

This article focuses on the implementation of closed process systems, controlled processing capabilities, and manufacturing flexibility.

## Trends in Biopharmaceutical Manufacturing Facility Design: What's Hot!

by Jeff Odum

The biotechnology industry is in the early stages of what many "experts" see as a period of tremendous growth and advancement. 2004 saw the approval of 20 new biotechnology products. Another 80 are in late stage development. The industry continues to develop technologies that will focus on genomics and the improvement in protein production techniques to increase efficiency and cost effectiveness. Many companies that had received approval of drugs in 2004 are embarking on substantial capital expansion programs.

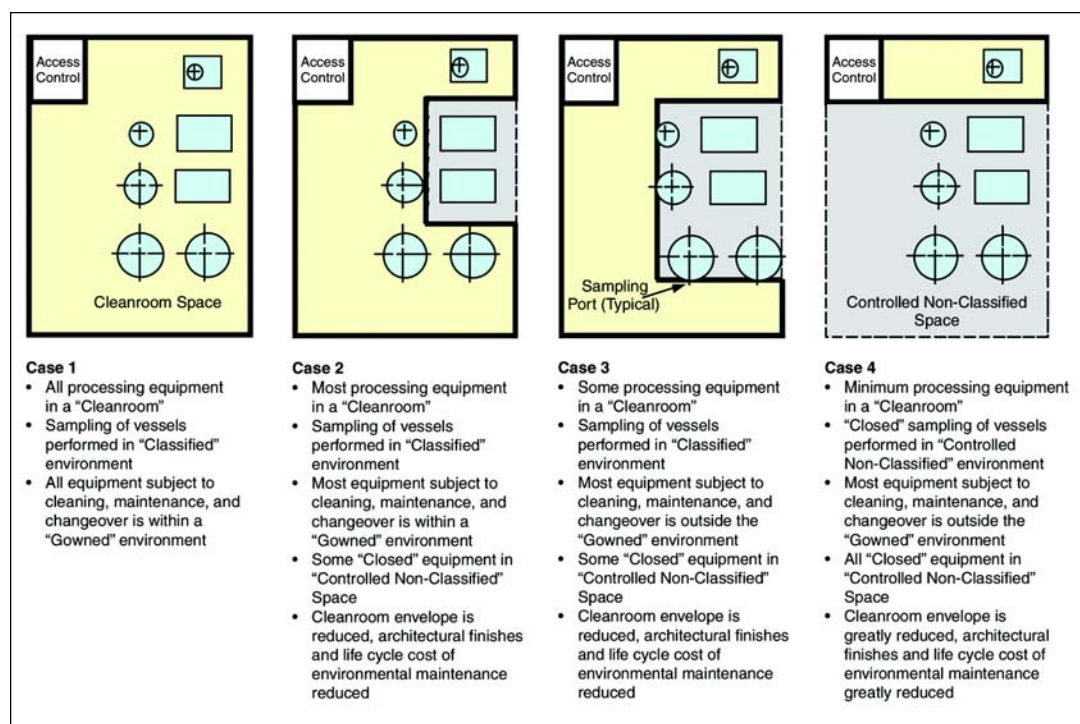
As the biotechnology industry moves forward, engineers are being challenged to find a "better way to build the mouse trap" in order to

drive down the cost of goods, reduce capital expenditures, and provide more flexibility in the way that biotechnology products are manufactured. At the same time, there is a move within the FDA to improve the process of validation and licensing of production facilities. So what trends are the focus of today's design efforts?

### Influences

In developing the *ISPE Baseline® Guide for Biopharmaceutical Manufacturing Facilities*,<sup>1</sup> the members of the task team made a concerted effort to define the primary influences that impact facility design. They defined these influences as:

Figure 1. Closed systems in "Controlled Non-Classified (CNC) space."



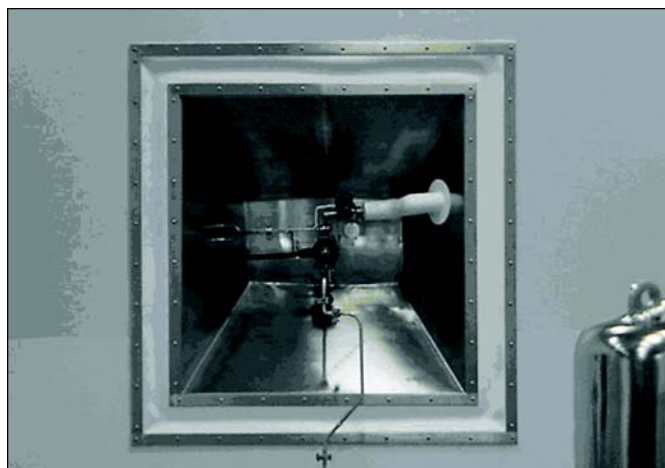


Figure 2a. CNC Space sampling alcove.

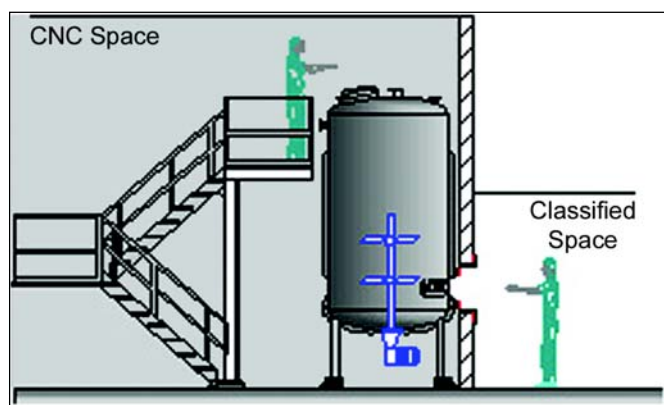


Figure 2b. CNC Space room schematic.

- **Product Attributes**
  - the physical characteristics of the product being manufactured
- **Process Attributes**
  - the materials, equipment, systems, methodologies, and techniques required to deliver the product
- **Facility Attributes**
  - the space allocations, environmental conditions, physical adjacencies, materials of construction, finishes, and operating procedures required to accommodate the manufacture of the product<sup>2</sup>

The understanding of these attributes led to some fundamental concepts of facility design that are key to successful design and operation. One of these concepts is that process design is linked to facility design. The implementation of closed process systems, controlled processing capabilities, and manufacturing flexibility are the focus of many of the trends discussed in this article.

## Layout Considerations

The construction and operation of classified manufacturing space is a costly undertaking. For many years, the dominant

philosophy within the industry was to perform all manufacturing operations inside classified space with at least a Class 100,000 (Grade C) environment.

Currently, there is a realization that layout design that complies with GMP can eliminate the need for classified space in many operational environments. It follows that if you can decrease the physical amount of classified space that must be operated, you can greatly reduce annual operating costs. Engineers are finding ways to do just that.

## Closed Systems

One of the fundamental foundations of bioprocess system design is the use of closed systems for production. While the GMPs do not provide a definition of a closed system,<sup>3</sup> it is a recognized concept that if you can totally close a system during its operation, you can, conceivably locate and operate that system outdoors.<sup>4</sup> The *ISPE Baseline® Guide* has provided examples of this philosophy through its definition of Controlled Non-Classified (CNC) Space.

Figure 1<sup>5</sup> provides four different layout considerations for closed systems in a CNC space. The first case represents the layout approach and classification philosophy that are the primary approach that is currently taken by industry; all process equipment is located in a classified space that is validated and under protocol control. The second case resembles the approach often referred to as “gray space” implementation, where some of the mechanical and “maintenance intense” components of process equipment are located in an unclassified space.

The third case represents a new approach that is being implemented with successful results. This approach places only key sample ports inside a clean vestibule space. This approach greatly reduces the amount of classified space required for operation. Figure 2 provides an example of this design philosophy in an operating environment.<sup>6</sup> The fourth case represents the operational philosophy of totally closed systems in a CNC environment. CNC-based facility design requires that the Owner defines what “controlled” represents. The common attributes of CNC space include:

- ventilated with filtered air (not necessarily HEPA filtered)
- some hierarchy to the airflow, such that outdoor contaminants cannot migrate to production areas easily
- access control for people, materials, and equipment
- special finishes or cleaning procedures are not required

A number of current facilities have implemented this design philosophy for media and buffer hold operations, bioreactor suites, and harvest areas. It is less common, but not unseen, for some media and buffer prep operations and initial purification to also be executed in a CNC space using closed system design.

## Multi-Product Applications

The concept of a multi-product manufacturing facility for biological products is not new,<sup>7</sup> and the advent of this type of facility has been a boon to the biotechnology industry. Com-

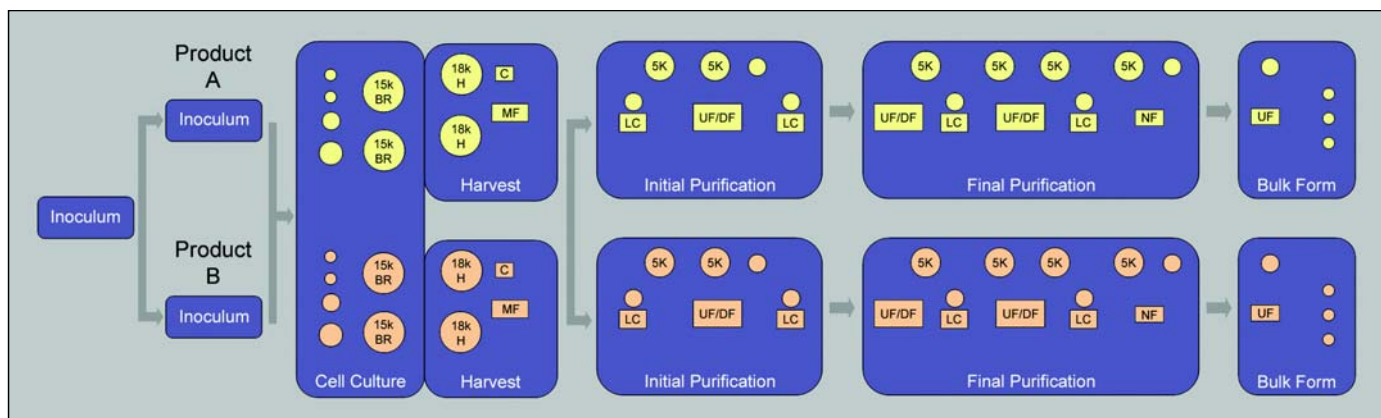


Figure 3. Concurrent manufacturing layout.

panies are now applying this approach to new business models; in some cases, as planned; in others, out of necessity.

Large scale production facilities are, generally, dedicated to specific *Escherichia coli* or other microbial processes that are product specific. Early and late stage clinical materials and production facilities are often operated on a single campaigned train, unless the pipeline is pushing more products through than a single train can accommodate. While a facility may be designed for multi-hosts, it is often operated as a single host facility.

One current trend in the industry is toward simultaneous multi-product production in fermenter/bioreactor areas with separate inoculum laboratories and harvest areas - *Figure 3*. Downstream operations are still, generally, designed for campaigned operation, but there are some licensed facilities that have moved to a concurrent manufacturing approach for both upstream and downstream operations. Such facility designs rely heavily on the “plug and play” concept for unit operations, closed system design, and a high level of automation and procedural control. This approach provides a definite cost advantage over a “greenfield” production approach for expansion. It is less expensive to add a new production train and increase utility/infrastructure needs. This flexible approach also provides benefit by allowing for a partial build-out to serve initial manufacturing needs, which can be expanded with increased market needs or new products.

The market for many biological products is very dynamic. Strategic planning for manufacturing capability is becoming quite a challenge, especially if companies are trying to outsource the manufacturing of their product. Many companies are using this fact as a driver in the development of their strategic plans. Multi-product facilities are being designed so that if in-house product manufacturing needs do not meet forecasts, excess capacity can be contracted to firms seeking an outsource partner. A number of companies have successfully used this approach.

### Equipment Design

There have been many advances in equipment design philosophy over the past few years. Many of these changes have been a result of the desire of manufacturing firms to move into more efficient multi-product manufacturing scenarios

and the move to increase production scale, particularly for Monoclonal Antibody (MAb) products. But the driver from a design standpoint is not new; it is cost effective design.

The following discussions focus on some current trends. Many of these selections are based on “cultural/religious” decisions of the manufacturer, i.e., there may be many factors other than technical or scientific data driving the decision.

### *Perfusion versus Fed Batch Reactors*

Fed batch reactors have been the mainstay of the industry for years. Their operating process is simple, they are very reliable, and they provide higher titers at concentrations of 1 to 3 g/L. Process development groups are pushing higher titer yields through large scale fed batch processes.

Perfusion reactors can provide a higher titer for cell concentrations below 10 g/L. They also can provide increases in productivity. However, they will usually require more equipment within the sterile boundary of the facility, and many process development scientists find there may be a potential for “process drift” when this reactor type is implemented.

### *Centrifugation versus Microfiltration*

With the current trend of increasing production scale, many companies are moving away from Microfiltration (MF) due to the requirement for large membrane systems and the cumbersome nature and expense of membrane change-out. Many MF harvest operations also require large volumes of expensive buffers for washing cells. In multi-product manufacturing facilities, this can become a very expensive operational cost.

With the improvement of low shear centrifuge design, many companies are moving into centrifuge operations for harvesting. But centrifuge applications also come with drawbacks. A centrifuge is a very complex piece of equipment. As with any complex machine, operation and maintenance issues must be carefully investigated. This complexity also introduces potential issues with cleaning and sterilization during changeover. One further review point is that there is a potential for product loss with cell debris as a result of the harvest operation. Washing steps may improve recovery yield, but are an added operational cost for each product batch.

## Purification Operations

As batch sizes increase, the issue of potential bottlenecks in the downstream purification operations becomes more of a problem. Many companies are decoupling upstream and downstream operations by collecting the cell-free harvest fluid or initial capture eluate and storing or “pooling” the product. Both perfusion and fed-batch processes can implement this approach. As appropriate, pooled product is sent into purification to match the harvest volume to the scale of the available purification equipment. This “sub-batching” approach can sometimes allow for larger batches to be processed through purification.

On-line dilution also has been successfully implemented as a means of reducing costs and improving efficiency of purification operations. The implementation of this approach will require a process development effort in order to verify the suitability for the targeted buffer systems that will be used. Since not all buffers are appropriate for this approach, this becomes a risk management decision for the company. The use of on-line dilution can reduce the need for large numbers of alloy tanks (only a single salt concentrate tank) and can eliminate the need for buffer tanks entirely if the philosophy of using disposable bags is implemented.

## Equipment Standardization

Many projects are realizing the benefits of taking a strong approach to standard design attributes including:

- standard Process and Implementation Diagrams (P&IDs) and equipment details
- implementation of S88 for code development<sup>8</sup>
- standardization of instrument and valve numbering schemes
- platform-based unit operations

The approach to standardization is very logical. Processes are developed to fit a given set of steps so that a process can be operated in any number of different locations. This allows for platform-based operations, where skids can be designed in a manner where it is easy to duplicate design (modularize the parts as much as possible), and allow for a quicker changeover to new products. Skids would be “plug-and-play” and easily changed out and instrument and valve numbers would be consistent; a sample valve would have the same identifier in every location application. Figure 4<sup>9</sup> provides an example of a large scale platform process.

## Modular Design

Modular facility design has become an over used “buzz phrase” in the industry. Many companies publicize the savings that can be realized by implementing a modular design approach. There also have been many articles written on the implementation of different strategies for modular design. It is important to understand that all modular approaches are not equal, and to identify the benefits and risks in implementing such an approach.

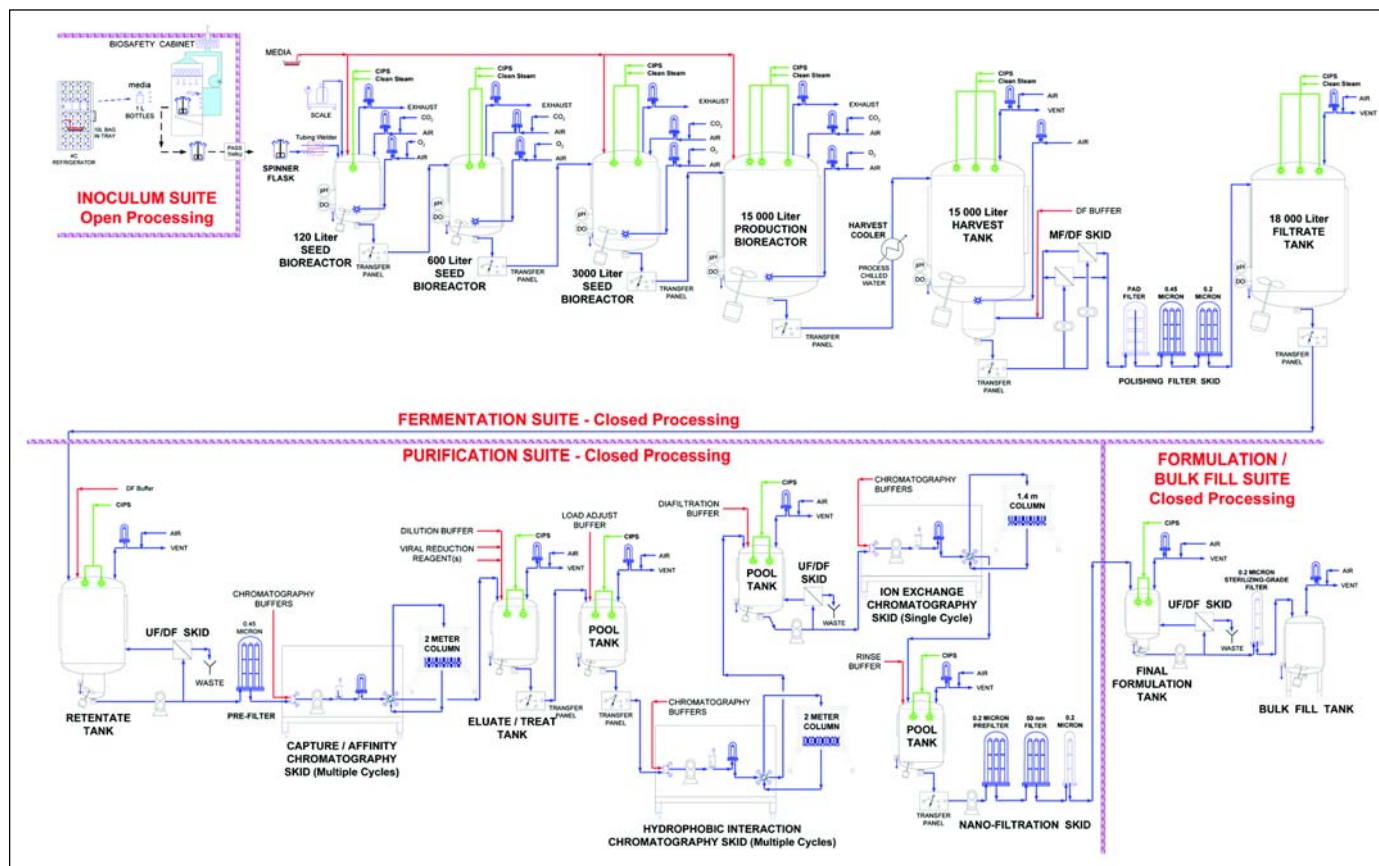


Figure 4. Large-scale cell culture process.

The design of a “module” can be defined as a simple skid, a combination of multiple skids, a series of multiple equipment items that form one or more unit operations, a segment of an entire room, or a complete room or suite. This listing goes from least to greatest complexity, both in terms of design effort and the integration of components. Depending on the type of equipment being modularized, it also, generally, follows a least-to-greatest cost impact scenario.

The benefits of modular design are well documented. Overall schedule improvements can be realized due to a more efficient division of labor between shop and field fabrication/installation activities. Schedule improvements also can come from a phased Factory Acceptance Testing (FAT) approach that will decrease the duration of Site Acceptance Tests (SATs). More flexibility in integrating automation code is another benefit, realized due to earlier opportunities to check automation during FAT visits. In addition, there is a general suggestion of improved component quality due to the greater fabrication controls found in a shop environment.

The risks are also well known. The coordination effort to define module boundaries is critical. The procurement of subcomponents and the phasing of their delivery are also critical; the design team will need to make some decisions very early on to make this work and there must be an acknowledgement that changes have an amplified impact during such an effort. If multiple vendors are involved, ensuring consistency of finished product is also critical. Many companies have elected to develop a dedicated group of resources to implement this approach on larger projects, which increases overhead costs.

## Disposable Technologies

Disposable technologies; bags, hoses, filter cartridges, etc., have been available to the industry for a number of years. Due to technological improvements of these components, more companies are implementing the use of disposables in their process development efforts.

The large capital investment that is required for fixed stainless steel vessels in biomanufacturing facilities is the target on which engineers have focused their efforts, providing more cost effective alternates in facility design. Single-use bag systems have had acceptance in small scale operations for a number of years; and at present, these systems are being used in ranges of 50 L to 3,000 L scale to provide numerous options in facility design.

Many companies have developed their processes around disposable bag systems for manufacturing operations such as product hold, sampling, media and buffer preparation and hold, and product storage. While current size limitations above 3,000 L have physical constraints that must be realized, smaller scale bag components do provide flexibility and cost savings.

Replacing stainless steel vessels with disposable bags can create dramatic capital cost savings. But beyond this trade-off, there are other economic advantages to disposable systems.

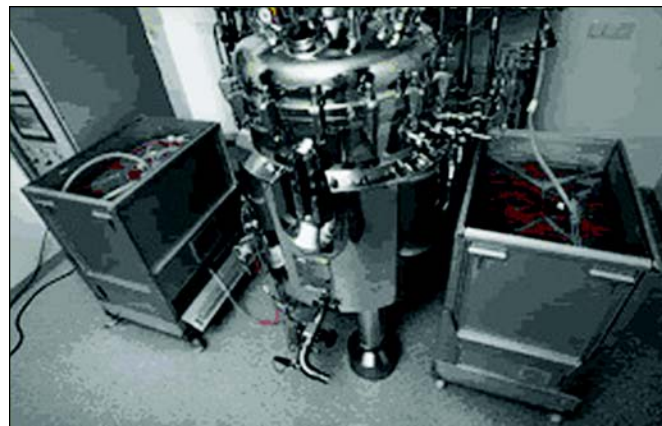


Figure 5. A single-use system.

- **Utility Consumption:** Reducing the number of fixed vessels that will require CIP and SIP will produce a dramatic reduction in annual operating costs for utility generation and waste treatment.
- **Flexibility:** Production processes are dynamic, as are many facilities that produce multiple products. Change is inevitable. Single-use bag systems provide a higher level of flexibility based on the reduction or elimination of piping configuration redesign, process control modifications, or the addition or elimination of equipment components.
- **Reduced Space:** Many single-use systems are designed to more efficiently use space<sup>10</sup>. *Figure 5*. These systems are easier to maneuver if change is required, and provide many options to the engineer regarding configuration. These reductions in expensive classified space can produce dramatic savings in areas such as media and buffer preparation/hold.

## Regulatory Review

A large number of companies are taking the FDA’s request for earlier review involvement to heart. Since the release of FDA Directive 135,<sup>11</sup> both large and small biotechnology firms are engaging the FDA to participate in early stage reviews of the design basis, preconstruction, and validation approach. While the FDA will not provide an endorsement of any design or approach, they will comment on items such as flows, contamination control philosophy, utility approach, structure of Master Plan execution, and qualification approach.

These meetings can provide valuable information for the design team and to the operations organization as project scope confirmation moves forward and baseline documents for the project are established. Having the opportunity to receive early regulatory comments will reduce the risk of potentially costly changes at later points in the project.

## Summary

There are a number of new, and old, approaches to tackling and solving project challenges that are being implemented in the industry today. Some involve new ways of thinking about

solutions to existing problems. Others simply involve improving a proven approach to solve a problem. Others are just common sense being raised to a new level of awareness. Whatever the case, companies would be wise to explore how to “improve the mouse trap” as their projects are in the early stages of development, when change causes the least impact, both from a cost and schedule perspective. Time wisely spent up front can reap significant dividends later in the project lifecycle.

## References

1. ISPE Baseline® Pharmaceutical Engineering Guide, Volume 6, Biopharmaceutical Manufacturing Facilities, First Edition, June 2004.
2. *ibid.*
3. Odum, Jeffery N., “Closed Systems in BioProcessing: Impact on Facility Design,” *Bioprocessing Journal*, January/February, 2005.
4. Guidance for Industry: Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients, US FDA.
5. ISPE Baseline® Pharmaceutical Engineering Guide, Volume 6, Biopharmaceutical Manufacturing Facilities, First Edition, June 2004.
6. Photo courtesy of Biogenidec, drawing courtesy of CRB Consulting Engineers.
7. Bader, Fredric and others, “Multiuse Manufacturing Facilities for Biologicals,” PMA Ad Hoc Committee on Multiuse Facilities; *BioPharm*, September, 1992.
8. Standard S88.
9. Drawing courtesy of CRB Consulting Engineers.

10. Photo courtesy of Stedim.

11. US FDA, ORA Field Management Directive No. 135.

## About the Author



**Jeff Odum** has been involved in the biopharmaceutical industry for more than 20 years. He is a nationally recognized author and speaker who provides industry insight in the areas of regulatory compliance, facilities and process design, and project management for biopharmaceutical companies. His experience in the biopharmaceutical

industry has included design and construction of many of the industry’s major manufacturing projects, as well as consulting roles for a number of the global biotechnology industry leaders. These projects represent a total capital investment of well over \$2 billion and produce many of the key biopharmaceutical therapeutics and vaccines currently in the marketplace. He is the author of more than 20 published works on industry critical issues, including process improvement and execution to meet regulatory guidelines issued by the FDA and other international regulatory bodies. These works include three books that are recognized industry reference guides. He was also one of the lead chapter authors for the recently published *ISPE Baseline® Guide for Biopharmaceutical Manufacturing Facilities*. He is the current Chairperson of ISPE’s North American Education Committee – the body that develops and executes international education programs for the biopharmaceutical industry, and a member of ISPE’s International Technical Training Staff. In this role, he leads several professional industry training courses, nationally and internationally, that are focused on engineering and regulatory compliance curricula. He can be contacted by telephone 1-919/852-5425 or by e-mail: [jeff.odum@crbusa.com](mailto:jeff.odum@crbusa.com).

CRB Consulting Engineering Inc., 1225 Crescent Green, Suite 300, Cary, NC 27511. 

This article presents a procedure for the validation of biological API manufacturing processes. It details each step of the procedure for biological processes applications, and covers the regulatory requirements for biological APIs.

# Procedure for the Validation of Biological Active Pharmaceutical Ingredients (APIs) Manufacturing Processes

by Josée Ethier

## Introduction

The validation of biological Active Pharmaceutical Ingredients (APIs) manufacturing processes is more complex compared to standard chemical APIs, due to the lack of both product and process characterization. The following definition of Process Validation can be found in ICH Guideline Q7A:<sup>1</sup> "Process validation is the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce an intermediate or API meeting its pre-defined specifications and quality attributes."

The objective of process validation is to:

- demonstrate process stability and reliability
- evaluate the impact of a variation in a critical process parameter on product quality

Not all manufacturing processes require validation. The examples mentioned hereafter usually require process validation:

- processes for which the product can not be fully characterized and/or verified
- processes for which the complete product characterization is very expensive or impossible to perform (in this case, product quality is assessed using process validation)
- processes for which the product quality is critical and for which a slight variation in its composition may result in severe reactions in the patient

Validation of processes involving micro-organisms probably present the highest difficulty degree due to the important variability of living organisms. Variations in the behavior and productivity level of the micro-organism used may result in differences in the composition of the culture media at the end of the production, which can, in turn, impact the purification process. Processes involving living micro-organisms are more sensitive to operating conditions and may show larger variability from one batch to another. Therefore, biological processes are more difficult to validate, and require more considerations. In addition, as stated by Kirrstetter,<sup>2</sup> the raw materials used in biological APIs manufacturing processes may result in microbiological contamination, and more stringent controls of equipment, utilities, and services are required to minimize the risk of contamination. Slight variations of the manufacturing conditions may be observed when undesired un-

Table A. Recommended procedure for the validation of API manufacturing processes.

Recommended Procedure for the Validation of API Manufacturing Processes
<ul style="list-style-type: none"> <li>• Formation of a Validation Committee</li> <li>• Description of the process manufacturing steps, utilities, services and equipment</li> <li>• Critical Analysis</li> <li>• Identification of critical process parameters and validation requirements</li> <li>• Elaboration of a Validation Master Plan (VMP)</li> <li>• Redaction of process validation protocols</li> <li>• Protocols execution</li> <li>• Reports</li> </ul>

characterized substances are found in the final product. Biological APIs are difficult to characterize and, are influenced by the numerous parameters involved in their manufacturing process.

As the biotechnology sector faces important growth with the increasing number of expiry patents,<sup>3</sup> the number of biological API manufacturing processes to validate will increase in the next few years, enhancing the importance of a structured procedure for process validation.

## Process Validation Requirements

Process validation is generally required prior to product commercialization to demonstrate that the process consistently results in a product having the required specifications

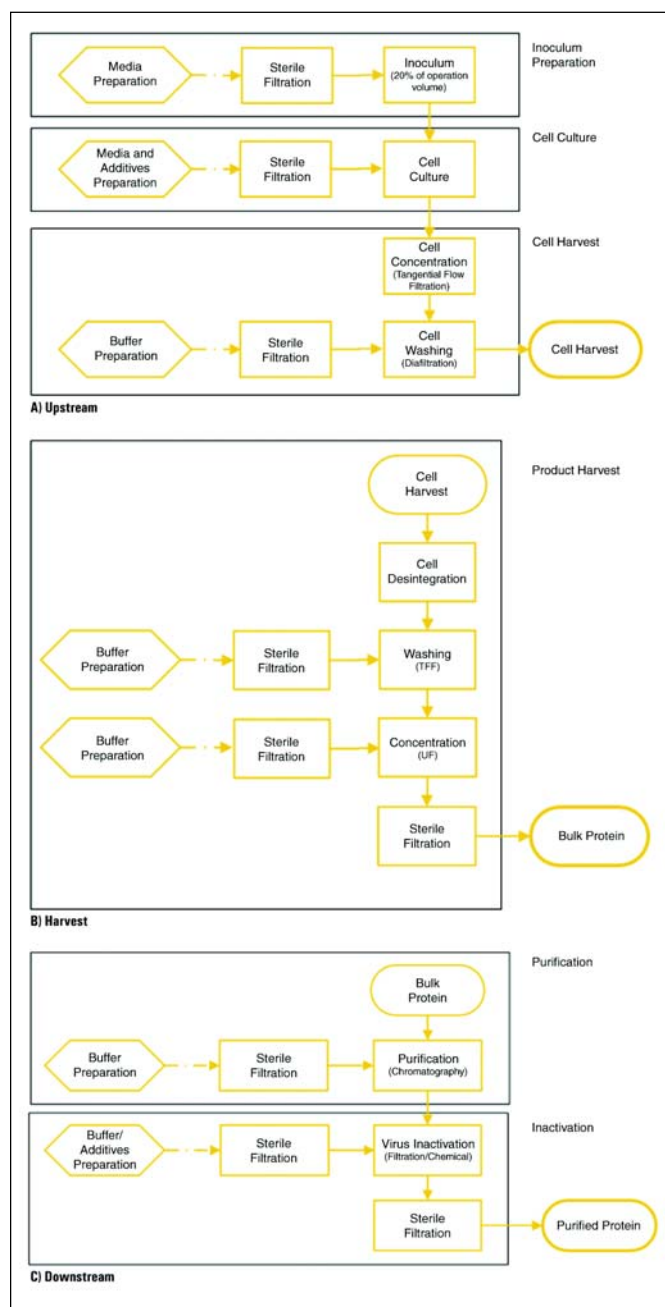


Figure 1. Typical flowchart for a cell culture process (and functional blocks).

and quality characteristics. Process validation was originally not required for clinical trial material manufacturing due to the numerous modifications brought to the procedures during process fine tuning and due to the limited number of batches produced at this stage.

The Annex 13 of European current Good Manufacturing Practices<sup>4</sup> has been modified in 2003 to require process validation for clinical material manufacturing.

The Canadian regulatory agency has decided to adhere to the new European directive.<sup>5</sup> FDA still maintains its position and requires process validation for commercial batches only. However, the US FDA appropriated control and monitoring of the critical process parameters and demonstrated traceability for clinical lots.

Process validation will now be required earlier, prior to the completion of process development. The validation procedure presented here constitutes a systematic approach that also can help in process development and optimization, and allow the initiation of process validation while its development is still in progress.

## Main Validation Steps

The proposed validation procedure for biological API manufacturing processes is described here. The procedure also can be applied to standard (non-biological) APIs.

Process validation may follow Installation, Operation, and Performance Qualification of equipment, utilities, and services, as a process can be developed and implemented in an existing premise using qualified equipment. However, the procedure presented here is more general and can be applied to new processes implemented in new premises using new services and equipment. As mentioned above, the proposed procedure can be initiated in early development stages and help in the identification of critical process parameters and improve process understanding. It also ensures that an appropriate distance has been taken to visualize the process as a whole and that equipment, utilities, services, process environment, and parameters impact have been properly considered and evaluated.

The main validation steps are described below and summarized in Table A.

## Formation of a Validation Committee

First, a validation committee should be formed and include people from the following departments: Quality Assurance, Engineering, Production, and Development (R&D). Representatives from additional departments could be included if required (Laboratories, Logistics, and Regulatory Affairs, as an example), depending on the nature of the process to be validated and the organizational structure. This committee is responsible for the management and the execution of process validation and to ensure compliance with regulatory authorities. The committee should meet on a regular basis as long as process validation is not completed and be involved earlier during process development.

The modified Annex 13 to the European cGMPs<sup>4</sup> requires the presence of a Qualified Person (QP) that plays a similar role.



## Process Description

Once the committee is formed, a complete and detailed description of the manufacturing process can be established and should include the following steps:

1. A Process Flow Diagram (PFD) should be prepared and functional blocks should be defined, each block having a clear and distinct function. Figure 1 illustrates a typical flow chart of a cell culture process and the corresponding suggested functional blocks. Typical unit operations involved in a biological API manufacturing process are: fermentation, inoculation, cell harvest, filtration, centrifugation, diafiltration, chromatography, formulation, filling, freeze drying, sterilization. Transfer steps should be included in the PFD.
2. The equipment, utilities, and systems required can be listed for each functional block. The corresponding specifications and validation status (if any) should be specified.
3. The In-Process Controls (IPC) with the corresponding tolerances should be identified.
4. Product final specifications with the corresponding tolerances should be identified.
5. The analytical methods, required instruments, and final specifications with tolerances should be specified. The corresponding validation status (if any) should be specified.
6. The process parameters which impact product quality should be identified.
7. Process inlets and outlets should be identified and illustrated using a cause and effect diagram ("Fish Bone," see Figure 2). The "Fish Bone" illustrates the impact of a variation in process parameters on product specifications and helps in process understanding.

## Critical Analysis

The validation of a Drug Product (DP) manufacturing process requires the qualification of each manufacturing step whereas the validation of an API manufacturing process requires the qualification of the critical manufacturing steps only.

To help in the identification of validation requirements and critical process parameters (and complete the lists prepared during the previous step) a Critical Analysis (or Risk Analysis) needs to be performed - *Table B*. Most product nonconformities result from either errors performed during manufacturing or from variations in process parameters or immediate environment.

A Critical Analysis consists of the identification of those possible sources of errors and process variations that could result in product non-conformity. Once the sources are identified, their impact on product quality and/or process safety (including environment and operators) are evaluated. The

Critical Analysis Results
<ul style="list-style-type: none"> <li>• Identification of the critical process parameters that must be monitored and controlled.</li> <li>• Identification of validation requirements: IQ, OQ, PQ, analytical methods, cleaning, operation, inactivation, process</li> <li>• Identification of the required characteristics: raw materials, final product, in-process samples, etc.</li> <li>• Identification of "markers" for process comprehension and follow-up.</li> </ul>



Table B. Description of the critical analysis results.

probability of detection (D), the possible occurrence of the problem (O), and the gravity of the resulting consequence (G) are evaluated (refer to the Failure Mode and Effect Analysis procedure).<sup>6</sup> The critical parameter ( $C = D \cdot O \cdot G$ ) can then be calculated, and represents a quantitative measure of the critical of each possible source of non-conformity. Appropriated solutions can be proposed for each possible source identified to reduce the critical (C) to an acceptable level, either by improving the detectability of the problem (and reduce factor D) and/or reducing the possible occurrence of the problem (and reduce factor O). The calculation of the Critical Factor (C) can be performed again, considering the solutions proposed.

Most of the time, the solutions proposed will allow the identification of critical process parameters and the definition of validation requirements: perform cleaning or design validation, add an in-process control, control the environment (by having a validated HVAC system as an example), etc. Table C illustrates an example of a part of a Critical Analysis (inoculation functional block). Four possible sources of nonconformities have been identified to illustrate the procedure (not exhaustive):

- the inoculum cell concentration could be out of specification
- the inoculum could be contaminated
- the transfer of the inoculum to the bioreactor could be deficient
- the bioreactor cleaning could be deficient

The impact of each source is then identified and evaluated. An out of specification inoculum cell concentration would result in unusual growth kinetics that could be detected using an in-process control prior to bioreactor inoculation. Accordingly, the possibility of detection (D) would be rated at 3, the occurrence (O) at 2, and the gravity (G) at 3 since the productivity level would be affected. The resulting critical factor (C) would then be 18 ( $3 \cdot 2 \cdot 3$ ). The proposed corrective action is the implementation of optical density verification prior to inoculation. The probability of detection (D) would then be rated at 1, the occurrence (O) at 1, resulting in a critical factor (C) of 3 ( $1 \cdot 1 \cdot 3$ ).

The final critical factor evaluation (rightmost column in Table C) allows the identification of most critical process parameters with a series of corrective actions that are required to keep the risks at a minimal level and ensure product consistency and quality, in addition to personnel safety and

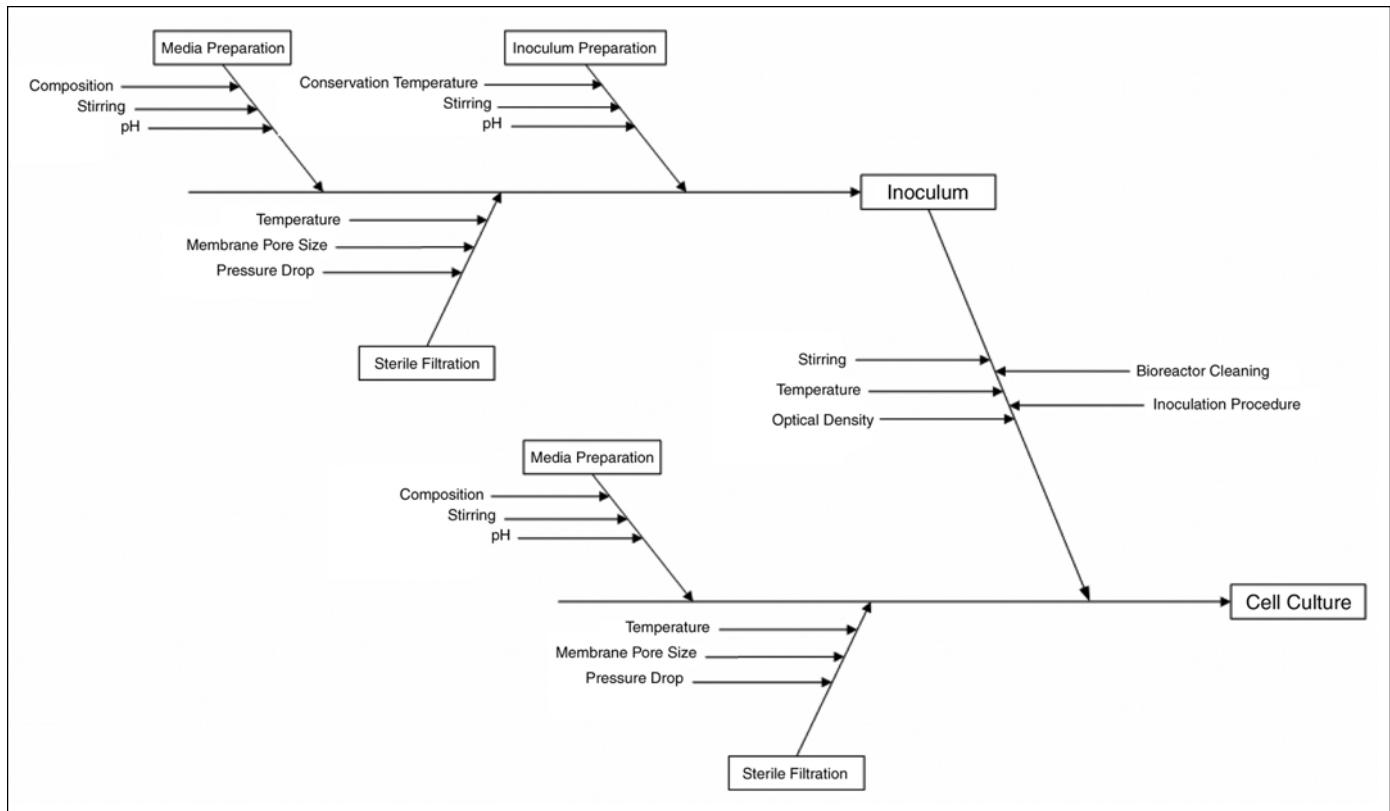


Figure 2. Example of a cause and effect diagram ("Fish Bone.")

environmental considerations. The corrective actions could be an in-process control, a standard operating procedure, a validation, a verification, personnel training, or any other action required to reduce the occurrence of the problem and/or improve its detectability.

Generally, the following process steps should be identified as critical for biological processes and be included in the Critical Analysis: equipment and instrument cleaning, raw material characterization (media, components, and cells), weighing, solution, and media preparation, inoculation preparation, bioreaction (pH, dissolved oxygen, stirring,...), harvesting, refolding (if required), purification, formulation (when applicable), filling, freeze-drying (when applicable), packag-

ing and labelling.

### Identification of Critical Process Parameters and Validation Requirements

The Critical Analysis is a very efficient tool that allows the identification of critical process parameters and the identification of validation requirements. Any possible source of non conformity is analyzed and solutions to control variability are proposed until the critical factor (C) is reduced to its minimal value. The acceptable operation range for each critical process parameter also can be defined. The risk to forget an important parameter or to omit a required qualification is reduced to its minimum, and benefits are reflected on the

Manufacturing Step	Source of Non-Conformity	Impact on Quality/Safety	D	O	G	C	Corrective Action	D	O	G	C
Bioreactor Inoculation	Out of specification cell concentration of the inoculum	Unusual growth kinetics	3	2	3	18	- In-process control of optical density before inoculation	1	1	3	3
	Contamination while inoculation	Presence of contaminant in the bioreactor	3	2	4	24	- SOP for inoculation - Installation of a laminar flow hood - SIP of inlet ports to be developed - Monitor optical density during growth phase	1	1	4	4
	Forget to open inlet port	Loss of inoculum	1	2	3	6	- SOP for inoculation	1	1	3	3
	Bioreactor cleaning deficient	Presence of contaminant in the bioreactor	3	2	4	24	- Cleaning validation required - TOC/swab prior to bioreactor inoculation	1	1	4	4
<b>LEGEND</b>			D = probability of detection		O = possible occurrence of the problem		G = gravity of the resulting consequence		C = critical factor		

Table C. Example of a critical analysis.

whole validation team, for which the validation/development objectives are clear even before the redaction of the Validation Master Plan. Some corrective actions could involve process development and/or engineering design.

Some “markers” can be chosen among the critical process parameters identified, based on their fair representation of the process condition, to limit in-process control related costs during process validation and commercial manufacturing (methods development and validation, as well as time and consumables). The optimal value of each marker should be identified and accompanied with the corresponding analytical method, sampling procedure, specification and tolerance, and a reference standard (if required). Markers are used mainly for not-well characterized biologics (mainly complex vaccines, blood products, viral vectors, and cell therapies)<sup>7</sup> to follow the product quality and consistency.

Of all unit operations, cell culture is the processing step resulting in most important variations. Living micro-organisms can show slight differences in growth characteristics and can release proteins and debris in the culture media that affect the growth curve. The Critical Analysis is therefore of major importance for biological processes validation.

Bioassays also are critical and should be qualified since they allow the determination of the product’s tertiary structure and activity.<sup>7</sup>

## Validation Master Plan

Now that the critical process parameters, critical manufacturing steps, markers, and validation requirements are identified, the preparation of a Validation Master Plan should constitute the normal following step of the process validation procedure.

For biological processes, cell stability and purity (including viral clearance) also need to be validated. The stability of the genetically modified micro-organism must be demonstrated, and the maximum cell division number identified. This can determine the longest continuous cell culture that could be performed before mutation or transformation occurs. Viral clearance is usually performed by inactivation (using pH, solvents and/or detergents, or heat) or removal (using filtration and/or chromatography).

For yeast and bacterial cultures, viral inactivation is not required since these micro-organisms are usually not in contact with viruses nor TSE (Transmissible Spongiform Encephalopathies).

## Process Validation Protocol Redaction

The structure of process validation protocol should be the same as for standard pharmaceutical processes. However, for biological processes, particular verifications are required to ensure process consistency and reproducibility.

The process validation protocols should include:

- a general decisional process flow chart
- a list of the equipment (both critical and ancillary) and instruments used, including their identification number and calibration state (if required)

### List of Biological Process Validation Pre-Requisites

- Defined raw materials
- Defined equipment, utilities and services
- Defined process parameters and acceptance range
- Standard Operating Procedures (SOPs)
- Process documentation
- Critical analysis (risk analysis)
- Validation Master Plan
- IQ/OQ/PQ for equipment, utilities and services with closed deviations and nonconformities
- Validated analytical methods
- Qualified instruments
- Maintenance and calibration programs
- Change control program
- Identification of critical process parameters and markers, with their respective acceptance range
- Bioassays defined and qualified

Table D. List of the information required prior to process validation.

- a description of all manufacturing steps and in-process controls, including packaging operations and acceptance limits for each process parameter
- the final product specifications

The following verifications should be included for a biological API manufacturing process:

## Bioreaction

As mentioned above, bioreaction is the most variable manufacturing step as micro-organisms are involved.<sup>7</sup> The process duration, temperature, pH, conductivity, nutrients, and product concentration should be characterized. The establishment and maintenance of the Working Cell Bank (WCB) is not covered by the ICH Q7A cGMP. However, it is recommended to perform the characterization of the Master and Working Cell Bank (MCB/WCB) to identify the history of the organism (media used, storage conditions, pressure factor used, etc.) and demonstrate the absence of virus and mycoplasma.

Growth kinetics, product formation rate, yields, cell density, stirring conditions, and optical density needs to be characterized for successful process scale-up and validation. The demonstration that the bioreactor sterility can be maintained during normal operation of the bioreactor (sampling, addition of antibiotics, etc.) should be included in the performance qualification.

Cleaning procedures are critical for bioreactors as they must eliminate any risk of cross contamination. It is strongly recommended to dedicate bioreactors to bacteria, yeast, or mammalian cell culture to avoid contamination.

Continuous operation of a bioreactor (including perfusion) is often preferred to batch and fed-batch operation for mammalian cell culture due to higher product yields obtained. However, validation is more difficult to perform on continuous systems since the production can last for months (compared to days/weeks for batch and fed-batch cultures). The cell line stability can be difficult to demonstrate. Cell mutation can occur and can be difficult to detect, resulting in complex validation. It may be difficult to determine when a lot begins and finishes, and the production of three distinct

batches can take a year to perform. In addition, if a contamination occurs, it will be detected only few days later, contaminating part of the lot.

Finally, it is important to characterize product stability for the holding period between bioreaction and harvest. The maximum holding duration and storage conditions need to be specified.

## *Harvest and Recovery*

Most unit operations used in harvest and recovery steps are centrifugation, microfiltration (tangential, diafiltration), disintegration, and refolding (for inclusion bodies). At the end of the recovery step, the product is most of the time inactivated using sterile filtration to eliminate any risk of contamination of the equipment used for downstream processing (mainly chromatography media) and to contain viable micro-organisms into the production room.

The efficiency of each filtration step should be characterized and verified. The filter integrity should be demonstrated before and after filter use using standard methods. Filter integrity also should be demonstrated before and after the sterile filtration step. Sterile filtration qualification should include the demonstration of absence of viable particles following filtration.

The acceptance range of each critical parameter needs to be specified for each unit operation involved in harvest and recovery operations. Refolding step should be defined and its consistency demonstrated.

The endotoxin and protein concentration shall be characterized at the end of the recovery step. And as previously specified, the hold period between recovery and purification needs to be characterized (maximal duration and storage conditions) to ensure product integrity and stability.

## *Downstream Processing*

Unit operations usually involved in downstream processing are chromatography (gel filtration, ion exchange, affinity, hydrophobic interaction), extraction, and ultrafiltration. Five to 10 purification steps are normally required to reach the required product purity level.

Chromatography requires several verifications to demonstrate process consistency and reproducibility and to guarantee product quality. Chromatography media is very difficult to clean, and is often used for different applications. Cleaning validation is critical for chromatography columns and media. The Total Organic Carbon (TOC) of the final rinsing water should be measured and be kept below the specification to demonstrate the absence of residues of cleaning agents and confirm the absence of resin leaching. The gel lifetime also should be determined. A procedure is required for column sanitization and needs to be rigorously followed by the personnel.

Chromatography resins should be considered as a raw material and therefore requires full characterization as well as acceptance specifications. Resins properties can vary considerably from one batch to another and the acceptance specification range should consider such possible variability.

Purification efficiency is closely related to chromatography operation parameters such as ionic strength, pH and flow rate of the elution solution, the column diameter, the bed height, and both the impurity and protein concentration of the inlet solution to be purified. The efficiency is also dependent on packing quality. The evaluation of the Height Equivalent to a Theoretical Plate (HETP) should be performed following each column packing to demonstrate the absence of channeling and assess packing quality. Finally, the non-specific binding of the protein to the chromatography resin should be quantified to confirm resin quality and safely process the target protein using this media.

For ultrafiltration operations, the maximum flow rate and membrane pore size should be characterized and an operating range specified. The non-specific binding of the protein on the membrane should be quantified as for chromatography resins.

The use of disposable filtration units eases the validation of filtration steps and reduces cleaning validation efforts.

## *Validation Execution*

ICH<sup>1</sup> requires three consecutive runs for prospective and concurrent process validation and from 10 to 30 consecutive runs for retrospective process validation. More runs may be required for complex processes. For prospective and concurrent validation, three different lots of raw materials should be used. Each run needs to be completely independent from the others: the inoculum and culture media should be fresh and the equipment cleaned using cleaning procedures in place between each run.

The application of the validation procedure described here ensures that all the information required to perform process validation is available - *Table D*.

Product characterization can be performed using the specified analytical methods. Data needs to be compiled and statistically analyzed.

Finally, a validation report comparing the product specifications with product characterization should be prepared. Deviations and nonconformities should be summarized in this report.

A change control procedure is required to follow and control any modification performed on the process and/or its utilities and services. Each modification should be evaluated commonly by the Validation Committee or by the Qualified Person, depending on the structure of the society. Process revalidation may be required when a major modification is performed on an equipment, a service, or an utility, on the premise itself or on the manufacturing procedure. Any deviations of the markers identified should result in a process investigation to quickly identify the source of the problem and reduce the risk of getting out-of-specifications product.

## **Conclusion**

The proposed procedure may seem time-consuming and heavy to implement. However, considerable reduction of both development and validation steps duration results from the use of this procedure. Qualification can be initiated prior to the

completion of process development and accelerate product marketing.

## References

1. ICH Harmonized Tripartite Guideline Q7A: GMP Guide for Active Pharmaceutical Ingredient, November 2000.
2. Kirrstetter, R., "Requirements for Process Validation of Biotech Active Pharmaceutical Ingredients (APIs)," *Pharmaceutical Engineering*, Volume 22, No. 3, May/June 2002.
3. ABN-AMRO, "Generic Biologics: The Next Frontier," June 2001.
4. EU Guide to GMP (Volume 4), Annex 13: Manufacture of Investigational Medicinal Products, July 2002.
5. Health Canada: Annex 2 to the Current Edition of the Good Manufacturing Practices Guidelines: Manufacture of Drugs Used in Clinical Trials, April 2004.
6. FMEA information centre (Failure Mode and Effect Analysis), [www.fmeainfocentre.com](http://www.fmeainfocentre.com)
7. Nash, Robert A. and Wachter, Alfred H., "Pharmaceutical Process Validation," Third Edition, Marcel Dekker, Inc., New York, 2003.
8. EU Guide to GMP, Annex 15: Qualification and Validation, July 2001.
9. ICH Harmonized Tripartite Guideline Q6B: Specifications: Tests Procedures and Acceptance Criteria for Biotechnical/Biological Products, March 1999.

## Acknowledgement


The author would like to thank Validapro Inc. for their support in the preparation of this article. Any questions regarding the content of this article may be addressed to Ethier or Validapro Inc. ([www.validapro.com](http://www.validapro.com))

## About the Author



**Josée Ethier** is Project Manager at ProMetic BioSciences Inc. She has a chemical engineering degree from École Polytechnique de Montréal (1992) (biotechnology specialty) and a Masters degree in chemical engineering processes also from École Polytechnique de Montréal (1996). She is involved in biological and chemical process design and validation

as well as cleanroom design. She has more than 13 years of experience in the biotechnology and pharmaceutical industry in the design, process development, User Requirement Specifications (URS) development, project management, and critical analysis. Ethier has filed two patent applications and is member of the Quebec Order of Engineers. She can be contacted by e-mail: [j.ethier@prometic.com](mailto:j.ethier@prometic.com) or by telephone: 1-514/341-2115.

ProMetic BioSciences Inc., 8168 Montview, Mont-Royal, Quebec H4P 2L7, Canada. [www.prometic.com](http://www.prometic.com) 

This article discusses some of the challenges, execution methods, and potential opportunities of Design Qualification (DQ).

Reprinted from  
PHARMACEUTICAL ENGINEERING®

The Official Journal of ISPE  
March/April 2005, Vol. 25 No. 2

# Do You DQ? Design Qualification Challenges and Considerations

by Allan MacDonald

## Why DQ?

**T**he regulatory authorities of the European Union, Japan, and the United States have come together to form the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH). ICH Q7A was the first Good Manufacturing Practice (GMP) guidance developed jointly by industry and regulators under the ICH umbrella. The document establishes one global GMP standard for Active Pharmaceutical Ingredients (APIs).

Following suit, the US Food and Drug Administration (FDA) has stated, “Q7A supersedes FDA’s draft API guidance.”<sup>1</sup> The ICH Q7A guidance defines DQ as “the documented verification that the proposed design of the facilities, systems, and equipment is suitable for the intended purpose.” This definition for DQ is the same as the one found in the Commission of the European Communities Guide for GMP.<sup>2</sup> This European Union (EU) document also states, “the first element of the validation of new facilities, systems, or equipment could be design qualification.”

The requirement for DQ can be debated since the above-mentioned documents use words like “could,” “should,” and “usually,” and because these are guidance documents only, not regulations. However, government guidance documents *usually* carry a lot of weight in a historically “risk-averse” environment like the pharmaceutical industry. Therefore, many companies are implementing DQ programs and procedures and are expecting others to support these efforts.

## Definition Before Qualification

To verify that a proposed design meets the intended purpose, we are required to under-

stand each of these terms. The challenge is that both the definition of the “purpose” and “design” evolve during the life of a project. So there is a temporal component to DQ that must be addressed. The pharmaceutical manufacturer should decide early in the project when a DQ will be executed.

The EU GMP and ICH Q7A both use the term “proposed design” in their DQ definition; however, this only reflects the status of a design at the time the DQ was performed. For a DQ to be valid, the Installation, Operational, and Performance Qualification (IQ, OQ, and PQ) each must be performed on the system or equipment that was constructed per the design that was qualified.

At a minimum, a DQ needs to be performed on the final design. But, from a project standpoint, waiting until the design is final before verifying that it meets the intended purpose is not practical. Rather, verifying the design along the way will allow for design corrections to be made with minimal impact on cost and schedule. Whether or not this verification is documented and included as part of DQ is up to the owner of the system or equipment to be qualified. However, documenting earlier efforts can reduce the effort required for the DQ on the final design.

A design can be defined by documents such as:

- Descriptions (Process, Basis of Design)
- Specifications (User Requirement, Functional, Design)
- Drawings (Process Flow Diagrams (PFD), Piping and Instrumentation Diagram (P&ID), Layout)
- Purchase Orders
- Contracts

## Specification Resource

There is a group in ISPE that focuses on GAMP in the Americas. A subgroup of that group was formed called the Joint Equipment Transition Team or JETT.

The group defines themselves on the JETT homepage at <http://www.jettconsortium.com> as the following. "JETT is a consortium of pharmaceutical users (manufacturers), equipment suppliers, and consultants seeking to improve communications between users and suppliers to more effectively meet the 'validation' requirements of the pharmaceutical industry."

This consortium has produced URS templates for various pieces of equipment that are available for download free of charge from the site. These templates have been created based on the GAMP 4 methodologies.

In addition to the many URS templates available, sample design and functional specification are included on the site.

A matrix on the sample documents Web page provides the status of current and future documents the JETT is working on.

For the execution of the DQ to be efficient, the user and designer need to define – in advance – the path a design will take for each type of equipment. The Code of Federal Regulations (CFR) requires manufacturers of medical devices to keep a Design History File (DHF).<sup>3</sup> Although this is not required for pharmaceuticals, a DHF could be used as part of a DQ. The user, designer, and validation group could agree on the types of documents to be in the DHF for the equipment or system that they will be designing. These documents are generated and copies should be collected during the design process.

Some of the documents in the DHF might be:

- the original user request
- emails and minutes from meetings and teleconferences
- calculations
- PFDs and P&IDs
- drawings

The items referenced in the DHF would be used to verify your design in a DQ.

## Specifications

Specifications are an important part of what defines the design of a system or piece of equipment. Companies within the pharmaceutical industry frequently use common terms for specifications that unfortunately may have different meanings, interpretations, and impacts.

For example, the User Requirement Specification (URS) as described in GAMP 4 is to be used for describing what a system is supposed to do.<sup>4</sup> This entire guide was written for

use with automated systems; however, the term URS is often being used broadly to include many, if not all, specifications being produced by the user or their designee. This can often be confusing once validation groups attempt to use the now classic "V-model" and arrange their PQ to verify all items in a URS.

GAMP 4 states in a section describing the URS that "a separate requirements specification should provide appropriate production process and product information, electrical and mechanical details, and performance requirements."<sup>5</sup>

It is also common for a firm to design a control system for a client and create a specification for bid that not only has the user's requirements, but also some functional and design specifications. This is so the proposals or bids received from potential suppliers can be tabulated and compared on an "apples to apples" basis.

Once a successful bidder is awarded the project, they then go on to create a complete Functional Specification (FS) and Design Specification (DS). In this case, what would the specification that was sent out for bid be called? It is more than a URS and it has elements of an FS and a DS. To minimize confusion on a project, the terms and accompanying definitions that will be used by all parties on a project should be identified. Check for instances that those involved not only all know what a URS is, but also agree on the same definition and where it will be applied.

Agreement in advance on what pieces of design will have a URS, FS, and DS and which ones will have another type of specification is an important step in the process.

Portions of the facilities, systems, and equipment that will undergo DQ may be specified using methods common in the construction trade such as those advocated by the Construction Specifications Institute (CSI). Mechanical, Electrical, Plumbing (MEP), Heating, Ventilation, and Air Conditioning (HVAC), and architectural building contracts are often specified using different methods than process system equipment or control systems. These differences should be addressed in advance so that all parties involved in the design and qualification of that design have the same expectations. The DQ procedures and forms also should allow for the use of construction contracts and documents.

## Design Qualification vs. Enhanced Design Review

The ISPE Baseline® Guide Volume 5 "Commissioning and Qualification" has adopted the term Enhanced Design Review (EDR).<sup>6</sup> EDR is a practice that the guide suggests to utilize to compliment Good Engineering Practices (GEP). As defined, an EDR is a documented review of the design, not necessarily limited to systems to be qualified and not a requirement of the FDA. This author highly recommends reading the material covered in the ISPE Commissioning and Qualification Baseline® Guide.

Although the ISPE Guide avoids the term "Design Qualification," the methods described for an EDR could be used as a DQ. Many firms, particularly those involved with international business, are developing or have developed DQ proce-

dures. At a minimum, when a documented design review is performed on systems or components that are to be qualified, the review should be performed as a DQ.

## Validation Plan

A validation plan is needed early in the project to determine how facilities, systems, and equipment will be validated. The validation plan should be shared with the project team, particularly with those that will be performing the design.

The validation plan should address an impact assessment and qualification rationale.<sup>7</sup> The plan determines what will be qualified; part of this qualification may be DQ. For example, the plan may state that “all elements of a design that have been determined to have a potential to impact product quality shall be qualified during a DQ.”

If applicable, the intent to perform DQs on a project should be decided before a Request for Proposal (RFP) goes out for bid to design firms.

## DQ Execution

The pharmaceutical manufacturer or their designee must provide a specific document that defines the user’s requirements to meet the intended purpose of the system or equip-

ment. The team needed to verify a design must understand the intended purpose and have the appropriate background to evaluate the proposed design. The DQ team may include:

- System User
- Designer of the System
- Validation
- Quality Assurance
- Project Management

DQ team members should have access in advance to the information that will be presented and evaluated during that DQ execution. Each team member also should know in advance what will be expected of them and what procedures will be followed during the execution of the DQ.

Each user requirement should be listed or referenced specifically in the DQ document. During a DQ, the design elements that meet each specific requirement in that user document should be verified, and each of the design documents being verified should be uniquely identified.

The history of a design should be known and available as a DQ is performed. The evolution of a design usually involves meetings, calculations, and correspondences that should all

<b>XYZ Inc.</b>		<b>User Requirement</b>	
<b>Project Name:</b> Yitsnotadrugatol Large Scale Production Facility		<b>Doc.No.:</b> URD-123589-4	<b>Rev:</b> A
<b>System Description:</b> Cyclization Reactor		<b>Project #</b> 123589	<b>Location:</b> Anywhere, CA
		<b>Page</b> <u>    </u> <b>of</b> <u>    </u>	<b>Date:</b> Jul/06/2004
Requirement Number	Requirement Description	May Impact Product Quality	Requirement Category
URD-23859-4-1	Cyclization Reactor to have sufficient volume for the conversion of 400 kg (880 lbs) of intermediate in a single batch.	Yes	Process
URD-23859-4-2	All wetted materials of construction to be compatible with the chemicals to be used in the reactor.	Yes	Process
URD-23859-4-3	Reactor transfer pump to be able to pump entire contents to the quench tank in the isolation room in less than 15 minutes.	Yes	Process
URD-23859-4-4	All electrical equipment on the reactor to be rated for a Class 1 Div1 Group C, D.	Not Directly	EH&S
URD-23859-4-5	Reactor Manway to have lift assist.	No	EH&S
<b>Notes:</b>			
Created By:			
<i>K. D. Davis</i>	<i>Kevin Davis</i>	<i>Operations Manager</i>	<i>Jul/12/2004</i>
Signature	Name (Print)	Title	Date
Reviewed By:			
<i>B. Strichter</i>	<i>Beatrice Stricter</i>	<i>Validation Manager</i>	<i>Jul/12/2004</i>
Signature	Name (Print)	Title	Date
Please note that the above is an example of a single page of a document that would include sections for information such as titles, document approvals, procedural references and places for the identification of signatures and initials.			

Figure 1. Example of a user requirement document.



<b>XYZ Inc.</b>		<b>Design Qualification</b>	
<b>Project Name:</b> Yitsnotadrugatol Large Scale Production Facility		<b>Doc.No.:</b> DQ-123589-4	
<b>Design Requirements to be Verified:</b> Cyclization Reactor system requirements as described in URD-123589-4, Rev: A., Jul/06/2004		<b>Project #</b> 123589	
<b>Note:</b> This DQ is limited to the requirements of the design that could have a direct impact on product quality. (See attached copy of URD)		<b>Location:</b> Anywhere, CA	
		<b>Page</b> <b>of</b>	
		<b>Date:</b> Oct/15/2004	
<b>Design Documents Verified (Include Revision/Date)</b>	<b>Design Verification Description</b>	<b>Pass/Fail</b>	<b>Verified By/Date</b>
D1- 12539 Rev 0 (Jul/28/2004) D2- 12539 Rev 0 (Aug/30/2004)	The Design Basis and Process Description represent a design that is suitable for the intended purpose as described in requirement URD-23859-4-1, URD-23859-4-2, and URD-23859-4-3.	PASS	AJM Oct/22/2004
PID-123589-4 Rev 0 (Aug/30/2004) PID-123589-5 Rev 0 (Aug/30/2004)	P&IDs represent a design that is suitable for the intended purpose as described in requirement URD-23859-4-3.	PASS	AJM Oct/22/2004
EA-123589-104 Rev 0 (Sept/01/2004) P-123589-104 Rev 0 (Sept/01/2004) P-123589-105 Rev 0 (Sept/01/2004) P-123589-106 Rev 0 (Sept/01/2004)	Equipment Arrangement and Piping drawings are consistent with the P&IDs and represent a design that is suitable for the intended purpose as described in requirement URD-23859-4-3.	PASS	AJM Oct/24/2004
SPE-12539-18111 Rev 1 (Sept/10/2004) SPE-12539-18222 Rev 1 (Sept/15/2004)	Engineering Purchase specifications for the Pump P-401 and the reactor R-401 represent a design that is suitable for the intended purpose as described in requirement URD-23859-4-1, URD-23859-4-2, and URD-23859-4-3.	PASS	AJM Oct/22/2004
<b>Design History Documents: (The documents listed below were used in the verification of the design documents above.)</b>			
<i>XYZ Meeting Minutes No. 52 (Aug/10/2004), pump and system pressure calculations by J. Smith, Aug/25/2004.</i>			
<b>Comments:</b>			
<i>Per meeting minutes No. 52, the quench tank T-402 will now be located in the same room as the reactor. The design team agreed that the intent of requirement URD-23859-4-3 was that the quench took place in under 15 minutes to avoid excessive reaction by products. The calculated transfer rate and equipment specifications of the design were consistent with this requirement and therefore the Equipment Arrangement and Piping drawings were verified as meeting the requirement.</i>			
<b>Reviewed By:</b>			
<i>B. Stricter</i>	<i>Beatrice Stricter</i>	<i>Validation Manager</i>	<i>Oct/30/2004</i>
Signature	Name (Print)	Title	Date
<i>K. D. Davis</i>	<i>Kevin Davis</i>	<i>Operations Manager</i>	<i>Oct/30/2004</i>
Signature	Name (Print)	Title	Date

Figure 2. Example of a design qualification form.

be documented and indexed so pertinent points can be specifically referenced.

The correspondences, calculations, and other supporting documents also should be created with unique references. These references will help in following the path of the design during a design qualification.

Systems can be used to track a design as it evolves through the use of a traceability matrix similar in concept to that described in GAMP 4.<sup>8</sup> This, however, may not be appropriate for designs that are unlike the control systems that lend themselves well to a tabular representation, such as a matrix.

The form, protocol, or document completed for a DQ should provide sufficient information to identify all of the documents used to verify the design. A method should be put in place in advance for maintaining documents to be used for review/DQ by those responsible for the design.

Strict change control involving user validation personnel needs to be instituted once a DQ process has begun on a given system. This is to ensure that the design documents remain in a qualified state.

Deviations or additional requirements that arise in meetings or in correspondences that were not in the initial user's

requirements or scope should be explained in the DQ document. Changes also should be submitted to the appropriate party to update the user's requirement or scope document.

The timing of the execution of a DQ is important to the schedule of a project. The final DQ on a system should be late enough so that all of the design documents have been completed, but early enough so that the fabrication or construction is not delayed. Project management should be aware that any fabrication or construction on a system that is to be qualified would be "at risk" if performed before a DQ had been completed on the proposed design.

## Sample Project with DQ

A pharmaceutical company (XYZ Inc.) has hired an engineering firm to design a large scale manufacturing system for their new product that they currently make on a smaller scale.

XYZ Inc.'s goals for the project were spelled out in an RFP for a conceptual study. A conceptual study was performed by a design firm with several options and an accompanying rough estimate for the different options. Project options were chosen and preliminary engineering began.

A preliminary design with drawings (PFDs, P&IDs, lay-

outs, etc.) and a  $\pm 20\%$  estimate was developed for capital cost approval. The estimate exceeded what XYZ Inc. had expected the cost to be. A “value engineering” exercise was then performed to reduce the scope and cost of the project. Once the estimate was within XYZ Inc.’s budgeted amount, the early design documents were revised to reflect the value-engineered scope of the project.

The documents were then used by XYZ Inc. to group portions of the project into systems. XYZ Inc.’s Quality Assurance group then had a Validation Master Plan (VMP) created. The VMP had a list of systems and whether they were to be considered a direct impact system. The VMP also stated that a DQ would be carried out on direct impact design elements only.

XYZ Inc. uses a document they call a User Requirement Document (URD) to convey their needs for the project. The document also designates which of those needs their process operations and validation groups feel could have an impact on the quality of the product on direct impact systems.

XYZ Inc.’s VMP states that a DQ will be performed on direct impact systems and equipment before design documents are approved for fabrication or issued for construction.

Once a direct impact system has successfully passed a DQ, the design documents for that system can be approved for fabrication or issued for construction. These same documents then become controlled documents under XYZ Inc.’s Quality Assurance program. Updates or revisions to these documents then require a QA/Validation evaluation as to whether they constitute a change to the executed DQ.

XYZ Inc. had required a DQ before construction of each design; however, the team would also be required to perform a design review at regular intervals during design to check that URD points for all systems are being met by the design.

The design team members were sent copies of the User Requirements document, URD-123589-4 Rev. A, that had been written earlier in the project in advance of the time set for the DQ of the Cyclization Reactor. See Figure 1 for an example page of the URD-123589-4 Rev. A document. A list of the design and design history documents that would be used in the DQ was also sent to the disciplines responsible for the documents.

During the execution of the DQ, the team members examined each of the design documents listed on DQ-123589-4 (Figure 2) and verified that the design documents will meet the requirements that may have an impact on product quality as listed in URD-123589-4 Rev. A.

A review of the pump calculations was required for requirement URD-23859-4-3 to determine that the right pipe and pump size had been specified.

The piping and layout drawings showed the quench tank T-402 as being in the same room as the reactor. Yet the requirement URD-23859-4-3 stated that the quench tank was to be in the isolation room. This turned out to be the only deviation so the meeting was adjourned and an investigation of the deviation was requested.

A review of meeting minutes was performed to determine why the location had been changed. The design team was

notified of the findings and agreed that the true requirement was in the transfer time and not the location of the quench tank. The design team agreed to pass the verification of the equipment arrangement and piping drawings. An explanation was added to the DQ form.

Once the DQ on the system was completed and approved by XYZ Inc.’s Quality Assurance group, the design documents for the Cyclization Reactor were released to be issued for construction.

## Design Firms and DQ

Most design firms have systems in place to review the design documents they produce. However, the needs of client companies can vary, and a design firm’s procedures need to be adaptable to the expectations for DQ.

Procedures explaining the expectations of the design firms for DQ should be included with any RFPs. Should a client have particular needs that would be outside of the normal scope of deliverables, any additional costs would be reflected in a design firm’s proposal.

Some of the systems and procedures that a client may request of a design firm for their DQ needs can help in controlling costs and “scope creep.” Specific user requirement documents with traceability can be used for defining a design basis. Any feature or item in a design without a design history traceable back to the user’s requirement could be flagged as a change for evaluation as a “must have” or a “nice to have.”

Information usually flows in many parallel paths between a client and the design firm. Project Managers can more effectively manage a project and control scope by using an approved user requirement document as the official mechanism.

Multiple design firms or multiple disciplines may be involved in a project. Often, a client has a representative from a certain discipline work with a particular group within a design firm to create a specification for the project. These two parties may be in agreement with each other, since they both “speak the same language;” but qualification and validation involves many disciplines, and a design qualification needs to address all of them. Design firm disciplines need to all agree on the deliverables that will be used for DQ.

## Summary

Pharmaceutical manufacturers may or may not have systems in place for performing DQ. The DQ procedures and expectations will vary from company to company. Design firms, vendors, and other support resources for pharmaceutical manufacturers need to understand the client’s DQ needs and have systems and methods adaptable to those needs.

A clear agreement on the expectations for how facilities, systems, and equipment will be specified and which elements will require DQ is required by the entire design team. This should be addressed for each type of system. In particular, the client should be aware of the typical methodologies within each discipline of a design team.

DQ practices can improve the control of a project. The execution of a DQ should clearly identify:

- the document that established the “intended purpose of the proposed design”
- the documents that define the design
- the documents that were used to develop the design

The purpose of this article was to provide concepts, considerations, and examples that pharmaceutical industry professionals can use to help create or improve procedures for dealing with DQ. Remember, DQ, as stated by the ICH Q7A, is “the documented verification that the proposed design of the facilities, systems, and equipment is suitable for the intended purpose.”

## References


1. FDA Presentation “ICH Q7A GMP Guidance for APIs and its Use During Inspections,” [http://www.fda.gov/cder/meeting/ICH\\_Q7A/index.htm](http://www.fda.gov/cder/meeting/ICH_Q7A/index.htm), 2002.
2. Commission of the European Communities. The Rules Governing Medicinal Products in the EC, Vol. IV, Good Manufacturing Practice for Medicinal Products, Annex 15 Qualification and Validation, Luxemburg Office for Official Publications of the EC, ISBN 92-828-2029-X, 1998.
3. Code of Federal Regulation, Title 21, Volume 8, CITE: 21CFR820.30, revised as of April 1, 2004.
4. GAMP 4 Guide for Validation of Automated Systems, ISPE, Appendix D1, page 1, 2001.
5. GAMP 4 Guide for Validation of Automated Systems, ISPE, Section 9.5.1, page 53, 2001.
6. ISPE Baseline® Pharmaceutical Engineering Guide, Volume 5, Commissioning and Qualification, page 75, First Edition, March 2001.
7. ISPE Baseline® Pharmaceutical Engineering Guide, Volume 5, Commissioning and Qualification, page 65, First Edition, March 2001.
8. GAMP 4 Guide for Validation of Automated Systems, ISPE, Appendix M5, page 3, 2001.

## About the Author



**Allan MacDonald** has more than 25 years of experience in the pharmaceutical industry. He is currently the Facilities Manager for Therion Biologics in Cambridge, Massachusetts. His experience includes major pharmaceutical company operations and engineering with design firms and equipment manufacturers. This article was written while

he was with Parsons in Boston, Massachusetts. He is currently on the ISPE Boston Chapter’s Board of Directors and has co-chaired the bulk pharmaceutical chemicals discussion forum (formerly SIG) for five years. MacDonald holds a BS in chemical engineering from McGill University in Montreal, Canada.

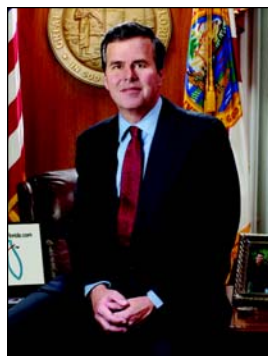
Therion Biologics, 76 Rogers St., Cambridge, MA 02142. 

The following interview with Governor Jeb Bush was conducted by Mark Mathis in November 2004. Mathis is the Communications Chair of the ISPE Carolina-South Atlantic Chapter and can be reached at Integrated Process Technologies, Inc., Tel: 1-919/345-4044.

Reprinted with permission from the ISPE Carolina-South Atlantic CASA Chapter newsletter.

## Interview with Florida Governor Jeb Bush

by Mark Mathis



Governor Bush, first I would like to thank you for taking the time to speak with us on the biotechnology/pharmaceutical market and your achievements in seeing Florida's growth in this industry. As you already

know, ISPE is a non-profit multinational organization supporting the growth of biotechnology/pharmaceutical professionals. ISPE's headquarters are in Tampa, Florida and we host many of our events in your state.

**Q** What percentage of annual new jobs does the biotechnology/pharmaceutical market account for in Florida? How does this factor in with your overall employment plan?

**A** Florida's life sciences industry is characterized by the specialization of small firms that are forming alliances with academic and private partners to support their growth and success. With Florida's productive technology transfer programs, Centers of Excellence, innovation infrastructure, and supportive business environment, more and more valued added enterprises, including those in the life sciences, are choosing to grow in Florida.

Florida's biosciences sector had about 1,800 establishments as of March 2004 with employment of about 38,000, up 800 jobs from the year before. Statewide, gains in the bioscience industry accounted for less than 1% of job growth.

As Florida strengthens its reputation as an environment that supports life sciences operations, and with our recent investments in the industry, we anticipate and are preparing for significant growth.

**Q** How does the growth of the biotechnology/pharmaceutical industry in Florida fit in with your other initiatives?

**A** Tourism, agriculture, and international trade will continue to play an enormous role in the future of our state, but our efforts to diversify Florida's economy, especially in emerging technologies, will also be critical to our long term success. As ISPE members know, biotechnology and the life sciences are integral to our state and nation's future. Catalysts like Scripps Florida, the Moffitt Cancer Center, the Institute for Human and Machine Cognition, wonderful public and private universities, and new and existing companies, will ensure Florida's position at the crossroads of innovation for the life sciences industry.

**Q** 2003 was a big year for Florida's biotechnology/pharmaceutical industry. A lot has been made of Scripps and the tax credits and other support of this company in relation to the biotechnology/pharmaceutical initiative. Now that some time has passed, what new ways or incentives will you use to attract other companies to the state? Are there any other large projects on the horizon?

**A** Scripps Florida is a unique opportunity. It combines the first-ever expansion of the highly regarded Scripps Research Institute (TSRI) with Florida's maturing life sciences industry and technology-rich academic infrastructure. Florida was able to capitalize on this opportunity by investing a portion of its one-time federal economic stimulus funds (which every state received) into the incubation of a sister campus for TSRI.

Although the scope and brand of Scripps is unique, the idea of investing state resources to catalyze success is not. For example, the James and Esther King Biomedical Research Pro-

gram recently awarded grants totaling \$9.2 million to research scientists from across the state's biotechnology industry, public and private universities, and clinical research institutes. To enhance this program, Florida Senate Bill 2002 adds \$6 million recurring dollars and Senate Bill 1278 gives the program a greater ability to offer multi-year grants to biomedical researchers in Florida. Ultimately, the goal is to invest close to \$100 million in biomedical research over the next 10 years.

In Florida, specific economic development projects are locally driven and evaluated on an individual basis. We have a competitive business climate and competitive incentives programs to assist economic development projects grow in Florida, and the State has taken a pro-active role in supporting the incentives requests of its local communities.

**Q** \$500 million in incentives is a big step forward for Florida, very similar in comparison to other states located in Biotech hot spots. Is it your intention to have Florida considered in the same market as the Northeast (New England), West Coast (Bay Area and San Diego), and North Carolina (Research Triangle Park)? If so, what can you say about the growth of such initiatives?

**A** The Florida legislature and I agreed that an investment in Scripps Florida as an engine for economic development was a wise use of the one-time, federal, economic stimulus dollars. The long term benefits that Scripps Florida will afford the state, in terms of attracting and keeping world-class scientists, in terms of fostering the development of advanced technologies required by Scripps and surrounding universities and private enterprises, in terms of growing and attracting early and late stage capital, and in terms of raising the bar for education in the life sciences for Florida students, is well worth the investment.

Florida is already a hot spot of technology development and we have good reason to believe we will not only compete with other technology centers, but also lead them in the future. People like to work where they like to live and Florida offers a superior quality of life, superb access to local and global innovation, and resources to fund growth. The nexus of these three assets will drive the future to Florida.

**Q** On the same note, many small biotechnology/pharmaceutical companies will not attract the interest of Venture Capitalist's. Would you comment on any state funded opportunities for companies interested in qualifying for grant money and loan programs?

**A** One of Florida's most successful grant programs for smaller firms is the state's Small Business Technology Transfer Research program. The program is designed to stimulate the commercialization of biomedical research in Florida. The grants fund joint projects between research institutions and small business enterprises. The most recent awards ranged from \$90,000 to \$100,000. Recipients are selected through a sophisticated multi-step process used to


rank applicants' projects. The Biomedical Research Advisory Council housed in the Florida Department of Health oversees the selection process. The Council is made up of nine respected scientists from across Florida.

**Q** How does the investment made in the biotechnology/pharmaceutical market compare with similar state funded programs for other industries in Florida?

**A** Florida is investing its resources in targeted industries and organizations that will help catalyze the quality economic growth Florida needs to compete in the years ahead. To guide to our efforts and investments, we established a strategic plan for economic development – *Roadmap to Florida's Future*. Our vision is to see Florida as a leader in knowledge-based jobs, leading edge technology, and competitive enterprises. We are addressing the priorities outlined in *Roadmap*, first, by focusing on quality economic growth, innovation, and globalization, second, by ensuring Florida is strong in multiple industry clusters and world markets in order to hedge against normal business cycles, and third, by integrating our education, workforce training, infrastructure, quality of life, and smart growth planning as integral elements to diversify Florida's economy. Our investments are aligned with opportunities to help us realize our vision. Florida's partnership with The Scripps Research Institute and the creation of Scripps Florida, for example, promises strong results in many of these categories. Other state investments in critical industries such as modeling, simulation, and training systems technology, aerospace and defense, information technology, and business and financial services will help Florida to prepare for the future.

**Q** Are there any state sponsored programs that integrate with scholastics in Florida's many colleges with the growth of the biotechnology/pharmaceutical industry?

**A** Florida is committed to building the types of academic and research facilities that are needed in order to be competitive in attracting life science companies. The state's universities perform nearly a *billion dollars* annually in sponsored research focused on various scientific and technological sectors. To link this research to our local industries, the State of Florida has established a \$30 million Technology Development Fund to create three new Centers of Excellence. The centers combine Florida's academic and industry sectors to bring local innovations to commercial viability. The centers are conducting research that is not only impacting Florida, but is also contributing to discoveries and applications on a worldwide basis.

- Center of Excellence in Regenerative Health Biotechnology at the *University of Florida*
- Center of Excellence in Biomedical and Marine Biotechnology at *Florida Atlantic University*
- Florida Photonics Center of Excellence at the *University of Central Florida* 

This article presents the advantages and opportunities of relocating or expanding a biotechnology company in the Southeastern United States.

Reprinted from *Business Facilities Magazine*.

Reprinted from  
PHARMACEUTICAL ENGINEERING®

The Official Journal of ISPE  
March/April 2005, Vol. 25 No. 2

## Biotech: A Wealth of Choices

by Thom Hallock

If you're seeking to expand or relocate a biotechnology company, you're blessed with a seemingly innumerable number of locations willing to bend over backwards for you. We'll help you sort through some of the more popular choices.

Year-end figures show that money flowed more freely into US biotechnology during 2003 than it has in recent years, according to the Bioworld Biotechnology State of the Industry Report 2004. The industry raised about \$16.5 billion, a sizable up-tick over the \$10.25 billion brought in a year earlier. While still down from the \$38 billion raised in 2000, biotechnology is clearly back and only getting stronger as the US economy recovers. After all, the 2003 figure ranks second in terms of total funds ever raised in the industry.

With more money becoming available, the question of whether you're in the right location becomes an issue you can take action on. Below are some of the most interesting places for biotechnology—many of which fly below the radar, but probably won't for long.

### Growing a Culture for Innovation

Located along Florida's Treasure Coast, just a few hours south of Orlando and a few hours north of Miami, St. Lucie County is one of the fastest-growing commercial and residential destinations in the Southeast. Once a quiet, rural area dotted with citrus farms and bedroom communities, St. Lucie County is today home to more than 200,000 residents and a booming economy focused on research and innovation.

In order to conduct revolutionary research on pharmaceuticals, biotechnology, and horticulture, St. Lucie County capitalizes on the area's foundation established by such organizations as Harbor Branch Oceanographic Institution, US Horticultural Laboratory, the Smithsonian Marine Station, and research programs at Florida Atlantic University (FAU)

and the University of Florida. These institutions have been key in encouraging biotechnology companies to relocate to the area.

St. Lucie County still has untapped potential for companies in the biotechnology industry. A number of companies currently cooperate on research efforts through The St. Lucie County Research and Education Coalition, a coalition of more than 100 PhD research scientists fostering new collaborations in research and technology. Additionally, local colleges and universities are adding biotechnology technician degree programs and joint degree programs to prepare local students for work in the pharmaceutical, biotechnology, and agricultural industries. For example, the recently announced Center of Excellence in Biomedical and Marine Biotechnology at FAU will work with institutions such as Harbor Branch and the Smithsonian Marine Station to help train the biotech workforce of Florida's future. Partnerships like these are sparking the interest of organizations looking to move to the area.

The recent relocation of The Scripps Research Institute to Palm Beach County, just South of St. Lucie County, is helping St. Lucie County and the surrounding areas to focus on the evolving economic development of their community—one that is growing into a mini biotechnology capital.

"We have a very favorable climate, and I'm not just talking about the weather," says Don Root, Executive Director of the Economic Development Council for St. Lucie County. "I am talking about an economic development climate, I'm talking about a lifestyle climate, and I'm talking about a climate for collaborative research in St. Lucie County that will attract people here."

St. Lucie County ranks highly on the quality of life scale, including affordable top-quality housing, innovative education, low traffic, safe city environments, and boundless cultural and recreational amenities.

Award-winning master-planned developer Core Communities has been working with government officials over the past five years to develop employment centers, commerce facilities, schools, and recreational facilities. Core Communities is planning a “jobs corridor” on 6,500 acres west of Interstate 95 and north of neighboring Martin County that will include housing and business space, all connected by a high-speed fiber optic network. The center also will be within walking distance of the local school.

In addition, the county is acquiring property near the USDA and University of Florida Institute of Food and Agricultural Sciences locations in Ft. Pierce to create a research and education park to accommodate new research opportunities.

This is just one example of the tremendous growth in business opportunity in St. Lucie County, a region with a keen focus on biotechnology. It’s one reason why economic development leaders claim St. Lucie County is growing a culture for innovation.

### **A Biotechnology Leader Yesterday, Today, and Tomorrow**

North Carolina ranks among the top five biotechnology regions in the US in several measures. The area spanning a 100-mile radius of Scotland County, NC, is known as the state’s southeastern region, and is home to the famed Research Triangle—the biotechnology leader of not just southeast North Carolina, but the entire southeastern US.

More than 140 of North Carolina’s 150 biotech companies are located within a 100-mile radius of Scotland County. The reason? How about a world-class research system; strong links between research and industry; a very highly trained workforce with many outlets available for further skills development; venture capital and seed funding in abundance; and available sites and buildings?

Back before “biotechnology” even existed as a word, the industry was getting its footing in the Research Triangle. The area was branded in the 1950s, capitalizing on its universities, researchers, and a proposed park within the triangle drawn by Duke University in Durham, NC State University in Raleigh, and the University of North Carolina at Chapel Hill.

What’s perhaps surprising is that there’s still plenty of room for new ventures and relocations, despite the region’s tremendous growth. More than 1.4 million people live within a 90-minute drive of Scotland County. The state of North Carolina has been incredibly pro-active about building upon its existing strengths; through programs like BioWork, it has ensured that there will be enough employees with the necessary skills to continue the growth of North Carolina biotechnology companies. The BioWork training is a 128-hour course that prepares students for entry-level jobs in bioprocessing plants producing biopharmaceuticals, amino acids, enzymes, vaccines, and other products. It’s intended for high school graduates, traditional manufacturing workers who have lost their jobs, or anyone interested in a new line of work. The course can even be customized and taught to those already employed at biomanufacturing plants.

### **World-Class Resources Come Together in Oak Ridge, TN**

Tucked away into an urban forest that was previously owned by the Department of Energy is Horizon Center, a new world-class business park in Oak Ridge, TN that has been created for pharmaceutical and biotechnology companies, high tech manufacturers, and innovative R&D companies.

Theragenics™ is the first company to locate in Horizon Center with its \$25 million medical isotope facility. The company makes a radioactive seed implant called TheraSeed® for the treatment of prostate cancer. Under its lease agreement, Theragenics was granted use of unique DOE isotope production technology. The company is heavily involved in research and development for treatment of other types of cancer and for production of other isotopes.

“Horizon Center was an easy choice for Theragenics,” says Christine Jacobs, Theragenics Chairman, President, and CEO. “The park’s high-tech vision, along with its close proximity to the unique resources that exist at the DOE’s Oak Ridge National Laboratory, fit perfectly with our long-term strategy.”

Horizon Center measures 1,000 acres, approximately half of which will remain in its natural state with wildlife, walking trails, and sculptures that create a campus-like setting. The center was created by the Community Reuse Organization of East Tennessee (CROET), a non-profit organization that works with previously government-owned properties to create an economic asset for the private sector.

Multiple building sites, measuring from 11 to 148 acres, have been identified in the Horizon Center master plan. Several projects are underway to make it easy for companies to locate in the park quickly. Several sites have recently been pre-graded, and a 40,000-square-foot speculative building is being developed this spring.

The upscale business park is fully equipped with a fiber optics network and dependable underground utilities. Conveniently located near the interstate system, Horizon Center tenants enjoy the convenience of being located within a day’s drive of approximately one-half of the U.S. population.

Carefully crafted covenants protect land owners’ and lessees’ investments in the park. In addition, CROET helps new tenants work with local organizations to obtain fair tax packages and to tap incentive packages that might exist.

Lawrence Young, President of CROET, notes that several high-tech clusters seem to find Oak Ridge particularly attractive. These include biotechnology, pharmaceuticals, waste management, homeland security, and transportation. Young says that several specialized areas, like radiological pharmaceuticals, are particularly exciting.

“A critical mass of technology companies already exists in Oak Ridge, and as a result, emergent radiological pharmaceutical companies like Theragenics are discovering the area’s world-class resources,” says Young.

Biotech and pharmaceutical companies in Oak Ridge include Allmeds, Apocom, Atom Sciences, Concorde Technologies, Coorstek, CTI, Deroyal Industries, Genomix Corp.,

***"The laboratory modules and related office space are available immediately for start-up businesses with commercial applications for life sciences products and processes."***

Identichem, Imtex, Ipath, Perkin Elmer, and others.

"It makes good economic sense for these companies to operate in the midst of the sophisticated facilities and intellectual power found in Oak Ridge," Young explains.

Workforce strengths of Oak Ridge include more than 2,300 PhDs, 45,000 information technology professionals, 9,000 students majoring in sciences, and 400,000 prospective employees, according to the Oak Ridge Economic Partnership.

World-class resources include Oak Ridge National Laboratory, the Russell Laboratory for Comparative and Functional Genomics, the Joint Institute for Biological Sciences, the University of Tennessee Center for Environmental Biotechnology, UT-Battelle, and the one-of-a-kind Spallation Neutron Source that comes on line in 2006. In addition, a wide range of organizations help foster a strong entrepreneurial spirit in Oak Ridge, including the Tennessee Biotechnology Association, the Office for Entrepreneurial Growth, and Technology 2020.

### **South Carolina Makes Serious Strides**

In South Carolina, biotech companies have the advantages of available skilled labor, an attractive business climate, a low-cost operating environment, and unparalleled quality of life. The state and its partners have taken serious measures to make sure South Carolina is a premier location for all sorts of biotechnology and life sciences companies.

South Carolina's 22,000-square-foot Biotechnology Incubation Facility, located in South Carolina's Lakelands Region, offers biotech entrepreneurs the unique opportunity to collaborate with the MD and PhD geneticists associated with the adjacent J.C. Self Research Institute of Human Genetics. The resources of South Carolina's three research universities (Clemson University, the Medical University of South Carolina, and the University of South Carolina) provide companies with competitive advantages through their commitments to research and access to technology and innovation. A 500-acre biotechnology park adjacent to the incubator facility will provide attractive sites to locate companies "graduating" from the incubator.

The first incubation facility, opened in September 2002, houses six laboratory modules, library, a conference center, offices, and support space. The laboratory modules and related office space are available immediately for start-up businesses with commercial applications for life sciences products and processes.

In an ongoing team effort to broaden the understanding of biotechnology and how to effectively recruit this industry to South Carolina, the Palmetto Biotechnology Alliance (PBA) presented the second statewide Palmetto Biotechnology Conference earlier this month. The conference featured many speakers representing leading biotechnology companies across the US, offering a unique perspective on industry trends and

factors that promote success in an increasingly demanding industrial sector. According to the PBA, South Carolina-the Palmetto State-has the research nucleus, natural resources, business environment, and professional expertise to successfully grow biotechnology.

Reliable, low-cost power generated by Santee Cooper, the state-owned electric and water utility, also has been pivotal in attracting these companies. Santee Cooper provides power to the state's 20 electric cooperatives in addition to its direct-service territories, so it serves as a major coordinator for economic development statewide.

While Santee Cooper is state-owned, Central Electric Power Cooperative represents the aforementioned 20 non-profit, customer-owned electric distribution cooperatives. The cooperatives provide engineering assistance, incentive rates, and loan and grant programs to encourage job creation. They offer new and expanding companies an incentive rate called the "Start Up Power Rider" (SUPR). To qualify for SUPR, the new connected load must be 750kW or more. With a 10-year contract, SUPR reduces the demand charge over the first three years of operation by 40% in the first year; 25% in year two; and 15% in year three. Grants for site preparation and/or building construction may be available depending on the number of jobs created, amount of capital investment, and characteristics of the new electric load. Santee Cooper and Central Electric Power Cooperative work together with the Palmetto Economic Development Corporation under the banner of the South Carolina Power Team to help businesses succeed in South Carolina.

### **Biotech Opportunity in Maryland has a Name: Hagerstown**

Maryland achieved international recognition with the completion of the sequencing of the human genome in 2000, a combined effort of one of the industry leaders, Celera Genomics, and one of Maryland's strategic scientific assets, the National Institutes of Health's Human Genome Project. Dubbed the genome "BioCapital," Maryland is home to "DNA Alley"- one of the largest concentrations of gene-based discovery companies in the world.

Although 42nd in geographical size, Maryland's success in the development of its high technology industries and the bioscience industry in particular has been noteworthy. Maryland is one of the 10 states selected as a 2002 Honor Roll State by the Corporation for Enterprise Development in its annual Development Report Card for the States. The Report Card provides an annual assessment of each state's economy and potential for future growth. Maryland received As in two major categories, performance and development capacity, and a B rating in business vitality.

The Hagerstown-Washington County, MD area is a perfect home to companies seeking to join the 300-plus biotechnology companies in Maryland. Hagerstown and Washington



County are actively recruiting companies within the industry. The community offers a location with a close proximity to the research institutions of the National Institutes of Health, Johns Hopkins University, and more that are situated in the Baltimore/Washington, DC metro area.


Those more than 300 diverse bioscience companies in Maryland and federal institutions provide easy access to innovation, technology transfer, and knowledgeable bioscience professionals. Maryland's biotechnology industry is now the third most concentrated among the states and second on a per capita basis. Hagerstown-Washington County offers the perfect way to tap into this strength with its productive, available workforce; attractively priced real estate; planned development areas; Enterprise Zones; 1,800-acre Foreign Trade Zone; affordable cost of living; and family-oriented lifestyle that so many highly skilled, well-paid researchers seek.

### Roanoke Valley, VA

The Roanoke Valley of Virginia is a vibrant community in the Blue Ridge Mountains of western Virginia. The largest metropolitan area west of Richmond-located equidistant between New York and Atlanta-the Roanoke Valley is within a day's shipping distance of most of the US population. The valley offers something for everyone: from a lively arts scene to award winning schools; from big-time college football at nearby Virginia Tech to a nationally recognized symphony; from hiking, boating, skiing, and golf to an entrepreneurial spirit that has fostered innovations for more than 150 years.

Whether your company is purely research oriented, involved in biomanufacturing, or both, the Roanoke Valley has a lot to offer. Its workforce is 320,000 people strong, coming from within a 60-mile radius. Nineteen colleges and universities are within an hour's drive, including Virginia Tech, one of the nation's top research universities. Many of the workforce in the area are graduates of these schools, meaning their skills are top-notch and in many cases very technical. Employees love to live in the Roanoke Valley not only for its natural beauty and quality of life, but for a cost of living (and doing business) that's 10% below the national average.

Electric rates that are also among the lowest in the nation, and for those needing distribution capabilities, you'll be glad to know that the Roanoke Valley has excellent market access, thanks to a Foreign Trade Zone and inland port, a jet-served airport, and Interstate 81.

Biotech and biomedical industry is an active target for the communities of the Roanoke Valley. Plenty of companies and resources that enhance the "bio atmosphere" are present in the valley, such as the Carilion Biomedical Institute. The institute, a partnership between Carilion Health System, Virginia Tech, and the University of Virginia, assists with commercialization and funding of biotechnology ventures, among other activities. Earlier this month, the institute showed off a new orthopedic device-a cordless, hand-held screw-hole locator. The device allows surgeons to fix metal pins through segments of a broken thigh bone without using X-ray images. It's just one example of the kind of progress being made in the Roanoke Valley of Virginia. 

This article presents an Extended Supply Chain System which encompasses all aspects of clinical supply information and provides study managers with a comprehensive picture of the supply flow.

Reprinted from  
PHARMACEUTICAL ENGINEERING®

The Official Journal of ISPE  
March/April 2005, Vol. 25 No. 2

# Optimizing the Extended Clinical Supply Chain: Strategic Advantages for Clinical Trials

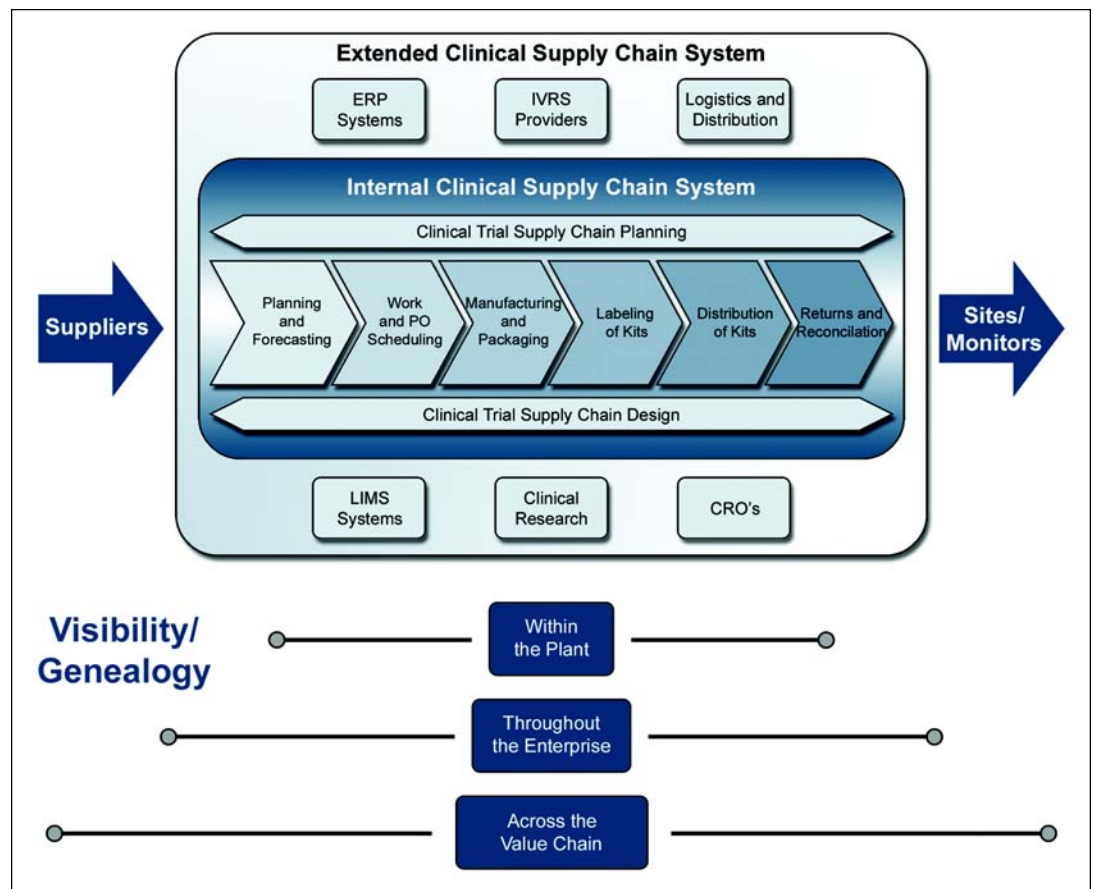
by Vikram Marla

## Introduction

The core of any good clinical supply chain is a supply management system that addresses all of the nuances of clinical supplies. Although Clinical Supply Management is often considered a back-office business unit for a sponsor, it is almost always on the critical path of the drug development process. The efficient, accurate, and timely delivery of material to the investigators is critical for a successful clinical trial. Given that

cost plays a key role in the drug development process, sponsor companies are attempting to minimize their investments by outsourcing many of their activities to vendors. As more and more vendors become involved, it becomes crucial for the sponsors to properly plan, manage, and control the activities occurring between the contractors and the sponsor. By having full control of their data and the necessary tools in place to plan and manage the flow of materials between the vendors and investigators, spon-

Figure 1. Key business process of an extended supply chain.



sor companies are able to realize possible strategic advantages over their competitors.

## Players

There are many processes of a clinical supply chain which can be accomplished internally. The key business units engaged with clinical supplies activities include:

- Manufacturing
- Packaging
- Pharmacy
- Quality
- Regulatory
- Clinical
- Analytics

Many of the business processes performed by these business units could potentially be outsourced. This is a trend being adopted by both big and small companies. Both physical and virtual pharmaceutical companies are increasing their outsourcing budgets to increase capital efficiency and enhance flexibility. The vendors commonly used to outsource clinical processes include:

- Clinical Research Organizations (CROs)
- Packaging and Labeling companies
- Interactive Voice Response (IVR) Vendors
- Contract Manufacturers
- Distribution Warehouses
- Site Monitoring Outsourcing companies
- Returns and Destruction companies

Another key player in the clinical trial arena is the investigator. The investigator performs the crucial task of dispensing the investigational drug to the patients and subsequently monitoring the reaction to the drug. The key tasks critical to clinical supplies being performed by an investigator include the following:

- dispensing the right drug to patients on a visit in a blinded study
- the return and reconciliation of both used and unused drug
- blind breaking in case of an adverse event

## Components of an Extended Supply Chain System

A good supply management system might track all manufacturing and packaging activities for in-house material and inventory management. A good supply chain system also would encompass planning, tracking, and distribution of materials from start to finish for the sponsor company. But only an Extended Supply Chain would allow the sponsor to plan, manage materials, track inventory, distribute to investigational sites, dispense drugs to patients and perform reconciliation across multiple vendors. Figure 1 illustrates an extended supply chain system.

## Benefits of an Extended Supply Chain System

Given that pharmaceutical and biotechnology companies are

increasingly using third party contractors and external IVR vendors for drug development, it is becoming more and more critical for sponsor companies to have real-time visibility across the entire clinical trials value chain.

If managed properly, this extended ecosystem of sponsors, contractors, and third party vendors provides numerous key benefits to all those involved, especially the sponsor:

- vendors become an extension of the enterprise
- improved capability for regulatory compliance
- accurate, real-time inventory visibility across the value chain, enabling real-time process flow
- end-to-end genealogy/visibility
- seamless integration - consolidation of manufacturing and packaging into a single system for subsequent data analysis
- load sharing/transfers across vendors while sponsors maintain visibility of the inventory

While there are numerous benefits for the sponsor, there are numerous benefits for the vendors as well:

- process efficiencies
- more focus on the core business and less on communicating information to the sponsors
- significant savings in resources - no more 'paper,' manual processes, or double reporting
- easy access to work order, batch records, and bill of material information
- ability to run queries
- ability to differentiate themselves to sponsors
- Part 11 compliance
- easy access to transaction history for tracking and genealogy

## Integration Challenges

The key to the extended supply chain system is its ability to integrate multiple vendors into a common platform and technology. Although there are many middleware and Enterprise Application Interface (EAI) technologies available, they generally only work when multiple parties agree on a common technology and are ready to make the investments needed to make their in-house systems communicate with the chosen technology. With rapidly changing technology and disparate systems existing between vendors and sponsors, there are various challenges for both the sponsors and the vendors:

- the technology needed to integrate the systems
- cost of implementing the chosen technology
- all vendors adopting a single messaging standard
- time to build and validate the integration effort

## Technology to Integrate the Systems

In order for companies to maximize value, sponsors and vendors must integrate and connect the disparate silos of information between them. Vendors face the immediate challenge of connecting their applicable systems in a flexible,

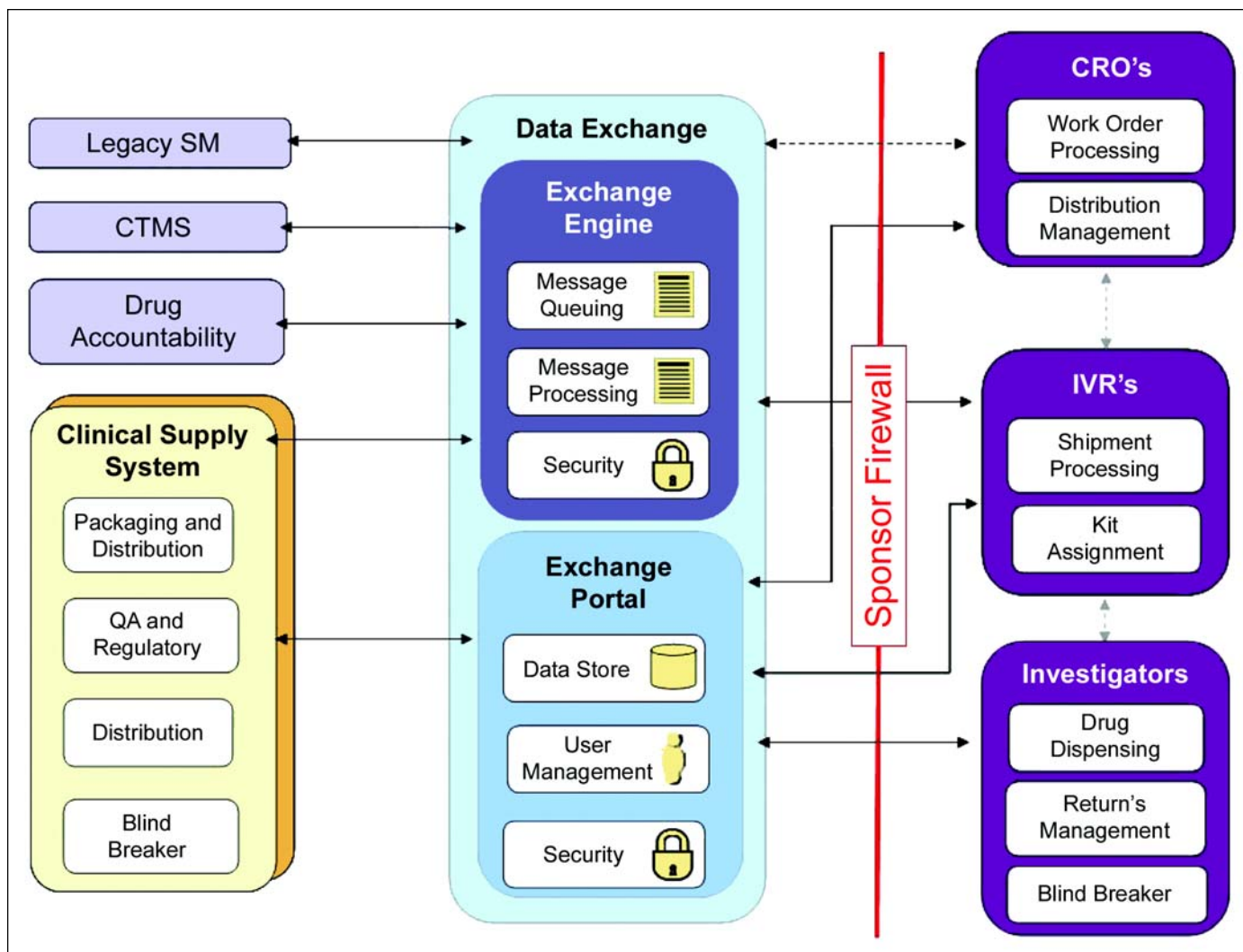


Figure 2. Clinical data exchange.

economical, manageable, and reliable manner.

Information is generally exchanged through the use of messaging. Every message serves as a packet to perform a specific function or set of functions. For example: an order request to ship 10 kits to an investigational site.

There are various issues that must be considered when it comes to integrating various systems. First and foremost a message written in an Extensible Markup Language (XML) should be understood by all vendors in the information chain. The structure of the message must be adoptable by all vendors, even when they are using their own in-house system or an enterprise level commercial system to integrate with external systems.

### Cost of Implementing a Technology

Integration is often the most underestimated task in information systems. In reality, integration takes a considerable amount of upfront analysis, a fair amount of time for scheduling and coordination of all parties involved, and a significant amount of effort to build the interface. Often, there is even the need for middleware software to connect the two parties. These factors have discouraged many vendors from

becoming early adopters or frontrunners when it comes to participating in integration efforts in this industry.

### All Vendors Adopting a Single Messaging Standard

Messages come with certain standards in terms of technology and specifications. Thanks to Clinical Data Interchange Standards Consortium (CDISC), there is already a certain amount of standardization that has been achieved and accepted for data exchange among different parties in the industry. However, every message will have specific standards to comply with in terms of its contents and its representation. Accepting and abiding by these standards can be an uphill battle and a drawn-out effort during integration analysis.

### The Challenge of Validating the Integration Effort

Clinical supply software packages must pass vigorous validation testing. As the software will be used for numerous non-repetitive activities, it requires a broad range of testing scenarios. Applications that are integrated with the clinical

supply chain system must be validated as well. Integration should be accomplished in such a way that all interfaced systems are not required to undergo validation each time one of the individual systems is upgraded and requires re-validation. This becomes a challenge when multiple contract vendors with different specifications are involved.

## **Solution to Overcome the Integration Challenges**

A possible solution to the many integration challenges is a Clinical Data Exchange (Figure 2) that is accessible by the CROs, IVR vendors, and Investigational Sites. The data exchange is a hub of information that the sponsor hosts for authorized vendors and investigators to access. The exchange can even be used by investigators to inquire and transact investigational site information, which can then be used for further processing.

The data exchange should have the ability to identify each message that is received from an external system and route it to the appropriate queue. Queues can be configured to be forwarded to a specific address or be stored in a local data store. Users can access the information in the data store using portal views accessed through the internet. The architecture of the data exchange module should be based on a Java 2 Platform Enterprise Edition (J2EE) compliant exchange which can be hosted on any J2EE-compliant server.

### **Use of a Clinical Data Exchange by CROs**

Using the above general architecture, sponsors can send messages to multiple CROs using the common Data Exchange. Message transfer intervals between the sponsor and the data exchange can be configured to be either on-line or at specific time intervals. The Clinical Data Exchange can queue the data for each CRO and will send the notification of the action to be performed. CRO vendors can access this data via the Web for further processing.

Vendors would have multiple ways in which to access the data and transact with the sponsors:

1. direct access using a portal
2. generic messaging and Web services

#### **Direct Access Using a Portal**

Vendors will be able to review, access, and enter data using Web portals. A CRO should be able to review manufacturing or packaging work orders, download batch records and instructions, gather data transfer information, or review inventory status information. Based on the batch record and the material received from the sponsor, the CRO can complete the batch and use the portal to enter manufacturing or packaging information directly into the exchange. Users accessing the portal will need to be set up by the sponsor. This would allow the sponsors to control the data being shared with the vendor.

#### **Generic Messaging and Web Services**

Generic messages can be built on demand for vendors to

access data from the data exchange. These messages built using XML technology will provide flexibility to the vendors to interface with various in-house systems. Messages would provide a means of passing information back from the vendor site to the exchange. Alternatively, Web services technology also may be used by vendors to access data from the exchange in an automated manner.

### **Use of a Clinical Data Exchange by IVR Vendors**

The exchange can be used to transfer IVR messages to its vendors. By doing this, IVR vendors can now set up the message queue in a Clinical Data Exchange to automatically download messages into their system. Vendors also will have the portal to view and review IVR data, message statistics, and history information. Messages from the IVR vendor's system are received into the data exchange and are sent back to the sponsor's supply management system.

### **Use of a Clinical Data Exchange by Investigators**

Investigators will be able to use the portal to perform various functions in relationship to clinical materials:

- dispense verification/assignments
- drug returns
- blind breakers

A Clinical Data Exchange can have its own data store capability for the system to capture shipment information and returned materials. The Clinical Data Exchange would send and receive messages from the sponsor's supply management system. In essence, the investigator interface would be independent of a supply management system and would have its own data store for drug reconciliation.

## **Data Exchange: The Leverage for Extended Supply Chain**

The Clinical Data Exchange is an important strategic tool and helps the sponsor optimize the extended supply chain by leveraging their drug development assets. There are many key benefits of this tool for both the sponsor as well as all the external parties in the supply chain ecosystem.

A few of the key benefits at the sponsor's end are as below:

**Standard Integration for all Vendors:** Basically, the sponsor will be putting secure data in a warehouse that is accessible to vendors with the proper security clearance. The sponsor no longer has to adopt or modify their integration techniques, depending on the middleware or system used by the vendor.

**Standardization of Data Exchange:** Irrespective of the techniques adopted by the vendors to exchange data between the exchange and their system, the data that enters the sponsor's system will be in one standard format.

**Validation Effort:** The sponsor will validate just the messages that go in and out of a Clinical Data Exchange. Because a Clinical Data Exchange acts as a buffer between the

internal system and the outside world, the sponsor's supply chain system will be transparent of changes in specifications that happen in the vendors' systems.

On the other hand, the vendors also would stand to gain tremendously:

**Cost of Compliance:** Vendors can avoid the cost of integrating messages into their in-house systems by using the portal to enter their data and review historic data.

**Option for Automated Interfaces:** Vendors have the option of configuring messages for automatic downloads and uploads. Once they are set up to accept and send messages, they have the option of configuring their profile in the Clinical Data Exchange for messages to interface with their system in an automated manner.

## Regaining Control and Visibility throughout the Extended Supply Chain


The types of players involved in the extended supply chain process is made up of a diverse set of suppliers, CROs, IVR vendors, distribution centers, in-house pharmacies, QA, site monitors, and investigators. There is an increasing trend of sponsor companies outsourcing more and more tasks to these entities going forward. Nonetheless, sponsor companies continue to be responsible for not only the efficiency and the accountability of the supplies dispensed to the patient, but for their accuracy as well. To manage the web of information exchanged between the players, it is important that sponsor companies be empowered with a strategic tool to leverage the benefits of an Extended Supply Chain System. This system would act as a hub of information where authorized vendors and investigators can access or upload data, giving study managers a comprehensive picture and the power to properly plan and manage their clinical supply flow. Only then can companies truly optimize their investments in clinical trials and accelerate their drug development efforts.

### About the Author



**Vikram Marla** has worked in information systems management for more than 20 years. He began his career in IT consulting as a systems analyst for Westinghouse Medical Software and soon joined the consulting division of Oracle Corporation where he worked his way to managing principal for clients from various biotech and health-related industries.

With his experience in the biotech and medical industry, he founded InfoPro Solutions, Inc. in 1995 and is President and CEO of the company. He received a Masters degree in computer science from the University of Memphis. He can be contacted by e-mail: [vikram\\_marla@infoprosolutions.com](mailto:vikram_marla@infoprosolutions.com).

InfoPro Solutions, Inc., 31365 Oak Crest Dr., Suite 250, Westlake Village, CA 91361. 

This article provides a review of controls associated with the manufacturing process, process development and validation, elucidation of structure, control of the drug substance, container closure system, and stability.

Part 1 of the article was published in March/April 2004.

# Pharmaceutical Drug Substance Due Diligence - A CMC Technical Assessment - Part 2

by Thomas J. DiFeo, PhD

## Introduction

**D**ue diligence is a vital activity in the acquisition or in-licensing of pharmaceutical compounds for market commercialization. Pharmaceutical product due diligence is a detailed investigation of the Chemistry, Manufacturing, and Controls (CMC) information associated with a drug substance and/or drug product. The investigation provides assurance that a given compound meets requisite technical and quality elements to allow for successful commercialization of the drug. This document provides an overview of CMC information which should be reviewed as part of due diligence activities for drug substance. This review follows the format of the Common Technical Document (CTD) for the Registration of Pharmaceuticals for Human Use: Module 3 Quality of the ICH Harmonized Tripartite Guideline<sup>1</sup> with some sections of the CTD template combined in order to simplify the presentation.

## **Manufacturing Process - Control of Materials**

The acceptance criteria and test methods for the starting materials, solvents, reagents, catalysts, and any other materials used in the manufacture of the drug substance are reviewed. The acceptance criteria for starting materials should consider those qualities critical to the operation. For example, the moisture content of a reagent may impact the formation of side-products.<sup>31</sup> A discussion of the controls selected for each reagent should indicate the rationale for acceptance criteria with regard to the quality impact on the drug substance.

## **Description of Analytical Methods**

The analytical methods used to control starting materials, reagents, and drug substance are reviewed. Sufficient detail should be provided so that the methods could be run in the laboratory. For example, HPLC methods should provide detail on the type of column used, run time, mobile phase composition, flow rate, and detection means. Adequate validation data should be available to assure the accuracy of the data used to support the physico-chemical properties of the drug substance. The ICH text on the validation of analytical procedures provides a good overview of the type of information that should be included in the validation package.<sup>32</sup> Key items include accuracy, linearity, precision (repeatability and intermediate precision), robustness, and specificity. While all of these aspects of validation may not be complete in early phases of development, some level of detail should be available to assure the accuracy of the information provided. In particular, the limit of quantitation should be at least 0.05% to provide adequate representation of the impurity profile.

Some compounds may have isomeric forms which can be characterized as structural (e.g., cis/trans isomers) or stereoisomers (e.g., enantiomers). Control of structural isomers is routinely accomplished by reversed-phase HPLC.<sup>33</sup> Compounds with molecular dissymmetry must have control methods that determine the enantiomeric purity (typically expressed as enantiomeric excess).<sup>34</sup> These separations are performed using chiral stationary phases (direct technique) or derivitization of the molecule to form diastereomers (indirect method) which



Figure 4. A summary check list of key CMC review aspects of drug substance - description of manufacturing process and process controls, solvents, reagents, and catalysts.

may in turn be separated on achiral stationary phases.<sup>35</sup> Since isomers may have different toxicological and pharmacological profiles, adequate control methods must demonstrate the purity of the drug substance.<sup>36,37</sup> A good overview of the use chiroptical spectroscopy in the characterization of pharmaceutical compounds can be found in the literature.<sup>38</sup>

## Solvents and Reagents

In reviewing the batch records of the lots of drug substance produced, the certificate of analysis for each solvent and reagent used is compared with any critical attributes identified in the process discussion. Certain solvents are rarely used in full-scale operations and should be avoided as the process moves from the laboratory to the pilot scale. These

include the solvents pentane, hexane, benzene, chloroform, carbon tetrachloride, 1,4-dioxane, and several ethers whose risks include safety and environmental issues.<sup>39</sup>

## Catalyst

A residual catalyst test is performed at the end of each process step where a catalyst is used. If these results are not available, a test should be performed for the drug substance. The levels of metallic catalysts are the subject of regulatory scrutiny and the limits should be based upon process capability and safety considerations. The European Agency for the Evaluation of Medicinal Products provides specific guidance on the limits of residual metal catalysts.<sup>40</sup> Typically, a heavy metals test is conducted for the drug substance. Figure 4 provides a summary check list for review of items concerning a description of the manufacturing process and process controls, solvents, reagents, and catalysts.

## Quality Control of Critical Manufacturing Steps

cGMP controls should be applied to all manufacturing steps beginning with the starting materials. Adequate process control is achieved when there is an understanding of each process step and its associated critical quality attributes. Critical Quality Attributes (CQA) are applied to those process steps that have an impact on the final quality of the drug substance. For each reaction step, the impact on the final drug substance should be determined. Some questions to be addressed are:

1. What process impurities are generated?
2. What process parameters influence the level of the process impurity?
3. How are the process parameters that influence product quality controlled?
4. Is the process control test reproducible?
5. Is there a clear correlation between the process control and the critical quality attribute?
6. Are the CQA results among batches consistent?

## Control of Intermediates

The requirements that apply to each CQA during the synthesis should be detailed. A review of the results for several batches will give an indication of the process robustness.

The analytical methods to control the CQAs should be given including any available validation data.

## Process Validation

Process validation is defined by ICH as the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce an intermediate or API meeting its predetermined specifications and quality attributes.<sup>41</sup> The approaches to validation of bulk drug substance are outlined in the ICH document as well as other regulatory guidance documents.<sup>42,43</sup> Some of the key aspects of validation are:



1. a validation master plan or protocol with objectives, scope, and responsibilities outlined
2. critical process parameters (key process variables) and their associated critical quality attributes must be identified
3. documentation of key process data during validation
4. acceptance criteria for key process intermediates and final drug substance
5. three consecutive successful production batches
6. reproducibility of the impurity profile
7. investigation of any atypical events or results occurring during validation runs

## Manufacturing Process Development

A review of the manufacturing process development includes an emphasis on the reproducibility of the impurity profile of the drug substance. Changes to the route of synthesis during development may lead to the formation of new impurities. The review focuses on any process changes made subsequent to the first toxicology study. All impurities must be qualified when they reach the ICH qualification threshold.<sup>44</sup> For a maximum daily dose of less than or equal to 2 grams/day, the qualification threshold is 0.15% or 1.0 mg per day intake (whichever is lower). For a maximum daily dose of greater than 2 grams/day, the qualification threshold is 0.05%. Qualification of impurities typically entails 28-day daily dosing study in mice. In addition, a package of genotoxicity assays is recommended including the bacterial mutation (Ames) test, the mouse lymphoma assay, and the rodent micronucleus test.<sup>45</sup> Figure 5 provides a summary check list for review of items concerning quality control of critical manufacturing steps, control of intermediates, process validation, and manufacturing process development.

## Elucidation of Structure

As discussed earlier in the General Information section of the Drug Substance description, specific data pertaining to structural elucidation is presented. Clear interpretation of the data should accompany the spectra. For mass spectrometry, the technique (e.g., electrospray ionization), instrument conditions, and sample preparation should be detailed. Major fragments should be identified and related to the proposed structure. NMR spectroscopy should include the sample solvent, operating conditions, and a narrative detailing the assignment of spectral peaks.

## Impurities

Impurities of drug substances may be classified into the following categories:<sup>8</sup>

- a. Organic Impurities
- b. Inorganic Impurities such as Heavy Metals (USP<231>)
- c. Residual Solvents

## Organic Impurities

Organic impurities can be produced during the manufacturing process and during the storage of the drug substance

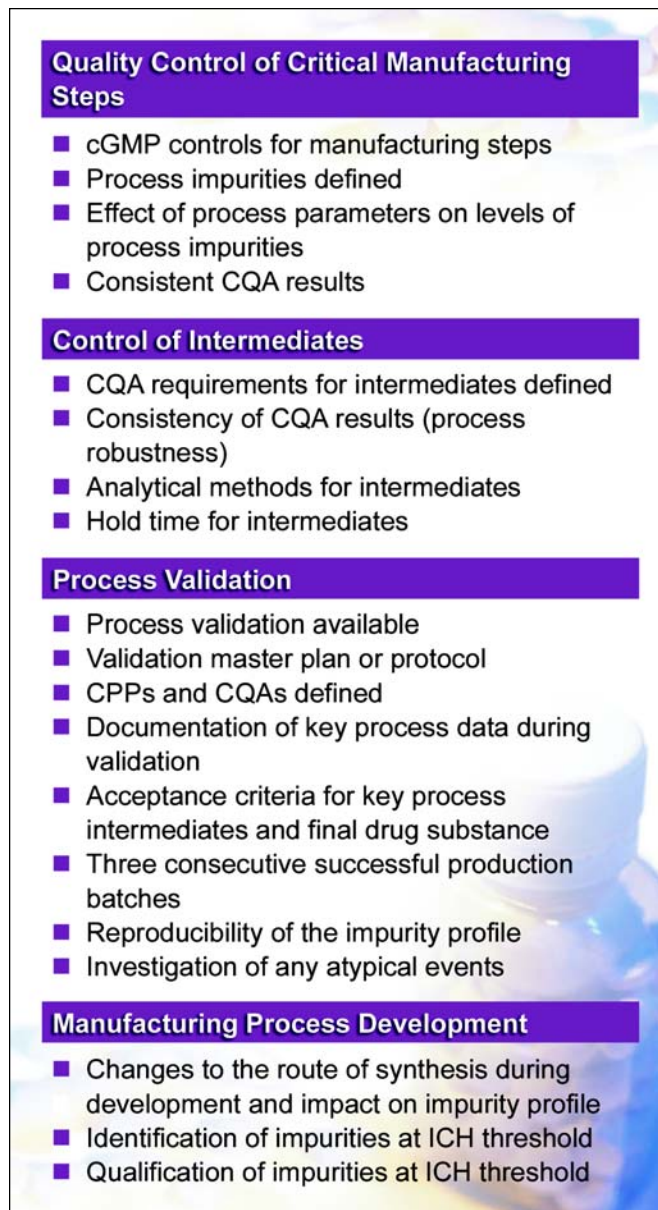


Figure 5. A summary check list of key CMC review aspects of drug substance - quality control of critical manufacturing steps, control of intermediates, process validation, and manufacturing process development.

(degradation products). Organic impurities include:

- Starting Materials
- By-Products
- Intermediates
- Degradation Products
- Reagents, Ligands, and Catalysts

The organic impurity profile of the drug substance includes the actual and potential impurities most likely to arise during the synthesis, purification, and storage of the drug substance. The results of all pertinent batches (especially toxicology study batches) should be given. The structure and source of the impurity should be discussed. For synthetic impurities, the side-reactions leading to the impurities should

<b>Elucidation of Structure</b> <ul style="list-style-type: none"><li>■ Specific data pertaining to structural elucidation</li></ul>
<b>Impurities</b> <ul style="list-style-type: none"><li>■ Control of organic impurities - starting materials, by-products, intermediates, degradation products<ul style="list-style-type: none"><li>• Inorganic Impurities - reagents, ligands, and catalysts, residual metals, salts, residual solvents</li><li>• Comparison of impurity profiles of toxicological and primary clinical batches</li></ul></li></ul>
<b>Control of Drug Substance</b> <ul style="list-style-type: none"><li>■ Description</li><li>■ Identification</li><li>■ Assay</li><li>■ Impurities</li><li>■ Melting point</li><li>■ Refractive index (chiral molecules)</li><li>■ Particle size</li><li>■ Polymorphic form</li><li>■ Loss on drying</li><li>■ Karl Fischer</li><li>■ Volatile Organic Impurities</li><li>■ pH of solution</li><li>■ Microbial limits</li></ul>
<b>Primary Packaging</b> <ul style="list-style-type: none"><li>■ A full description of the primary package</li><li>■ Qualification of the packaging component</li><li>■ Critical packaging component parameters identified</li></ul>
<b>Stability</b> <ul style="list-style-type: none"><li>■ A review of all stability batches</li><li>■ The treatment of drug substance with light, heat, moisture, acid/base, and peroxide</li><li>■ The degradation pathway elucidated for the drug substance</li></ul>

Figure 6. A summary check list of key CMC review aspects of drug substance - elucidation of structure, impurities, control of drug substance, primary packaging and stability.

be detailed and the relevance of any process controls used to minimize the impurities given. Potential organic impurities (degradation products) also may be predicted by degradation studies of the drug substance.

Similar to studies carried out for the structural elucidation of the active drug substance, studies detailing the structural identity for each impurity should be given.

An impurity profile should be available for each drug substance lot used in toxicological evaluation, primary clinical studies, stability evaluations of both drug substance and drug product, validation of the manufacturing process, and the development of the drug product. A comparison of impurity profiles across lots is performed.

### ***Inorganic Impurities***

Inorganic impurities can result from the manufacturing process and include:

- Reagents, Ligands, and Catalysts
- Residual Metals
- Salts
- Other Materials (e.g., Filter Aids, Charcoal)

An impurity profile should be available regarding the inorganic impurities for each drug substance lot used in toxicological evaluation, primary clinical studies, stability evaluations of both drug substance and drug product, validation of the manufacturing process, and the development of the drug product. A comparison of impurity profiles of these lots is performed and where any differences are noted, the implications regarding quality impact on the drug substance are assessed.

### ***Residual Solvents***

Solvents are used in the preparation of solutions or suspensions during the synthesis of a new drug substance. The maximum levels of residual solvents should be limited by ICH guidance.<sup>46</sup> Information on residual solvents should be available for all of the lots discussed above.

## **Control of Drug Substance**

### ***Specifications***

Specifications consist of test methods and their associated acceptance criteria. Each drug substance specification should be presented with a rationale for the limits specified. The following tests and acceptance criteria are applicable to all drug substances:<sup>47</sup>

- a. Typically, a qualitative statement or description regarding the appearance of the drug substance is given. The drug substance acceptance criteria entails the observed drug substance meeting the given qualitative criteria.
- b. Identification testing should distinguish between the drug substance and closely related compounds. Typically, two identification tests are performed with one test being the HPLC retention time match with a reference standard material. The second test is typically a spectroscopic technique such as IR. It should be noted that UV-Vis absorbance spectra are not generally specific enough to distinguish related compounds.
- c. The most common assay procedures for drug substances are titration methods and HPLC methods. If a titration

method is employed for assay, an additional specific, stability-indicating method should be employed to control impurities in the drug substance.

- d. HPLC methods are commonly used to control impurities in drug substance. The methods should be specific and stability-indicating.

There are additional specifications that may be applicable depending upon the nature of the drug substance and drug product. These specifications include:

1. Particle Size
2. Melting Point
3. Refractive Index (Chiral Molecules)
4. Polymorphic Form
5. Loss on Drying
6. Karl Fischer
7. Volatile organic impurities

For drug substances used in suspensions and solutions, additional physico-chemical characteristics of the drug substance may impact the drug product formulation. These characteristics include:

1. pH of Solution
2. Microbial Limits

### **Analytical Procedures and Validation**

As detailed previously for the control of starting materials, reagents, and drug substance, sufficient detail should be provided in order that the methods could be adequately run in the laboratory. Control methods derived from compendial references should clearly detail any requisite sample preparation requirements. A review of the method validation package should ensure that all ICH guidelines are met.

### **Batch Analyses**

Test results for all batches made (including lab scale batches) are reviewed. A comparison of results for those batches used in toxicology studies with those batches made for clinical use is pursued. The level and type of impurities in the clinical batches typically should not exceed that of the toxicology batches. If the levels of impurities in the clinical batches exceed that of the toxicology batches, a full review by the toxicology group is performed to assure that the level of impurities in batches proposed for the clinic are qualified.

### **Justification of Specifications**

Drug substance specifications provide comprehensive control of identity, purity, quality, and potency. The specifications for the drug substance should be consistent with current process capability and drug safety study results. Specifications for impurities in early development will be controlled primarily by qualification limits determined by toxicology studies. During early stages of development, full justification of specifications is not available as final specifications are deter-

mined by the comprehensive development experience. If the drug substance is in Phase III of development, draft final specifications should be justified with regard to the historical experience with the process at the current scale and synthetic route. At Phase III, the drug substance process should be well-defined and not open to any significant changes since Phase III stability batches and pivotal clinical studies will use drug substance from the current process.

### **Reference Standards or Materials**

The validity of the analytical results provided is, in part, reliant upon the use of appropriate reference standards. Reference standards used in the analysis of drug substance, starting materials, and intermediates must have additional testing to verify the identity and purity of the reference standard. Typically, the reference standard is fully characterized including structural elucidation data as well as extended testing for impurities. Once the reference standard is fully characterized, a secondary reference standard may be tested against the primary standard and used for routine testing.

### **Container Closure System (Packaging Material)**

A full description of the primary package used to store drug substance should be given. The potential for any incompatibility between the package and drug substance is reviewed.

The chemical and physical reactivity of the drug substance will dictate the type of packaging needed. For example, hygroscopic drug substances may require the inclusion of desiccants in the primary package. For drug substances sensitive to environmental conditions, (e.g., heat, light, moisture), data on the qualification of the packaging component should be given. Once the critical packaging parameters are identified, these parameters should be tested routinely upon receipt of the container prior to its use in the holding of drug substance. A minimum of identification testing should be performed for the packaging material regardless of the sensitivity of the drug substance. Techniques such as FT-IR identity for PolyVinyl Chloride (PVC) films is commonly applied.<sup>48</sup>

### **Stability Batches Tested**

A review of all stability batches is performed. Special attention is given to any increase in impurities or appearance of a new degradation product. The amount of variability seen between batches in the level of degradation products may be indicative of the robustness of the process. The appearance of new impurities or changes in impurity levels are consistent with poorly controlled processes. The degradation pathway for the drug substance and any critical intermediate should be elucidated.

### **Summary of Forced Degradation Studies and Stability Studies Under Stress Conditions**

Typically, as part of method development, forced degradation studies of the drug substance are performed. The treatment

of drug substance with light, heat, moisture, acid/base, and peroxide enable the analyst to demonstrate that the analytical method to control the drug substance is indeed specific and stability indicating. The data produced in accelerated studies also provide information to the assessment team regarding potential processing issues (e.g., light protection) that might be necessary in the manufacture of the drug product. Ideally, some level of degradation should be produced (~5-10%) during forced degradation studies in order to demonstrate the specificity of the method and provide information on the degradation pathways of the drug substance. Therefore, depending upon the intrinsic stability of the molecule, it may be necessary to adjust the relative intensity of the degradation conditions. Figure 6 provides a summary check list for review of items concerning elucidation of structure, impurities, control of drug substance, primary packaging, and stability.

## Conclusion

Pharmaceutical drug substance due diligence is a detailed investigation of the Chemistry, Manufacturing, and Controls (CMC) information associated with a drug substance and serves to assure that an adequate level of quality exists for the given compound to allow for successful commercialization of the drug. A scientific review of the pertinent development data provides the necessary information to assure that informed decisions are made regarding the in-licensing of a development compound.

## References

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality - M4Q, Quality Overall Summary of Module 2, Module 3: Quality, *Step 4* of the ICH Process, 9 November 2000.
2. Lim, Chang-Kee, and Lord, Gwyn, "Current Developments in LC-MS for Pharmaceutical Analysis," *Biological and Pharmaceutical Bulletin*, Vol. 25, No. 5, 2002, pp. 547-557.
3. Food and Drug Administration, Department of Health and Human Services, Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances, Center for Drug Evaluation and Research, February 1987.
4. Reddy, K.V.S.R. Krishna et al., "Isolation and Characterization of Process-Related Impurities in Linezolid," *Journal of Pharmaceutical and Biomedical Analysis*, Vol. 30, 2002, pp. 635-642.
5. Streng, W. H., "Physical Chemical Characterization of Drug Substances," *Drug Discovery Today*, Vol. 2, No. 10, 1997, pp. 415-426.
6. Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Guidance for Industry for the Submission of Chemistry, Manufacturing, and Controls Information for Synthetic Peptide Substances, November 1994.
7. Bastin, R.J., Bowker, M.J., and Slater, B.J., "Salt Selection and Optimisation Procedures for Pharmaceutical New Chemical Entities," *Organic Process Research & Development*, Vol. 4, 2000, pp. 427-435.
8. International Conference on Harmonisation of Technical Requirements For Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Q3A(R), Impurities in New Drug Substances, *Step 4* of the ICH Process, 7 February 2002.
9. McCrossen, S.D. et al., "Comparison of LC detection methods in the Investigation of non-UV Detectable Organic Impurities in a Drug Substance," *Journal of Pharmaceutical and Biomedical Analysis*, Vol. 17, 1998, pp. 455-471.
10. Hilhorst, M. J., Somsen, G.W., and de Jong, G.J., "Capillary Electrokinetic Separation Techniques for Profiling of Drugs and Related Products," *Electrophoresis*, Vol. 22, 2001, pp. 2542-2564.
11. Sallam, E. and Orr, N., "Studies Relating to the Content Uniformity of Ethinylloestradiol Tablets 10 µg: Effect of Particle Size of Ethinylloestradiol," *Drug Development and Industrial Pharmacy*, Vol. 12, No. 11-13, 1986, pp. 2015-2042.
12. Carr, R.L., "Particle Behavior, Storage and Flow," *British Chemical Engineering*, Vol. 15, No. 12, 1970, pp.1541-1549.
13. Stephenson, G.A., Forbes, R.A., and Reutzel-Edens, S.M., "Characterization of the Solid State: Quantitative Issues," *Advanced Drug Delivery Reviews*, Vol. 48, 2001, pp. 67-90.
14. Otsuka, M., Ofusa, T., and Matsuda, Y., "Physicochemical Characterization of Glybuzole Polymorphs and Their Pharmaceutical Properties," *Drug Development and Industrial Pharmacy*, Vol. 25, No. 2, 1999, pp. 197-203.
15. Bartolomei, M. et al., "Physico-Chemical Characterisation of the Modifications of I and II of (R,S) Propranolol Hydrochloride: Solubility and Dissolution Studies," *Journal of Pharmaceutical and Biomedical Analysis*, Vol. 21, 1999, pp. 299-309.
16. Jahansouz, H. et al., "Investigation of the Polymorphism of the Angiotensin II Antagonist Agent MK-996," *Pharmaceutical Development and Technology*, Vol. 4, No. 2, 1999, pp. 181-187.
17. Matsuda, Y. et al., "Pharmaceutical Evaluation of Carbamazepine Modifications: Comparative Study for Photostability of Carbamazepine Polymorphs using Fourier-transformed Reflection-Absorption Infrared Spectroscopy and Colorimetric Measurement," *Journal of Pharmacy and Pharmacology*, Vol. 46, 1994, pp. 162-167.

18. Burger, A. and Koller, K.T., "Polymorphism without IR and Raman-spectroscopic Differences: Tiaprofenic Acid, Three Modifications," *Pharmazie*, Vol. 54, No. 5, 1999, pp. 365-368.
19. Smith, J. et al., "Application of Two-Dimensional <sup>13</sup>C Solid-State NMR to the Study of Conformational Polymorphism," *Journal of the American Chemical Society*, Vol. 120, 1998, pp. 11710-11713.
20. Haleblan, J. and McCrone, W., "Pharmaceutical Applications of Polymorphism," *Journal of Pharmaceutical Sciences*, Vol. 58, No. 8, 1969, pp. 911-929.
21. Brittain, H.G. et al., "Physical Characterization of Pharmaceutical Solids," *Pharmaceutical Research*, Vol. 8, No. 8, 1991, pp. 963-973.
22. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Q6A, Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances, Step 4 of the ICH Process, 6 October 1999.
23. Kushida, I. and Ashizawa, K., "Solid State Characterization of E2101, A Novel Antispastic Drug," *Journal of Pharmaceutical Sciences*, Vol. 91, No. 10, 2002, pp. 2193-2202.
24. Tiwary, A.K. and Panpalia, G.M., "Influence of Crystal Habit on Trimethoprim Suspension Formulation," *Pharmaceutical Research*, Vol. 16, No. 2, 1999, pp. 261-265.
25. de Villiers, M.M. et al., "Correlation Between Physico-Chemical Properties and Cohesive Behavior of Furosemide Crystal Modifications," *Drug Development and Industrial Pharmacy*, Vol. 21, No. 17, 1995, pp. 1975-1988.
26. Carlton, R. A. et al., "Preparation and Characterization of Polymorphs for an LTD4 Antagonist, RG12525," *Journal of Pharmaceutical Sciences*, Vol. 85, No. 5, 1996, pp. 461-467.
27. Byrn, S.R., et al., "Solid-State Pharmaceutical Chemistry," *Chemistry of Materials*, Vol. 6, 1994, pp. 1148-1158.
28. American Conference of Governmental Industrial Hygienists, Guide to Occupational Exposure Values, Publication #0380, Cincinnati, OH: ACGIH Signature Publications, 2002.
29. Mura, P. et al., "Investigation of the Effects of Grinding and Co-grinding on Physicochemical Properties of Glisentide," *Journal of Pharmaceutical and Biomedical Analysis*, Vol. 30, 2002, pp. 227-237.
30. Committee for Proprietary Medicinal Products (CPMP), Committee for Veterinary Medicinal Products (CVMP), Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products, 31 May 2001.
31. Zdrojewski, T. and Jonczyk, A., "Application of <sup>13</sup>C NMR Spectroscopy and <sup>13</sup>C-Labeled Benzylammonium Salts to the Study of Rearrangements of Ammonium Benzylides," *Journal of Organic Chemistry*, Vol. 63, 1998, pp. 452-457.
32. International Conference on Harmonisation of Technical Requirements For Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Q2B, Validation of Analytical Procedures: Methodology, Step 4 of the ICH Process, 6 November 1996.
33. DiFeo, T. J. and Shuster, J. S., "Mixed-mode Gradient HPLC Analysis of a Tyrosine Kinase Inhibitor, its Isomers and Other Potential Impurities," *Journal of Liquid Chromatography*, Vol. 16, No. 18, 1993, pp. 3903-17.
34. Shah, R.D. and Nafie, L. A., "Spectroscopic Methods for Determining Enantiomeric Purity and Absolute Configuration in Chiral Pharmaceutical Molecules," *Current Opinion in Drug Discovery and Development*, Vol. 4, No. 6, 2001, pp. 764-775.
35. Haginaka, J., "Pharmaceutical and Biomedical Applications of Enantioseparations using Liquid Chromatographic Techniques," *Journal of Pharmaceutical and Biomedical Analysis*, Vol. 27, 2002, pp. 357-372.
36. McWilliams, M. L., Chen, G-D., and Fechter, L.D., "Characterization of the Ototoxicity of Difluoromethylornithine and its Enantiomers," *Toxicological Sciences*, Vol. 56, No.1, 2000, pp. 124-132.
37. Mayer, J.M. and Testa, B., "Pharmacodynamics, Pharmacokinetics and Toxicity of Ibuprofen Enantiomers," *Drugs of the Future*, Vol. 22, No. 12, 1997, pp. 1347-1366.
38. Brittain, H.G., "Applications of Chiroptical Spectroscopy for the Characterization of Pharmaceutical Compounds," *Journal of Pharmaceutical and Biomedical Analysis*, Vol. 17, 1998, pp. 933-940.
39. Anderson, N., (ed), Practical Process Research and Development, San Diego, CA: Academic Press, 2000.
40. Committee for Proprietary Medicinal Products (CPMP), Note for Guidance on Specification Limits for Residues of Metal Catalysts, London, 27 June 2002.
41. International Conference on Harmonisation of Technical Requirements For Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Q7A, Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients, Step 4 of the ICH Process, 10 November 2000.
42. Committee for Proprietary Medicinal Products (CPMP), Committee for Veterinary Medicinal Products (CVMP), Note for Guidance on Process Validation, London, 1 March 2001.
43. Center for Food and Drug Evaluation, Center for Biologics Evaluation and Research and Center for Devices and Radiological Health, Guideline on General Principles of Process Validation, May, 1987.


44. International Conference on Harmonisation of Technical Requirements For Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Q3A(R), Impurities in New Drug Substances, Step 4 of the ICH Process, 7 February 2002.
45. Lee, R., "Identification and Determination of Impurities in Drugs," *Progress in Pharmaceutical and Biomedical Analysis*, Vol. 4, 2000, pp. 23-37.
46. International Conference on Harmonisation of Technical Requirements For Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Q3C, Impurities Guideline for Residual Solvents, Step 4 of the ICH Process, 17 July 1997.
47. International Conference on Harmonisation of Technical Requirements For Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Q6A, Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances, Step 4 of the ICH Process, 6 October 1999.
48. Laasonen, M. et al. "Near infrared Reflectance Spectroscopy for the Fast Identification of PVC-based Films," *The Analyst*, Vol. 126, 2001, pp. 1122-1128.

## About the Author



**Thomas J. DiFeo, PhD**, is the Global Director of the ChemPharm CMC Sciences and Dossier Management Department at Johnson & Johnson Pharmaceutical Research and Development in Spring House, Pennsylvania and Beerse, Belgium. He received his BS in chemistry from Saint Joseph's University in Philadelphia, PA and his MS and PhD in

physical chemistry from Drexel University, Philadelphia, PA in 1990. Prior to his current position at Johnson & Johnson, Dr. DiFeo was a senior regulatory scientist and cGMP compliance manager at Merck & Co. He has held positions at Park-Davis Pharmaceutical as a stability lab section manager and at Rhone-Poulenc Rorer as an associate research fellow in the Analytical and Physical Chemistry Department. Dr. DiFeo was elected to USP Pharmaceutical Analysis Expert Committee by USP Council of Experts 2000-2005, and is a scientific reviewer for the Drug Development and Industrial Pharmacy Journal. He can be contacted by e-mail: [tdifeo@prdus.jnj.com](mailto:tdifeo@prdus.jnj.com).

Johnson & Johnson Pharmaceutical Research and Development, E2020 Welsh & McKean Roads, Spring House, PA 18944. 



- In August 1980, a group of six men met at American Airlines' Admiral Club at La Guardia airport to discuss the formation of an engineering society whose primary purpose would be focused on:

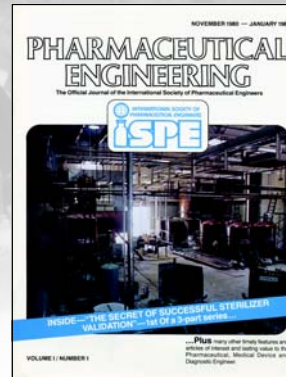
- Education
- Networking
- Exchange of information

- The conception of the Society continued to unfold as validation became more and more of a reality with an expanded need for consistency within the industry.
- Formation of the Society was complete when the name "International Society of Pharmaceutical Engineers" was decided upon.
- There were three staff members when ISPE began: Diane Simmons, Executive Director/Editor; C. David Boyer, Managing Editor; and Cheryl A. Conroy, Administrative Assistant.
- The first issue of *Pharmaceutical Engineering* (November 1980 - January 1981) was published. This quarterly publication was known as the "Official Journal of ISPE".

1980



*The Early Years...*



- The 1980 Board of Directors included:
  - Charles W. Newcomb – President
  - Paul Simmons – Executive Vice President
  - James O'Brien – Vice President
  - Peter A. Merrett – Treasurer
  - Thomas P. Henry – Secretary
- ISPE's relationship with the FDA began in 1981 when the Society asked the FDA to speak at a seminar.
- The first official seminar took place in February 1981 at the Tampa Host Hotel and was attended by 106 people. The panel of speakers included representatives from the US Food and Drug Administration as well as professionals in the industry. The topic of the seminar was "Upgrading to Meet cGMPs."
- In the first year, membership grew to 430.
- The first Annual Membership Meeting and Awards Banquet was held on 11 November 1981 in the Warwick Hotel, Philadelphia, Pennsylvania and was attended by more guests than paying attendees. The Meeting was held in conjunction with PACK INFO '81, 11-12 November at the Philadelphia Civic Center presented by the Packaging Machinery Manufacturers Institute (PPMI).

1980-1981



The first Annual Meeting, November 1981.

*FDA relationship...*



- Ron Hall became Executive Director in 1982.
- *Pharmaceutical Engineering* began to publish bi-monthly with the July/August 1982 issue.
- Bob Best became ISPE's Executive Director in 1985.
- ISPE began to publish a newsletter for members only.
- ISPE Expo was held for the first time in Philadelphia in June 1985.
- In 1985, the first North American Chapter was formed in New Jersey.
- ISPE sponsored its first International Pharmaceutical Engineering Forum during the 1986 Annual Meeting held 16-19 November in St. Petersburg Beach, Florida.
- Membership grew to 1,000 in 1986.
- ISPE's first European venture, the International Congress of Pharmaceutical Engineering, took place on 26-28 September 1989 at the Scandic Crown Regency Hotel in Brussels.
- The first two affiliates were formed in 1989-1990 in the UK and Ireland.

1982-1989



Bob Best



ISPE Annual Meeting in 1987.



**NEW JERSEY CHAPTER ISPE**



*First European venture...*

- In 1990 the Society name was changed slightly from "International Society of Pharmaceutical Engineers" to "International Society for Pharmaceutical Engineering."
- Staff is up to nine employees.
- ISPEAK was unanimously chosen by the ISPE Editorial Committee as the official name of the ISPE newsletter in March 1990. The name was chosen as a result of a "Name the Newsletter" competition won by Thomas J. Novitsky of Associates of Cape Cod.
- The New Jersey Institute of Technology became ISPE's first official Student Chapter at a dinner meeting held on 24 February 1991.
- ISPE opens European office in the Hague, Netherlands in 1992 and adds six more employees to the total.
- In 1992, volunteer leaders from North America and Europe wrote the first strategic plan and mission statement for the Society.
- In February 1993, ISPE implements strategic objectives by establishing North American and European Operating Committees.

1990-1993



*NJIT Students...*



The Hague, The Netherlands.

*ispeak*  
*ispeak europe*

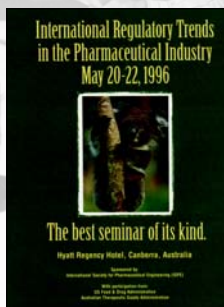


- The Germany/Switzerland Affiliate was ISPE's first multi-national affiliate and organized its first programs in 1993. Unlike other ISPE affiliates, this group is organized not nationally, but regionally, holding meetings in southwestern Germany and northern Switzerland.

1993-1996



- ISPE membership reached 5,000 in 1993.
- In 1994, industry leaders developed industry-wide guidance for suppliers to assist in the management and development of computer systems. The result was the GAMP Guide which is now in its fourth edition. More than 10,000 copies have been distributed globally in four different languages.
- The Career Center was begun in 1995.
- At the 1995 Annual Meeting, ISPE introduced the Pharmaceutical Engineering Baseline® Guide Series with the draft of Volume 1, Bulk Pharmaceutical Chemical Facilities.
- ISPE held its first event in Australia on 20-22 May, 1996 at the Hyatt Regency Hotel in Canberra. The program was titled "International Regulatory Trends in the Pharmaceutical Industry."



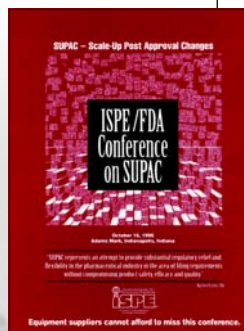
Career Center at the Annual Meeting.



*5,000 members...*

- During the ISPE Pharmaceutical Advisory Council (PAC) meeting 4 June 1996 in Valley Forge, a presentation was made by the FDA's Matthew Lewis, District Director, and Joseph Phillips, Deputy Regional Food and Drug Director, proposing another partnership effort between ISPE and FDA. In this project, ISPE committed to develop the list of equipment, by functionality categories, to specify similar equipment as referenced by the new Scale-Up and Post-Approval Changes (SUPAC) regulations. **SUPAC is one of the most significant regulatory changes ever to benefit the industry.** SUPAC gives guidance to aid the industry on how to file and significantly reduces the filing burden in many circumstances. Some changes that once needed an approved supplement might now properly be submitted as a change being effected or in the next annual report under SUPAC terms. Determining similar equipment was the task that the FDA asked ISPE to undertake.
- In response to member demands, ISPE created its Web site, [www.ispe.org](http://www.ispe.org), which was effective as of 1 November 1996.

1996



*World Wide Web...*



- ISPE re-designed the logo to better show the Society as "international."
- As reported in the January/February 1997 issue of *Pharmaceutical Engineering*, ISPE signed an agreement with Reed Exhibition Companies as official sponsor of INTERPHEX events. Said ISPE's President Larry Kranking at the time of the partnership: "INTERPHEX has long been the trade show of choice for most ISPE members."
- As reported in the July 1997 issue of *ISPEAK*, Sharon Smith Holston, Deputy Commissioner for External Affairs, FDA, presented the FDA Commissioner's Special Citation "in appreciation of outstanding cooperation with the Food and Drug Administration in providing vital support to the industry through educational and special projects, nationally and internationally." Bob Best accepted the award on behalf of ISPE and received the Harvey W. Wiley Medal, the father of the Pure Food and Drug Law.

1997



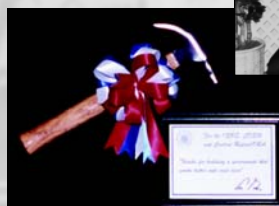
Trade show sponsor...



Bob Best, Sharon Smith Holston, and Jim Murphy.

- At the 1997 Annual Meeting, ISPE was honored with Vice President Al Gore's Hammer Award that was presented to the ISPE-FDA team that developed a list of "similar equipment" needed for efficient implementation of Scale-Up and Post-Approval Changes (SUPAC) guidance for products in immediate release – solid dosage form.
- On Friday, 21 November 1997, ISPE was honored by the Center for Drug Evaluation and Research (CDER) with a special Recognition Award.
- ISPE membership reached 10,000 members in 1997.
- On 7 October 1998 ISPE held its first official activity in South America (Brazil) in conjunction with the launch of Reed Exhibition Companies' INTERPHEX South America trade show. The event was attended by more than 100 industry professionals.
- In 1999, the ISPE European Office in The Hague closed and ISPE established a relationship with an association management company (GIC) and opened an office in Brussels, Belgium which is operating today.
- ISPE sponsored first INTERPHEX Japan in 1999.

1997-  
1999



10,000 members...



ISPE European office today.

- First global edition of ISPEAK was published in July/August 1999.

1999-  
2002

- ISPE staff reaches 31 employees in 2000.
- ISPE acquired the GMP Institute effective 1 January 2000 and began ISPE's training division.
- The first educational conference in Singapore took place 12-13 June 2000 at Pan Pacific Hotel in conjunction with Reed Singapore. This was the first educational conference in Asia.
- In June 2000, the ISPE Singapore Affiliate was officially launched and was the first Affiliate in Asia.
- The U.S. Department of Commerce chose ISPE to offer a four-week intensive training program jointly led by the GMP Institute, consultant Dale McMillen, and the American Association for the Advancement of Science (AAS) from 14 January to 8 February 2002. The course provided basic knowledge and training on current Good Manufacturing Practices (GMPs) to enable former bio-chemical scientists from the Novosibirsk region of Russia to adapt from their current manufacturing standards to internationally acceptable manufacturing practices.



Jim Wulfeck and Bob Best.



*Still growing...*



- The inaugural event of the Japan Affiliate was held in June 2002 at the Edogawa Ward Civic Center in Tokyo and attended by 350 industry representatives.
- *Pharmaceutical Engineering* introduced a new feature, Country Profile, highlighting the pharmaceutical industry in countries where an international ISPE affiliate exists; this feature has been expanded in 2005 to include North America.
- In 2003, the ISPE International Board of Directors approved the new emerging economy membership category.
- The India Affiliate held its inaugural on 15-16 April 2004.
- Thailand is ISPE's newest Affiliate and had its inaugural event on 8 January 2004. A conference took place in April 2004.
- ISPE reached 20,000 members in 2004.

2003-  
2004



*More to come...*

Currently, the FDA has invited ISPE to play a leading role in its transition to changing the way it has regulated the industry for decades and in the incentives being offered to companies to innovate.



India Affiliate inaugural event.

Specifically, the FDA is asking ISPE to change its current operating procedure in several ways:

1. publish a new science-based, peer-reviewed journal
2. in collaboration with universities and the FDA, develop a training program to be utilized by both Industry and Regulators
3. establish a Certification program that sets a standard for Pharmaceutical Manufacturing Science and Technology competency
4. work through ASTM to establish standards that must be referenced by the FDA

Other new initiatives in 2005 include the Facility of the Year Award, the formation of ISPE Communities of Practice, and the culmination of ISPE's 25<sup>th</sup> anniversary celebration taking place at the 2005 Annual Meeting in November.

2004-  
2005



ISPE today includes:

- 49 staff at ISPE Headquarters in Tampa, Florida
- Seven staff in the ISPE European Office, Brussels, Belgium
- Ten advisors located around the world
- 21,530 international members
- 24 regional chapters
- 18 international Affiliates
- 38 student chapters, with 13 more in the process of forming

**Come celebrate ISPE's 25th Anniversary at the 2005 Annual Meeting!!!**

## SAVE THE DATE!



25th Anniversary  
**INNOVATE**  
1980 - 2005  
**CELEBRATE**

**ISPE ANNUAL MEETING**

6-10 NOVEMBER 2005 ■ SCOTTSDALE, ARIZONA ■ USA ■ [www.ispe.org](http://www.ispe.org)