



by Ron Ball

# Proposed Changes to U.S. Pharmacopoeia (USP) / National Formulary (NF)

## If the USP makes its reference standards the only acceptable method, many firms will suffer significant financial hardship

The United States Pharmacopeia (USP) is a nongovernmental, standards-setting organization that advances public health by ensuring the quality and consistency of medicines, promoting the safe and proper use of medications, and verifying ingredients in dietary supplements. USP standards are developed by a unique process of public involvement and are accepted worldwide. In addition to standards development, USP's other public health programs focus on promoting optimal health care delivery and include USP Verification Program, Health Care Information, and Patient Safety. USP is a nonprofit organization that achieves its goals through the contributions of volunteers representing pharmacy, medicine, and other health care professions, as well as science, academia, the U.S. government, the pharmaceutical industry, and consumer organizations.

Members and volunteers consist of the following groups:

- About 650 elected scientists and practitioners comprise USP's scientific decision-making body by serving as members of the Council of Experts (CoE) or on expert committees.
- Eleven elected officers and trustees have fiduciary responsibilities for the management and policies of the organization.

- About 400 members represent state associations and colleges of medicine and pharmacy; the federal government; national and international professional, scientific, and trade organizations; the pharmaceutical industry; and consumer organizations. USP members meet once every five years to adopt resolutions and to elect the CoE and USP's Board of Trustees. The next member meeting will be held in Washington, D.C., in 2005.

### *Evolution of Monographs*

The USP is the official compendia of standards, which establish the monographs for all pharmaceuticals sold in America. Each monograph contains the analytical techniques, storage and packaging requirements, as well as other vital information about each drug. In 2003, the USP proposed a number of changes to the medical gas monographs. While there were some positive changes, such as making the paramagnetic analyzer the official USP test of medical oxygen, the industry had concerns over the changes to analytical methods for many of the other medical gases. GAWDA and CGA worked together to submit comments to USP; and as of the writing of this article, USP has not formally responded to the medical gas industry.

The proposed changes to the USP/NF

monographs are summarized in Table I.

The potential implications for Gas Manufacturers are as follows:

**Oxygen:** No changes for companies who have validated paramagnetic method.

**Nitrogen:** For companies using electrochemical method, they will need to re-conduct equivalency validations against the paramagnetic method.

**Medical Air:** Most companies now use and have validated the paramagnetic method; they will incur no changes.

**Helium and Nitrous Oxide:** GC equipment operating parameters and system suitability parameters (precision, resolution, etc.) will be explicitly specified. Most companies will only have to reconcile the new specific parameters with any differences to their current parameters and revise their SOP's appropriately.

**Carbon Dioxide:** Companies will need to evaluate any specific GC requirements in the new method to determine if any additional equivalency validation is required.

### *Reference Standards*

Historically the medical gas industry has ensured the accuracy of their analytical instruments by calibrating them using a cylinder of known properties, specifi-

GAS	Test	Current Methodology	Proposed Change
<b>Oxygen</b>	Identification	Acceptable Orsat test Detector tube (carbon dioxide)	Acceptable paramagnetic assay
	Assay	Liquid chemistry (Orsat)	Paramagnetic method
<b>Nitrogen</b>	O <sub>2</sub> and Assay Gas chromatograph		Paramagnetic method and calibration standard from O <sub>2</sub> /He to O <sub>2</sub> /N <sub>2</sub>
<b>Medical Air</b>	Assay Electrochemical cell analyzer		Paramagnetic method
<b>Helium</b>	Identification	Wood splinter test & balloon test	Gas chromatograph
	Assay Gas chromatograph		GC Column, parameter changes, and addition of GC system suitability tests
<b>Nitrous Oxide</b>	Identification	Pressure-difference CO <sub>2</sub> detector tube Pyrogallol liquid chemistry	GC column CO <sub>2</sub> detection tube
	Assay Gas chromatograph		GC column, parameter changes, addition of GC system suitability tests, and standard from Air/He to Air/n <sub>2</sub> O <sub>2</sub>
<b>Carbon Dioxide</b>	Assay	Liquid chemistry (Orsat) (Zahm Nagel)	Gas chromatograph, addition of GC system suitability tests, & addition

cally prepared and tested. Industry refers to these as calibration gas cylinders.

Many welding and gases distributors have laboratories with the necessary equipment to prepare calibration cylinders, and enjoy a substantial business making and selling these products.

This practice is unlike the pharmaceutical industry, which typically relies on USP reference standards to calibrate their analytical equipment. For instance, a firm that makes aspirin tablets would purchase a reference standard from USP to test how quickly their tablets dissolve when taken, against a known standard.

In May of this year, USP proposed to eliminate the use of medical gas calibration cylinders, and to require manufacturing firms to use USP medical gas reference standards. USP has already begun sending out sample reference standards to labs for review.

This proposed change is troubling in a number of different areas. First off, there are more than 3000 FDA registered manufacturers of medical gases in 50 states.

The logistics of supplying all these manufacturers and to all corners of the United States, along with the costs of shipping these cylinders is a significant concern. Secondly, the test reference standard cylinders we have seen have all

been small disposable cylinders. Typically medical gas calibration standard cylinders are large (nominal 300 scf) cylinders.

It is not clear if USP appreciates the fact that medical gas firms may calibrate their analyzers multiple times a day. The small volume of the USP reference standard cylinders means that firms will have to change calibration cylinders frequently, and could run out if the supply logistics system can not keep up with demand.

Thirdly, while USP has not announced proposed pricing for medical gas reference standards, we can draw some comparisons from the USP/NF website. It appears that not only will USP medical gas reference standards come in much smaller cylinders than typically supplied today, they could cost significantly more than current calibration cylinders provided by a specialty gas lab.

Finally, with USP making their reference standards the only acceptable methods to calibrate a medical gas analyzer, companies that engage in making and selling calibration cylinders for medical gas use would no longer have access to that market. Losing access to this market would be a significant financial hardship for many firms, many of whom have been providing high quality calibration standards to the medical gas industry for

decades.

Mandating the medical gases industry switch from a proven source of calibration gases to USP reference standards will not increase the safety or effectiveness of either the medical gas or the analytical technique used to assay the gas. Through CGA, the industry has made their objection to this proposed change known to the USP. As of the writing of this article, USP has not formally responded to the medical gas industry.

Analytical methodology is a key FDA requirement, and firms need to maintain appropriate testing activities. If your testing methodology differs from the methods stated, you will need to prove, by validation, that your method is equivalent to the "official" method. ■

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