For many years, the pharmaceutical industry and the US Food & Drug Administration (FDA) accepted the fact that, while myriad new drugs were being invented, the processes and techniques for manufacturing those drugs were inferior to those employed by manufacturers of products such as soap and snack foods. Even faced with large numbers of drug recalls (176 in 1998, 248 in 2001 and 354 in 2002), this inconsistency represented the status quo.

The FDA, charged with protecting the user community, took the view that it was more important to manufacture (via an established protocol) a drug precisely on specification than to investigate and possibly take advantage of newer, more sophisticated manufacturing models. The pharmaceutical industry, with billions of dollars of revenue at its disposal, had a greater financial incentive to invest in locating, evolving and marketing new drugs than in re-tooling existing manufacturing processes, equipment and methodology.

Faced with the inevitable conclusion that the pharmaceutical industry was in drastic need of new and innovative process improvements, the FDA – for the first time in over 25 years – overhauled its regulations governing drug manufacturing. The pharmaceutical industry, with billions of dollars of revenue at its disposal, had a greater financial incentive to invest in locating, evolving and marketing new drugs than in re-tooling existing manufacturing processes, equipment and methodology.

The FDA, charged with protecting the user community, took the view that it was more important to manufacture (via an established protocol) a drug precisely on specification than to investigate and possibly take advantage of newer, more sophisticated manufacturing models. The pharmaceutical industry, with billions of dollars of revenue at its disposal, had a greater financial incentive to invest in locating, evolving and marketing new drugs than in re-tooling existing manufacturing processes, equipment and methodology.

For the first time in over 25 years – overhauled its regulations governing drug manufacturing. The FDA's draft guidance for the industry, 'PAT – A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance', was the first step in facilitating the development, implementation and regulation of manufacturing processes based on fundamental process understanding. The need has now progressed to defining and developing a series of process-based (rather than product-based) ‘best practices’ to advance the scientific approach to addressing process knowledge and flexible manufacturing.

The FDA has encouraged the pharmaceutical industry to take an active role in identifying and drafting such practices for one fundamental reason – if the FDA were to develop such practices solely, the experience and expertise within the pharmaceutical industry could not be engaged to the level desired. Thus, the aim is to gather broad representation from the pharmaceutical industry, identify appropriate topics for discussion and create an appropriate structure for drafting a series of consensus standards. The FDA has stated that these collaborations will lend credence to and general acceptance of the developed practices, as well as establish a foundation for the implementation and regulation of PAT. Finally, the early implementation of a series of process-oriented standards would lead to a greater understanding of the variables associated with product performance, which would (in turn) help create consistency – thereby lowering production expense.

**WHY STANDARDS AT ALL?**

Standards are far from a purely academic exercise. A product of strategic debate and consensus building, standards are essential for the evolution of any industry as they contribute directly to the bottom line. Conversely, the lack of standards can cost an industry revenue – as well as constrain future growth into new and potentially lucrative markets. A sound standardisation philosophy will enable an industry to meet its challenges head-on and enjoy the benefits of efficiency, cost-savings and the capability to leverage assets and create new products. By actively participating in the work of standards-developing organisations like ASTM International, becoming aware of which business activities require new or improved standards, and making standards consideration a regular component of upper-level strategic thinking, an individual or organisation can usher these benefits into their own specific marketplace. Ultimately, the understanding and adoption of business-critical standards can serve to power through existing industry log-jams, and

**ASTM International Committee E55 will serve as a catalyst through which the widely diverse interests of the pharmaceutical community will be focused to produce full consensus PAT (process analytical technology) standards.**

**By Pat A Picariello, Director, Development Operations at ASTM International**

Pat A Picariello is Director, Development Operations at ASTM International. In this role, he oversees the exploration, planning, organisation and management of all aspects of new standards development activity and outsourcing service areas for ASTM International. Mr Picariello has experience with ASTM related to standards development and strategic standardisation initiatives from both a national and global perspective. He holds a BA from Dartmouth College (Hanover, NH) and a JD from Temple University School of Law (Philadelphia, PA). He is a member of the Standards Engineering Society and the American Society of Association Executives.
help an industry reach and maintain an era of revenue growth and profitability.

ABOUT ASTM INTERNATIONAL

ASTM International, a not-for-profit corporation organised in 1898, is a management system for the development of standards and related technical information for materials, products, systems and services. It provides a legal, administrative and publications forum within which producers, users, ultimate consumers and representatives of government and academia can meet on a common ground to develop standards that best meet the needs of all concerned.

ASTM’s technical committee structure is made up of main committees, subcommittees and task groups. The task groups initiate draft standards, which sub- and main committees ballot following the consensus procedures described in the ‘Regulations Governing ASTM Technical Committees’. The ASTM procedures, based on due process, ensure that the standards produced are technically sound and rest on a solid legal foundation with appropriate concern for legal issues, such as restraint of trade and volunteer liability.

FDA BRIEFING

In response to the market conditions described above, the FDA’s Center for Drug Evaluation and Research (CDER) contacted ASTM in December 2002, with a request for a briefing and orientation regarding the ASTM process.

The ASTM process is based on openness and transparency; these are extremely attractive attributes to industry. Even more attractive is the fact that any interested party not only has the opportunity to participate on an ASTM committee, but also the luxury of enjoying an equal seat at the standards development table. With regard to pharmaceutical PAT standards (Committee E55, see below), this means that the regulator, the regulated, the academic community, and every other conceivable member of this diverse and extremely important industry sector holds 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. Additionally, the decision as to which standard is used in the marketplace is best driven by the stakeholders – and not by a standards-developing organisation 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.

In July 2003, ASTM again met with FDA representatives to discuss the possible development of an industry-driven consensus standards programme. This meeting resulted in a request (by the FDA) for ASTM to hold a planning meeting of a select group of key industry stakeholders to discuss the need for standards in the area of process improvement and control.

At a planning meeting held on October 3rd 2003 at ASTM International Headquarters, key members of the pharmaceutical industry – including manufacturers, users and the US FDA – unanimously agreed to hold an organisational meeting for the development of this new activity within ASTM International. Various disciplines – including consumers, manufacturers, suppliers, trade and professional societies and federal agencies – were invited to participate. The attendees at the planning meeting also recognised the need to evolve their manufacturing processes to be more consistent, efficient and cost-effective.

At an Organisational Meeting held December 1st-2nd 2003 at ASTM International Headquarters, over 60 representatives of the pharmaceutical industry voted (without dissent) to organise a full-consensus standardisation activity within ASTM; this activity carries the alphanumeric designation of E55.

COMMITTEE E55

Committee E55 – or to give it its full title, ASTM International Committee E55 on Pharmaceutical Application of Process Analytical Technology – was subsequently formed. It was agreed that the scope of the Committee should be:

“... the development of standardized nomenclature and definitions of terms, recommended practices, guides, test methods, specifications, and performance standards for pharmaceutical application of process analytical technology. The Committee will encourage research in this field and sponsor symposia, workshops, and publications to facilitate the development of such standards. The Committee will promote liaison with other ASTM Committees and other organizations with mutual interests.”

Three subcommittees were formed: E55.01 on PAT System Management, E55.02 on PAT System Implementation & Practice, and E55.91 on Terminology.

Committee E55 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 organisations and academia. At present, 164 members
are involved in this multinational initiative – all participating actively within the three-tiered subcommittee structure described above.

CURRENT WORK PROGRAMME
The current work programme for E55 is listed below; details are also available on the E55 homepage (http://www.astm.org/COMMIT/COMMITTEE/E55.htm). It is important to remember that this represents a snapshot of the items currently under development and should not be viewed inclusively.

WK4185: Test Method for Thermal Efusivity of Solids, Powders, Liquids, and Composite Samples Using the Modified Hot Wire Transient Technique (Date Initiated: 12 Feb 2004)
This test method describes a general procedure for the rapid, quantitative, non-destructive 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.

WK4694: Standard Guide to Assure Fitness-for-Use of a Measurement System to Determine or Control Process or Product Quality Attributes (Date Initiated: 15 April 2004)
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 and/or referenced by the US FDA.

WK5015: Pharmaceutical Process Design (Date Initiated: 30 May 2004)
The scope of this Work Item comprises the following:

a) Define for pharma what ‘pharmaceutical process design’ means in context with PAT for assessing and controlling variability / risk

b) Describe the process for ‘pharmaceutical process design’. List and describe aspects, items and activities that should be considered for ‘pharmaceutical process design in a PAT context

c) 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):

◆ 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.

This terminology covers process analytical technology in the pharmaceutical industry and terms are defined as they are used relative to the pharmaceutical industry. Terms that are generally understood and in common usage, or adequately defined in other readily available references, are not included except where particular delineation to process analytical technology may be more clearly stated. No complete collection of terms for this application (pharmaceutical) of PAT exists.

CONCLUSION
The pharmaceutical manufacturing community has recognised that PAT standards are the bed-rock it currently lacks – a foundation on which its future operations must be anchored. ASTM International Committee E55 (and its 164 current members) will serve as a catalyst through which the widely diverse interests of this community (including manufacturers, users, regulators, trade associations, consultants and academia) will be focused to produce industry-driven, market-relevant, full consensus standards.

The author can be contacted at ppicarie@astm.org