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PHARMACOPEIAL FORUM VOL. 35 NO. 3

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**USP ANNOUNCES REVISION TO AMANTADINE HYDROCHLORIDE CAPSULES MONOGRAPH.**

The Biopharmaceutics Expert Committee (BPC) has approved the addition of *Dissolution Test 2* to the Amantadine Hydrochloride Capsules *Interim Revision Announcement* monograph. This monograph was previously printed as an *In-Process Revision* in *Pharmacopeial Forum* volume 35(1). The approved *Interim Revision Announcement* supersedes the monograph printed in *USP 32–NF 27* until the monograph is printed in the *USP 32–NF 27, Second Supplement*, which will be released June 1, 2009 and will become official December 1, 2009. The chromatographic procedure in this test was validated using the RTX-1 or DB-1 brand of G1 phase. The retention times for naphthalene and amantadine hydrochloride are approximately 6 and 7 minutes, respectively.

Should you have any questions on the Amantadine Hydrochloride Capsules Monograph, please contact Margareth Marques, Ph.D. at 301-816-8106 or mrm@usp.org.

**USP ANNOUNCES REVISION TO BUPROPION HYDROCHLORIDE EXTENDED-RELEASE TABLETS MONOGRAPH.**

The Biopharmaceutics Expert Committee (BPC) has approved the addition of *Dissolution Test 8* to the Bupropion Hydrochloride Extended-Release Tablets *Interim Revision Announcement* monograph. This monograph was previously printed as an *In-Process Revision* in *Pharmacopeial Forum* volume 35(1). The approved *Interim Revision Announcement* supersedes the monograph printed in *USP 32–NF 27, First Supplement* (released February 1, 2009 and official August 1, 2009) until it is printed in the *USP 32–NF 27, Second Supplement*, which will be released June 1, 2009 and will become official December 1, 2009.

Should you have any questions on the Bupropion Hydrochloride Extended-Release Tablets Monograph, please contact Margareth Marques, Ph.D. at 301-816-8106 or mrm@usp.org.

**STAGE 4 AND STAGE 6 HARMONIZED STANDARDS ARE NOW FEATURED IN TWO SEPARATE PF SECTIONS.**

USP publishes monographs and general chapters that are undergoing international harmonization by the Pharmacopeial Discussion Group (PDG) at Stage 4 and Stage 6. The Stage 4 documents are published for public comment. The Stage 6 documents have received PDG approval. These documents are being published to inform readers of their PDG sign-off status.

To make clear the distinction between Stages 4 and 6, USP has revised the Harmonization section of *Pharmacopeial Forum (PF)* by separating the two types of documents.

Stage 4 documents are published in *PF* in draft form and are available for public comment. The Japanese and the European Pharmacopoeias and the USP analyze comments and revise the general chapters and monographs accordingly. The documents are revised based on the comments received and then forwarded to the next stage.

The Stage 6 documents are provided in *PF* as an informational resource, and these documents will be published in the next available official publication. The Stage 6 documents published in *PF 35(3)* will be official in *USP 33–NF 28*.

**PHARMACOPEIAL FORUM PUBLIC REVIEW AND COMMENT PERIOD DEADLINES.**

The USP welcomes and encourages interested parties to submit comments and data regarding potential, proposed, or adopted (official) standards. In accordance with the Rules and Procedures of the 2005–2010 Council of Experts, USP has implemented a 90-day comment period by providing a deadline for each issue of *PF* unless otherwise stated in the individual briefing. The listing of comment period deadlines and the targeted official publications appears below.

Pharmacopeial Forum	Comment Deadline	Targeted Official Publication	Release Date	Official Date
PF 35(2)	June 15, 2009	USP 33–NF 28 1st Supplement	February 2010	August 1, 2010
PF 35(3)	August 15, 2009			
PF 35(4)	October 15, 2009	USP 33–NF 28 2nd Supplement	June 2010	December 1, 2010
PF 35(5)	December 15, 2009			
PF 35(6)	February 15, 2010	USP 34–NF 29	November 2010	May 1, 2011
PF 36(1)	March 31, 2010			

All official revisions are published in the annual edition or *Supplements* to *USP–NF* (twice yearly). Between these publications, official revisions are published in *PF* in the *Interim Revision Announcement* section and incorporated in the upcoming *Supplement* or book. They may also be published as *Revision Bulletins* on [www.usp.org](http://www.usp.org) in the “New Official Text” section. The official publication in which an *IRA* is incorporated will depend upon publica-

tion deadlines. See the table below. The electronic version of *USP–NF* is updated as each *Supplement* becomes available and, therefore, contains all official text up to and including the contents of the latest *Supplement*. The table below outlines the publications and their release and official dates, and the book or supplement which supersedes them.

### Publication Schedules

Publication	Release Date	Official Date	Superseded by
<i>USP 32–NF 27</i>	November 1, 2008	May 1, 2009	<i>1st Supplement to USP 32–NF 27</i>
<i>IRA [PF 35(1)]</i>	January 1, 2009	February 1, 2009	<i>2nd Supplement to USP 32–NF 27</i>
<i>1st Supplement to USP 32–NF 27</i>	February 1, 2009	August 1, 2009	<i>2nd Supplement to USP 32–NF 27</i>
<i>IRA [PF 35(2)]</i>	March 1, 2009	April 1, 2009	<i>2nd Supplement to USP 32–NF 27</i>
<i>IRA [PF 35(3)]</i>	May 1, 2009	June 1, 2009	<i>USP 33–NF 28</i>
<i>2nd Supplement to USP 32–NF 27</i>	June 1, 2009	December 1, 2009	<i>USP 33–NF 28</i>
<i>IRA [PF 35(4)]</i>	July 1, 2009	August 1, 2009	<i>1st Supplement to USP 33–NF 28</i>
<i>IRA [PF 35(5)]</i>	September 1, 2009	October 1, 2009	<i>1st Supplement to USP 33–NF 28</i>
<i>IRA [PF 35(6)]</i>	November 1, 2009	December 1, 2009	<i>2nd Supplement to USP 33–NF 28</i>
<i>USP 33–NF 28</i>	November 1, 2009	May 1, 2010	<i>1st Supplement to USP 33–NF 28</i>

**PRIORITY NEW MONOGRAPH ITEMS.** USP is seeking monographs for the following drug substances and drug products that are or soon will be off patent and thus are of the highest priority. USP also is seeking monographs for the excipients listed below. Monographs are marked “Received” upon receipt of monograph proposal. Received monographs are removed from this list upon publication in *Pharmacopeial Forum* or when posted in the Pending Monographs section of the USP website

(<http://www.usp.org/standards/pending/>). This list has been updated as of February 20, 2009; monographs received since the last update to the list are noted in bold.

Monograph sponsors should consult USP’s Guideline for Submitting Requests for Revision to the *USP–NF* at <http://www.usp.org/USPNF/submitMonograph/subGuide.html>.

For additional information, contact Karen A. Russo, Ph.D., [kar@usp.org](mailto:kar@usp.org).

### Small Molecules (Drug Substances)—As of February 20, 2009

1. Allopurinol Sodium	2. Aminopropazine Fumarate	3. Aminopterin Sodium
4. Anagrelide Hydrochloride <b>(Received)</b>	5. Arsenic Trioxide	6. Auranfoin
7. Azelaic Acid <b>(Received)</b>	8. Balsalazide Disodium <b>(Received)</b>	9. Bentoquatam
10. Benzphetamine Hydrochloride	11. Bivalirudin <b>(Received)</b>	12. Calcipotriene
13. Calcium Trisodium Pentetate	14. Calfactant	15. Candesartan Cilexetil <b>(Received)</b>
16. Ceftibuten	17. Cetorelix	18. <b>Cevimeline Hydrochloride</b> <b>(Received)</b>
19. Chloroxine	20. Choline Salicylate	21. Cysteamine Bitartrate
22. Dalfopristin	23. Dapirazole Hydrochloride	24. Desirudin
25. Desonide <b>(Received)</b>	26. Dexrazoxane	27. Difenoxin Hydrochloride
28. Entacapone <b>(Received)</b>	29. Epoprostenol Sodium <b>(Received)</b>	30. Erythromycin Phosphate
31. Erythromycin Thiocyanate	32. Esmolol Hydrochloride <b>(Received)</b>	33. Estazolam <b>(Received)</b>
34. Estramustine Phosphate Sodium	35. Ethanolamine Oleate	36. Etomidate <b>(Received)</b>
37. Etoposide Phosphate	38. Exemestane	39. Famciclovir <b>(Received)</b>
40. Felbamate <b>(Received)</b>	41. Fluoromethane F 18	42. Fosfomycin Tromethamine <b>(Received)</b>
43. Gadobenate Dimeglumine	44. Gadopentetic Acid	45. Gallium Nitrate

## INSTRUCTIONS TO AUTHORS

Contributions in the form of original research reports, evaluations of new and existing compendial methods, and other commentaries and articles relevant to drug standards or to *USP–NF* revision will be considered for publication in *Pharmacopeial Forum* under the section *Stimuli to the Revision Process*. Manuscripts are received with the explicit understanding that they have not been published previously in any language or medium and that they are not simultaneously under consideration by any other publication.

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## Drug Product Performance and Interchangeability of Multisource Drug Substances and Drug Products

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**ABSTRACT** Multisource drug products may contain drug substances and drug products that meet *USP–NF* monograph standards of strength, quality, purity, and identity. Pharmaceutical equivalence per se does not ensure equivalent drug product performance as demonstrated by bioequivalence, nor does it ensure therapeutic equivalence. This *Stimuli* article examines pharmaceutical equivalence and suggests that multisource drug products that meet *USP* monograph requirements may not be pharmaceutical equivalents and/or may not have the same drug product performance.

### INTRODUCTION

Multisource drug products are products marketed by more than one manufacturer that contain the same active pharmaceutical ingredient (API) or drug substance in the same dosage form and are given by the same route of administration. Many of these multisource drug products contain drug substances that meet *USP–NF* monograph standards of strength, quality, purity, and identity. However, drug substances and drug products that solely meet the same *USP–NF* monograph standards should not be considered automatically as interchangeable products. The objective of this *Stimuli* article is to provide an understanding of interchangeability and substitutability of drug substances and drug products that meet *USP–NF* monographs.

Pharmaceutical equivalents are drug products that contain the same active ingredient(s), are of the same dosage form, are administered by the same route, and are identical in strength or concentration. Pharmaceutically equivalent drug products are formulated to contain the same amount of active ingredient in the same dosage form and to meet the same or compendial or other applicable standards (i.e., strength, quality, purity, and identity), but they may differ in characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, and preservatives), expiration time, and, within certain limits, labeling.

Multisource drug products that meet *USP–NF* monographs may not be pharmaceutical equivalents and/or may not have the same drug product performance. Designation of multisource drug products for interchangeability (substitution) generally is a matter of governmental (regulatory) approval. Regulatory approval for interchangeable multisource generic drug products is not identical in all countries. The US Food and Drug Administration (FDA) has very strict rules for the approval and marketing of generic drug products. These regulations must be considered during the devel-

opment of both branded and generic drug products. Drug product performance also must be considered if any changes occur in the finished dosage form, including scale up, site changes, process changes, or other modifications that could have an effect on the drug product. Only multisource drug products that are pharmaceutical equivalents, bioequivalent, and therapeutic equivalents that have been approved by the appropriate regulatory agency (e.g., FDA), may be marketed as interchangeable. *USP* General Information Chapter *In Vivo Bioequivalence Guidances* (1090) discusses the basis for therapeutic equivalence.

*USP–NF* contains science-based standards for drugs, biologics, dietary supplements, and excipients used in dosage forms and products. A *USP–NF* monograph for an official substance or preparation includes applicable standards of strength, quality, purity, and identity, including also the article's definition, packaging, storage, and other requirements and specifications. The specification consists of a series of universal (description, identification, impurities, and assay) and specific tests, one or more analytical procedures for each test, and acceptance criteria.

Ingredients are defined as either drug substances or excipients. An excipient is any component, other than the active substance(s), intentionally added to the formulation of a dosage form. Excipients are not necessarily inert and may affect the performance of the finished dosage form (drug product). Quality standards are important attributes that must be built into the drug product. Products that meet *USP–NF* standards are accepted globally as articles with an assurance of high quality.

In addition to meeting *USP–NF* quality standards, multisource drug products must meet certain in vivo and/or in vitro performance standards to be considered therapeutically equivalent and interchangeable (see *USP* General Information Chapter (1090)). Drug product performance may be defined as the release of the active pharmaceutical ingredient (API) from the drug product dosage form, leading to systemic availability of the API necessary to achieve a desired therapeutic response.

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## Topical and Transdermal Drug Products

The Topical/Transdermal Ad Hoc Advisory Panel for the USP Performance Tests of Topical and Transdermal Dosage Forms: Clarence T. Ueda (Chair), Vinod P. Shah (USP Scientific Liaison), Kris Derdzinski, Gary Ewing, Gordon Flynn, Howard Maibach, Margareth Marques (USP Scientific Liaison),<sup>a</sup> Howard Rytting,<sup>b</sup> Steve Shaw, Kailas Thakker, and Avi Yacobi.

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**ABSTRACT** This *Stimuli* article provides general information about the test methods that should be employed to ensure the quality and performance of topical and transdermal drug products. The term *topical drug products* refers to all formulations applied to the skin except transdermal delivery systems (TDS) or transdermal patches that will be addressed separately.

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### INTRODUCTION

Drug products topically administered via the skin fall into two general categories, those applied for local action and those for systemic effects. Local actions include those at or on the surface of the skin, those that exert their actions on the stratum corneum, and those that modulate the function of the epidermis and/or the dermis. Common products in the former category include creams, gels, ointments, pastes, suspensions, lotions, foams, sprays, aerosols, and solutions. Creams, ointments, and gels generally are referred to as semisolid dosage forms. The most common drug products applied to the skin for systemic effects are referred to as self-adhering transdermal drug delivery systems (TDS) or transdermal patches.

Two categories of tests, product quality tests and product performance tests, are performed with drug products to provide assurances of batch-to-batch quality, reproducibility, reliability, and performance. Product quality tests are performed to assess attributes such as assay, identification, content uniformity, pH, microbial limits, and minimum fill and are part of the compendial monograph. Product performance tests are conducted to assess drug release from the finished dosage form.

This *Stimuli* article provides general information about the test methods that should be employed to ensure the quality and performance of topical and transdermal drug products. The term *topical drug products* refers to all formulations applied to the skin except transdermal delivery systems (TDS) or transdermal patches that will be addressed separately.

Topical dosage forms include solutions (for which release testing is not indicated), collodion, suspensions, emulsions (e.g., lotions), semisolids (e.g., foams, ointments, pastes, creams, and gels), solids (e.g., powders and aerosols), and sprays. The physical characteristics of these dosage forms vary widely.

Therefore, the in vitro release test for those products also may differ significantly and may require different types of apparatus. At present, a product performance test exists only for semisolid formulations, specifically creams, ointments, and gels. That test employs the vertical diffusion cell (VDC) system. The VDC system is simple to operate and yields reliable and reproducible results when employed by properly trained laboratory personnel.

TDS or transdermal patches are physical devices applied to the skin and vary in their composition and method of fabrication. Therefore, they release their active ingredients by different mechanisms.

### GLOSSARY OF TERMS

Definitions of topical drug products, some aspects related to the manufacture of these products, and a glossary of dosage form names commonly used can be found in General Information Chapter *Pharmaceutical Dosage Forms* (1151).

#### Collodion

Collodion (pyroxylin solution; see *USP* monograph), is a solution of nitrocellulose in ether and acetone, sometimes with the addition of alcohol. As the volatile solvents evaporate, a dry celluloid-like film is left on the skin. Because the medicinal use of a collodion depends on the formation of a protective film, the film should be durable, tenacious in adherence, flexible, and occlusive.

#### Creams

Creams are semisolid dosage forms that contain one or more drug substances dissolved or dispersed in a suitable base. This term traditionally has been applied to semisolids that possess a relatively soft, spreadable consistency formulated as either water-in-oil or oil-in-water emulsions. However, more recently the term has been restricted to products consisting of oil-in-water emulsions or aqueous microcrystalline dispersions of long-chain fatty acids or alcohols that are water washable and more cosmetically and aesthetically acceptable.

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## Performance-based Monographs

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**ABSTRACT** This *Stimuli* article describes a performance-based monograph (PBM) that specifies tests and acceptance criteria for articles in the *US Pharmacopeia (USP)* and *National Formulary (NF)*. For selected tests of the monograph, a certified reference material (CRM) from USP would be provided to assist analysts in developing sound procedures. Availability of a default procedure in association with the PBM is considered, pros and cons of the approach are presented, and comments are solicited.

### INTRODUCTION

A *US Pharmacopeia (USP)* specification for a drug substance, excipient, or product contains four universal tests (Definition, Identification, Assay, and Impurities) and certain specific tests, with accompanying procedures and acceptance criteria. Each manufacturer develops a unique specification for its ingredients and products. Specifications developed by multiple manufacturers of the same ingredient or product may include tests and acceptance criteria that are similar, but the procedures used in the tests may not be the same. Despite this, USP's intent is to present a monograph establishing a standard specification that encompasses all legally marketed ingredients and products, where appropriate. The procedures presented in *USP* traditionally have been provided by the innovator of a drug substance. As additional manufacturing sources of ingredients and products become available, these original procedures can become too restrictive, causing the *USP–NF* monograph to be out of step with current industry practice. This has led to the development of flexible monographs (1) and the need for alternative suppliers of information and reference materials (RMs) to provide evidence that their procedures are adequate for all marketed products (2).

In contrast to the current approach wherein all elements of the monograph's specification are explicitly provided, a performance-based monograph (PBM) provides a specification for a drug substance that includes a *Test* and *Acceptance criteria*, but the *Procedure* would define only the criteria needed to show that the procedure used is acceptable. The universal tests and acceptance criteria generally are consistent between monographs [e.g., Assay, 98.0%–102.0%; Identification with IR or chromatography; impurities, not more than (NMT) 0.10%; and others] and rarely differ significantly. Therefore, in the case of most drug substances, a default set of tests and acceptance criteria could be used. An example of a performance-based monograph appears in *Appendix 1* in the form of a PBM for Acamprosate Calcium. The general approach fits well within the concepts articulated

under the general term *quality by design*, where knowledge and design space requirements conclude with an understanding of the private control space pertinent to a particular ingredient and product (3, 4). The control space for the public standard may be viewed as the total array of tests and acceptance criteria of the monograph.

The application of a PBM approach would involve a number of important changes in the way that *USP–NF* monographs and related General Chapters are created, used, and interpreted. The major components of this concept include the PBM itself, to include a definition of an acceptable procedure, primary certified reference materials (CRMs), and, when available, appropriate screening procedures. Initially, only new monographs would be targeted for the PBM approach. In some instances, the performance-based procedure may appear in a General Chapter (5).

### ACCEPTABLE PROCEDURES

What defines an *acceptable procedure*? There are several means to define an acceptable procedure, including equivalent or better, and others described by Hauck et al. (6). In that article, the term *acceptable procedure* is described as a procedure that "meets a set of minimum performance requirements." The term acceptable also means that a procedure is suitable for its intended use. An acceptable procedure also has been defined as a procedure that is validated as described in USP General Chapter *Validation of Compendial Methods (1225)* (7). This General Information Chapter provides a set of criteria (reproduced herein as *Table 1*) but does not provide the minimum performance criteria necessary to define an acceptable procedure. Using these criteria as a starting point, one can see that the type of test directly affects the set of performance requirements. In this discussion, we focus on International Conference on Harmonization (ICH) universal tests for ingredients, with the understanding that many of the applications also pertain to drug products.

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## Acceptable, Equivalent, or Better: Approaches for Alternatives to Official Compendial Procedures

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**ABSTRACT** The *General Notices* in the *US Pharmacopeia (USP)* permit analysts to use acceptable (suitable) alternatives to an official procedure. In a revision that will be effective May 1, 2009, the *General Notices* will require that the alternative procedure be demonstrated to give results that are equivalent to or better than those obtained by the official procedure. This *Stimuli* article discusses approaches for determining equivalent or better procedures. The concepts and tests discussed in this paper may become one or more *USP* General Chapters. The preceding *Stimuli* article speaks to approaches that determine an acceptable procedure without requiring a study to document equivalent or better.

### INTRODUCTION

In its *General Notices*, the *US Pharmacopeia (USP)* states: "Compliance may be determined also by the use of alternative methods, chosen for advantages in accuracy, sensitivity, precision, selectivity, or adaptability to automation or computerized data reduction or in other special circumstances. Such alternative or automated procedures or methods shall be validated (1).<sup>b</sup> The *General Notices* requirement for validation means the analyst using the alternative procedure has determined the procedure is acceptable (suitable) for its intended use in the specified monograph test. The wording of the *USP General Notices* presumes that the alternative procedure possesses *some* property for which there is an advantage, however defined—otherwise why use it? But the *General Notices* statement does not require comparison to the compendial procedure on advantageous properties. A priori, one would think that the alternative procedure should be not be worse, however defined, than the compendial procedure, but this is not stated in the current *General Notices*. A revision to the *General Notices* (3) that will be official May 1, 2009, calls for the alternative procedure to "give equivalent or better results" by comparison with the compendial procedure. In addition, elsewhere the *General Notices* state: "Proportionately larger or smaller quantities than the specified weights and volumes of assay or test substances and Reference Standards may be taken, provided the measurement is made with *at least equivalent accuracy*... [emphasis added]" (1). General Chapter *Validation of Alternative Microbiological Methods* (1223) states, "The critical question is whether or not the alternat[iv]e meth-

od will yield results *equivalent to, or better than*, the results generated by the conventional method [emphasis added]" (1, p. 681). *USP* does not provide a definition or approaches for alternative procedures, whether they are deemed acceptable, equivalent, or better.

The Food and Drug Administration (FDA) and ICH employ similar language regarding alternative procedures. The Code of Federal Regulations, in the section that covers requirements for Equivalent Methods and Processes for biological products, requires "that the modification will provide assurances of the safety, purity, potency, and effectiveness of the biological product *equal to or greater than* the assurances provided by the method or process specified in the general standards or additional standards for the biological product [emphasis added]" (4). FDA also uses a similar phrase in its draft guidance, *Analytical Procedures and Methods Validation: Chemistry, Manufacturing, and Controls Documentation* (5). In discussing alternative analytical procedures this guidance notes, "A validated alternative analytical procedure should be submitted only if it is shown to perform *equal to or better than* the regulatory analytical procedure [emphasis added]" (5). ICH Q6A, 2.7 *Alternative Procedures*, states, "Alternative procedures are those which may be used to measure an attribute when such procedures control the quality of the drug substance or drug product to an extent that is *comparable or superior* to the official procedure [emphasis added]" (6). In MAPP 5310.7, FDA's Office of New Drug Quality Assessment states the following policy for its reviewers: "If there is no USP/NF monograph for an excipient, drug substance, or drug product, and the applicant proposes to use an analytical procedure from the BP, EP, or JP in a specification in lieu of the corresponding analytical procedure in the General Chapters of the USP/NF, the BP, EP, or JP procedure is considered an alternative analytical procedure and may be used provided the analytical procedure in the BP, EP, or JP is *equivalent to or better than* the corresponding analytical procedure in the USP/NF [emphasis added]." "Equivalent" is used in this paper rather than the "equal" of 21 CFR 610.9(c) in order to avoid the connotation of *equal as meaning identical* (7).

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<sup>b</sup> Using terminology of the International Conference on Harmonization (ICH), the US Pharmacopeial Convention (USPC) uses the term *procedure* to describe the steps to be followed by the analyst in conducting a test. This is in agreement with the *International Vocabulary of Metrology (VIM)* (2), which describes a measurement procedure as a detailed description in contrast to a measurement method, which is a generic description (such as "indirect, a direct method, or an instrumental method"). This *Stimuli* article thus will use the terminology *comparison of procedures* rather than *comparison of methods*.