

In Defense of *USP* Singlet Testing

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The United States Pharmacopeia should not change its philosophical position on singlet testing.

Some in the pharmaceutical industry have begun to question the philosophical underpinnings of the United States Pharmacopeia's (USP) position on compendial standards and singlet testing.

That philosophical position is clearly stated in *USP 28*:

Compendial standards define what is an acceptable article and give test procedures that demonstrate that *the article* is in compliance. These *standards* apply at any time in the life of the article from production to consumption. ... Thus, when tested from the viewpoint of commercial or regulatory compliance, *any specimen* tested as directed in the monograph for that article shall comply. ... Tests and assays in this Pharmacopeia prescribe operation on a *single specimen*, that is, the *singlet* determination," (Italics added.) (1)

The key concept to understand is that the *USP* provides standards and not specifications. There is a substantial philosophical and practical difference between the two.

Standards, by definition, are absolute. For a standard, no acceptable risk or probability of failure exists.

Specification criteria are relative to a specific company and a product. Specifications recognize and contain a risk of failure. This risk usually can be predetermined by using historical data and an appropriate statistical analysis.

For example, every USP-grade aspirin tablet is expected to "... contain not less than 90.0% and not more than 110.0% of the labeled amount of aspirin (C₉H₈O₄)" (2). This standard applies to all companies and all lots. A typical lot may contain one to two million tablets. If stored correctly, all tablets are expected to meet the criteria at any

point in time until the expiry date. The *USP* test method can be conducted in any qualified laboratory by a qualified analyst using validated equipment according to current good manufacturing practices (CGMPs). Indeed, the US Food and Drug Administration has a program of sampling product from the pharmacy shelf and testing it in its own laboratories.

Recognizing that there are sources of variability, *USP* section <905> provides a standard to judge the content uniformity of tablets. Again, <905> is not a specification, but an absolute standard of what must be met (not how it is to be met), by a company for a given product. It should be noted that for content uniformity and other *USP* standards, Bergum has solved this specification issue. He states that, "Acceptance limit methodology is given which assures that a future sample will have at least P% chance of passing a multiple stage test" (3). Bergum's method is a specification designed to meet the *USP* standard. Content uniformity is addressed in his paper and in Chow and Liu (4).

The *USP* philosophical position as a standard is very clear, and the aspirin example shows that the *USP* does not specify how a standard should be achieved in practice by each company for a given product.

Some have stated that it is unreasonable for billions of tablets made by dozens of companies to all meet the criteria. Suggestions have been made that the *USP* should define a more practical acceptance criteria using statistical approaches such as statistical sampling plans to incorporate the element of risk or the probability of failure.

At first consideration, this suggestion seems reasonable. Variability is a recognized reality in almost all aspects of life, and all sampling plans and specifications contain a finite and small (one hopes) risk of failure. The field of statistics validates the predictability and the science of variation. Thus, a statistical approach seems logical.

Several arguments can be made, however, against changing the *USP* philosophy regarding singlet testing. The *USP* itself addresses this approach directly:

Interpretation of results from official tests and assays requires an understanding of the nature and style of compendial standards.... [that is, the philosophical position stated above.] ... in addition to an understanding of the scientific and mathematical [*i.e.*, statistical] aspects of laboratory and quality assurance for analytical laboratories.

Confusion of compendial standards with release tests and with sampling plans occasionally occurs. ... These procedures should not be confused with statistical sampling plans. ... The manufacturer's release specifications, and compliance with good manufacturing practices generally, are developed and followed to assure that the article will indeed comply with compendial standards until its expiration date when stored as directed. ... Repeats, replicates, statistical rejection of outliers, or extrapolations of results to larger populations are neither specified nor proscribed by the compendia; such decisions are dependent on the objectives of the testing. (5)

The *USP* defines the legal standard and then companies are required to find a way to meet the requirements, whatever it takes. The *USP* is also very clear about not adjusting the standard:

The tolerances and limits stated in the definitions in the monographs for pharmaceutical articles allow for such overages and for analytical error, for unavoidable variations in manufacturing and compounding, and for deterioration to an extent considered acceptable under practical conditions. (6)

Because *USP* standards are law and enforceable by FDA, *USP* compendial limits are a go/no-go gauge. The product either passes or fails. If a product sample fails, anywhere, any time, an investigation and corrective action may be required by the company or by FDA, or by both. Like the law, there cannot be uncertainty in the decision.

Failures drive improvements to products and processes. If the samples are fail-

ing, then physical changes must be made to the components, the product, the process, or the laboratory testing procedures. These changes would rightly focus on reducing variability and could include:

- redeveloping and revalidating the process to increase process capability;
- redeveloping and revalidating the product to reduce variation;
- redeveloping and revalidating the test methods to improve precision;
- redefining the company's definition for the reportable value for the test method to reduce variation;
- retraining employees to be more consistent in their performance;
- requiring suppliers to provide materials that are less variable.

If statistical procedures were given in the *USP*, companies would have little incentive to develop better procedures.

Each manufacturer is responsible for the success of its unique products and processes. Manufacturers must develop and implement specific tools and techniques that best fit their needs. It is obvious that this should include statistical tools, but those tools certainly are not required. If statistical procedures were given in the *USP*, companies would have little incentive to develop better procedures specific to their situations or to change as new statistical techniques are developed.

Further, managers are responsible for determining a risk posture for the company. Managers develop risk strategies that they believe they and their stockholders can tolerate. It can be argued that the current *USP* position will encourage most managers to strive for more conservative risk positions. It is common for quality assurance departments to develop and implement tests, techniques, and internal re-

lease criteria that give them a high degree of assurance that the risk of failure after shipping is low. Usually, this means they do more than is required by the *USP* standard. The absolute certainty of the standard and FDA's interpretation of the standard provides benefits to the industry and, ultimately, increased protection for the patient.

Finally, companies must comply not with the good manufacturing practices, but with *current* good manufacturing practices. As science improves, practices considered up-to-date a few years ago become obsolete. Continuous improvement is expected as a normal course of business. *USP* should not be in a position of defining what is *current* in the CGMPs; that is best left to the industry and FDA.

Conclusions

The *USP* philosophical position on singlet testing is clear and should not be changed. The role of the *USP* is to set a clear absolute standard for the industry. Each individual company's role is to meet that standard. Although statistics obviously have a significant role to play, that role lies in the company's efforts to meet the standard, not in having the *USP* specify statistical procedures.

References:

1. *United States Pharmacopeia 28—National Formulary 23* (US Pharmacopeial Convention, Rockville, MD, 2005), p. 8
2. *United States Pharmacopeia 28—National Formulary 23* (US Pharmacopeial Convention, Rockville, MD, 2005), p. 18.
3. J.S. Bergum, "Constructing Acceptance Limits for Multiple Stage Tests," *Drug Dev. Ind. Pharm.* **16** (14), 2153–2166 (1990).
4. S. Chow and J. Liu, *Statistical Design and Analysis in Pharmaceutical Science* (Marcel Dekker, New York, NY, 1995), p. 161.
5. *United States Pharmacopeia 28—National Formulary 23* (US Pharmacopeial Convention, Rockville, MD, 2005), p. 8.
6. *United States Pharmacopeia 28—National Formulary 23* (US Pharmacopeial Convention, Rockville, MD, 2005), p. 4. **PT**