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FEATURE ARTICLE

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Process analytical technologies in the pharmaceutical industry: the FDA's PAT initiative

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Introduction

Two branches exist in pharmaceutical production: the manufacture of active pharmaceutical ingredients (APIs), also known as drug substances, and the manufacture of drug products. Whereas with API manufacturing, the active ingredient is synthesized during the course of many individual chemical reactions, drug product manufacturing involves carrying out a formulation of the active ingredient with excipients in order to produce the drug.

Techniques have been applied for decades in API manufacture, which had previously been understood as being part of process analytical chemistry (PAC) [1]. Process control has in particular been the classical application area for PAC in API manufacturing, involving such parameters as temperature, pressure, pH, moisture, solvent drying, redox probes, and such spectroscopic techniques as UV, IR, NIR, Raman, etc. [1]. Chemometrics have however also been applied to process monitoring, modeling, and control [2]. Synthesis robots, workstations, and automated reactors for automated process optimization with statistical experimental design as well as multivariate data analysis are already being applied for the purpose of process understanding in development [3]. Many of those tools for which applications have been discovered in the manufacture and development of APIs are also to be found in the initiative on process analytical technology (PAT), which was started up a few years ago by the American Food and Drug Administration (FDA) [4]. In addition to API manufacture, however, this initiative is primarily concerned with drug product manufacturing. Analytical tools have evolved to such an extent that they are now capable of dealing with the complex matrix of multiple dosage forms and of providing data in a meaningful way. For example, near-infrared spectroscopy (NIR), radio frequency, and microwaves have been applied for moisture determination [5]. A veritable NIR boom has been triggered ever since AstraZeneca and Pfizer successfully deployed NIR for on-line monitoring in the critical pharmaceutical process areas of raw materials receipt, drying, blending, and tableting [6, 7].

As a result of the FDA's PAT initiative, PAT is now being promoted in the pharmaceutical industry. The present article explores the ramifications of this initiative.

Regulatory and business environment

On average, it takes between 10 and 15 years and costs more than 800 million dollars in research and testing to bring a new medicine to patients [8]. This includes the testing by researchers of thousands of chemicals to determine their biochemical activity in the body. Even after a medicine has been discovered, its development may fail because it proves to be impossible to manufacture the drug on a large scale safely or to the proper specifications. In clinical trials, which may take years and involve thousands of patients, it must be demonstrated that a new medicine really works and that it does not cause unacceptable side effects. Nevertheless, only 20% of the medicines that enter clinical trials are eventually approved for patient use by the FDA [9]. Once a patent is granted, a company has only a limited period in which it has exclusive right of sale. It is during this time that one has the opportunity of potentially recouping the hundreds of millions of dollars invested in the research and development of a new medicine. "Most compounds discovered never earn FDA approval. Developing a new medicine is time-consuming and expensive, and few products earn revenues equal to or greater than the average cost for research and development. Only a few blockbuster successes cover the losses on many other projects," stated Henry G. Grabowski of

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Duke University [9]. It is for these reasons that more funds are devoted to the investigation of new medications than are being spent on efficient manufacture.

The requirements of good manufacturing practices (GMP) became a legal standard in 1962. The Assistant General Counsel for Food and Drugs is on record as having stated that [10] "the purpose of this provision is to require that all drugs are prepared in proper facilities, with adequate equipment, and with all needed control procedures." Ever since then, pharmaceutical manufacturing has gone hand-in-hand with the implementation of government regulations.

Because of both the effort involved and the associated costs that are required to maintain compliance with government agency requirements, manufacturers avoid making any process changes after phase II clinical trials, thus locking in production methods and costs at an early stage [11]. The Wall Street Journal reported the following commented about this practice [12]: "in other industries, manufacturers constantly fiddle with their production lines to find improvements. But FDA regulations leave drug-manufacturing processes virtually frozen in time. As part of the drug-approval process, a company's detailed manufacturing plan—and even the factory itself—must pass FDA muster. After approval, even a tiny change to how a drug is made requires another round of FDA review and authorization, requiring time and paperwork. The process discourages updating by the companies, which worry they will face a production delay that could cost them heavily."

For all of these reasons, the pharmaceutical industry has always lagged behind others in terms of efficient manufacturing.

Development of the FDA's PAT initiative

The FDA initiated a proactive approach to introduce innovation and the public health benefits associated with it into the pharmaceutical manufacturing process.

An initiative was developed at the FDA's Center for Drug Evaluation and Research (CDER), which was intended to encourage manufacturers to incorporate modern PAT into pharmaceutical production and quality control. The PAT initiative was then discussed publicly for the first time at an FDA Advisory Committee for Pharmaceutical Science (ACPS) meeting in July 2001, at which representatives from industry and science also participated. A formal presentation to the FDA's Science Board took place in November 2001, after which the Board endorsed the CDER's plan [13].

The agency formed a subcommittee on PAT under the CDER's ACPS. In addition to FDA representatives, the subcommittee also included industry experts (e.g., from Pfizer, Bristol-Myers Squibb, and AstraZeneca) and representatives from academia (e.g., Purdue University). The tasks of the subcommittee, which was chaired by Tom Layloff, were defined as follows [11]:

- Current status and future trends involving PAT in pharmaceutical development and manufacturing. This includes available technologies, applications in domestic and foreign plants, and perceived and real regulatory hurdles.
- General principles for regulatory application of PAT, including methods validation and specifications and feasibility of parametric release concepts.
- Case studies about PAT, most likely using NIR technologies.
- Research and training needs of FDA and the industry.

The subcommittee was divided up into four working groups to handle specific topics involved in the implementation of PAT [13, 14].

A guiding force in the FDA's PAT movement was the CDER's Office of Pharmaceutical Science (OPS) Deputy Director, Ajaz Hussain, who is the chair of the PAT steering committee.

The agency was conducting internal research on PAT in co-operation with other federal agencies and with industry. This means that there is a PAT research team within the FDA Office of Testing and Research, which conducts research to provide information for policy development. During the compilation of guidelines on PAT, Ajaz Hussain also worked closely with Mel Koch of the Center for Process Analytical Chemistry (CPAC), which played a pioneering role in the integration of process analysis and process control. The idea of founding the CPAC, an industry–university co-operative research center, had already occurred to a group of researchers at the University of Washington in the 1980s [15, 16].

Similarly, a "Co-operative Research and Development Agreement" was signed between the FDA and Pfizer in 2003 that will allow the two to collaborate on chemical imaging studies. In a further development, the FDA works together with the National Science Foundation's Center for Pharmaceutical Processing Research to develop expertise in the area of real-time process monitoring. In addition to three other representatives of CDER's OPS, Ali Afnan, an industrial chemist hired by the FDA in May 2003 who had previously been employed at AstraZeneca, was also active in the original PAT Policy Development Team. He is one of three pharmaceutical/chemical engineers with expertise in PAT who was recruited by the FDA [17].

The FDA's guidance for industry on PAT

To further facilitate PAT, the FDA was preparing to release a guidance on the subject. The comments and recommendations made by the subcommittee working groups were used for this purpose, leading to the announcement of a draft version of guidance for industry on the subject of PAT on 3 September 2003. The draft was finalized within a single year and the final version was published in September 2004 as "Guidance

for Industry: PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance [18].'' Several important changes were made to the original draft, such as the coverage of biological products in the final guidance and the explicit introduction of the term ''development'' in the title.

In addition, there were also other smaller changes made, so that, e.g., specific types or technologies (such as NIR spectroscopy) were no longer mentioned in the final version. Instead of being a set of guidelines, the document was deliberately structured as a guidance to provide a framework for allowing companies to come up with their own solutions. ''Instead of telling them how to do things, we've given companies all the flexibility they need,'' said Ajaz Hussain [19].

The term PAT is defined within this framework as follows: ''the agency considers PAT to be a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality. It is important to note that the term *analytical* in PAT is viewed broadly to include chemical, physical, microbiological, mathematical, and risk analysis conducted in an integrated manner [18].''

The expression ''timely measurements'' used in the definition is a misconception from a chemistry point of view because it means measurements that have been done in time. It would be better to refer to ''real-time measurements''—as defined by International Union of Pure and Applied Chemistry (IUPAC)—because it means measurements that are concurrent with events.

When one studies the PAT applications, one could gain the impression that PAT is to be considered the equivalent of replacing classical off-line analyses (e.g., HPLC) with on-line NIR spectroscopy [20, 21]. That would however be incorrect. The PAT goes far beyond process analyzers and PAC techniques. The FDA's PAT guidance itself states: ''transfer of laboratory methods to on-line, in-line, or at-line methods may not necessarily be PAT [18].'' When one studies the background of the PAT philosophy, one finds for example the application of on-line analyzers, which are used with the objective of imposing measurement values from which one can make inferences concerning product quality. This process puts one in the position of being able to alter the process at an early stage to ensure that it will result in the desired product quality. Consider, e.g., the pharmaceutical blending process. Instead of blending by recipe for a fixed time, you would blend until the mixture is homogenous, monitored on-line by NIR. This is also shown in the statement contained in the PAT guidance ''quality cannot be tested into products; it should be built-in or should be by design [18],'' which means that, at the present time, one only determines the quality of the finished product and undertakes corrective action where needed. On the other hand, however, the goal should be to control and monitor the process in such a way that, in the end, only the correct quality can result. The FDA's Ali Afnan commented: ''therefore, analyses of tablets alone, with no correlation or relationship to the manufacturing process and starting materials (i.e., for such attributes as assay or content uniformity), should not be regarded as PAT. Such a procedure can only 'assure' the status quo, and has no impact on quality, even with 100% inspection of product. It is 'monitoring' only, not control, and thus should be considered an alternate method [22].''

Different tools are available for facilitating the goals of the PAT initiative—process understanding and process control, including at-line, in-line, or on-line [23] measurement devices, statistical and information technology tools, and a scientific systems approach for data analysis to control processes to ensure production of desired quality (Fig. 1).

One of the main goals of the PAT initiative is to achieve process understanding. As the FDA guidance states: ''the goal of PAT is to enhance understanding and control the manufacturing process, which is consistent with our current drug quality system: quality cannot be tested into products; it should be built-in or should be by design. A process is generally considered well understood when

1. all critical sources of variability are identified and explained;
2. variability is managed by the process; and,
3. product quality attributes can be accurately and reliably predicted over the design space established for materials used, process parameters, manufacturing, environmental, and other conditions [18].''

The accomplishment of complete understanding of a process begins as early as the development phase of a project. One of the main tasks of chemical and pharmaceutical development has always to distinguish between key process indicators and those aspects which have little or even no influence on the process.

PAT and the ICH, EMEA, and ASTM

The PAT initiative is part of a broader process, namely the initiative announced in August 2002 entitled ''Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach,'' and continues within the ICH process (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use), specifically in the new draft guidelines ''ICH Q8—Pharmaceutical Development'' and ''ICH Q9—Quality Risk Management.'' It is the Q8 effort in particular which focuses on designing quality into process and product development. The FDA is actively supporting the ICHs efforts in this area [25].

The European Medicines Agency (EMEA) also reacted to the PAT initiative of the FDA and formed an EMEA PAT team in January 2004 to review the implications of PAT to ensure that the European regulatory

- Multivariate tools for design, data acquisition and analysis

  These tools include such widely used statistical techniques as design of experiments and multilinear regression analysis, which enables a quantitative understanding of the effects of different inputs upon the output of a system.

- Process analyzers

  Modern process analyzers/process analytical chemistry tools could be placed on- or in-line and are nearly instantaneous, such as near-infrared and raman spectroscopy.

- Process control tools

  These tools provide a means for measuring process parameters and acting on those measurements.

- Continuous improvement and knowledge management tools

  These tools constitute information systems that integrate data and make them available to users, offering a basis for sustainable improvement.

Fig. 1 Tools which are included in the PAT framework [18, 24]

framework and the authorities are prepared for and adequately equipped to conduct thorough and effective evaluations of PAT-based submissions. To avoid confusion, the European regulators will be using the PAT definition contained in the FDA guidance: "PAT is a system for designing, analyzing, and controlling manufacturing through timely measurements of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality [26]."

Notes concerning the topic of PAT are already to be found in a whole series of European documents, as has been pointed out by Christina Gaffner of the Swedish Government Drug Agency [27]. Thus, e.g., "parametric release" is mentioned in the 5th edition of the European Pharmacopeia, just as Annex 17 to the EU Guide to GMP concerns itself exclusively with parametric release. Formulations are also to be found in the European "Note for Guidance on Development Pharmaceutics" (CPMP/QWP/155/96) that reflect the basic ideas of PAT, namely that of process understanding.

The American Society for Testing and Materials (ASTM) established the Committee E55 on Pharmaceutical Application of PAT in February 2004. This committee addresses issues related to process control, design, and performance, as well as quality acceptance/assurance tests for the pharmaceutical manufacturing industry. Around 150 members, including representatives of academia, federal agencies, manufacturers of pharmaceuticals and equipment, and software vendors, are working together in the executive subcommittee and or in the three subcommittees on PAT system management, PAT system implementation and practice, and terminology. They are developing standardized language and definitions of terms, recommended practices, guides, test methods, specifications, and performance standards for PAT applications in pharmaceuticals. Within a single year, nine work items and one active standard have thereby come into being. The first approved standard, which covered terminology, was ASTM E2363-04a, "Standard Terminology Relating to PAT in the Pharmaceutical Industry [28, 29]." Approximately 75 PAT-related terms are defined there, such as "acceptance criteria", "deviation", "on-line measurements", "process control", and "risk assessment" as they relate to PAT.

Implementation of PAT

The PAT concept of process understanding and control has long been implemented in the semiconductor, petrochemical, automotive, and food and beverage industries. Investments have always been made in these branches of industry to improve quality and reduce cost. Drug companies often put resources into developing the next new product that may offer the chance of being sold without competition. David Lerner, Co-Director of the Rusco process technology consulting group, gave an example of this thinking [28]: "if I am a CEO of a company, I could spend resources to save 10 million dollars (by implementing PAT, e.g.). That is nothing to sneeze at, but I could use the same resources to have a chance to develop a new drug that could make a billion

dollars.'' According to the Wall Street Journal [12], however, laboratories are currently producing fewer new drugs, which means that the payoff from investing in drug discovery is diminishing. At the same time, sales forces have hit the saturation point and savings from improving manufacturing processes make more sense as a way to boost profits. As a result, attention is now being focused on investment in more efficient manufacturing through the use of PAT.

According to Rusco [28], there are three beneficial opportunities for the implementation of PAT tools:

- processes that have long processing times, low efficiency, or generate high levels of waste;
- new products, where PAT can provide more data for use in development and scale-up;
- processes which have to be improved enough to compete with generic drug manufacturers once the time of market exclusivity ends.

But it should be stated that not every PAT area is appropriate for every product or every company. FDA officials have also stated in talks with the industry that PAT will not be considered mandatory [30]. Similarly, industry consultant Peter Smith (KMI) agrees that PAT is not practical for low-volume products and is probably not economically feasible for small companies [30]. But PAT makes good business sense for pharmaceutical companies which produce large numbers of batches annually in dedicated facilities or in dedicated lines. This opinion is also shared by Gerd Fischer of Sanofi–Aventis, who said at the IFPAC 2005 Conference [31] that products for a PAT pilot project should amount to more than 100 t per year for API and more than 1,000 batches per year for drug products.

Nonetheless, according to a statement made by Ajaz Hussain that is quoted in the November 2004 issue of *The Gold Sheet* [32], a number of PAT submissions have already arrived at the agency. Sanofi–Aventis received approval as early as December 2004 for a submitted change in the adoption of PAT [31].

The PAT Guidance for Industry is proposing various options for implementation [18]:

- PAT can be implemented under the facility's own quality system. The cGMP inspections by the PAT team or PAT certified investigator can precede or follow PAT implementation.
- A supplement can be submitted to the agency prior to implementation, and, if necessary, an inspection can be performed by a PAT team or PAT certified investigator before implementation.
- A comparability protocol can be submitted to the agency outlining PAT research, validation and implementation strategies, and time lines. Following approval of this comparability protocol by the agency, one or a combination of the above regulatory pathways can be adopted for implementation.

A similar comparability protocol (CP) was also utilized by Sanofi–Aventis to manage manufacturing changes to PAT. As reported by Gerd Fischer of Sanofi–Aventis [31], the company began its PAT pilot project in January 2003, and was already presenting its project to the FDA in May of that year. In doing so, it was complying with the FDA's call to companies to present PAT projects at an early date. Various draft CP versions were discussed afterwards with the FDA PAT team. The PAT CP was submitted in October 2004, following a pre-operational site visit by the FDA in August 2004, and approval was granted two months later.

In addition to implementation, thought must also be given to validation of the PAT systems. ''Revalidation is not an issue,'' as FDA's Ajaz Hussain has said. ''With PAT, we said, you don't validate it, you control it, using validated controls. This approach makes the whole system modular and based on the level of understanding. It allows you to distinguish between what's important and what isn't, so you can focus on what is [19].'' The PAT guidance [18] formulates this as follows: ''in a PAT framework, validation can be demonstrated through continuous quality assurance where a process is continually monitored, evaluated, and adjusted using validated in-process measurements, tests, controls, and process end points.''

PAT review and inspection

The final guidance on FDA's PAT initiative [18] states, ''the regulatory implementation strategy includes creation of a PAT team approach to chemistry manufacturing and control (CMC) review and current good manufacturing practice (cGMP) inspections as well as joint training and certification of PAT review and inspection staff.''

The ''PAT Review, Inspection and OPS (Office of Pharmaceutical Science) Policy Development Team'' (PATRIOT) was assembled in late 2002 for that purpose. The FDA PAT team consists of representatives from the CDER, the Office of Regulatory Affairs (ORA), and the Center for Veterinary Medicine (CVM) and is subdivided into the following groups: PAT Steering Committee, PAT Policy Development Team, PAT Training Coordinators, and PAT Review/Inspection Team. The 15-person-strong PAT review/inspection team is made up of investigators, compliance officers, and reviewers.

A training program for the team was developed in coordination with several academic National Science Foundation centers and included two didactic sessions, as well as three advanced practicums. The didactic sessions provide knowledge about pharmaceutical processes, PAC, multivariate analysis, and process control, and include case studies. The practical training programs were held at the Universities of Washington, Purdue, and Tennessee, with focus on sensor technology

1. Is this a PAT system?
2. Does it have aspects of design, measurement and manufacturing control?
3. Are PAT principles and tools used?
4. Which tools specifically are used for manufacturing control?
5. How is continuous improvement and knowledge management performed?
   - Systems in place and design for the future
6. What risk-based approach has the company taken – assessment, prevention and management?
7. How are the PAT systems integrated?
8. What kind of real-time release is being proposed or used?
9. What regulatory process is being considered?
   a) Can the companies' quality system manage the PAT change?
   b) Are the submission proposals appropriate and justified?
10. What are the critical aspects that should be looked at during site visits/inspections?"

Fig. 2 Ten questions that the FDA would like to have answered in connection with a changeover to PAT and/or the implementation of PAT were presented by Albinus D'Sa of the Office of Compliance, DMPQ CDER, FDA at the IFPAC 2005 Conference [33]

and utilization, multivariate analysis, and process control and capability [17, 33].

The first PAT team will continue its training, and a second PAT team will be selected to begin training for CMC review and cGMP inspections of applications that utilize PAT. Invitations will be extended to the Canadian, Japanese, and European regulatory agencies to participate in the second PAT training program, as stated by the FDA [34].

This training strategy appears to lead to a change of direction. This was the gist of comments made by David Radspinner of Sanofi–Aventis at the IFPAC 2005 Conference [35], who noted that the pre-operational site visit of the FDA to the company's PAT application was not the equivalent of a formal inspection but proceeded instead in a very science-oriented manner. Questions were posed for example regarding models for data assessment, risk evaluation, and measurement system performance verification (Fig. 2).

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