

The Application of Uncertainty to USP's Compendial Reference Standards Program: Certified Reference Materials

Reference Standards Expert Committee Subcommittee on Certified Reference Materials,* Ronald G. Manning, Steven Lane, Shawn Dressman, Walter W. Hauck,† Roger L. Williams, USP

ABSTRACT USP creates comprehensive, practical, relevant, and timely documentary standards and reference materials (RMs) to help ensure the strength, quality, and purity of medicines (drugs, biologics, and excipients) and foods (dietary supplements and food additives). These standards may be adopted by governmental and nongovernmental bodies, including most notably the United States (US) Federal government, which recognizes the *United States Pharmacopeia (USP)* and *National Formulary (NF)* in the Federal Food Drug & Cosmetic Act as official compendia of the US. USP's RMs are closely tied to USP's documentary standards and arise through collaborative and other studies, from which resulting information is forwarded to the Council of Experts' Reference Standards Expert Committee (RSEC) for a decision. If that decision is positive and unanimous RMs become official USP Reference Standards. During the past several years the RSEC and staff have considered amplifying this laboratory work so that official USP Reference Standards may be labeled as Certified Reference Materials (CRMs). This *Stimuli* article provides information to support further discussion and results from a pilot study. USP encourages comments.

INTRODUCTION

As part of its public health mission to establish useful pharmaceutical standards based on the best possible science, USP intends to develop selected RMs as Certified Reference Materials (CRMs). The development of USP CRMs results from increasing national and international acceptance of modern metrological principles and approaches. This paper discusses the rationale and operational details of USP's emerging CRM program, as well as the compendial and regulatory applications of uncertainty of measurement and other relevant information associated with CRMs.

BACKGROUND

Scientific and technical discussion of USP's CRM program occurs in the Reference Standard Expert Committee (RSEC) of the Council of Experts. During the 2000–2005 cycle the RSEC worked with Project Team 4 of the Prescription/Non-prescription Stakeholder Forum to advance the discussion, with input from the US national metrology institute—the National Institute of Standards and Technology (NIST)—and the International Organization for Standardization (ISO). Based on these discussions USP published a report providing 1) an overview of metrology concepts as they relate to USP's standards, 2) a history of and description of USP's RM collection, 3) value assignment decisions of the RSEC based on recommendations from Project Team 4, and 5) scientific issues and opportunities (1). That report provides an introduction to this *Stimuli* article, as illustrated by the following statement from the report:

USP's monographs and official USP Reference Standards are most commonly used in . . . quality control laboratories [to allow release of a batch into the marketplace].

USP does not engage in testing itself but rather provides the "measurement study" (monograph) and official USP Reference Standard [in support of "technically and administratively correct decisions."] The hypothesis of a quality control laboratory is that the article [medicine or food or their ingredients], when tested, yields a result that either does or does not fall within a monograph's acceptance criteria. If results fall within the acceptance criteria, the article is deemed acceptable [i.e., its identity has been established relative to its name]. If not, the result may be deemed "out of specification" (p. 11).

Beyond USP's efforts, NIST and ISO approaches are of increasing interest. FDA's new guidance on GMPs reflects ISO 9001 approaches (2). An FY 2006 goal for FDA's Office of Regulatory Affairs (ORA) was to establish and maintain a laboratory quality system that meets the requirements of ISO 17025, *General Requirements for the Competence of Testing and Calibration Laboratories* (3). The ultimate FDA goal is to achieve and maintain accreditation for all 13 ORA laboratories (4). USP's Rockville, MD, headquarters and India laboratories are both ISO 9001 and 17025 certified. USP plans for all of its laboratories worldwide to be certified to both standards. Manufacturers of medicines and foods are also advancing toward ISO approaches.

ISO Guide 17025 provides guidance to owners and operators of laboratories regarding both quality management in a laboratory environment and technical requirements for the proper operation of a testing laboratory. Guide 17025 includes sections on uncertainty (uncertainty should be properly estimated), traceability (results should be traceable to an internationally agreed reference such as the *Système International d'Unités*, the international system of units based on the meter, kilogram, second, ampere, kelvin, candela, and mole), and quality control (each result should be demonstrably valid within its stated uncertainty). An important section of 17025 discusses the purpose for which the result will be used, including any legal aspects of the work. Also included in 17025 are requirements for periodic proficiency testing. ISO 17025 further references ISO Guide 43, Parts 1 and 2, regarding proficiency

* For membership see Appendix.

† Correspondence should be addressed to: Walter W. Hauck, PhD, Senior Scientific Fellow, US Pharmacopeia, 12601 Twinbrook Parkway, Rockville, MD 20852-1790; phone: 301.816.8390; e-mail: wh@usp.org.

test programs and the need for and use of CRMs (5). The general framework for certifying reference materials is discussed in ISO Guides 30–35 (6). Guide 34, amended in 2003, specifically addresses requirements for the competence of reference material producers.

According to ISO, an RM is sufficiently homogeneous and stable with respect to one or more specified properties and has been established to be fit for its intended use in a measurement process for value assignment, i.e., the content of the RM for the measurand under test is specified (ISO Guides 30 and 31). RM is a generic term, and RM properties can be quantitative or qualitative: e.g., they may be associated with the identity of substances or species. Uses may include the calibration of a measurement system, assessment of a measurement procedure, assigning values to other materials, and quality control. An RM can be used only for specific purpose(s) in a given measurement. RM is a general, umbrella concept—a family name. Many different kinds of RMs exist, including CRMs. A CRM is an RM that is characterized by a metrologically valid procedure for one or more specified properties, accompanied by a certificate that provides the value of the specified property, its associated uncertainty, and a statement of metrological traceability. Annex A of ISO Guide 34 provides an elaboration of various ways in which this traceability can be achieved, including the interlaboratory approach described in this paper. The concept of *value* includes qualitative attributes such as identity or sequence. Uncertainties for such attributes may be expressed as probabilities. Metrologically valid procedures for the production and certification of reference materials are given in, among others, ISO Guides 34 and 35. ISO Guide 31 gives guidance regarding the contents of certificates.

PILOT STUDY

USP executed a pilot study on five candidate RMs. The pilot study involved the following steps:

1. Acquire bulk candidate RM
2. Homogenize bulk by blending
3. Subdivide bulk into vials

4. Pull samples from early, middle, and late stages of packaging runs
5. Submit test protocols and samples to three USP-qualified laboratories
6. Analyze results to determine content, uncertainty, and homogeneity of samples
7. Draw conclusions and plan for next steps.

Following blending of received material, candidate RMs were subdivided and packaged into standard vials. Samples were pulled from early, middle, and late portions of the packaging run for multilaboratory testing. Value assignment relied on mass balance using usual USP approaches (*Table 1*), calculated as follows:

$$\text{mg of analyte/mg of material} = (100.0\% - \text{sum of percentage of } \textit{dry basis} \textit{ impurities})(100.0\% - \text{sum of percentage of } \textit{as is} \textit{ impurities})/10,000$$

where *dry basis* impurities are those that are measured as a percentage of the dried sample or as a percentage of total response for a technique that does not respond to water or residual solvents and *as is* impurities are those that are measured as a w/w percentage of the sample taken without drying. For this study the *dry basis* impurities were related compounds of the analyte measured by compendial high-performance liquid chromatographic (HPLC) procedures expressed as a percentage of the total detectable area, and the *as is* impurities were measured by techniques such as *Loss on Drying* (731), *Water* (921), *Residual Solvents* (467), and *Residue on Ignition* (281). On the label of its Reference Standards USP includes instructions for use. Some USP Reference Standards are labeled with instructions to dry before use or to determine water content at time of use. In such cases the Loss on Drying, Residual Solvents, or Karl Fischer results are excluded from the mass balance calculation in order to avoid double counting. Using only the measurements involved in the mass balance determinations, researchers conducting the pilot study measured uncertainty according to approaches described in ISO Guide 98, *Guide to the Expression of Uncertainty in Measurement* (7).

Table 1. Methods Included in the Mass Balance Calculation for the Five Standards in the Study

CRM 1	HPLC impurities, LOD*
CRM 2	HPLC impurities, ROI†
CRM 3	HPLC impurities, ROI, LOD
CRM 4	HPLC impurities, ROI, LOD
CRM 5	HPLC impurities, ROI, Residual Solvents, Water

* = loss on drying.

† = residue on ignition.

Results of the multilaboratory testing are shown in *Table 2*.

Table 2. Total Expanded Uncertainties in Comparison to the Associate Monograph Acceptance Criteria

	“Certified” Value (mg/mg)	Total Expanded Uncertainty (mg/mg)	Monograph Acceptance Criteria	Uncertainty as Percentage of Monograph Assay Range
CRM 1	0.997	0.0006	98.0–102.0%	3%
CRM 2	1.000	0.0005	98.0–102.0%	3%
CRM 3	0.999	0.002	98.0–102.0%	10%
CRM 4	0.997	0.002	90.0–110.0%	2%
CRM 5	0.939	0.004	945–1030 µg/mg	13%*

* Using symmetrical acceptance criteria of 970–1030 µg/mg to calculate percentage

UNCERTAINTY CONSIDERATIONS

USP conducts collaborative studies to determine the assigned value for each of its RMs (official USP Reference Standards) and, for CRMs, the expanded uncertainty. USP does not believe it is sufficient simply to determine the uncertainty for a CRM—that uncertainty must be small for the RM’s intended use. The following describes considerations for determining what is small enough. The perspective is for a customer using a USP CRM as a standard in its analytic work. Uncertainty in the assigned value of a USP RM becomes part of the uncertainty of a quality control laboratory’s assignment of value to a measurand, e.g., the content of the active pharmaceutical ingredient and/or its impurities in a drug substance. The impact of an RM uncertainty, unless it is negligible, is that it will alter

the likelihood that a quality control laboratory will make an incorrect administrative decision—passing an item that does not meet its acceptance criteria (consumer risk) or failing to pass an item that does (producer risk). *Figure 1* shows the probability of failing an item as a function of the true value for the item. The curve is for a 0.5% coefficient of variation (CV) in the laboratory for the single determination and for no error in the assigned value of the Reference Standard. The acceptance criterion is taken here to be (98.0%, 102.0%) as in the case of an active pharmaceutical ingredient (API). USP rounding rules are applied, so the effective acceptance interval is (97.95%, 102.04%) as shown by the vertical lines in *Figure 1*.

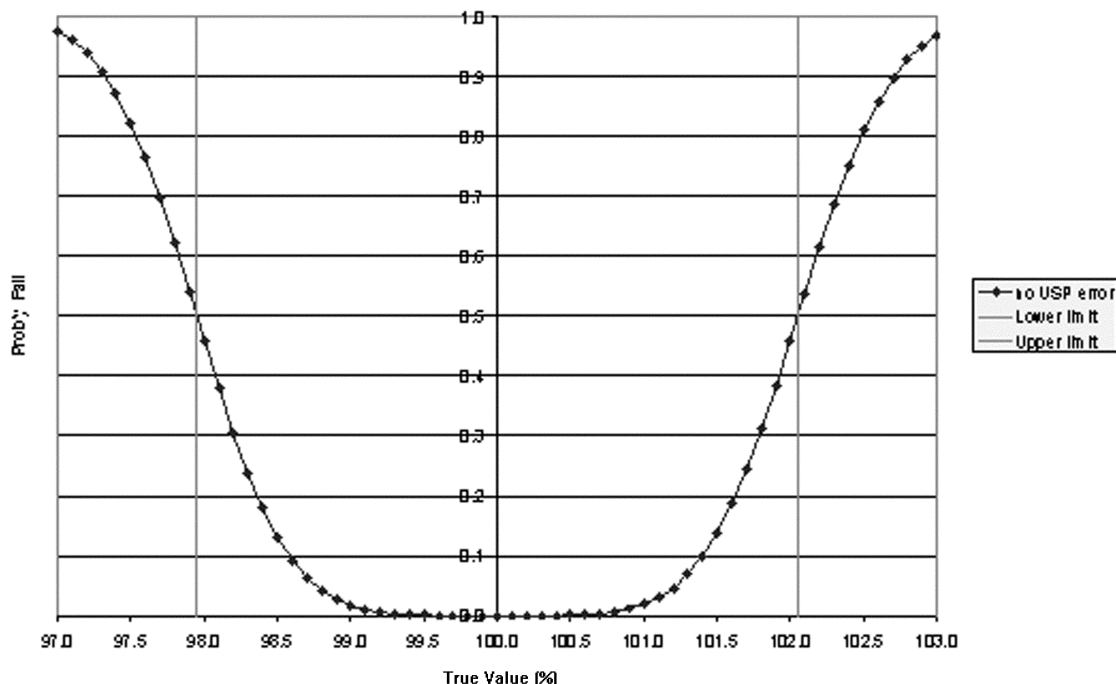


Figure 1. Probability of failing an item—no error in Reference Standard assigned value (CV = 0.5%).

Figure 1 shows that the probability of failing the item is essentially 0.0 for a value near 100%. The probability eventually increases as the value deviates from 100% and reaches 50% at the effective acceptance limits (the vertical lines). Outside the

acceptance limits the probability continues to increase, eventually reaching the asymptote of 1.0. An ideal curve would be

0.0 for all values within the limits, thus passing all acceptable items, and 1.0 for all values outside the limits, thus failing unacceptable items.

Figure 2A repeats Figure 1 but with the addition of two curves representing possible choices of maximum uncertainty in the CRM. The expanded uncertainty for a CRM is the half-width of a 95% confidence interval for the assigned value. A worst-case scenario occurs when the actual content of the Reference Standard is at one of the ends of the confidence interval for the assigned value. For example, if a CRM has an assigned

value of 99.3% and an expanded uncertainty of 0.3%, the 95% confidence interval is (99.0%, 99.6%), and either 99.0% or 99.6% would then be the worst-case error in the assigned value. For the calculations underlying Figure 2, we assume that the laboratory determines a ratio—such as that of areas—and multiplies that ratio by the assigned value of the Reference Standard. In the log scale, then, an error in the assigned value of the Reference Standard is an additive error. The impact is to narrow the acceptance interval by the magnitude of that error.

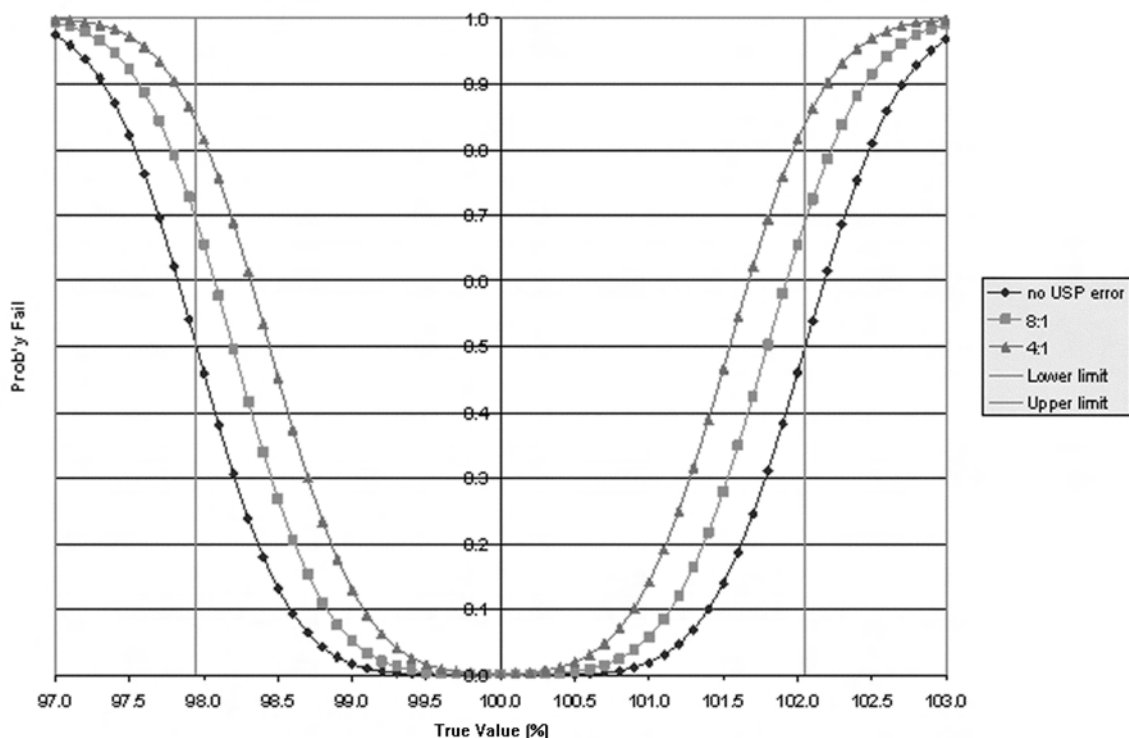


Figure 2A. Probability of a failing result with a worst-case error in the CRM (CV = 0.5%).

The allowed maximum error is typically expressed in one of two ways: The first is for the ratio of the \pm limits of the acceptance interval to the expanded uncertainty. For example, if the acceptance interval is $\pm 2\%$, then a 4:1 ratio means the expanded uncertainty of the RM needs to be less than one-fourth of 2%. This ratio is sometimes referred to as the test accuracy ratio (TAR) or test uncertainty ratio. We will use this form in the present manuscript. The second form of expression is the ratio of the acceptance interval width to the expanded uncertainty. For symmetric acceptance limits, the second form is twice the first ratio. That is, a 4:1 TAR means the expanded uncertainty should not be more than one-eighth of the acceptance interval width.

A criterion for maximum uncertainty of the CRM assigned value can then be considered in terms of the relationship between the expanded uncertainty and the acceptance criteria. Figure 2 considers two options: a TAR of 4:1 (e.g., 0.5%

for $100.0\% \pm 2.0\%$) and a TAR of 8:1 (e.g., 0.25% for $100.0\% \pm 2.0\%$). The choice of 4:1 is commonly used and was part of MIL-STD 45662A, although the latter was cancelled in 1995. The American Society of Mechanical Engineers (ASME) document (8) suggests a range of 10:1 to 3:1, and 4:1 and 3:1 have been more commonly used in recent years. Based on these considerations, a choice of 4:1 seems to be a reasonable default choice and is the TAR used by the *European Pharmacopeia* (U. Rose, written communication, June 2007.). To understand the implications of this choice, Figure 2 also shows results for 8:1. In terms of expanded uncertainty, a 4:1 criterion corresponds to an expanded uncertainty no more than one-eighth the width of the acceptance interval, and an 8:1 criterion corresponds to one-sixteenth the width of the acceptance interval.

Figures 2B and 2C repeat the curves of Figure 2A with increased laboratory CV (1.0% and 1.5%, respectively).

STIMULI TO THE REVISION PROCESS

Stimuli articles do not necessarily reflect the policies of the USPC or the USP Council of Experts

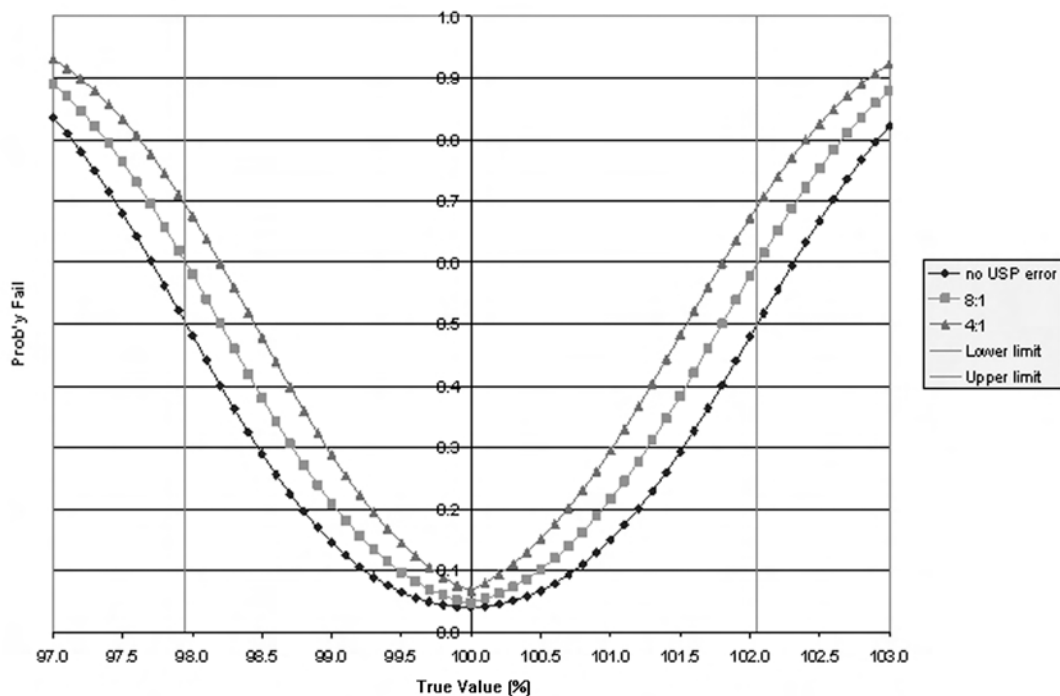


Figure 2B. Probability of a failing result with a worst-case error in the CRM (CV = 1.0%).

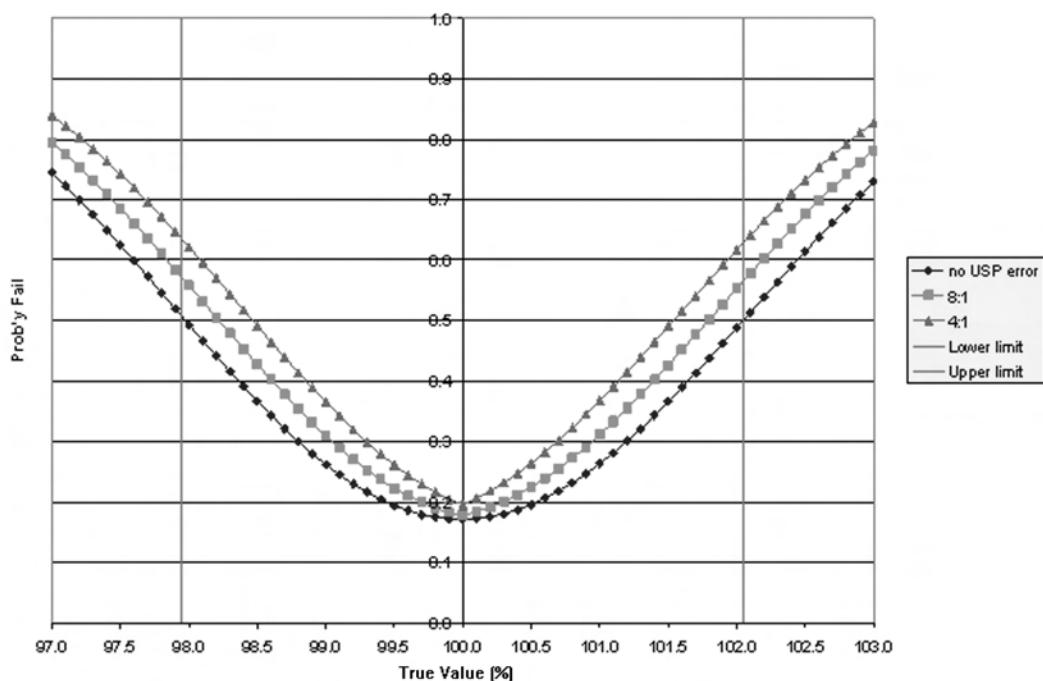


Figure 2C. Probability of a failing result with a worst-case error in the CRM (CV = 1.5%).

The curves shown in *Figure 2* choose the maximum error for the assigned value in order to increase the probability of failing the item. Thus these curves show only the effect of

falsely failing items that should pass. Other curves, not shown, could demonstrate the probability of failing, thus increasing the probability of not failing items that should fail.

PILOT RESULTS AND CERTIFICATE OF ANALYSIS

The results described above have focused on the measurement of uncertainty, but another key requirement for a CRM is a certificate of analysis. The certificate must include the certified values for the material, demonstration of the traceability of the values to an SI unit of measure, expression of the uncertainty of the certified value, and an explanation of how the certified values and uncertainties were measured. An example of such a certificate for candidate material #1 appears in *Figure 3*. USP understands the need for a certificate as a requirement for a CRM but has not reached a decision about how to make this certificate publicly available.

DISCUSSION

As shown in *Table 2*, expanded uncertainty for the candidate RMs in the pilot study was extremely low and perhaps could be considered negligible. This is expected to be true of many of USP's RMs, which are highly purified chemicals drawn from pharmaceutical production. USP is aware, however, that some of its RMs exhibit greater uncertainty, e.g., some potency standards that are defined by a unit of activity, such as enzymes and antibiotics. This observation, however, does not yield a conclusion about what is small enough. It may be that—as with many acceptance criteria—an a priori decision will be useful in determining what is small enough, e.g., a 4:1 TAR approach. This would yield a quality boundary for USP's RM collection. If the a priori limit were to be exceeded, USP would do additional studies to assure the public that an RM uncertainty would not be greater than the specified amount. When the uncertainty was likely to be very low, USP might design smaller multilaboratory studies than would be needed for candidate RMs with higher expected uncertainty.

At times, quality control laboratories may qualify secondary standards to primary national or international standards. When this occurs, the uncertainty of the secondary standards includes the uncertainty of the primary standard. Thus the uncertainty of the secondary standard is larger than that of the primary standard. Because the uncertainty is based on a confidence interval, this uncertainty can be overcome with increased testing.

SUMMARY

The Strategic Plan of USP's Board of Trustees speaks to the importance of accelerating introduction of new RMs in pace with monograph development and maintaining the quality of RMs that are currently available. The quality of a USP RM is evaluated and expressed by the provision of information discussed in this *Stimuli* article. The scientific aspects of this information are the responsibility of the RSEC of the Council of Experts—and of the entire Council of Experts—working with staff. A consensus has developed in the RSEC that these approaches are sound. This *Stimuli* article reflects that consensus and articulates a scientific way forward for USP to offer CRMs in accordance with ISO Guide 34. Although further experience will be beneficial, the pilot study has concluded, and

the five articles studied have been placed in commerce without publication of uncertainty values. USP will continue to apply the new approach with selected additional candidate materials, thus allowing the pilot approach to become increasingly routine. Beyond this publication, staff will advance further needed communications and training: e.g., the Prescription/Nonprescription Stakeholder Forum may wish to consider a Project Team devoted to the topic. USP has not concluded an approach that will make available a certificate required for a CRM. This has important implementation aspects that require careful staff consideration. Pending implementation of a certificate, the public will not know which RMs offered by USP have the requisite testing that would support a CRM. For this reason, USP intends rapidly to advance consideration of a certificate. Overall, USP's advances in ensuring the quality of its RM collection are intended to align with regulatory and manufacturing approaches to ensure that patients and practitioners have available official articles (ingredients and products) of the most optimal and relevant quality.

REFERENCES

1. Williams RL, Project Team 4, the 2000–2005 Reference Standards Committee of the USP Council of Experts and Its Advisory Panel, USP Staff, Consultant. Official USP reference standards: metrology concepts, overview, and scientific issues and opportunities. *J Pharm Biomed Anal.* 40;2006:3–15.
2. FDA. Pharmaceutical CGMPs for the 21st century—a risk-based approach. September 2004. www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4078B1_08_CGMP-Report.pdf. Accessed 07 June 2005.
3. ISO. *Guide 17025—General Requirements for the Competence of Testing and Calibration Laboratories*. Geneva, Switzerland: ISO; 2005.
4. FDA. Disposition of FY 2006 performance goals. www.fda.gov/oc/oms/ofm/budget/2007/HTML/3DispositionTable.htm. Accessed 07 June 2007.
5. ISO. *Guide 43—Proficiency Testing by Interlaboratory Comparisons. Part 1: Development and Operation of Proficiency Testing Schemes and Part 2: Selection and Use of Proficiency Testing Schemes by Laboratory Accreditation Bodies*. Geneva, Switzerland: ISO; 1997.
6. ISO. *Guide 30—Terms and Definitions Used in Connection with Reference Materials* (1992); *ISO Guide 31—Reference Materials—Contents of Certificates and Labels* (2000); *ISO Guide 32—Calibration in Analytical Chemistry and Use of Certified Reference Materials* (1997); *ISO Guide 33—Uses of Certified Reference Materials* (2000); *ISO Guide 34—General Requirements for the Competence of Reference Material Producers* (2003); *ISO Guide 35—Reference Materials—General and Statistical Principles for Certification* (2006). Geneva, Switzerland: ISO; [dates as shown].
7. ISO. *Guide 98—Guide to the Expression of Uncertainty in Measurement (GUM)*. Geneva, Switzerland: ISO; 1995.
8. ASME. Guidelines for decision rules: considering measurement uncertainty in determining conformance to specifications. ASME B89.7.3.1-2001. New York, NY: ASME; 2001:4.

STIMULI TO THE REVISION PROCESS

Stimuli articles do not necessarily reflect the policies
of the USPC or the USP Council of Experts

Pharmacopeial Forum
Vol. 33(6) [Nov.–Dec. 2007]

8

Appendix: Reference Standards Expert Committee Subcommittee on CRMs

Philip J. Palermo, PhD—Chair
Private Consultant

Matthew W. Borer, PhD
Eli Lilly and Company

David Fay, PhD
Tyco Healthcare/Mallinckrodt

Antony Raj Gomas, MS
Dr. Reddys Laboratories, Ltd.
Hyderabad, Andhra India

Shaohong Jin, BA
National Institute for the Control of
Pharmaceutical and Biological Products
China

Judy Lee, PhD
Purdue Pharma, LP

Maria Ines Santoro, PhD
University of Sao Paulo
Sao Paulo, Brazil 05508-900

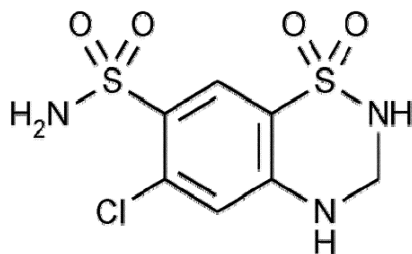
Figure 3. Sample certificate of analysis.



U.S. Pharmacopeia
The Standard of Quality™

Certificate of Analysis

USP Hydrochlorothiazide RS
LOT J0F070



Molecular Formula

C₇H₈ClN₃O₄S

Molecular Weight

297.74

CAS Number

58-93-5

Produced and Certified by:	The UNITED STATES PHARMACOPEIA 12601 Twinbrook Parkway Rockville, MD 20852-1790
Catalog Number:	1314009
Nominal Package Size:	200 mg
Appearance:	Clumpy white powder
Hazards:	N/A
Storage:	Controlled Room Temperature
Release Date:	December 2006
Instructions for Use:	Do not dry. For quantitative applications, use a value of 0.997 mg of hydrochlorothiazide per mg of material. Keep container tightly closed.
Certified Content Value:	Standard Uncertainty 0.997 ± 0.0002 mg/mg on the as is basis Expanded Uncertainty 0.997 ± 0.0006 mg/mg on the as is basis

STIMULI TO THE REVISION PROCESS

Stimuli articles do not necessarily reflect the policies
of the USPC or the USP Council of Experts

Pharmacopeial Forum
Vol. 33(6) [Nov.–Dec. 2007]

	Confidence Level: 95% k = 2.8
Uncertainty Values:	Uncertainties are provided for informational purposes only. They are not to be used in assessing conformance to Compendial requirements.
Period of Validity:	Continued Suitability for Use studies of historical batches of USP Hydrochlorothiazide RSs indicate that the Certified Value of Lot J0F070 is expected to remain valid through the anticipated lifetime of the lot. Further studies at appropriate intervals will be conducted to confirm this Period of Validity.
Homogeneity Assessment:	During the production of end use vials, samples were collected from the Early, Middle, and Late segments of the filling operation. Three laboratories analyzed each. The resulting content determinations were evaluated using a Two-Way ANOVA calculation. The values obtained: F = 0.71, and P = 0.54 > alpha (0.05) Therefore, the Early, Middle, and Late segments are statistically equal, and the material is considered homogeneous
Traceability:	The declared content value of this Certified Reference Material was obtained using standard methods for Hydrochlorothiazide found in <i>USP–NF</i> and is therefore traceable to the strict adherence to those methods by all collaborating laboratories. In addition, all direct measurements of mass were performed on balances whose calibration certificates were traceable to NIST traceable calibration weights and are therefore traceable to the kg.

Certification Details

Three Laboratories evaluated three samples each of the candidate material in order to assign a value. The Mass Balance approach was used, i.e., 100% – Total Impurities%. Impurities were determined by USP HPLC (Hydrochlorothiazide Related Compounds) and *LOD <731>* methods for this material. All collaborating laboratories used a common protocol. The analysis of each detected impurity was treated as a separate experiment and the grand mean of means was used in uncertainty calculations.

HPLC

Reference:	<i>USP 29</i> , page 1061
Column:	C18, 5 cm x 4.6 mm; 3 μ m
Mobile Phase:	Gradient elution of Solution A and Solution B Solution A: acetonitrile and methanol (3:1) Solution B: anhydrous formic acid in water (5 in 1000)
Sample Concentration:	0.32 mg/mL
Diluent:	Sodium phosphate and acetonitrile (7:3)
Injection Volume:	10 μ L
Flow Rate:	1.0 mL/min
Run Time:	20 min
Column Temperature:	35°
Result:	0.0024 mg/mg Total Chromatographic Impurities

Loss on Drying

Reference:	<i>USP 29</i> , page 1061
Conditions:	Dry at 105° for 1 hour
Result:	0.00022 mg/mg

STIMULI TO THE REVISION PROCESS

Stimuli articles do not necessarily reflect the policies
of the USPC or the USP Council of Experts

Additional Tests

Infrared Absorption, (IR, FTIR)

Reference: Identification-A, *USP 29*, page 1061
Result: Conforms

Ultraviolet Absorption

Reference: Identification-B, *USP 29*, page 1061
Result: Conforms

Elemental Analysis

Result: Consistent with theory

Assay

Reference: *USP 29*, page 1061
Result: 100.6% vs. *USP Hydrochlorothiazide RS*, Lot I

Scope of Certification: This certification was conducted according to the guidelines in ISO Guides 30-35 and is valid only for the Official Uses of this particular Reference Standard found in the current version of the *USP-NF*. The use of this information for any other purpose is the responsibility of the user.

Intended Use:

This is an established *USP Reference Standard*. Its official applications in *USP 29–NF 24* and proposed applications (marked by *) in *PF 31(4)*, p. 1123 [July–August 2005], *PF 30(6)*, p. 2006 [November–December 2004], and *PF 29(4)*, p. 1036 [July–August 2003] (copies attached) are listed below. This list is subject to change in the normal *USP* revision process.

Monograph	ID	Related compounds	Chromatographic purity	Limit of captopril disulfide	Drug Release	Dissolution	Uniformity of dosage units	Assay
Amiloride Hydrochloride and Hydrochlorothiazide Tablets	TLC, HPLC					UV	HPLC	HPLC
Bisoprolol Fumarate and Hydrochlorothiazide Tablets	TLC, HPLC		HPLC			HPLC	HPLC	HPLC
Captopril and Hydrochlorothiazide Tablets	HPLC			HPLC **		UV	HPLC	HPLC
Enalapril Maleate and Hydrochlorothiazide Tablets	HPLC					UV	UV	HPLC
Fosinopril Sodium and Hydrochlorothiazide Tablets *	IR, HPLC					HPLC	HPLC	HPLC
Hydrochlorothiazide Hydrochlorothiazide Tablets	IR, UV IR, HPLC	HPLC ** HPLC **				UV	HPLC	HPLC
Irbesartan and Hydrochlorothiazide Tablets *	HPLC					HPLC	HPLC	HPLC
Methyldopa and Hydrochlorothiazide Tablets	HPLC					UV	HPLC	HPLC
Metoprolol Tartrate and Hydrochlorothiazide	UV					UV	UV	HPLC

STIMULI TO THE REVISION PROCESS

Stimuli articles do not necessarily reflect the policies
of the USPC or the USP Council of Experts

Pharmacopeial Forum
Vol. 33(6) [Nov.–Dec. 2007]

Tablets								
Propranolol Hydrochloride and Hydrochlorothiazide Extended-Release Capsules	IR, HPLC				UV	UV	UV	HPLC
Propranolol Hydrochloride and Hydrochlorothiazide Tablets	IR					UV	UV	HPLC
Reserpine, Hydralazine Hydrochloride, and Hydrochlorothiazide Tablets	IR, UV						UV	UV
Reserpine and Hydrochlorothiazide Tablets	TLC					UV	UV	UV
Spironolactone and Hydrochlorothiazide Tablets	HPLC					HPLC	HPLC	HPLC
Timolol Maleate and Hydrochlorothiazide Tablets	TLC					UV	HPLC	HPLC
Triamterene and Hydrochlorothiazide Capsules	TLC, HPLC					UV, HPLC	HPLC	HPLC
Triamterene and Hydrochlorothiazide Tablets	TLC, HPLC					HPLC	HPLC	HPLC
Valsartan and Hydrochlorothiazide Tablets *	TLC, HPLC	HPLC				UV	HPLC	HPLC

** Used in system suitability as a resolution probe and peak identifier.

USP certifies that the USP Reference Standards Expert Committee, in accordance with their rules and procedures, determined that this USP Reference Standard lot is suitable to assess compliance with the monograph standards for which it is specified. The critical characteristics of this lot are usually determined independently in three or more laboratories, including USP, government, academic, and industrial collaborators.

QA Director

LEGAL NOTICE

USP MAKES NO REPRESENTATION OR WARRANTY WITH RESPECT TO THE ACCURACY, COMPLETENESS, OR CURRENTNESS OF THIS CERTIFICATE; AND USP SPECIFICALLY DISCLAIMS ANY OTHER WARRANTY, EXPRESS, IMPLIED, OR STATUTORY, INCLUDING, BUT NOT LIMITED TO, THE IMPLIED WARRANTIES OF MERCHANTABILITY AND FITNESS FOR A PARTICULAR PURPOSE. USP DOES NOT WARRANT THAT THE INFORMATION CONTAINED HEREIN MEETS THE CUSTOMER'S REQUIREMENTS. USP SHALL NOT BE LIABLE ON ACCOUNT OF ANY SUCH ERRORS OR OMISSIONS.

STIMULI TO THE REVISION PROCESS

Stimuli articles do not necessarily reflect the policies
of the USPC or the USP Council of Experts

USP Reference Standards are not intended for use as drugs,
dietary supplements, or as medical devices.
This document is not a Material Safety Data Sheet.

This certificate may not be reproduced without
the express written permission of USP.

Copyright 2007 The United States Pharmacopeial Convention, Inc. All rights reserved.

STIMULI TO THE REVISION PROCESS

Stimuli articles do not necessarily reflect the policies
of the USPC or the USP Council of Experts

Pharmacopeial Forum
Vol. 33(6) [Nov.–Dec. 2007]