

## Validation Viewpoint

**Specifications establish the criteria to which a drug substance or product should conform to be considered acceptable for its intended use. Setting specifications requires justifications and the application of different types of tests under different circumstances, each with their own acceptance criteria. This month's "Validation Viewpoint" column discusses the general concepts and highlights some specific guidelines and testing used in the process of setting specifications.**

**Michael Swartz and  
Ira Krull**

*Validation Viewpoints Editors*

# Setting Specifications

In all our years of lecturing, teaching, and writing on the subject of method validation, the most fertile ground for questions we have received concerns setting specifications. Specifications that establish tests, procedures, and acceptance criteria play a major role in ensuring the quality of new drug substances and products at release and during shelf life. But who determines specifications? How does one find or establish acceptance criteria? In a regulated laboratory, setting specifications and acceptance criteria generally is left up to the originator. That is, only the originator (applicant, manufacturer) can determine and justify what is appropriate for a particular product, test, or procedure for eventual approval by a regulatory agency. However, help is available. Recently, the U.S. Food and Drug Administration (FDA) adopted an International Conference on Harmonization (ICH) guideline (1) on specifications for new drug substances and products (2). This guideline addresses the process of selecting tests and methods, setting specifications for the testing of drug substances and dosage forms, and includes several flow-chart decision trees for different types of tests. And while this month's column will discuss the FDA guidance in some detail, the reader is encouraged to consult the references for additional details. The guideline was written to establish global specifications for marketing approval of new drug substances and products of synthetic chemical origin and new drug products produced from them that have not been registered in the U.S., European Union, or Japan. FDA guidance documents are available through the Freedom of Information Act and are always a good source of information because they are prepared for review staff to establish policies intended to achieve consistency in FDA policy and regulatory approach and to establish inspection and enforcement policies and procedures.

So just what exactly is a specification? Quite simply, a specification is defined as a

list of tests, references to analytical procedures, and appropriate acceptance criteria for the test described (for example, numerical limits, ranges, or other criteria to which a drug substance or product should conform to be considered acceptable for its intended use). Specifications ensure product quality and consistency and are just one part of a total control strategy. Also necessary are thorough product characterization during development and adherence to good manufacturing practices (for example, suitable facilities, validated manufacturing processes and test procedures, raw material testing, and stability testing). When proposing specifications, justification is needed for each procedure and acceptance criteria. Justification should include related data from development, pharmacopeial standards, test data from toxicological and clinical studies, and results from accelerated and long-term stability studies. When justifying a specification, normal or acceptable analytical or manufacturing variability should be taken into consideration. The final goal is "conformance to specifications" which means that the drug substance or drug product satisfies the listed acceptance criteria when tested according to the documented analytical procedure.

### General Concepts

An understanding of several types of testing concepts is necessary in order to develop and set specifications. These concepts include: Limited Data Available at Filing, Periodic or Skip Testing, Release Versus Shelf-Life Acceptance Criteria, In-Process Tests, Parametric Release, and Pharmacopeial Tests. Not all of these tests are applicable universally, but each needs to be considered as circumstances warrant. Test design and development considerations also should take into account data and experience acquired during the development of a new drug substance or product. Sometimes this experience can lead to justifying exclusion or replacement of specific tests.

### Limited Data Available at Filing

Many times, only a limited amount of data is available when an application is filed, and the basis for setting acceptance criteria focuses on safety and efficacy. Until additional data and experience manufacturing a drug substance or product is obtained, it might be necessary to propose revised acceptance criteria. This situation necessitates reviewing initial approved tests and acceptance criteria as more data are collected. After review, modifications involve loosening and tightening the acceptance criteria as appropriate.

### Periodic or Skip Testing

Periodic or skip testing is the performance of specific tests on preselected batches at predetermined intervals as opposed to testing every batch. Of course, it is understood that all of the untested batches still must conform to the acceptance criteria for that product. Batch selection and intervals must be justified and approved by the regulatory authorities prior to test implementation. Because many times only a limited amount of data is available when an application is filed, this concept generally is implemented postapproval.

### Release Versus Shelf-Life Acceptance Criteria

Sometimes, for drug products, more-restrictive acceptance criteria are set for release of the drug product than are applied to the shelf-life. This concept sometimes is applied to assay and impurity (degradation product) testing levels. Sometimes an applicant might choose to have tighter in-house limits at the time of product release to provide additional assurance that the product will remain within the regulatory acceptance criteria throughout its shelf-life.

### In-Process Tests

In-process tests are performed during the manufacture of the drug substance or product, as opposed to the traditional prerelease testing. When the acceptance criteria are identical to or tighter than the release specification, the in-process test can be included in the release specification. However, this approach must be validated to show that the characteristics of the product do not change from the in-process stage to final release. In-process tests that are used only to adjust process parameters within an operating range normally are not included in the specifications.

### Parametric Release

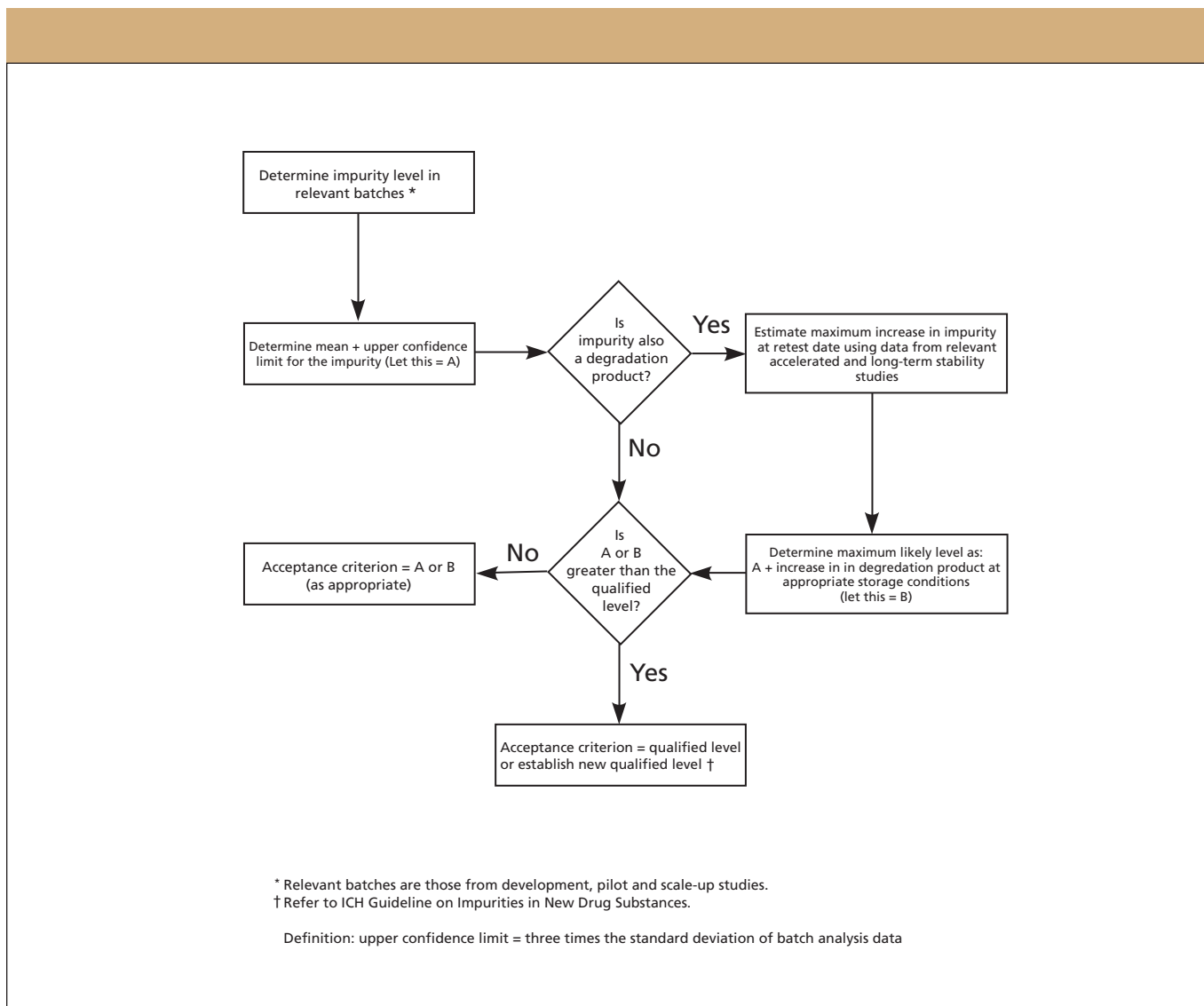
Parametric release testing involves monitoring of specific batch parameters (for example, temperature, pressure, and time) as an alternative to routine release testing. Appropriate physical or chemical laboratory tests also can be included in parametric release testing. Sometimes these parameters can be controlled and measured more easily than, for example, sterility. The parametric release process should be maintained in a validated state, as demonstrated by revalida-

tion at established intervals, and the attribute that is controlled indirectly, together with the associated parametric test procedures, should be included in the specifications.

### Pharmacopeial Tests

Wherever they are appropriate, pharmacopeial procedures should be followed. One of the main goals of the ICH process is harmonization of procedures on a global basis, and the U.S., Japan, and European phar-





**Figure 1:** Establishing acceptance criteria for a specified impurity in a new drug substance.

macopeias all have expressed a commitment. Eventually, all three pharmacopeias will be considered equivalent and interchangeable.

### Universal Tests and Criteria

There are some tests that are considered universal for setting specifications for new drug substances and products. These universal tests include: description, identification, assay, and impurities. Implementation of tests in this category also should take into account general method validation guidelines found in other USP and ICH documents (3–5). A *description* constitutes a qualitative statement about the state and color of the new drug substance. *Identification testing* should be able to discriminate between compounds of closely related structure that might be present, and should be specific for the new drug substance.

Chromatographic retention time, for example, is not specific; however the addition of an advanced detection technique, such as photodiode array detection or mass spectrometry (MS), generally is acceptable. An *assay* to determine the new drug substance content should be specific and stability indicating. Impurities (organic and inorganic impurities, and residual solvents) are governed by additional ICH guidelines (6–8). Two recent “Validation Viewpoint” columns also have addressed this topic and should be consulted for more detail (9,10). Organic impurities that are degradants of the new drug substance and process-related impurities from the new drug product should be monitored, along with acceptance limits.

For many of these tests, reference standards are used that in most cases are characterized more stringently than the sub-

stance being regulated. Reference standards should be accompanied by a certificate of analysis from a reputable source and have a quality appropriate for their intended use, including control of impurities by procedures not usually applied in routine testing.

### Specific Tests and Criteria: New Drug Substances

In addition to the general tests mentioned earlier, the following specific tests might be considered for new drug substances:

**Physicochemical properties:** Used to measure properties such as pH, melting point and range, and refractive index, these tests are determined by the physical nature of the drug substance and its intended use.

**Particle size:** For many formulations, particle size can have a significant effect on dissolution rates, bioavailability, and stabil-

Table I: Summary of decision tree attachment to the guideline for setting specifications and acceptance criteria

Decision Tree	Title	Comments
One	Establishing Acceptance Criterion For a Specified Impurity in a New Drug Substance	Relevant batches are those from development, pilot, and scale-up studies.
Two	Establishing Acceptance Criterion For a Degradation Product in a New Drug Product	Refers back to decision tree #1.
Three	Establishing Acceptance Criterion For Drug Substance Particle Size Distribution	Helps to determine if acceptance criterion for particle size is required.
Four	Investigating the Need to Set Acceptance Criteria for Polymorphism in Drug Substances and Products	Establishes criteria or justification for exclusion of test.
Five	Establishing Identity, Assay, and Enantiomeric Impurity Procedures for Chiral New Drug Substances and New Drug Products Containing Chiral Drug Substances	Numerous footnotes that should be consulted for more detail.
Six	Microbiological Quality Attributes of Drug Substance and Excipients	Establishes criteria or justification for exclusion of test.
Seven	Setting Acceptance Criteria For Drug Product Dissolution	Justification for dissolution versus disintegration; acceptance criteria for single versus multiple point rate-release profiles.
Eight	Microbiological Attributes of Non-Sterile Drug Products	Establishes criteria or justification for skip-lot testing or exclusion of test.

ity. Testing should be performed using an appropriate procedure, and acceptance criteria should be provided.

**Polymorphic forms:** Differences in polymorphic forms can affect quality or performance of the product in some cases, because different crystalline forms can alter

physical properties. In the cases where differences are known to exist, the appropriate solid state should be specified. Physicochemical techniques such as melting point (including hot-stage microscopy), solid-state infrared (IR), X-ray powder diffraction, thermal analysis (procedures such as

differential scanning calorimetry and thermogravimetric analysis), Raman spectroscopy, and solid-state nuclear magnetic resonance (NMR) often are used to determine if multiple forms exist.

**Drug substance chirality:** When a new drug substance is developed as one enan-



tiomer, the other enantiomer generally is treated in the same way as other impurities. However, sometimes technical limitations prevent the same limits of quantitation from being applied. Nevertheless, an assay for the enantioselective determination of the drug substance should be a part of the specification (11). The determination can be achieved either by a chiral assay procedure or by the combination of an achiral assay together with an appropriate method to control the enantiomeric purity. For a drug substance developed as a single enantiomer, criteria should be included in the specification when the specific test has an impact on quality for batch control. Identity tests should be capable of distinguishing both enantiomers and the racemic mixture. In general, there are two cases where a stereospecific test is appropriate for release and acceptance testing: where there is a significant possibility that the enantiomer might be substituted for the racemate and where there is evidence crystal-

lization might lead to unintentional production of a nonracemic mixture.

**Drug product chirality:** Unless racemization has been shown to be insignificant during manufacture of the dosage form and on storage, stereospecific control for the analysis of degradation products is necessary. On assay, where there is no racemization, an achiral assay might be sufficient. Otherwise, a chiral assay should be used or alternatively, the combination of an achiral assay plus a validated procedure to control stereospecificity. For identification, a stereospecific test generally is not employed unless racemization is a concern. Then it is more appropriately covered at the drug substance stage.

**Water content:** When the new drug substance is known to be hygroscopic, a test for water content is important. Justification of the specification should include data on the effects of hydration and moisture absorption. A detection procedure specific for water (for example, Karl Fis-

cher titration) is preferred, but in some cases, a loss-on-drying procedure might be sufficient.

**Inorganic impurities:** Inorganic impurities commonly arise from catalysts used in the manufacturing process. The need for tests and acceptance criteria usually is determined during development based upon knowledge of the process. Pharmacopeial procedures and acceptance criteria exist for sulfated ash-residue on ignition. Other appropriate techniques, such as atomic absorption spectroscopy, are used commonly for other inorganic impurities.

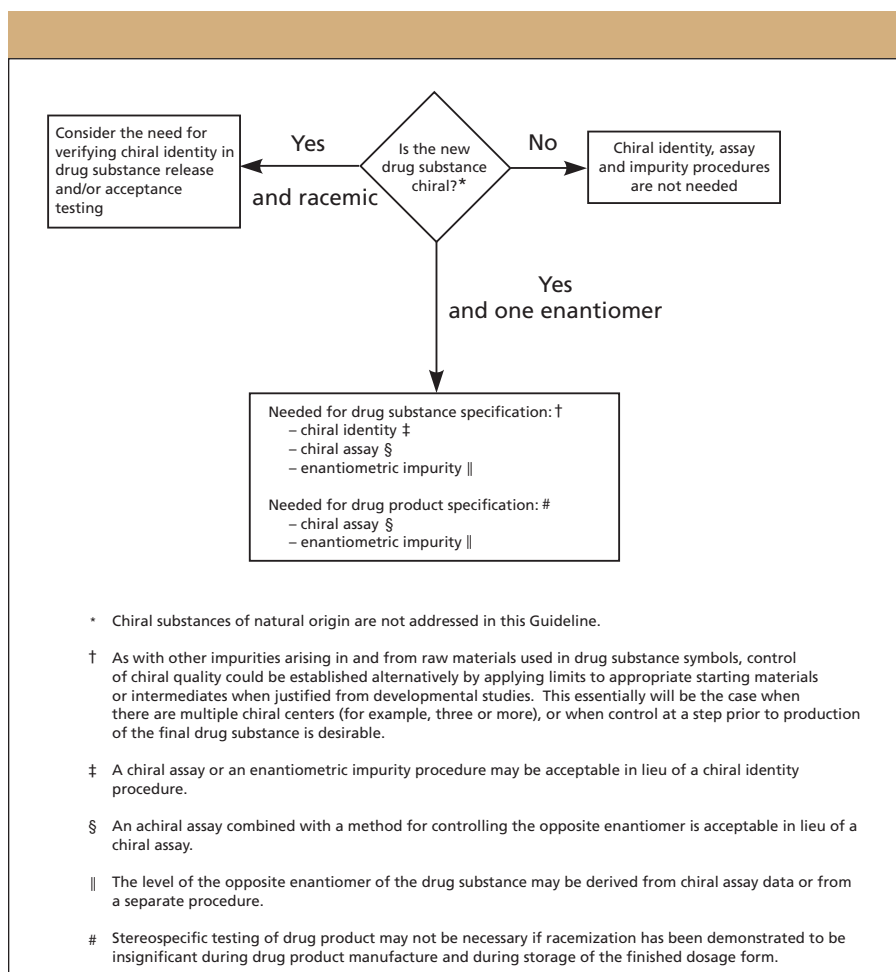
**Microbial limits:** Where needed, pharmacopeial procedures are used to specify parameters like the total aerobic microorganism count, the total count of yeast and molds, and the absence of specific objectionable bacteria. The choices of the type of microbial tests and acceptance criteria are based upon the nature of the drug substance and method of manufacture.

### Specific Tests and Criteria: New Solid Oral Drug Products

For some new drug products, additional testing might be needed, depending upon the dosage form. The specific dosage forms highlighted in the guidance include solid and liquid oral drug products and parenterals. For solid oral drug products, specific additional tests include dissolution, disintegration, hardness-friability, and uniformity of dosage units.

**Dissolution:** Specifications for solid oral dosage forms usually include a test to measure release of the drug substance from the drug product by dissolution. For immediate release formulations, single-point determinations commonly are used. For modified release formulations, appropriate test conditions and sampling procedures must be established. In general, multiple time-point rate-release curves are called for when testing extended or delayed release formulations. In instances where the rate of release can be demonstrated to affect bioavailability significantly, batch tests that can discriminate between acceptable and unacceptable bioavailability are needed. In this instance, *in vitro*-*in vivo* correlation can be used to establish acceptance criteria. In practice, the variability in mean release rate at any given time point should not exceed a total difference of  $\pm 10\%$  of the labeled content of the drug substance (that is, a total variability of 20%; a requirement of 50% means a range of 40–60%).

**Disintegration:** Disintegration can be substituted for dissolution for rapidly dis-



**Figure 2:** Establishing identity, assay, and enantiomeric impurity procedures for chiral new drug substances and new drug products containing chiral drug substances.

solving (dissolution > 80% in 15 min at pH 1.2, 4.0, and 6.8) highly soluble (dose–solubility volume < 250 mL from pH 1.2 to 6.8) new drug products. Disintegration also is appropriate in a case where a relationship to dissolution has been documented.

**Hardness–friability:** Hardness–friability normally is performed as an in-process control (addressed previously). It usually is necessary only to include these attributes in the specification if the characteristics of hardness–friability have a critical impact on product quality (for example, with chewable tablets).

**Uniformity of dosage units:** Uniformity of dosage units in this context refers to both the mass of the dosage form and the content of the active ingredient in the formulation. In general, the *Pharmacopeia's* methods should be used (12).

### Specific Tests and Criteria: New Oral Liquid Drug Products

For oral liquid drug products (and powders intended to be re-constituted as oral liquids), many of the same tests as for solid dosage forms are still appropriate (for example, uniformity, dissolution, and water content), but additional tests include pH (acceptance criteria and proposed range justified), antimicrobial and antioxidant preservative content, extractables, alcohol content, particle size distribution, redispersability, rheological properties, and reconstitution time. More details concerning each of these tests also can be obtained directly from the guidelines, as space allows only a brief summary here.

For formulations using an antimicrobial or antioxidant, criteria for preservative content should be established. Criteria for preservative content usually are established by shelf-life stability testing according to established guidelines (13).

Extractables normally are evaluated during development and stability, and after levels are shown to be consistently below acceptable, safe values, elimination of the test is acceptable. For products containing alcohol as declared on the label, content should be specified and quantitative results obtained by assay or calculation.

Some liquid dosage forms can settle on storage, necessitating specifications for redispersability, requiring either mechanical or manual shaking for a predetermined length of time. For viscous solutions or suspensions, specifications governing rheological properties, such as viscosity, might be appropriate. Both the test and the

acceptance criteria should be stated.

A reconstitution specification is appropriate for powder products that require reconstitution. The choice of diluents should be justified.

### Specific Tests and Criteria: Parenteral Drug Products

In addition to some of these tests, several tests specific to parenteral products must be considered, including a test for endotoxins and pyrogens (typically a limulus amoebocyte lysate test), particulate matter (an acceptance criteria for visible particulates and solution clarity), functionality testing of delivery systems (test procedures and acceptance criteria for the functionality of prefilled syringes or cartridges), and osmolarity.

**Decision trees:** In an attachment to the specifications guideline, several decision trees are included to help determine appropriate courses of action to establish acceptance criteria. These decision trees are excellent sources of protocol. Table I summarizes the eight decision trees included in the guidance. Figures 1 and 2 show examples of two of the decision trees; Figure 1 for establishing acceptance criteria for a specified impurity in a new drug substance and Figure 2 for establishing identity, assay, and enantiomeric impurity procedures for chiral new drug substances and products containing chiral drug substances.

### Conclusion

Many of the concepts and tests outlined in this column are important in the development of harmonized specifications. They are neither universally applicable nor all-encompassing. Tests other than those listed here and in the guideline might be needed in particular situations or as new information becomes available. New analytical technologies are being developed constantly, and their use is encouraged where justified. In general, proposals to implement the concepts outlined here and in more detail in the guideline should be justified by the applicant and approved by the regulatory agency before implementation.

Whether the topic is setting acceptance criteria, system qualification, or method validation, the discussion will eventually turn to suitability and acceptability for the intended use. And as with all validation topics, the common denominator is doing good science.

### References

(1) "ICH Q6A: Specifications for New Drug Sub-

stances and Products: Chemical Substances," International Conference on Harmonization of Technical Requirements for the Registration of Drugs For Human Use, Geneva, Switzerland, March 1995 (see also www.ICH.org under topic of Quality guidelines).

- (2) *Federal Register* **65**(251), 83,041–83,063 (December 29, 2000) (see also www.fda.gov/cder/guidance/index.htm under the topic of ICH Quality Guidelines).
- (3) "ICH Q2A: Text on Validation of Analytical Procedures." International Conference on Harmonization of Technical Requirements for the Registration of Drugs For Human Use, Geneva, Switzerland, March 1995.
- (4) "ICH Q2B: Validation of Analytical Procedures: Methodology," International Conference on Harmonization of Technical Requirements for the Registration of Drugs For Human Use, Geneva, Switzerland, May 1997.
- (5) *The United States Pharmacopeia 25/National Formulary 20*, 2256–2259 (2002).
- (6) *Federal Register* **68**(68), 6924–6925 (February 11, 2003).
- (7) *Federal Register* **68**(220), 64,628–64,629 (November 14, 2003).
- (8) *Federal Register* **68**(219), 64,352–64,353 (November 13, 2003).
- (9) J.D. Orr, I.S. Krull, and M.E. Swartz, *LCGC* **21**(7), 626 (2003).
- (10) J.D. Orr, I.S. Krull, and M.E. Swartz, *LCGC* **21**(12), 1146 (2003).
- (11) *Chirality* **4**, 338–340 (1992).
- (12) *The United States Pharmacopeia 25/National Formulary 20*, 2082–2084 (2002).
- (13) *Federal Register* **68**(225), 65,717–65,718 (November 21, 2003).

### Michael E. Swartz

"Validation Viewpoint" Co-Editor  
Michael E. Swartz is a Principal Scientist at Waters Corp., Milford, Massachusetts, and a member of LCGC's editorial advisory board.



### Ira S. Krull

"Validation Viewpoint" Co-Editor  
Ira S. Krull is an Associate Professor of chemistry at Northeastern University, Boston, Massachusetts, and a member of LCGC's editorial advisory board.

