

Process Analytical Technology A First-Birthday Standardization Update

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The author describes the efforts of the standards committees to establish guidelines for PAT implementation and the impact of the guidelines on the industry.

ASTM E55 Committee Overview

This committee addresses issues related to process control, design, and performance, as well as quality acceptance/assurance tests for the pharmaceutical manufacturing industry. Stakeholders include manufacturers of pharmaceuticals and pharmaceutical equipment, federal agencies, design professionals, professional societies, trade associations, financial organizations, and academia. More than 140 members are involved in this multinational initiative; all participating actively within a three-tiered subcommittee structure focusing on PAT system management, PAT system implementation and practice, and PAT terminology.

Introducing process analytical technology (PAT) has been like delivering a baby, with proud parents (the standard-setting bodies, led by the US Food and Drug Administration's deputy director of pharmaceutical science, Ajaz Husain), arguments over the name (several were considered before settling on P-A-T, a always pronounced letter-by-letter), baby showers (the series of advisory committee meetings and draft publications through 2002 and early 2003), and a birth (publication of the FDA draft guidance, weighing in at 21 pages, on 3 September 2003).

Since then, there have been ups and downs, sleepless nights, exciting firsts, and countless adjustments to a new way of life. PAT has taken its first steps, and most, if not all, of the Top 20 pharmaceutical firms have active PAT programs.

Teaching PAT to talk

Just as babies must learn to speak to make themselves understood to the world around them, the newborn PAT must also learn to talk.

Although it's sometimes natural to focus on the technology in PAT, communication is the key: at the device level, it's communication between the sensors and the analyzers. At the highest (and yet most fundamental) level, it's communication between industry and regulators. Thus, the effort to standardize the PAT lexicon takes center stage.

PAT standardization began in January 2004, with key elements of the PAT vocabulary, including nomenclature, definitions, recommended practices, guides, test methods, specifications, and performance standards. Glynis Foster Roberts of Barr Laboratories (Woodcliff Lake, NJ) and a member of ASTM E55, sums this up by saying, "PAT involves moving to a new paradigm in pharmaceutical manufacturing and process understanding. It is therefore important to have a common comprehension of the concept, the expectations, and the ultimate goal in implementing PAT."

Colin M. Minchom of Patheon* (Mississauga, ON) concurs: "We view PAT as an innovative tool that will enhance pharmaceutical development and manufacturing processes. Standardization is critical to the development of the tool, and its acceptance across the pharmaceutical industry and with regulators."

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Two volunteer standards-making bodies, ASTM International (formerly the American Society for Testing and Materials) and the US Pharmacopeia (USP) are each building a language around PAT. The two organizations come from different perspectives, with different historical roles in the pharmaceutical industry. USP is well established in the industry; ASTM is new to many, even though it has served the standardization needs of more than 100 industries since it was established in 1898. ASTM was formed when a forward-thinking group of engineers and scientists met to address frequent rail breaks in the burgeoning railroad industry. Their work led to standardization on the steel used in rail construction, ultimately improving railroad safety for the public.

“Following the introduction of PAT, the needs of the pharmaceutical industry have evolved toward the definition and development of process-based ‘best practices’ to advance a scientific approach toward process understanding and flexible manufacturing,” reads ASTM’s statement on the creation of Committee E55 on Pharmaceutical Application of PAT. “To establish the foundation for PAT implementation, and to lend credence and general acceptance to the developed best practices, FDA encouraged the pharmaceutical industry to take an active role in drafting these practices through consensus and broad-based stakeholder representation and input.”

The ASTM process is based on openness and transparency. Any interested party has the opportunity to participate on an ASTM committee, with an equal voice at the standards development table. Through Committee E55, the regulator, the regulated, the academic community, and every other member of this diverse industry sector hold the same degree of access to the standards development process.

“ASTM committees (and the standards they produce) are living entities, capable of modification to mirror the evolution of their respective industries. It is in this way that ASTM standards remain relevant,” commented Pat A. Picariello, director, developmental operations at ASTM and the staff manager for E55. “In addition, the decision as to which standard is used in the marketplace is best driven by the stakeholders, and not by a standards developing organization or political entity. A multiple-path approach, responding to the needs and requirements of various industrial sectors, empowers users to make the choice that’s right for them. Toward this end, ASTM is extremely pleased that the pharmaceutical industry has chosen to work under the ASTM umbrella via Committee E55 to develop full-consensus standards for the pharmaceutical application of process analytical technology.”

The initial creation and success of Committee E55 (the standard “E2363—Standard Terminology Relating to Process Technology in the Pharmaceutical Industry” was recently approved four months after its registration as a work item) attests to the value of looking outside the box.

An ASTM committee organizes new-standard development into work items. When a new work item is created, a notice is published on the committee Web site with sufficient description to encourage participation from the broadest possible group. Interested parties are encouraged to seek out the technical contact for that standard. The contact can supply details

on joining the subcommittee responsible for the activity or potentially the focused 8–15-member task group. The task group drafts a proposed standard document, which is presented to the larger audience through a multitiered balloting process. At the end of July 2004, there were four work items in progress within ASTM E55 (see Table I).

USP also supports PAT initiatives. As the pharmaceutical industry adopts PAT practices and ASTM standards, new technologies will emerge on the horizon. USP introduces new technologies to the pharmaceutical community through its Council of Experts and communicates with stakeholders and interested parties through the *Pharmacopeial Forum*. (see “Decoding the US Pharmacopeia,” *Pharmaceutical Technology*, July 2004). USP has been performing this function for the pharmaceutical industry for 184 years. When the USP General Chapter (1073) “Effusivity” appeared in *Pharmacopeial Forum* in July/August 2004, it was the second example of a PAT system Chapter in the USP. The first, the linked chapters (643) “TOC for USP Purified Water” and (645) “Conductivity for Water for Injection,” appeared in 1997.

Industry report card

To obtain a broader perspective on the impact of PAT standardization efforts on the industry, I talked to a dozen active thought-leaders on the topic, including representatives from:

- regulatory and standards bodies
- large pharmaceutical, generic, and contract manufacturers
- ASTM and non-ASTM members
- industry and academia
- formulation and engineering disciplines.

Each person was sent a draft of the article and presented with the following questions:

- Why is PAT standardization important to your organization?
- Are today’s efforts and progress sufficient?
- If not, what is lacking?
- What message would you like to send the industry related to standardization efforts?
- Should ASTM and USP both play a role in this activity? Will there be confusion/redundancy or rather are the audiences different (manufacturing/engineering versus research/chemists/pharmacists)?

A few key themes arose out of the conversational “report card” on our PAT offspring. One stakeholder commented that the industry members “don’t know how to play well together.” The industry has been under heavy regulatory load for a long time and is now hearing that it has a voice. The voice and social skills to interact for the broader good—like standardization activity—is new. Like a toddler at a playgroup, hanging on to her mother’s leg, several industry representatives to the standardization process have, so far, participated only in observer mode. The new freedom that comes from having a voice and a vote equal to FDA’s is a culture shock. This is not a state that is expected to last indefinitely and the timidity will diminish as the brave venture forward.

Another comment on the report card was that companies have an “inability to share their toys.” Early adopters of PAT systems may be holding too much data and learning close to their vests, rather than sharing information for the benefit of the

Table I: Work items in progress within ASTM E55.

Title: WK4187 Standard Terminology Relating to Process Analytical Technology in the Pharmaceutical Industry

Developed by subcommittee: E55.91

Date initiated: 19 February 2004

Scope: This standard defines PAT terms as they are used relative to the pharmaceutical industry. Terms that are generally understood are not included except where particular delineation to PAT may be more clearly stated. No complete collection of terms for this application of PAT exists. It is hoped that FDA finds value in, and ultimately adopts or references this standard.

Title: WK5015 Pharmaceutical Process Design

Developed by subcommittee: E55.02

Date initiated: 30 May 2004

Scope: Define what "process design" means in context with PAT for assessing and controlling variability and risk.

- Describe the process for "pharmaceutical process design." List and describe aspects, items, and activities that should be for "pharmaceutical process design" in a PAT context.
 - Propose an ASTM guidance document for approval of E55/E55.02. Reference existing documents (not necessarily specific to pharmaceutical application) where appropriate.
- Pharmaceutical Process Design encompasses (based on transformations of materials at each step of a process) items such as
- assessment of process understanding as a function of risk management/mitigation
 - process measurements and controls
 - best practices for pharmaceutical manufacturing
 - goal of process design.

A high-level guidance document is needed to enable industry interpretation of implementation requirements for PAT-process design.

Title: WK4694 Standard Guide to Assure Fitness-for-Use of PAT Systems for Measurement of Pharmaceutical Process or Product Quality Attributes

Developed by subcommittee: E55.02

Date initiated: 15 April 2004

Scope: Qualification procedures and recommendations in this guide are intended to assure fitness for use of a PAT system regardless of the specific technology being used for measurement of a pharmaceutical process or product quality attribute of interest. Procedures for initial qualification and subsequent continuous qualification of PAT system performance are described. PAT system qualification requires measurements of physical or chemical characteristics (process or product quality attributes) of pharmaceutical processes or products specified by the user. No such document exists. It is anticipated that the standard will be adopted or referenced by FDA.

Title: WK4185 Test Method for Thermal Effusivity of Solids, Powders, Liquids, and Composite Samples Using the Modified Hot Wire Transient Technique

Developed by subcommittee: E55.02

Date initiated: 12 February 2004

Scope: This test method describes a general procedure for rapid, quantitative, nondestructive determination of thermal effusivity of samples using the modified transient hot wire technique. Effusivity in general can be used to monitor blending, drying, wet granulation, and segregation in the tablet press hopper. It has been shown to monitor over-lubrication as well. All of these are on- and off-line applications. ASTM plays a strong educational role, and at this point, we would like consistency in the understanding of the tool in general.

larger industry. A wide-spread (though, we hope, mistaken) belief holds that PAT implementation excellence could be a competitive advantage. The deeply ingrained IP-and-patents mentality appears to overflow into the approach taken with PAT. This could be problematic. Vendors and users all lose under this scenario. "Standards development must take place prior to or in parallel with applications development, which ultimately leads to innovation as multiple users are not continually reinventing the wheel. The industry must achieve a balance between competition and standardization," commented ASTM E55.02 subcommittee and effusivity task group member Stephen Closs.

The automotive industry faced this same problem before their consolidated effort to institute a unified quality system, QS9000. Before the Big Three automakers agreed on quality standards for their suppliers, each supplier kept separate sets of quality records to comply with the specific requirements of each customer. The burden was preventing the dramatic margin shifts that were needed in the industry. Once the automakers realized that they needed to concentrate on their designs and features as their differentiator in the marketplace, QS9000 was created.

Drum makers must gain the same insight for standardization efforts to really work. While public discussions focus on the goal of a standard practice or method in PAT, possessiveness about the results and a disinclination to "share the toys" still lurks behind the scenes. The toys that make up the majority of PAT systems come with "some assembly required." As such, they are likely to be frustrating, if not downright useless, without a good set of instructions, in the form of standards, ready to hand. Success, to one commentator, would be "a day when a blender could be specified much like a pump and the trial and error of scale-up was eliminated."

To round out the school-yard metaphor, the industry seems to be looking for its familiar "security blanket." While the pharmaceutical industry might desire to grow up and mature in the adoption of PAT through ASTM and measurement-centered practices, to many industry members, USP is the "tried and true." Some industry observers predicted that "until it is in USP, it won't be adopted widely." When we presented this view to other stakeholders, however, we often found diametric disagreement. In the end, there are advantages to covering all the bases and having both ASTM and USP creating standards. The participant pool for the two voluntary committees is limited, however. And the people in the pool all have day jobs, not least of which is to lead the PAT initiatives within their own organizations. One respondent commented that "in a day when British, Japanese, and European Pharmacoepias and USP are making efforts to harmonize, why not start off on the right foot with a level of harmonization in the USP and ASTM standardization activity if both are going to be active."

Join in

Raising PAT will take time and patience, but it will bring rewards, from simple satisfaction to a bright career path for those bringing PAT into new processing lines. The standards committees will be the ones making sure PAT grows up strong, and there is always room for more helping hands. **PT**