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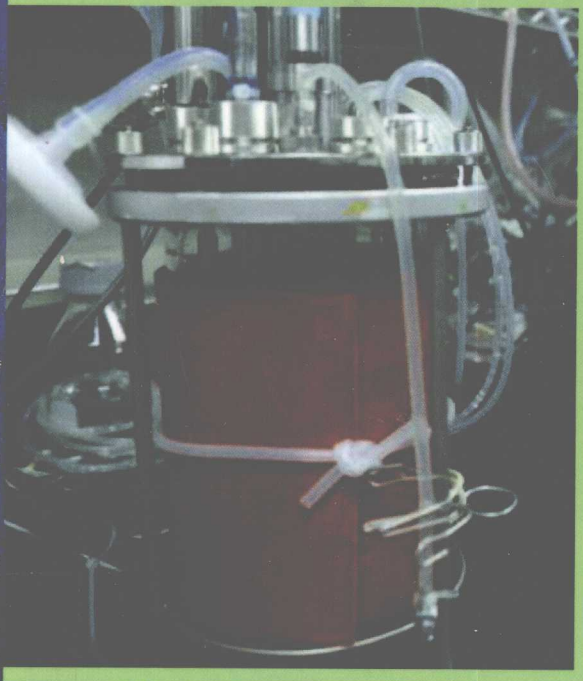
PAT Applied in Biopharmaceutical Process Development and Manufacturing

An Enabling Tool for Quality-by-Design



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Foreword

The publication of the draft of the guidance on Process Analytical Technology (PAT) on September 3, 2003 was a milestone for a much needed change for the pharmaceuticals and biopharmaceuticals industry. Energy and resources had been dedicated and applied to the process of drafting the guidance and finalizing it a year later in September 2004. The guidance was the culmination of collaboration between the regulators and the regulated, and the fruit of knowledge and experience of many years.

For the FDA the guidance was a first: it was historic; it was not prescriptive; it challenged the industry to re-evaluate its operations and knowledge of the manufacturing processes; it challenged the regulators world-wide as well as the industry to cease operating in silos and to collaborate across functions. A desired 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.*

Nearly a decade later its application is not universal for several reasons such as:

- Benefits of real-time control are neither appreciated nor understood;
- The regulatory process has not been explored sufficiently to facilitate and allow change;
- There is still confusion as to what the PAT framework is and how to implement it.

Continued success of the pharmaceutical industry requires innovation and efficiency. PAT is one framework capable of facilitating innovation and efficiency, thus assuring success of pharmaceuticals and biopharmaceuticals industries. As tenets of quality by design are consistent with PAT procedures, implementing the PAT framework can enable quality by design, can reduce the risk to quality and regulatory concerns whilst improving efficiency.

This book is a first comprehensive text on the PAT for biologics. It covers all aspects of the framework from different angles and perspectives. It is a rich offering for those who have not yet tried PAT in changing the research, development, and manufacturing within the industry. And it is useful for practitioners as a reference book.

Ali Afnan, PhD

* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070305.pdf.

Introduction to Process Analytical Technology in Biopharmaceuticals

Mel Koch and Ray Chrisman

1 INTRODUCTION

In the past few years, the field of bioprocessing has experienced a major increase in interest, as products resulting from this field are having an impact on their respective markets. As a result, significant growth in research and development and a dramatic expansion of production capacity have occurred. The significant increase in research and development is principally in the pharmaceutical and biotechnology industries, which have recognized bioprocessing as a potential source of a whole new range of bioactive materials. The capacity expansion has been led by the rapid growth in bio-ethanol and other fuels-related production. Adding to the general increase in interest in bioprocessing is the fact that other industries such as chemicals are exploring the potential of a biological approach for a more sustainable source of materials.

However, bioprocessing brings a whole new range of challenges to the process development team. These may include constantly varying quality of raw materials, optimization, and control of organism-mediated molecular production and postproduction concentration and purification steps. In addition, most bioprocesses require sterile operating conditions.

Biopharmaceutical production often has additional challenges in that the desired component may be trapped inside the cell, requiring a lysing step and filtering. Protein therapeutics impose additional conditions such as working with large and heat- and shear-sensitive molecules. Moreover, there are various, sometimes subtle, factors that can alter the post-translational modifications of the proteins, which can have undesirable effects on efficacy.

As with all of pharmaceutical production, the regulatory environment for the production of therapeutics has been changing. This change is a direct result of the implementation of the U.S. Food and Drug Administration (FDA)–initiated quality by design (QbD) guidelines and corresponding activity from other regulatory agencies and the International Committee on Harmonization (ICH) activities, notably Q8, Q9, and Q10. Given the rapid growth in the biopharmaceutical area and the complexity of the molecules, the optimum utilization of these concepts is still being developed, which requires the team to be very proactive in their efforts to satisfy regulatory requirements during process development. Fortunately, the development

and utilization of process analytical technology (PAT) has also been growing rapidly in this field. This book will offer many examples of the ways in which design teams are using PAT to not only speed up process development for biopharmaceutical production but also how it is being used to ensure high-quality production with enhanced regulatory compliance.

2 OVERVIEW OF BOOK STRUCTURE

The goal of this book, *PAT Applied in Biopharmaceutical Process Development and Manufacturing: An Enabling Tool for Quality-by-Design*, is to provide the reader with an up-to-date overview of the rapidly growing field of process analysis in bioprocessing. As such, Chapter 1, "Scientific and Regulatory Overview of Process Analytical Technology in Bioprocesses," begins the book by defining the concept of PAT from a regulatory point of view. Validation implications are outlined for the future use of PAT tools in biomanufacturing of drug substance and final dosage form.

Chapter 2, "Strategic Vision for Integrated Process Analytical Technology and Advanced Control in Biologics Manufacturing," describes how integrating PAT into biologics manufacturing requires a strategic vision and plan for advanced control. Experience with small-molecule production is a valuable starting point here. Achieving advanced control usually requires the implementation of multivariate analytical techniques (more than one variable per measurement, e.g., multispectral techniques like infrared or chromatography or combinations of measurements) during the process development phase. The chapter finishes with an example where PAT data are used for the control of glycosylation patterns of proteins.

Statistical treatment of the data from the design of experiments is used to predict a design space for process operation and is described in Chapter 3, "Multivariate Techniques in Biopharmaceutical Process Development." A variety of techniques, including fault detection and identification, predictive monitoring, partial least squares, principal component analysis, and spectral approaches, are reviewed. The chapter finishes with an example of the impact of PAT tools on effective production operations and a look at the future of process characterization.

Another facet of overall plant operation for process control is described in Chapter 4, "Analysis, Monitoring, Control, and Optimization of Batch Processes: Multivariate Dynamic Data Modeling." Several historical examples of successful modeling based on handling process data are described.

The focus of the book then shifts in Chapter 5, "Multivariate Data Analysis in Biopharmaceuticals," to the use of multivariate data analysis (MVDA) for problem solving and model development at the pilot scale and demonstrates how this knowledge can flow into uses for production control. The chapter also describes the various potential problems in modeling and how the appropriate use of MVDA can help solve them.

Chapter 6, "Process Analytical Technology Advances and Applications in Recombinant Protein Cell Culture Processes," focuses on the challenges in applying PAT to recombinant protein production processes. This involves regulatory

perspectives, tool selection, and knowledge management. The chapter finishes with applications to recombinant protein production.

Chapter 7, "Process Analytical Technology Applied to Raw Materials," begins with the characterization of the extreme complexity of raw material feeds and how chemometrics and MVDA can help ensure product quality given the variations in the feed. These points are enhanced by the use of several examples, including yeast extracts and fermentation, insulin micronization design development, and the media influences on glycosylation in mammalian cell cultivation.

Given the importance of cleaning to ensure product quality and safety and reduce production holdups, the use of PAT for this production phase is reviewed in Chapter 8, "Process Analytical Technology for Enhanced Verification of Bioprocess System Cleaning." Its utilization to enhance product release and ensure compliance with regulatory requirements is described. The efforts required to ensure cell culture quality are explored in Chapter 9, "Cell Culture Process Analytical Technology Multiplexing Near-Infrared," via techniques of multiplexing near-infrared technology.

One of the most significant processing areas from a time and capital investment perspective is the whole area of bioseparations. The treatment of the subject in the next chapter demonstrates the value of PAT utilization in the area to ensure optimum operation. Thus, Chapter 10, "Process Analytical Technology for Bioseparation Unit Operations," reviews PAT applications in major harvest and purification operations, such as centrifugation, filtration, homogenization, and chromatography.

To give a broader understanding of the applications of PAT to the unique challenges of using biomaterials for production, an overview of its use in biofuels is described in Chapter 11, "Process Analytical Technology Use in Biofuels Manufacturing," to point out the many new and expanding applications to production processes in the bioprocessing field.

In Chapter 12, "Application of Microreactors for Innovative Bioprocess Development and Manufacturing," a major effort is made to help the reader understand the utility of the growing use of microscale technology to explore the broad parameter space covered by modern-day bioprocessing. The description demonstrates not only the utility of PAT for characterization of organism growth, but also serves as a reminder of the number and complexity of interactions of the parameters that affect their growth.

A key unit operation that is somewhat unique to bioprocessing is lyophilization. PAT tools useful for process control in this section of the process are described in Chapter 13, "Real-Time Monitoring and Controlling of Lyophilization Process Parameters through Process Analytical Technology Tools." This chapter demonstrates how the use of PAT can enhance the performance of the sometimes overlooked intricacies of lyophilization by describing the process parameters and the PAT tools available to monitor them.

Chapter 14, "Process Analytical Technology's Role in Operational Excellence" takes a broader view and evaluates all data flowing from the bioprocess to facilitate manufacturing excellence and lean manufacturing concepts. As an example, the idea of PAT-based predictive maintenance is presented.

The book then closes in Chapter 15, "Conclusions, Current Status, and Future Vision of Process Analytical Technology in Biologics," with a brief look to the future of PAT in the biopharmaceutical production area. It builds its vision of the future based on current uses of PAT in bioprocessing and then describes expected technology developments and how they may impact process design, monitoring, and control.

3 BRIEF BACKGROUND OF PAT IN BIOPHARMACEUTICAL PRODUCTION

There is growing global interest in the concepts of product and process optimization and quality assurance based on PAT to ensure public safety and product efficacy. The efforts are rapidly gaining support from both governments and industry as the various advantages of effective PAT utilization are more fully understood. Current implementation projects have clearly demonstrated improvements in not only quality but also cost of manufacture, environmental impact, energy efficiency, and the safety and security of operations.

The positive impacts of technological advances in PAT that have been seen in small-molecule drug development and manufacturing are a significant part of the reason that the concepts are now being applied to biopharmaceutical manufacturing. Thus, even though biomolecule production is one of the oldest areas of effective production, as evidenced by the use of fermentation through the ages, there are still significant improvements being discovered. These improvements are a result of new technology, enabling a more fundamental understanding of how bioprocesses work and what influences their efficiency.

What is now known is that there are many complexities in bioprocessing relative to the organism used, the media, the makeup and quality of the nutrients, the processing conditions, and the harvesting of the product. With this level of complexity, a key part of the advancement in understanding is based on the application of statistical data analysis to relate the multivariate analytical measurements to the broad parameter space to facilitate a much better process understanding. This powerful information analysis approach leads to actionable process understanding to advance the goal of process improvements mentioned above. This book will focus more on the methods and value of relating data to functional parameters throughout the process than it will on the specifics of the measurement science techniques used. However, because the appropriate measurements for the problem are a key part of analytical success, sufficient time will be spent in technique description to ensure that the reader understands and appreciates the justification for the approach chosen.

In addition to the traditional uses of bioprocessing in foods and beverages, there is rapid growth in its emerging use for biopharmaceuticals, biofuels, and bio-based production of chemicals. Though PAT for bioprocessing overall is still in its infancy, the rapid growth in several of the related fields has led to several new implementations of the technology. Bioprocessing, as it is related to bioenergy, has received a strong emphasis recently due to rising energy costs, largely due to increasing fossil fuel prices.

The use of biomaterials as a source for hydrocarbons has presented many challenges to the process engineer. As an example, new approaches to process separations

are needed for both the removal of the water from the product and also in separating the product from other components in the mixture. Bioethanol is a good example where the cost of removing the water from the product is the most expensive cost in the process other than buying the raw material, corn. These separation unit operations need to have analytical measurements for monitoring purposes to be controlled for optimum operation.

Because some of the key unit operations and their control are common across these related bioprocessing fields, Chapter 11 is included to describe the use of PAT in the biofuels area. It is expected that some of the learnings developed for the use of PAT in the production of biofuels will be useful to broaden the general understanding of successful applications of the technology.

One of the key differences in the application of PAT to biopharmaceutical process development from its historical bioprocessing uses has been the utilization of the technology to develop a more fundamental understanding of the underlying organism growth. As part of the effort to apply the concepts of QbD and fully characterize the operating range of a bioprocess, the utilization of PAT is proving to be indispensable for the development of the needed understanding. This understanding is then being utilized to optimize the process to improve productivity, reduce environmental impact, increase energy efficiency, and enhance process safety.

One approach that is being utilized to much more efficiently explore the wide range of variables that can impact organism growth is the use of microscale reactors. This technology can be highly automated and parallelized to run a significant number of experiments to grow organisms under an extremely wide range of conditions. The coupling of the approach with PAT generates very large data sets that profit from the use of the statistical analysis to understand the impact of changes in operating parameters. Chapter 12 is devoted to examining this powerful new approach that may be new to many who are working in the bioprocessing field.

As mentioned above, the ability to do more organism growth experiments aids the new push for process understanding that is part of the QbD concept embraced by the U.S. FDA pharmaceutical regulatory agency and advocated by regulatory agencies around the world. A key part of the QbD concept that will be described in more detail later in this introduction is the need to understand process variability as a function of process parameters.

However, this enhanced understanding is necessary for all aspects of the manufacturing process and is not limited to the organism growth sections. Thus, in addition to the bioreactor, the other unit operations, such as lyophilization, separation, and cleaning, are each described in much more detail to help the reader appreciate the PAT needed for characterization of the corresponding unit operations. The descriptions are taken through data analysis to help build awareness of the approaches that lead to the desired process knowledge for optimization of the steps.

Just as composition variability in a barrel of oil can dramatically change the efficiency of operation of a refinery, the variability of the raw material feed of a bioprocess can have a significant impact on process performance. Chapter 7 presents the state-of-the-art in measuring this variability and then describes how to use the information for optimized process operation.

As with any process design, care must be taken to avoid suboptimization of the process. A review of the contributions of PAT to the development of operational excellence in the analysis of the whole process is included in Chapter 14. Part of the uses of the approach is to ensure that the understandings that are developed in one unit operation are compatible with needs of other processing steps.

Another key theme that is present throughout the book is that as the manufacturing process is being designed, there is a need to ensure the scalability of information. PAT is proving to be very important to facilitate effective scale-up. In fact the inability to move from one scale to another has been a real problem for quality production as new small-molecule processes are implemented. To solve this problem in the small-molecule drug area, the microreactor world uses the concept of numbering up. The idea is that instead of building bigger reactors, scale-up is achieved by adding more microscale reactors so that process conditions such as heat and mass transfer do not change (Hessel et al. 2009).

This number up concept has proven to work and alleviate many of the problems with scaling to meet product launch or rapidly expanding product demand. However, it is now being demonstrated that the microscale equipment coupled with PAT can be used to characterize the underlying chemistry to the point that first principles types of process models can now be built (Koch et al. 2007). The ability to develop these models that are deconvoluted from the effects of the processing equipment enables the choice of processing equipment based on cost-effective performance to optimize the underlying chemistry as opposed to having to do extensive and expensive testing of the reaction at each new scale. The ability to more precisely understand the chemistry is a relatively new concept that is still evolving and is expected to become more important as companies work to achieve more cost-effective manufacturing. Although it is unclear if these first principles types of models can be developed for biopharmaceutical manufacturing, it is clear that PAT will have a significant impact on better model development for process scale-up.

Finally, the effective use of PAT also provides data that can greatly improve process understanding and facilitate the regulatory filing process. As this is a significant part of any new drug development process, we begin the book with a detailed look at how PAT can be effectively used to help biomanufacturing in this needed effort.

4 OVERVIEW OF PROCESS ANALYTICAL TECHNOLOGY

For more than 70 years, PAT (McMahon and Wright 1996; Gregory et al. 1946) has been practiced to monitor materials production. Initially, PAT was used to follow the progress of chemical reactions, but it also proved useful for problem-solving purposes if the process ever went into an upset condition. The first analytical tools that were taken to the process environment were the instruments that historically were used in the laboratory to characterize the product being produced.

The instruments were taken out of the laboratory and put on-line due to the realization that taking samples and transporting them to a central analytical laboratory was not only dangerous and costly, but it also resulted in inaccurate representation of the process—as the dynamics of the process were often missed because of the time required to make the measurement. It rapidly became clear that the same instrument

that gave data on the parameters of the final product when used in the lab could, if successfully placed on-line, represent process intermediates, many of which could predict product quality.

As PAT has matured, sampling techniques have improved to enable many measurement tools to be used in an at-line or in-line mode, which has reduced the need for manual sampling. However, sampling still remains the largest source of problems with on-line installations. This sampling problem is magnified with the often multiphase character of bioprocesses.

As the need for PAT grows, the types of instrumentation being implemented on-line continue to expand the breadth of analytical tools being utilized. It spans an increasing range of optical spectroscopy, various new approaches in separation science, a growing list of tools such as mass spectrometry, chemical sensors, acoustics, chemical imaging, and light scattering (Workman et al. 2009). Moreover, developments in PAT are coming from a wide range of laboratories, including the traditional analytical chemistry labs as well as many significant advancements coming from engineering, biological sciences, and computer science.

A key problem with this wide-ranging PAT development is that it is increasingly difficult for any one technical organization to follow all of the innovations in PAT. The developments are occurring across the whole range of processing industries as well as in government, and academic laboratories. This has become an increasingly more important problem as the need for PAT in a broader range of unit operations has risen and the implementing organizations continue to have limited resources of funding, man power, and time.

As such, most organizations are forced to look outside their company for help in following and implementing developments in PAT and QbD. This is evident in the increasing participation in symposium-based forums such as the International Foundation for Process Analytical Chemistry (IFPAC) and in a growing number of workshops and technical presentations in the fields of PAT and QbD that are being offered on a global basis by professional societies (including ISPE, PDA, and AAPS), standard setting groups (such as ASTM and ASME), and other commercial organizations (such as IBC, CHI, and IQPC).

A powerful additional strategy to stay abreast of the broad-ranging PAT field is the concept of leveraging activity via an industrial consortium. In this approach, members of a consortium are able to follow developments in related industries and leverage their resources to fund research projects in selected areas for the development of new PAT tools.

The Center for Process Analysis and Control (CPAC) at the University of Washington in Seattle, Washington (www.cpac.washington.edu), is one of the earliest and long standing examples of industrial-academic consortia from which several concepts in PAT emerged and were further developed.

The reason an academic consortium of industrial organizations survives is the ability to leverage scarce resources. In the pharmaceutical area, it has proved to serve as a benchmarking tool to understand how QbD can be a cost-effective approach to accomplish process and product optimization. Leveraging also occurs in a consortium because industry is exposed to additional members of a broad academic research team which is needed to develop modern PAT.

5 PAT CHALLENGES THAT ARE UNIQUE TO BIOPHARMACEUTICAL PRODUCTION

In a general sense, there are a series of fairly straightforward, simple steps that are taken in the chemical and related product areas that have proven to be quite useful to gauge the feasibility of a PAT implementation on a selected unit operation. The first step in a successful PAT implementation is finding the appropriate measurement tools that can characterize the components in the selected unit operation. This requires matching the speed of analysis, the specificity, and the quantitative precision and accuracy of the chosen technique to the rate of change and the compositional complexity of the unit.

Presently in biopharmaceutical operations, many conventional sensors (pH, conductivity, UV, etc.) are used but they have limitations related to fouling and nonspecificity for the desired product. Understanding more complex signals from advanced measurement instruments (Raman, NIR, IR, etc.) is challenging, but their use shows promise (see Chapters 6, 7, and 9). Work continues to show underlying correlations to 'cause and effect' in an attempt to achieve process understanding. As well, there is a challenge to develop methods for rapid microbiological testing to determine viability of a batch at an early step of processing.

It is worth mentioning at this point that in addition to the traditional approach just mentioned, newer data analysis approaches enable correlating instrument response to a broader range of process parameters such as product quality, process performance, and even equipment performance. Thus, the information from an in-process measurement, when properly analyzed, can provide a wealth of information leading to higher levels of product quality, enhanced process control, and even information leading to advanced strategies for preventative maintenance.

Once the needs are understood, the next step is developing a sampling strategy. This in many respects is the hardest part of the preliminary evaluation and as mentioned earlier is the source of failure in most implementations. This can be even more of an issue in biopharmaceutical applications as the streams can be far more complex than in the more traditional PAT applications in the small-molecule area.

The seemly rather straightforward role of the sampling system is to take a representative sample from the process stream and prepare it or condition it for analysis by the analytical device. The sample conditioning may include an initial separation to remove liquids from a solid sample or solids from a liquid sample. It must then adjust the temperature, pressure, and concentration to be compatible with the requirements of the analysis device. It may also need to adjust pH, change solvents, add additional components such as standards or other reagents, and possibly do an initial molecular or salt separation to reduce interferences. These steps all need to be done reproducibly as well as fast enough for needed control requirements. They must also be automated with minimal and preferably no operator intervention. It must also do these steps day and night, summer, and winter for extended periods of time with no loss of precision of the measurement.

Of course there are other issues like materials of construction and external environment. The environmental conditions such as temperature, power quality, and other external feeds can have a major impact on long-term system drift. Other issues

such as dust, humidity/rain, insect and animal infestations, and mechanical vibrations have also been known to cause problems with system performance. The point is that the list of potential problems is long and being constantly expanded. The key to handling the long list of potential problems is to develop a rugged reliable design based on the wealth of existing experience in the field.

Unfortunately, the design problem for biopharmaceutical production processes can be even more complicated by issues such as multiple phases in, for example, a bioreactor. Not only are there the organisms but there may be solids in the nutrient feed and potentially gas bubbles. Something as simple as media saturated with air in the bioreactor can cause flow inconsistencies in tubing and filters or bubble buildup on optical surfaces. In addition, the molecule of interest may still be inside the cells, which means that a cell lysis step must be added. All of these problems are solvable, but they do require a careful design to ensure that the on-line system produces the required data quality in a timely fashion. A system must be proven to be reliable to be useful and believed by the operating staff.

In order to improve sampling systems reliability, standardized flow path approaches were developed by a working group facilitated by CPAC that enabled the use of modularized and miniaturized sampling components in the petrochemical world (collective effort called New Sampling and Sensor Initiative, NeSSI) (CPAC 2011).

Although the NeSSI sampling system approach is viable for biopharmaceutical production, the implementation is currently not compatible with some important though unique concerns to pharmaceutical production processes. Even though solutions are known that would solve the problems, it has so far not been commercially reasonable to retool equipment designs to provide sampling system components that are qualified for use in pharmaceutical production. It is hoped that this problem will be resolved in a timely fashion to enable more rapid and reliable implementations of PAT in biopharmaceutical production processes.

Finally, to complete the design phase for a process analyzer, the system must be designed to ensure that process sterilization concerns are met both during operation and also during any system maintenance. If the sampling system design seems to be able to meet the various operational needs and the analysis system can perform the needed analysis, then it is reasonable to begin the process of system development. This description is meant to demonstrate that there is much more to a successful implementation than just running a test sample in the lab, or in other words, the name PAT is no misnomer.

It should be pointed out that each unit operation has its own challenges when it comes to on-line analyzers such as physical properties, analysis time, and sample complexity. It should also be pointed out that the operation of the particular step must also be understood to ensure that the data from the analyzer is of value for control of the unit.

Another aspect that is often mentioned in technical meetings by control engineers is that process analytical chemists will develop a system that provides information on component concentrations and assume that the problem is solved. However, the process often has no control point for directly changing product concentration and thus a process model needs to be developed to relate concentrations to controllable parameters like valve settings and motor speeds. The process model may suggest that reducing/raising the temperature may improve yield or that changing residence

times or agitation rate or some feed flow rate or all of the above may change the concentration but a model must be built to understand what to change at what rate to alter the concentration. Fortunately, if the data are available, it becomes much more possible to do but it is not necessarily easy to do.

6 REGULATORY ASPECTS OF PAT RELATIVE TO QBD

With the FDA's recent emphasis on quality, cost, and productivity, the use of PAT has emerged as a key resource to accomplish QbD. The general description of PAT encompasses the system that surrounds the measurement tools. It involves the sampling of the process, the sample conditioning needed for the effective measurement, the measurement, the data pretreatment, the data handling, and connection to the process control system. This has been described in an FDA Guidance.

The FDA has also worked with the ICH to outline an approach for describing QbD for the small-molecule area. In fact, this outline is an excellent template for all industries to follow in their process development and optimization activities.

The sample QbD approach (as incorporated in the International Harmonization document Q8R) was presented by a FDA representative (Nasr 2008) in Siena, Italy, in 2008. It involved:

1. Targeting the product profile
2. Determining critical quality attributes (CQAs)
3. Linking raw material attributes and process parameters to CQAs and performing risk assessment
4. Developing a design space for operating the process
5. Designing and implementing a process control strategy
6. Managing product life cycle, including continual improvement

It was emphasized that the application of PAT tools is useful for optimizing these steps in operating an effective process.

Large-molecule (biological) production can learn from successes in small-molecule manufacturing where "design space" was calculated based on designed variable experimentation. This often involved varying raw material quality, stoichiometry, and process conditions. Moreover, the value of monitoring was seen in establishing process control systems from effective process models. Monitoring was also the key to continuous improvement activities. In addition, as mentioned earlier, there are challenges for manufacturing of large (biological) molecules that include: diverse reaction media, sterilization concerns, equipment cleaning, size of unit operations, and process development activities, all of which can be aided by appropriate PAT.

7 INDUSTRY PERSPECTIVE ON THE NEEDS AND FUTURE OF PAT

Much of what is being pursued presently in the biopharmaceutical industry regarding areas around PAT is summarized in Figure 1 (Thomas 2009). There is a need for improved fundamental scientific understanding to improve process productivity. Much more of this knowledge can be gained by designing studies that are more

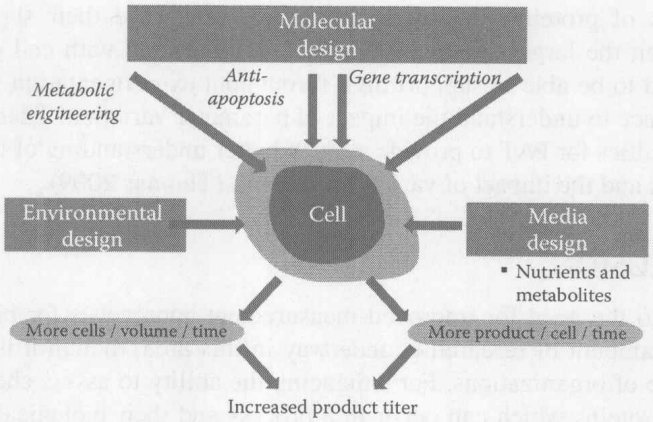

FIGURE 1 Greater productivity requires improved fundamental scientific understanding (Thomas 2009).

productive with the utilization of PAT in the process development phase (Thomas 2009).

Various processing steps are involved in the process development, and improvements can be made throughout the sequence of steps to bring a protein therapeutic into production. Although it is clear that these are very complex materials to manufacture, it is also clear that significant improvements have been made and are continuing to be made in their production (Thomas 2009).

Bioreactor operation is one of the most critical steps in producing proteins, and improvements are needed in molecular design, as well as in the characterization of the media and bioreactor conditions to improve productivity. Again, these can be facilitated by PAT (Thomas 2009).

However, there are significant barriers in measuring the products of bioprocessing as reflected in Thomas' presentation. Challenges and trends in measuring protein therapeutics include, as summarized by Thomas (2009),

1. Greater sensitivity and more specificity
   a. Peak profile (i.e., cation exchange chromatography (CEX)) does not identify specific chemical changes
   b. Move toward more informative assays
2. Elimination of subjectivity
   a. Visual inspection, presence of particles, color
   b. Move toward automated instrument-based inspection
3. Focus on CQAs
   a. Move toward specific chemical change and the site of modification
   b. Move toward understanding the biological importance of chemical changes

In conclusion, Thomas (2009) stated that technical opportunities for improving bioprocessing include the ability to more specifically measure the post-translational

modifications of proteins and to more rapidly understand their significance. In addition, given the large number of parameters associated with cell growth, PAT methods need to be able to support high-throughput experimentation for exploring parameter space to understand the impact of parameter variation. There are significant opportunities for PAT to provide a much better understanding of the quality of raw materials and the impact of variations in them (Thomas 2009).

8 CONCLUSION

In response to the need for improved measurement approaches for bioprocessing, a significant amount of research is underway in this area, though it is spread over a broad range of organizations. For enhancing the ability to assess chemical modifications of proteins which can occur in a process and their biological relevancies, new measurement platforms are being considered. There is no doubt that, based on continued successful advances in miniaturization technology, most of the new measurement needs will be solved.

In addition, novel microfabrication approaches are now being demonstrated in the production of devices, which can reduce measurement time and cost. With these advancements now being incorporated into devices, manufacturing new high-throughput tools for process development can be considered. These developments will have broad-based effects on the scope of PAT, which includes sampling, sensing, control, and eventual data communication.

It is expected that those practicing in the bioprocessing field will find the contents of this book to be very timely and relevant to their efforts as it explores the wide range of applications of PAT to bioprocessing.

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