pyrvinium pamoate	30	30	...
Quinacrine hydrochloride	30	30	...
Quinidine sulfate	30	30	...
Reserpine	60	30	30
Riboflavin	30	30	...
Sodium aminosalicylate	30	30	...
Sodium bicarbonate (gastric)	30	30	...
Sodium chloride	30	30	...
Sodium levothyroxine	30	30	...
Sodium liothyronine	30	30	...
Sodium salicylate	30	30	...
Sodium sulfoxone (enteric-coated)	150	60	90
Sodium warfarin		30	
Spironolactone		30	
Succinylsulfathiazole		30	
Sulfadiazine	30	30	...
Sulfamethoxypyridazine	30	30	...
Sulfapyridine	30	30	...
Sulfisoxazole	60	30	30
Thiamine hydrochloride	30	30	...
Thyroid	30	30	...
Tolbutamide	30	30	...
Trihexyphenidyl hydrochloride	30	30	...
Tripelennamine hydrochloride	30	30	...
Trisulfapyrimidines	30	30	...

[a] Transferred from NF XI without change in disintegration time.

same manufacturer (56, 57). Related studies have illustrated the effects of dosage form variation on the physiological availability of drugs (58, 59).

So far, pharmacopeial standards for tablet dissolution have not been formulated. The need for such standards will grow since tablet dissolution is of more fundamental importance than tablet disintegration for determining drug availability. The disintegration test merely measures the time required for a tablet to break up into granules smaller than a given size, but it tells nothing about how rapidly the drug is released from these granules into the substrate. Dissolution, on the other hand, has been shown to control the rate of build-up of many drugs in the blood stream and has been correlated more accurately than disintegration time with therapeutic efficacy.

Undoubtedly, dual tests comprising coordinated *in vivo* and *in vitro* evaluation of drug products are becoming the most critical parameters of

TABLE XII—TABLET DISINTEGRATION TIMES SPECIFIED IN THE NATIONAL FORMULARY

Tablet	NF XI (1960)	USP XVI (1960)	NF XII (1965)	Reduction, min.
Acetaminophen	30		30	...
Aluminum hydroxide gel		30	30	...
Aminobenzoic acid			30	
Amodiaquine hydrochloride		30	30	...
Amphetamine phosphate	30		15	15
Amphetamine sulfate	30		15	15
Anileridine hydrochloride			25	
Apomorphine hydrochloride	30		15	15
Arecoline hydrobromide	30		30	...
Aspirin, phenacetin, and caffeine	15	10		5
Azacyclonol hydrochloride	30	20		10
Benzestrol	30	15		15
Benztropine mesylate	15	15		...
Betamethasone			30	
Bismuth subnitrate	60		60	...
Three bromides (NH4Br, KBr, and NaBr)	30		30	...
Brompheniramine maleate			30	
Citrated caffeine	30		30	...
Calcium aminosalicylate	120		30	90
Calcium carbonate (gastric)	30		30	...
Calcium cyclamate and calcium saccharin			30	
Calcium cyclobarbital			30	
Calcium lactate	60		30	30
Calomel			30	
Carbinoxamine maleate	30	15		15
Cascara	90		60	30
Chlormerodrin			30	
Chlorothen citrate	30		30	...
Chlorothiazide		30	30	...
Choline dihydrogen citrate	60		30	30
Cocaine hydrochloride	30	15		15
Codeine sulfate	30	15		15
Cortisone acetate		30	30	...
Cyclophosphamide			30	
Cycrimine hydrochloride	30		30	...
Dehydrocholic acid		30	30	...
Dexamethasone			30	
Dexchlorpheniramine maleate			15	
Dextroamphetamine phosphate	30		15	15
Dextromethorphan hydrobromide	120		30	90
Dienestrol		30	30	...
Diethylstilbestrol dipropionate	30		30	...
Dihydroxyaluminum aminoacetate	60		30	30
Diphemanil methylsulfate	15	10		5
Diphenadione	30		30	...
Doxylamine succinate		30	30	...
Ephedrine hydrochloride	60		30	30
Ephedrine sulfate	30		30	...
Estradiol	120	15		105
Ethinamate	30		30	...
Ethisterone		30	30	...
Ethoheptazine citrate			15	
Ethyl biscoumacetate			15	
Ferrous gluconate		60	60	...
Glutethimide	30		30	...
Glycobiarsol		30	30	...
Halazone	15	10		5
Hexavitamin	120		30	90
Homatropine methylbromide		30	30	...
Hydralazine hydrochloride	30		30	...
Hydrocodone bitartrate			30	
Hydromorphone hydrochloride			30	
Hydroxyzine hydrochloride	30		30	...
Imipramine hydrochloride (gastric)			30	
Iodoalphionic acid	60	15		45
Iodochlorhydroxyquin		30	30	...
Lanatoside C	60	15		45
Levorphanol tartrate	45		30	15
Magnesium hydroxide (gastric)	30		30	...
Menadiol sodium diphosphate		60	60	...
Meperidine hydrochloride		30	30	...
Mephenesin	30		15	15
Mephobarbital		30	30	...
Meprobamate		30	30	...
Mercurophylline	60		30	30
Mercury bichloride large poison		15		
Methacholine bromide	30		30	...
Methantheline bromide	30	15		15
Methapyrilene hydrochloride	30		30	...
Metharbital	15	10		5
Methenamine	30		30	...
Methenamine and sodium biphosphate	30		30	...
Methionine (gastric)	30		30	...
Methscopolamine bromide			30	
Methylphenidate hydrochloride			30	
Methylprednisolone			30	
Methyltestosterone		30	30	...
Methylthiouracil		30	30	...
Methyprylon	45		30	15
Morphine and atropine sulfates	30	15		15
Niacin			30	
Nylidrin hydrochloride	30		30	...
Papaverine hydrochloride		30	30	...
Penthienate bromide	30		30	...
Phenindamine tartrate		60	60	...
Pheniramine maleate	60	15		45
Phenmetrazine hydrochloride		10		
Phenolphthalein	60		30	30
Phenoxymethyl penicillin				
Phentolamine hydrochloride	60		60	...
Phenylbutazone			45	
Phthalylsulfacetamide	60	15		45
Pipradrol hydrochloride	30		30	...
Polymyxin B sulfate		30		
Potassium phenethicillin				
Potassium warfarin			30	
Progesterone (buccal)				
Promazine hydrochloride			30	
Pyrilamine maleate		30	30	...
Pyrrobutamine phosphate			30	
Quinine sulfate	60		30	30
Rauwolfia serpentina	60		30	30
Rescinnamine	30		30	...
Salicylamide	30		30	...
Scopolamine hydrobromide	30		30	...
Sodium butabarbital		15		
Sodium carboxymethylcellulose		120	120	...
Sodium chloride and dextrose	60		30	30

TABLE XII—(*Continued.*)

Tablet	NF XI (1960)	USP XVI (1960)	NF XII (1965)	Reduction, min.	Tablet	NF XI (1960)	USP XVI (1960)	NF XII (1965)	Reduction, min.
Sodium cyclamate and sodium saccharin					Syrosingopine			30	
Sodium pentobarbital			30		Tetracycline hydrochloride	30			
Sodium phenobarbital			30		Thenyldiamine hydrochloride	30		30	...
Sodium saccharin					Theophylline	60		30	30
Sulfacetamide	60	15		45	Theophylline sodium acetate	60		30	30
Sulfacetamide, sulfadiazine, and sulfamerazine	60		30	30	Theophylline sodium glycinate	60		30	30
Sulfadiazine and sulfamerazine	60		30	30	Thonzylamine hydrochloride	30		30	...
Sulfadimethoxine			30		Tridihexethyl chloride (gastric)	30		30	...
Sulfamerazine	60		30	30	Trimethadione	60		30	30
Sulfamethizole	60		30	30	Urethan		30	30	...
					Dried yeast	120		60	60

TABLE XIII—COMPARISON OF DISINTEGRATION TIME DATA GIVEN IN USP XVII AND NF XII

	USP XVII	NF XII
Total number of tablets covered in monographs	117	139[a]
Tablets for which disintegration time was reduced	11 (9.4%)	36 (33.1%)
Tablets for which disintegration time was reduced by 50%	9 (7.7%)	29 (20.9%)
Tablets for which disintegration time was reduced by more than 50%	1 (0.8%)	9 (6.5%)
Tablets for which disintegration time was reduced by less than 50%	1 (0.8%)	8 (5.8%)
Tablets for which disintegration time was increased	1[b]	...
Tablets required to disintegrate in 30 min.	97 (82.9%)	91 (65.5%)
Tablets required to disintegrate in less than 30 min.	7 (6.0%)	30 (21.6%)
Tablets (nonenteric coated) permitted to disintegrate in more than 30 min.	9 (7.7%)	9 (6.5%)
Enteric-coated tablets for which disintegration times are specified	2[c]	...
Tablets for which disintegration times are not given in monographs	1	7 (5.0%)[d]

[a] Includes 26 preparations deleted from USP XVI. Disintegration times for 24 of these were left unchanged. [b] Probenecid. [c] Ammonium chloride and sodium sulfoxone. [d] Tablets of calcium cyclamate and calcium saccharin, phenoxymethyl penicillin, polymyxin B sulfate, potassium phenethicillin, sodium cyclamate and sodium saccharin, sodium saccharin, and tetracycline hydrochloride. Disintegration times were specified, however, for tablets of polymyxin B sulfate and sodium saccharin in USP XVI and for tablets of tetracycline hydrochloride in NF XI.

objective studies on humans together with *in vitro* disintegration and dissolution parameters reflecting the clinical performance of a dosage form are clearly emerging as prerequisites in the manufacture of drug products justifiably claimed to be safe and therapeutically effective. Any change in product formulation made subsequent to such standardization requires that both sets of data be reassembled so that adequately calibrated *in vitro* data alone may be utilized with confidence as monitors of quality control, gauging not only physicochemical variability within and between lots, but allowing also for interpretation of product safety and efficacy.

For certain dosage forms physiological availability data are already legal requirements. It is mandatory, for example, that in accordance with regulations of the Canadian Food and Drugs Act and Regulations "the manufacturer of a drug in oral dosage form represented as releasing the drug at timed intervals or in sustaining quantities over a period of time shall (a) conduct such investigations, using an acceptable method, as may be necessary to demonstrate that the drug is released

TABLE XIV—SPECIFICATIONS FOR BULK DRUGS OF THE UNITED STATES PHARMACOPEIA XVII

Assay Limits, %	No. of Compd.	Assay Limits, %	No. of Compd.
73–81	1	97.5–100.5	4
88–100.5	1	97.5–101	1
		97.5–102	1
90–100.5	2	97.5–102.5	1
93.5–101.5	1	98–100.5	25
95–100.5	5	98–101	14
95–101	1	98–101.5	7
95–103	1	98–102	17
95–105	7		
96–100.5	5	98.5–100.5	14
96–101	1	98.5–101	7
96–104	1	98.5–102	2
96.5–101	1	99–99.5	1
		99–100.5	16
97–100.5	6	99–101	8
97–101	1		
97–101.5	4	99.5–100.5	2
97–102	10	99.5–101	1
97–103	13	99.5–102.5	1

pharmaceutical quality control. Physiological availability data obtained through properly designed

and is available as represented, and (b) on request submit the record of such investigations to the Director" (*Reference 7*, Section C.01.012).

More and more companies, realizing the need for such studies to ensure the safety and clinical effectiveness of a pharmaceutical formulation, are submitting to the Director-General on their own accord experimental evidence documenting the physiological availability of new drugs as defined in Section C.08.001 of the Food and Drugs Act and Regulations (7). It is merely a question of time until such data will become official requirements.

Great strides are being made in the field of biopharmaceutics and it is essential that they be evaluated periodically in order to determine whether pharmacopeial tests and specifications for drug efficacy can be established that are more meaningful and informative than those upon which we must rely at the present time.

ASSAYS OF BULK DRUGS AND COMPRESSED TABLETS

Bulk Drugs—Assay limits for bulk drugs[9] specified in the United States Pharmacopeia, the National Formulary, and the British Pharmacopoeia are summarized in Tables XIV–XVI. As a rule, limits are given in the form of a statement defining

TABLE XV—SPECIFICATIONS FOR BULK DRUGS OF THE NATIONAL FORMULARY XII

Assay Limits, %	No. of Compd.	Assay Limits, %	No. of Compd.
91.5–100.5	1	98–100.5	45
		98–101	12
93–107	1	98–101.5	1
		98–102	26
94–100.5	2		
94–106	1	98.2–100.5	1
95–100.5	6	98.2–100.7	1
95–102	1		
95–103	3	98.5–100.5	13
		98.5–101	3
96–100.5	4	97.5–101.5	2
96–102	1		
96–104	2	98.8–100.7	1
96.5–100.5	1	99–100.5	14
		99–101	5
97–100.5	7	99–101.8	1
97–101	4	99–102	1
97–102	4	95.5–101	1
97–103	11		
97.5–102.5	1	99.7–100.5	1

that the drug contains not less than a certain percentage and not more than a certain percentage of the chemical compound specified in the monograph. For many products only lower limits are given. In each such instance, the upper limit is considered be 100.5%.

The distribution of ranges most frequently specified in USP XVII, NF XII, and B.P. 1963 is shown in Table XVII. For all three pharma-

TABLE XVI—SPECIFICATIONS FOR BULK DRUGS OF THE BRITISH PHARMACOPOEIA 1963

Assay Limits, %	No. of Compd.	Assay Limits, %	No. of Compd.
87.5–100.5	1	98–100.5	54
90–100.5	3	98–101	17
		98–101.5	4
94–100.5	2	98–102	13
95–100.5	11	98–104	1
95–101	1		
95–105	1	98.5–100.5	30
		98.5–101	9
96–100.5	3	98.5–101.5	4
96–101	1	98.5–102	1
96–104	13	98.5–102.5	3
97–100.5	6	99–100.5	50
97–101	1	99–100	18
97–101.5	1	99–101.5	4
97–102	3	99–102	1
97–103	14	99–103	1
97.5–100.5	4	99.5–100.5	6
97.5–101.5	1	99.5–101	1
97.5–102	1	99.5–104.5	1

TABLE XVII—FREQUENCY OF SPECIFIC ASSAY LIMITS FOR BULK DRUGS OF THE USP XVII, NF XII, AND B.P. 1963

Drug Content, %	Compd., %		
	USP XVII	NF XII	B.P. 1963
98–100.5	13.7	25.3	18.9
98.5–100.5	7.7	7.3	10.5
98–102	9.3	14.6	4.6
99–100.5	8.7	7.9	17.5
99–101	4.4	2.8	6.3
98–101	7.7	6.7	6.0

copeias, the most popular range extends from 98–100.5%. The second most popular range specified in the USP XVII and NF XII is 98–102% (9.3 and 14.6% of the compounds listed, respectively), while that of the B.P. 1963 extends from 99–100.5% (17.5% of compounds listed).

The Pharmacopoeia of the U.S.S.R. (English edition) designates lower limits for all drugs, but specifies upper limits for only a few.[10] For compliance, 97 drugs out of 150 (64.7%) must assay 99–101%, 34 must assay 98–102%, 7 must assay 97–103%, and 3 must assay 95–105%. These requirements are more stringent than those of the USP, NF, or B.P.

Assay limits specified for bulk drugs included in both the USP and B.P., or B.P. and NF, are shown in Table XVIII. Differences in either upper or lower limits of at least 1% were considered prerequisites for entry of compounds into this table. The data recorded illustrate the magnitude of interpharmacopeial drug content variations.

Thus, phenylephrine hydrochloride B.P. assays 98.5–100.5%, whereas phenylephrine hydrochloride USP may assay 97.5–102.5%. Methylprednisolone NF XII assays from 97–103%, but methylpredni-

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[9] Antibiotics, inorganics, and multicomponent drugs, *e.g.*, aminophylline (theophylline + ethylenediamine) are not included in this survey.

[10] The authors are indebted to Dr. A. N. Klimov, Division of Biology and Pharmacology, World Health Organization, Geneva, Switzerland, for advising that in the absence of specifications for complete tolerance ranges, upper limits of 100.5% apply.

TABLE XVIII—ASSAY LIMITS FOR BULK DRUGS INCLUDED IN THE
UNITED STATES PHARMACOPEIA, NATIONAL FORMULARY, AND BRITISH PHARMACOPOEIA

Compd.	USP XVII	NF XII	B.P. 1963
Acetazolamide	98–102		99.0–100.5
Amodiaquine hydrochloride		97–102	98.0–101.5
Amphetamine sulfate		98–100.5	99.0–100.5
Benzocaine		98–101	99.0–100.5
Calcium lactate		98–101	97.0–103.0
Chloral hydrate	99.5–102.5		99.0–100.5
Chloroquine phosphate	98–102		98.0–100.5
Chlorothiazide		97–100.5	98.0–100.5
Chlorpromazine hydrochloride	98–101.5		99.0–101.0
Chlorpropamide	97–103		99.0–101.0
Codeine phosphate	98–101.5		98.0–100.5
Cortisone acetate		97–103	96.0–104.0
Desoxycorticosterone acetate	97–103		96.0–104.0
Dextroamphetamine sulfate	98–100.5		99.0–100.5
Dextromethorphan hydro- bromide		98–100.5	99.0–100.5
Dichlorphenamide	97–100.5		98.0–100.5
Dienestrol		98–100.5	98.5–101.5
Diethylstilbestrol	97–100.5		98.5–101.5
Diiodohydroxyquin	96–100.5		97.0–100.5
Epinephrine	97–100.5		99.0–100.5
Epinephrine bitartrate	97–102		99.0–100.5
Ergonovine maleate	98–101		95.0–100.5
Folic acid	98–102		95.0–100.5
Glutethimide		98–100.5	99.0–100.5
Guanethidine sulfate	95–105		99.0–101.0
Hydralazine hydrochloride		98–100.5	98.0–102.0
Hydrochlorothiazide	97–101.5		98.0–100.5
Hydrocortisone	97–103		96.0–104.0
Hydrocortisone acetate	97–103		96.0–104.0
Hydrocortisone sodium succinate	97–103		96.0–104.0
Hydroxychloroquine sulfate	98–102		98.0–100.5
Imipramine hydrochloride		98–102	98.0–100.5
Iopanoic acid	97–101		98.0–101.0
Levarterenol bitartrate	97–102		99.0–101.0
Meclizine hydrochloride	97–100.5		98.0–100.5
Meperidine hydrochloride		98–101	99.0–100.5
Mercaptopurine	97–102		98.0–100.5
Methylene blue	98.5–100.5		96.0–101.0
Methylergonovine maleate	97–103		95.0–105.0
Methylprednisolone		97–103	96.0–104.0
Methylthiouracil		97–100.5	98.0–100.5
Neostigmine bromide	98–102		98.5–100.5
Neostigmine methylsulfate	98–102		98.5–100.5
Phenindamine tartrate		98–101.5	98.5–100.5
Phenolsulfonphthalein	95–105		94.0–100.5
Phentolamine hydrochloride		98–100.5	99.0–100.5
Phentolamine mesylate	98–102		99.0–100.5
Phenylbutazone		98–100.5	99.0–100.5
Phenylephrine hydrochloride	97.5–102.5		98.5–100.5
Prednisolone	97–103		96.0–104.0
Prednisolone acetate	97–103		96.0–104.0
Prednisone	97–103		96.0–104.0
Primaquine phosphate	98–102		97.5–100.5
Primidone	98–102		99.0–100.5
Promethazine hydrochloride	97.0–101.5		98.5–102.0
Quinidine sulfate	98–100.5		99.0–101.5
Reserpine	96–101		97.0–101.5
Riboflavin	98–102		97.0–102.0
Sodium aminosalicylate	98–101		99.0–101.0
Sodium indigotindisulfonate	96–100.5		90–100.5
Stibophen	98.5–102		98.5–101.0
Thiamine hydrochloride	98–102		98.5–100.5
Thimerosal		97–101	98.0–100.5
Tolbutamide	98–101		99.0–101.0
Undecylenic acid		95–100.5	96.0–100.5

solone B.P. may assay 96–104%. Ergonovine
maleate USP must contain 98–101% of the alk-
aloid, but ergometrine maleate B.P. (ergonovine
maleate) may assay 95–100.5%. Chlorpro-
pamide assaying 97–103% meets USP specifications,
but fails to meet B.P. requirements (99–101%).

Tolerance ranges for some drugs may differ by as much as 8%, *e.g.*, guanethidine sulfate B.P. assays 99–101%; guanethidine sulfate USP assays 95–105%. The following ranges apply to promethazine hydrochloride: USP 97.0–101.5%, B.P. 98.5–102.0%, State Pharmacopoeia of the U.S.S.R. (diprazine) 99.5–101.0%.

Diethylstilbestrol assaying not less than 97% meets USP specifications, samples assaying not less than 98.5% comply with B.P. requirements, and products assaying not less than 99.0% will meet specifications of the State Pharmacopoeia of the U.S.S.R. Sodium suramin (B.P. and USP) must contain not less than 97.5% (volumetric analysis) of the antitrypanosomal drug, but may assay 92.5% (gravimetric analysis) or 93.5% (volumetric analysis) to meet specifications of the State Pharmacopoeia of the U.S.S.R. (naganin).

It should be pointed out that bulk drugs are also covered in pharmacopeial monographs lacking methods of assay, *e.g.*, progesterone NF XII,[11] oestradiol B.P. 1963, cortisone acetate State Pharmacopoeia of the U.S.S.R.,[12] colchicine USP. Yet quantitative methods of analysis and tolerances may be specified for pharmaceutical dosage forms containing such drugs as active ingredients, *e.g.*, progesterone tablets NF XII (90–110%), oestradiol benzoate injection B.P. 1963 (90–110%), cortisone acetate tablets, State Pharmacopoeia of the U.S.S.R. (90–110%), colchicine tablets USP (90–110%). It is essential that reliable assays for bulk drugs used in the manufacture of such products be developed and tested collaboratively in pharmaceutical quality control laboratories.

Variations between assay limits for bulk drugs common to different pharmacopeias are, in part at least, due to differences in methodology. Thus ergonovine maleate USP is determined titrimetrically, but ergometrine maleate B.P. (ergonovine maleate) is assayed colorimetrically. Imipramine B.P. is determined by Kjeldahl analysis, imipramine NF by nonaqueous titration. Acetazolamide USP is assayed by infrared, acetazolamide B.P. by ultraviolet spectrophotometry. Phenylephrine hydrochloride USP is assayed iodometrically, phenylephrine hydrochloride B.P. is determined by nonaqueous titration. Chlorpropamide USP is estimated by ultraviolet spectrophotometry, chlorpropamide B.P. by Kjeldahl analysis. Guanethidine sulfate B.P. is assayed by column chromatography, guanethidine sulfate USP by colorimetry. Promethazine hydrochloride, State Pharmacopoeia of the U.S.S.R. (diprazine), is estimated by aqueous titrimetry, and promethazine hydrochloride USP by nonaqueous titrimetry, and promethazine hydrochloride B.P. by ultraviolet spectrophotometry. Diethylstilbestrol USP is assayed colorimetrically, stilboestrol B.P. (diethylstilbestrol) and diethylstilbestrol State Pharmacopoeia of the U.S.S.R. are determined titrimetrically following acetylation in pyridine.

Compressed Tablets—The drug content of compressed tablets covered in pharmacopeial monographs is usually given in the form of a statement indicating upper and lower limits. The tolerances allow for sampling variations, errors inherent in

analytical methodology, variations due to compounding, differences in bulk drug uniformity, and losses in active strength during storage. The general nature and scope of the assays has been described under *Drug Content.*

Relationships between drug content and permitted variation in compressed tablets for which symmetrical tolerances are specified in the USP, NF, B.P., and the State Pharmacopoeia of the U.S.S.R. are depicted schematically in Fig. 1. It can be seen that the USP endorses six and the NF seven different ranges. Only three of these are frequently applied (95–105%, 93–107%, and 90–110%). The B.P. recognizes but three limits of variability (95–105%, 92.5–107.5%, and 90–110%), and the State Pharmacopoeia of the U.S.S.R. allows for just two such ranges (95–105% and 90–110%).

The length of the bars shown in the illustration is proportional to the number of tablets to which the specified relationship between drug content (dosage) and permitted variation applies. For example, only one product is listed in the B.P. containing 500 mg. of active ingredient for which a tolerance of ±7.5% is permitted. Three products to which this tolerance applies contain 300 mg. of active ingredient. Five, nine, and 17 products meeting this specification contain 250 mg., 200 mg., and 100 mg. of active ingredient, respectively. Similarly, only one product is found to contain 100 mg. of active ingredient to which a tolerance of ±10% applies.

For 17 products containing this concentration of active ingredient, tolerances of ±7.5% are permitted and for 11 such products, variations of only ±5% are allowed. Thus, Fig. 1 readily demonstrates the overlap in dosage levels between tablets subject to identical dosage variations as well as the overlap in dosage variation between products of identical drug content. In general, dosage variations are maximal for products containing only small concentrations of active ingredients.

Totals shown in Fig. 1 represent both different drug products as well as different dosage levels of the same drug product. Thus, for phenobarbital tablets USP, dosage levels of 15 mg., 30 mg., 60 mg., and 100 mg. are included in the data, while for phenobarbitone tablets B.P., dosage levels of 15 mg., 30 mg., 60 mg., 100 mg., and 125 mg. have been recorded.

Ranges of 93–107% and 95–105% are most frequently specified in the USP (49 and 48 products, respectively, or about 30%). Variations ranging from 90–110% are most often applied in the NF (52 products or 29.9%). The B.P. recognizes limits of 92.5–107.5% for most medications (115 products or 42.4%), allowing for an extension of these limits if assays are based on less than 20 tablets. While the USP and NF specify, furthermore, unsymmetrical ranges for a few dosage forms containing overages of drugs prone to deterioration on prolonged storage, the B.P. does not follow this practice. The most often used limits of drug content specified in the State Pharmacopoeia of the U.S.S.R. extend from 95–105% (52 products or 70.3%). Thus, as for bulk drugs, limits for solid oral dosage forms are generally also narrower and more exacting in this pharmacopeia than in the USP, NF, or B.P. Formulations composed of antibiotics, inorganics, and mixtures of drugs are not included in these data.

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[11] A gravimetric assay for the steroid is given in the State Pharmacopoeia of the U.S.S.R. (98.5–100.5%) and an ultraviolet method described in the B.P. (97.0–103.0%).
[12] A colorimetric assay is given in both the B.P. (96–104%) and NF (97–103%).
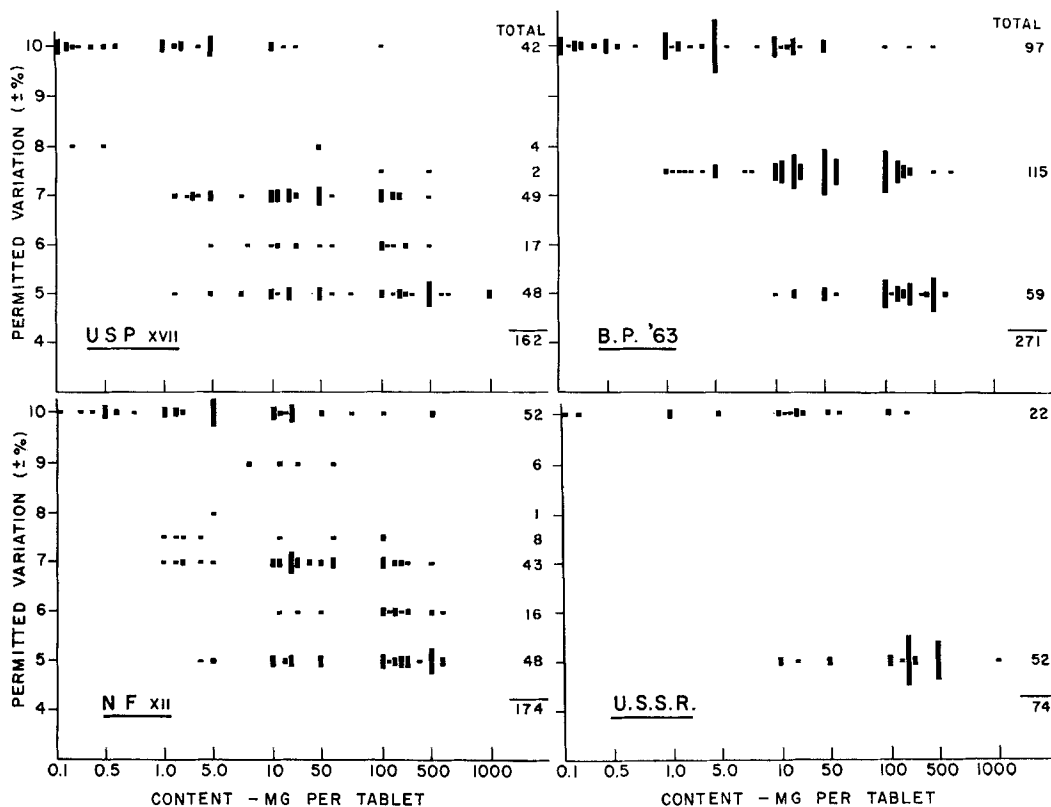
Fig. 1—Drug content tolerances for tablets included in pharmacopeial compendia.

Tablets for which different limits with regard to drug content are specified in different pharmacopeias are listed in Table XIX. Products for which symmetrical limits have been specified are given in part *A* and those for which unsymmetrical limits have been specified in at least one pharmacopeia are shown in part *B* of this table. Deviations of at least 1% in either lower or upper assay limits were considered prerequisites for compilation. Of all products thus screened—112—no less than 61 (54.5%) satisfied this requirement. Comparison of the data reproduced illustrates the extent of variation which exists between pharmacopeial specifications for products subject to identical label claims for drug content.

It is difficult to assess some of these discrepancies. They cannot always and solely be ascribed to different analytical methods. For example, guanethidine tablets USP as well as B.P. are assayed colorimetrically, yet their assay limits range from 95–105% and 90–110%, respectively. Phentolamine hydrochloride tablets B.P. and NF are both assayed gravimetrically, yet pharmacopeial limits vary from 90–110% and 93–107%, respectively. Similarly, diethylcarbamazine citrate tablets USP and B.P. are determined titrimetrically, yet assay tolerances extend from 95–105% to 92.5–107.5%, respectively. On the other hand, products may be examined by different methods yet comply with identical specifications for drug content. Thus, primidone tablets USP, B.P., and State Pharmacopoeia of the U.S.S.R. (hexamidine) (95–105%) are analyzed by either ultraviolet spectrophotometry

or gravimetry. Acetylsalicylic acid tablets USP, B.P., and State Pharmacopoeia of the U.S.S.R. (95–105%) are determined by either ultraviolet spectrophotometry or by titrimetry. Similarly cyclizine hydrochloride tablets USP (93–107%) are subjected to spectral analysis, whereas cyclizine hydrochloride tablets B.P. (92.5–107.5%) are assayed by nonaqueous titrimetry.

Examples illustrating different specifications for drug content based on different methods of analysis may also be cited. Tolbutamide tablets USP (95–105%) are assayed by ultraviolet spectrophotometry, but tolbutamide tablets B.P. (92.5–107.5%) are assayed by Kjeldahl analysis. Nitrofurantoin tablets USP (95–105%) are examined by polarography. Nitrofurantoin tablets B.P. (90–110%) are examined spectrophotometrically. Sodium aminosalicylate tablets B.P. (90–110%) are analyzed by titration with nitrous acid, but sodium aminosalicylate tablets, State Pharmacopoeia of the U.S.S.R. (95–105%), are analyzed by iodimetry. Thus, limits may range from 10–20% for pharmacopeial products subject to identical label claims for drug content.

Finally, examples illustrating identical specifications based on identical methods of analysis can also be given. Diethylstilbestrol tablets USP, B.P., and Pharmacopoeia of the U.S.S.R. are all assayed colorimetrically (drug content limit 90–110%). Cortisone acetate tablets NF, B.P., and State Pharmacopoeia of the U.S.S.R. are all analyzed spectrophotometrically (assay limit 90–110%). Similarly, sulfadiazine tablets USP and B.P. are

TABLE XIX—SPECIFICATIONS FOR TABLETS INCLUDED IN TWO OR MORE PHARMACOPEIAS

Tablet	Assay Limits, %			
	USP XVII	NF XII	B.P. 1963	State Pharmacopoeia U.S.S.R. IX
A—Symmetrical				
Acetazolamide	95–105		92.5–107.5	
Amobarbital	94–106		92.5–107.5	
Amodiaquine hydrochloride		93–107	95.0–105.0	
Amphetamine sulfate		90–110	90.0–110.0	95–105
Busulfan	93–107		90.0–110.0	
Calcium cyclobarbital		94–106	95.0–105.0	
Calcium lactate		94–106	95.0–105.0	
Chlorambucil	93–107		90.0–110.0	
Chlorothiazide		93–107	95.0–105.0	
Chlorpromazine hydrochloride	95–105		92.5–107.5	
Chlorpropamide	95–105		92.5–107.5	
Dapsone	92.5–107.5		95.0–105.0	
Dehydrocholic acid		94–106	...	95–105
Dextroamphetamine sulfate	93–107		90.0–110.0	
Dextromethorphan hydrobromide		90–110	92.5–107.5	
Diethylcarbamazine citrate	95–105		92.5–107.5	
Digoxin	92–108		90.0–110.0	
Diiodohydroxyquin	95–105		92.5–107.5	
Ephedrine hydrochloride		93–107	92.5–107.5	95–105
Ferrous gluconate		93–107	90.0–110.0	
Guanethidine	95–105		90.0–110.0	
Hydralazine hydrochloride		95–105	92.5–107.5	
Isoniazid	93–107		95.0–105.0	
Lucanthone hydrochloride	93–107		95.0–105.0	
Mepacrine hydrochloride			95.0–105.0	90–110
Meperidine hydrochloride		95–105	92.5–107.5	
Methamphetamine hydrochloride	93–107		90.0–110.0	
Methylprednisolone		92.5–107.5	90.0–110.0	
Methyprylon		95–105	92.5–107.5	
Nitrofurantoin	95–105		90.0–110.0	
Phenacetin	94–106		...	95–105
Phenobarbital	94–106		92.5–107.5	95–105
Phenolphthalein		92.5–107.5	92.5–107.5	95–105
Phentolamine hydrochloride		93–107	90.0–110.0	
Phenylbutazone		93–107	95.0–105.0	
Phthalylsulfathiazole	94–106		95.0–105.0	95–105
Probenecid	92.5–107.5		95.0–105.0	
Prochlorperazine maleate	95–105		90.0–110.0	
Proguanil hydrochloride			95.0–105.0	90–110
Propantheline bromide	95–105		92.5–107.5	
Pyridostigmine bromide	95–105		92.5–107.5	
Quinidine sulfate	94–106		95.0–105.0	
Quinine sulfate		94–106	95.0–105.0	95–105
Sodium aminosalicylate	95–105		90.0–110.0	95–105
Sodium warfarin	95–105		90.0–110.0	
Tolbutamide	95–105		92.5–107.5	95–105
Trihexyphenidyl hydrochloride	93–107		90.0–110.0	
Tripelennamine hydrochloride	93–107		90.0–110.0	
Sodium barbital			95.0–105.0	95–105
B—Unsymmetrical				
Ascorbic acid	95–115		92.5–107.5	95–105
Ethinyl estradiol	90–115		90.0–110.0	
Folic acid	95–115		90.0–110.0	
Meclizine	95–110		92.5–107.5	
Mepacrine hydrochloride			95.0–105.0	95–110
Mercaptopurine	93–110		90.0–110.0	
Niacin		95–115	92.5–107.5	
Nitroglycerin	80–112		85.0–115.0	86–116
Promazine hydrochloride		95–110	90.0–110.0	
Promethazine hydrochloride	95–110		92.5–107.5	90–110
Sodium amobarbital			92.5–107.5	93–105
Sodium barbital			95.0–105.0	93–105
Sodium pentobarbital		90–105	92.5–107.5	90–105

both examined titrimetrically and, to comply with specifications for drug content, must assay 95–105%.

Further comparisons of pharmacopeial specifications for drug content of compressed tablets are made in Table XX. The compilation illustrates that 45 products for which specifications are found in the B.P. are covered in other compendia as well. Only 11 such products are included in the Russian pharmacopeia. It is also seen that of the four pharmacopeias surveyed, the USP contains the

TABLE XX—PHARMACOPEIAL SPECIFICATIONS FOR DRUG CONTENT OF COMPRESSED TABLETS

	USP XVII	NF XII	B.P. 1963	U.S.S.R. IX
No. of tablets listed in one or more pharmacopeial texts	29	17	45	11
No. of tablets with potency limits narrower than specified in other pharmacopeial texts	20	6	12	6
No. of tablets with potency limits equal to those specified in other pharmacopeial texts	1	0	2	4

highest proportion of products (covered in other compendia as well) with narrowest limits. On the other hand, the State Pharmacopoeia of the U.S.S.R. commands the highest ratio of products (for which monographs are given in other compendia as well) with limits narrower than or equal to those of the USP, NF, and B.P. (10 products out of 11).

Of the four reference compendia, the State Pharmacopoeia of the U.S.S.R. appears to be the most rigorously standardized. It allows for only two ranges and very few dosage levels of the same product. It specifies, moreover, all substances which may be incorporated as excipients into solid oral dosage forms and states their concentrations as normally used. Thus, tablet manufacture and pharmaceutical quality assurance are more strictly controlled.

SUMMARY

Considerable differences exist between pharmacopeial specifications applied in the quality control of bulk drugs and solid oral dosage forms. Often experimental results obtained by different national laboratories in accordance with national standards cannot be readily compared. Methodology and compliance vary significantly for even a test as simple as weight variation. Only a few common features characterize the disintegration test. Products meeting one pharmacopeia's standard may therefore fail to meet specifications, and be rejected, if tested by another pharmacopeia's standard.

Progress in drug evaluation, advances in drug therapy, and improvement of international drug trade would be facilitated immeasurably if a code of pharmaceutical specifications could be sanctioned internationally and adopted universally.

These objectives can and must be reached. They are embodied in the resolution adopted by the World Health Assembly at its recent plenary session and endorsed by the World Health Organization (60, 61). This resolution "requests the Director-General (a) to continue his assistance to Member States for the improvement of the quality control of pharmaceutical preparations, and for the establishment of quality control laboratories for national or regional purposes where such laboratory

facilities are insufficient; (b) to implement the proposals made in his report; particularly in regard to the establishment of general principles for the quality of pharmaceutical preparations and the quality control of the products entering into international commerce; and (c) to report on the results to the Executive Board and the Twentieth World Health Assembly."[13]

It should be the solemn duty of all privileged to participate in these programs to do their utmost so that collectively they may be brought to fruition. There are indeed no higher stakes—the health and happiness of mankind.

REFERENCES

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Determination of Antimony in Talc

By HARVEY D. SPITZ and ALEXANDER J. GOUDIE

A method has been developed to determine trace amounts of antimony present in talc. The spectrophotometric method is based upon the reaction of antimony (V) with rhodamine B in isopropyl ether after extraction of the antimony from 1.5 M hydrochloric acid.

RECENTLY, the Food and Drug Administration set limits for antimony in certain foodstuffs and dyes at 2 p.p.m. Because of the possible extension of this regulation to talc, a method has been developed for the semiquantitative determination of antimony in talc in the concentration range of 2 p.p.m.

Several methods have been developed to determine micro amounts of antimony. Iodide ion in acid solution (1, 2) or with iodide and pyridine (3) have been used, but not with the sensitivity of some other chromophoric reagents. Busev (4, 5) and his co-workers have developed a sensitive method using antipyrine dyes. However, the unavailability of these noncommercial dyes negated any work with them. Matulis and Guyon (6) have recently developed a sensitive system of analysis based on the enhancement by antimony of a blue hue due to the reduction of the molybdate aggregate near pH 1.4.

The most common technique has employed rhodamine B (7–14). A relatively simple and moderately accurate method for the determination of antimony in talc has been developed with rhodamine B as the chromophoric reagent.

EXPERIMENTAL

Apparatus and Reagents—A Zeiss PMQ II spectrophotometer employing 1-cm. silica cells was used.

Hydrochloric Acid, 6 M—Dilute 500 ml. of concentrated hydrochloric acid with sufficient purified water to make 1000 ml. of solution.

Hydrochloric Acid, 1 M—Dilute 20.8 ml. of concentrated hydrochloric acid with sufficient purified water to make 250 ml. of solution.

Sulfuric Acid, 0.5 M—Dilute 2.8 ml. of concentrated sulfuric acid with sufficient purified water to make 100 ml. of solution.

Ceric Sulfate—Dissolve 3.3 Gm. of anhydrous ceric sulfate in 100 ml. of 0.5 M sulfuric acid.

Hydroxylamine Hydrochloride—Dissolve 1 Gm. of hydroxylamine hydrochloride in 100 ml. of purified water.

Hydroxylamine Hydrochloride, Acidic—Dissolve 1 Gm. of hydroxylamine hydrochloride in 100 ml. of 1 M hydrochloric acid.

Isopropyl Ether (Peroxide Free)—Saturate the isopropyl ether with 1 M hydrochloric acid.

Rhodamine B Reagent—Dissolve 0.02 Gm. of rhodamine B in 100 ml. of 1 M hydrochloric acid.

Sodium Sulfite—Dissolve 1 Gm. of reagent grade sodium sulfite in 100 ml. of purified water.

Antimony Postassium Tartrate, Reagent Grade—[K(SbO)C₄H₄O₆·¹/₂H₂O].

Preparation of Standard—Weigh to the nearest tenth of a milligram a 274–mg. sample of antimony potassium tartrate into a 100-ml. volumetric flask. Dissolve the sample in and make up to the mark with 6 M hydrochloric acid. Pipet 10.00 ml. of this solution into a 100-ml. volumetric flask and dilute