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Mitigate Risk, Facilitate Project Delivery, Integrate Sustainability, and Improve Maintainability for Advanced Technology Facilities

by Allan Chasey, PhD, PE

This article presents a project management vision that uses the reduction of risk, value-added sustainability, and improved operations and maintenance to minimize conflicts, waste, and costs.

Introduction

Building Information Modeling (BIM) is a process gaining traction within the Architect, Engineer, and Construction (AEC) industry as a method to improve the project delivery process. The fundamental characteristic of BIM is the development of critical information through a feedback loop that can continue throughout a facility's lifecycle. BIM combines the ability to develop a virtual model of a facility, beginning with design (space planning), then move to construction execution (cost, scheduling, interference detection), and finally, operations and maintenance (asset management). Even though the technology for implementation of BIM will change, and probably change rapidly, the process and underlying concepts will likely change very little. BIM allows a project team to visualize, understand, communicate, and collaborate as seen in Figure 1[1]: visualizing to "see" the project, understanding to know the project elements, communicating to ensure that understanding, and finally collaborating to provide the necessary input at the proper time. These benefits of collaboration also can be the greatest challenge. BIM requires openness among the team players to share information that will support the project goals.

Although many of the benefits of BIM are viewed as direct benefits, perhaps the greatest benefits are actually indirect. Direct benefits include such items as improved visualization and the centralization of project and building information. The indirect benefits include the necessity of collaboration, resulting in better project understanding and reducing project risk. Risk reduction comes through improved understanding and coordination in the management of a project by decreasing construction conflicts, eliminating construction waste, and ultimately reducing project cost.

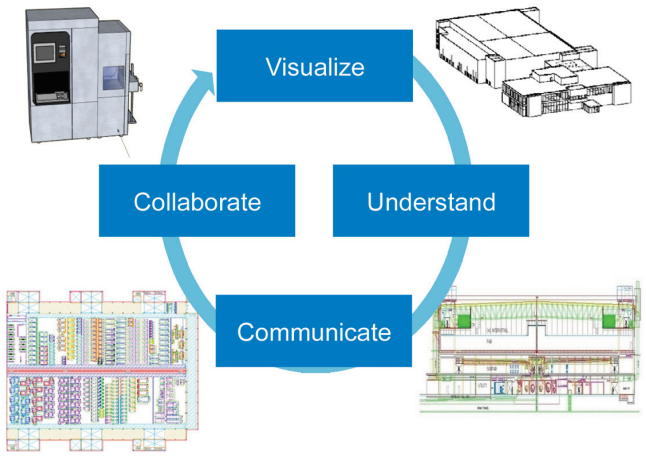


Figure 1. The process of building information modeling.

Project Risk

Most owners want their projects to be delivered on time, on budget, and without injury. Project risk comes in many forms:

- Financial – project costs too much due to scope uncertainties or complex technical issues affecting business profitability, competitiveness, and/or internal rate of return.
- Schedule – project delivered too late to meet a market window, which could put pressure on the project team for acceleration, affecting quality, safety, performance, market share, and/or cost.
- Quality – poor overall project quality due to materials, installation, or project acceleration affecting performance, functionality, and/or reliability.
- Safety – construction hazards due to installation requirements affecting insurance premiums, regulatory compliance, cost, and/or reputation.
- Technical – project complexity due to the manufacturing process requirements, hazardous materials, or multiple systems that require coordination for installation and operation affecting process performance, reliability, and/or maintainability.
- Environmental – regulatory compliance for emissions, hazardous waste, or product safety affecting the business profitability, product safety, or market share.
- Teamwork and organizational – the people side of project, teams working together that might not have worked together or do not understand the complexity of the project.

As shown in Figure 2, the cost of errors made during the design phase due to project complexity, time pressure, or environmental requirements increase dramatically the further the project progress in the stages of the project. Errors and omissions emanating from paper based methods cause field conflicts that are expensive and time consuming to correct and result in loss of productivity. The earlier any errors can be detected, the lower the cost to correct. If this can be done during the design phase, in coordination with the project team, the reduction in risk is evident as the facility can be built with few, potentially no changes or Requests For Information (RFI), unless there is a change requested by the owner due to changes in process or product.

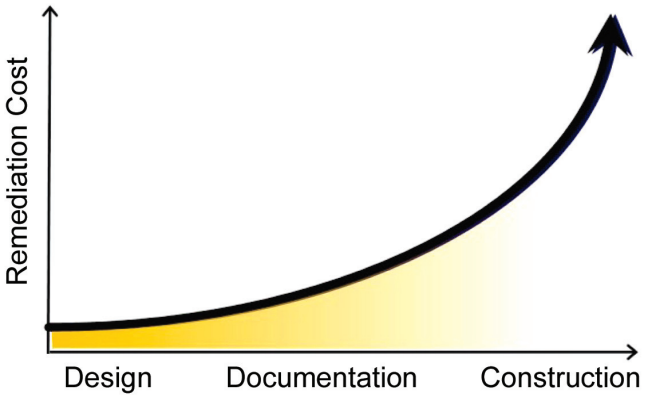


Figure 2. Cost of design errors.

Understanding Building Information Modeling

Building Information Modeling (BIM) is a valuable tool that can continue throughout a facility's lifecycle, including conceptual, schematic, design, construction, turnover, operation, even demolition at end of life. As a facility model

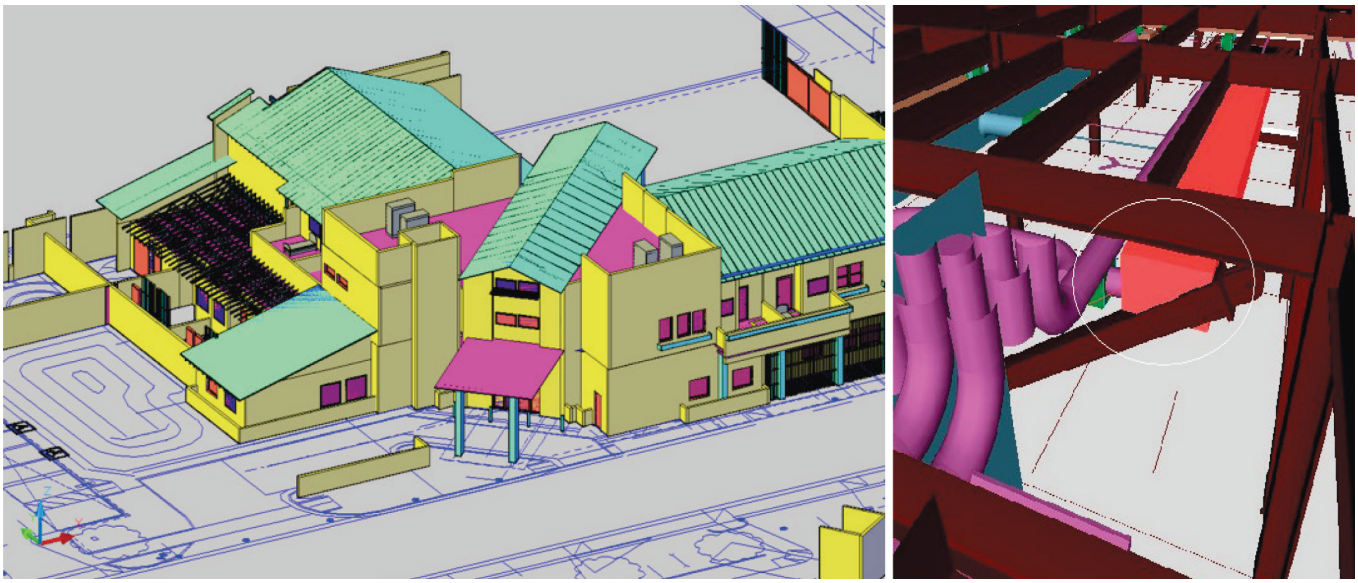


Figure 3. 3D modeling and clash detection.

Figure 4. Prefabricated piping sections.

progress through the development cycle, additional BIM uses and processes can be defined. The use of the BIM is different for the different players involved in the process. The owner's ultimate goal is to be able to extract detailed information that can help enhance systems and reduce operational costs. Designers are developing models that contain the information necessary for coordinating and constructing the buildings. The product manufactures assembled their projects in model format to position themselves in the marketplace and make them more attractive for designers to specify into their projects. The software vendors are adding more and more technical building data into their programs so design professionals will utilize their programs. And finally, the trade organizations are defining standards and guidelines that can easily be incorporated into the software as well as adopted as the norm within the industry. All of the BIM stakeholders essentially require the exchange of accurate and efficient information for each of their processes to ensure interoperability.

Most construction is still accomplished utilizing conventional two-dimensional (2D) drawings. When the third dimension (3D) is added, a virtual facility can be modeled promoting visualization and understanding of the facility/project composition. Adding the dimension of time, the fourth dimension (4D), a sequence of installation activities can be determined allowing visualization of a proposed construction schedule. Building the facility on "paper" before commitments are made in the field promotes effective construction sequencing. As shown in Figure 3, investigating interferences ("clash" detection) between systems and structure reduces the possibility of changes occurring in the field, reducing project risk for all parties involved.

As the models increase in detail, quantity take-offs become more accurate due to the dimensional correctness of a virtual model. Estimating (often referred to as 5D) can then be accomplished with greater accuracy in less time. It should be noted that quantities can be extracted from the model, but productivity measures (labor hours, equipment, etc.) must still be determined based on a company's processes. Due to the dimensional accuracy of the models, many piping spools can be prefabricated, as shown in Figure 4, in a more controlled environment, increasing the quality of the installed elements, while reducing the cost and increasing the speed of construction.

Additionally, a facility model also can be used to investigate sustainability and/or resource conservation ideas, such as shading, acoustics, daylighting, and energy usage with less risk during the preconstruction phase, resulting in additional savings, more than just energy. The impact of different types of materials can be modeled, estimated, and the impact on construction can be determined before construction begins. Different "what if" construction schedules can be investigated to find the most productive and efficient

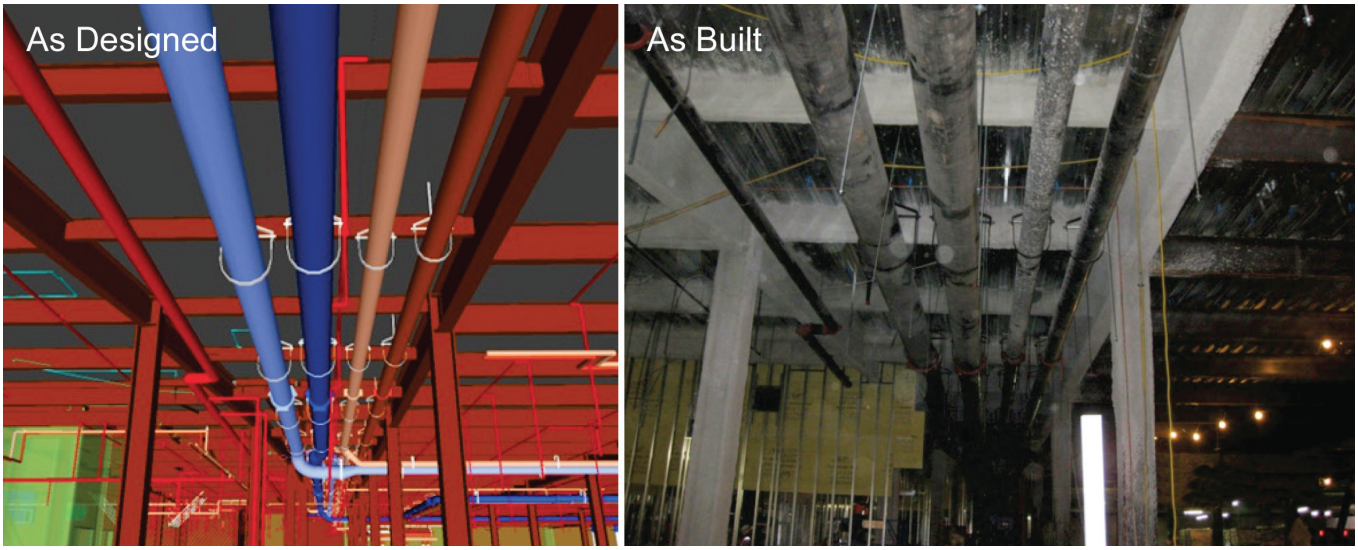


Figure 5. Quality control using BIM.

schedule. The model can be used for quality control (see Figure 5) to ensure that the installation is done according to the agreed upon model.

Parametric design, the basis for BIM, involves the definition of a facility as a set of objects, a virtual representation consisting of 3D objects with embedded information about that component or object.

The BIM also can be used during the commissioning process making a virtual model the basis for operations and maintenance information to track installed equipment, maintenance schedules, and operating information. With all the information regarding the equipment attached to the model, operations and maintenance information is readily available to operators and technicians so equipment can be operated the most efficiently, reducing operating costs and improving reliability. The National Institute for Standards and Technology (NIST) study of the additional cost incurred by building owners as a result of inadequate interoperability indicates that insufficient interoperability accounts for an increase in construction costs by $6.12 per SF for new construction and an increase in $0.23 per SF for Operations and Maintenance (O&M), resulting in a total added cost of $15.8 billion.[2] The study involved both the exchange and management of information, in which individual systems were unable to access and use the information imported from other systems. It was determined that additional costs associated with redundant computer systems, inefficient business process management, manual reentry of data, inefficient Request For Information (RFI) management can be attributed to insufficient interoperability and resulted in increased project costs. It was estimated that 68% of these additional expenses ($10.6 billion) were incurred by building owners and operators.[2]

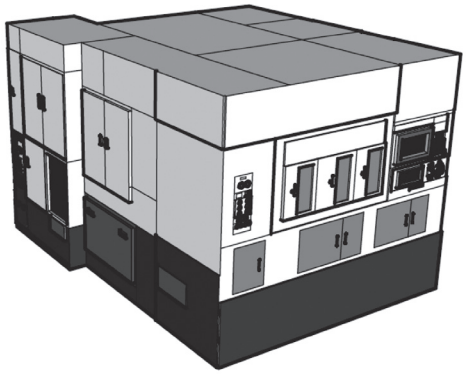
The final step is a virtual as-built model, which can be the basis for an intelligent facility model allowing integration of facility operations with manufacturing operations. The incorporation of an intelligent facility model can then provide decision support tools that will impact lifecycle cost and increase manufacturing effectiveness, provide real time O&M information exchange, automate critical performance factors, simulate factory performance, and develop predictive maintenance/performance models.

Intelligent Facility and Tool Models

Parametric design, the basis for BIM, involves the definition of a facility as a set of objects, a virtual representation consisting of 3D objects with embedded information about that component or object. These objects, due to their fixed geometries and parameters, can be defined once and used for multiple purposes throughout the facility's lifecycle. As a design is developed, embedded information becomes more specific depending on the project needs. The challenge is to develop an easy-to-use and consistent means of defining objects and instances appropriate for current and later use.

The 2D and 3D geometric representations of physical objects, such as doors, windows, and/or higher level assemblies such as walls, roofs, and floors are Building Element Models (BEMs). For process equipment, the information embedded in BEMs can create a tool model library that would become a strategic asset for an owner, representing the knowledge available about a tool or tool set. The risk of errors regarding tool installation for example, would decrease as higher quality models are developed and utilized as intelligent tool models.

For example, within the semiconductor industry, the diversity and complexity of process equipment creates difficult challenges for facilities design, and equipment installation. To help facilitate the necessary exchange of information,



Data Sheet Number	Data Sheet Title
100	Equipment Identification
200	Environmental Conditions
300	Physical Characteristics
400	Electrical Power
500	Water
600	Bulk Chemicals
700	Drains
800	Gases
900	Vacuum
1000	Exhaust

Figure 6. Building element model – intelligent tool model.

SEMI E6, Guide for Semiconductor Equipment Installation Documentation,[3] benefits equipment suppliers and semiconductor manufacturers by communicating information necessary to install process equipment. As seen in Figure 6, support utilities, such as power, water, and/or gases and chemicals, as well as the tool's physical characteristics (weight, height, length) can be provided in a standardized format. The tool model with embedded information with the Points Of Connections (POC) located on the tool model can greatly improve the communication of necessary data for tool accommodation and hook-up.

However, the SEMI E6 Guide only applies to the facility interface with the semiconductor equipment. Another SEMI Guide, SEMI E51, Guide to Typical Facilities Services and Termination Matrix, was conceived to provide the equipment supplier with an understanding of the "typical" support facilities available at the tool POCs, giving the tool manufacturer a much better basis for tool design. The objective of SEMI E51 is to help provide timely and cost-effective tool installation with minimum impact on existing customer facilities, systems, and services, and to ensure that the quality of infrastructure supplied (e.g., water, gases, chemicals, power) is not compromised once connected to the tool.[4] When typical facility services are considered by tool manufacturers during tool design, additional cost and lead times associated with customizing each tool installation could be minimized resulting in reduced costs to build and install semiconductor equipment.

SEMI E51 is not intended to be site-specific, but rather to identify utilities, performance, and connections available at a "typical" semiconductor facility, giving the tool manufacturers a range of operating conditions (see Figure 7). Site specific data can be provided to the tool manufacturer during the procurement process to ensure that the equipment purchased will operate within specific facility parameters or note areas where the facility infrastructure may not support a specific tool. Each tool would then be supplied in a "facility ready" state to work within the parameters of a specific facility. A site specific facilities service and termination matrix can become the basis for an intelligent facility model, which is linked to the tool matrix data to support the process layout during the concept and programming stage.

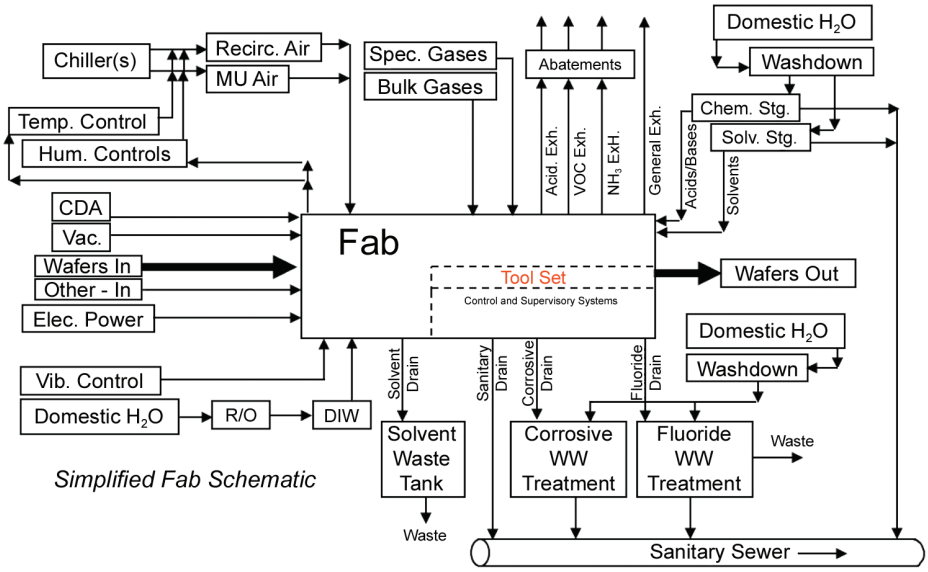
The reference to the site specific facilities services (E51 data) provides a basis for understanding that can be established to resolve installation issues prior to tool arrival. Additional facility requirements not identified by site specific information can be reviewed before a tool is purchased. Utilizing an electronic form of data collection and storage provides a basis for integration into a BIM that can be used during the facility lifecycle.

Intersection of Facility and Process Tool Data

Utilizing the standard terminology established by these guideline documents provide a basis for developing the methodology for data transfer between the tool manufacturers, the owner, the design and construction community, and various suppliers. Figure 8 illustrates the intersection of the two databases and how they can be integrated into a building information model.

Intersection Diagram

The site specific document generally refers to the "base build" portion of the main facility structure. Base build typically includes the buildings (manufacturing space, central utility building and all other support buildings such as offices, warehouse, restrooms etc.), the architectural, electrical, mechanical, HVAC and process systems, systems piping



Service Category Number	Service Category Description
100	Facility Characteristics
400	Electrical Power
500	Water
600	Bulk Chemicals
700	Drains
800	Gases
900	Vacuum
1000	Exhaust

Figure 7. Facility data for site specific services.

and ductwork for utility mains.

The process equipment document refers to the tool and the configurations needed for hookup to the facility systems. Hook-up is the final connections made from the utility systems to the process equipment as well as the interconnections made during tool installation.

Figure 8 provides a schematic of how the facility and tool guidelines intersect and how the terminology from the two documents can be used within the BIM. The clouded portions illustrate how tool data relates to facility data.

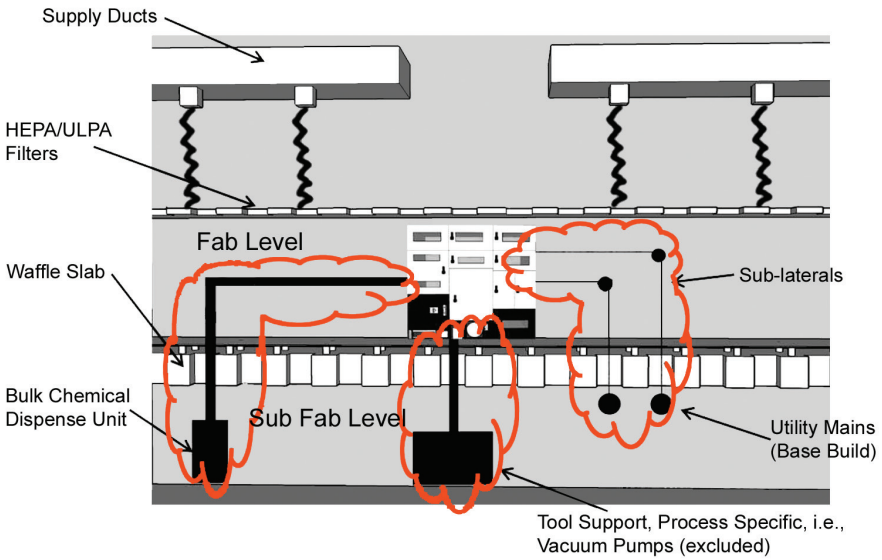


Figure 8. Intersection of tool and facility.

Conclusion

The future of BIM in the capital projects industry is the development and use of an automated project and facility management environment that is fully integrated from programming, through design and construction, through operations and maintenance, ultimately through the end of the buildings life. Data-rich 3D models, whether the data is physical (dimensions, location) or parametric (distinguishing one object from another similar object), whether it is in BIM, single building modeling, parametric modeling, or any other type of computer modeling, must be used in an intelligent fashion. The activities conducted throughout the lifecycle of any facility generates an enormous quantity of data that needs to be stored, retrieved, communicated, and usable by all parties involved. Advances in technology have increased the opportunities for gathering, providing access to, exchanging, and achieving all of this information for future reference. Continuing advances in smart building technologies, BIM technologies and construction practices have not only increased the amount and detail of data generated and exchanged, but also have further raised expectations about its use and value as an asset. The AEC industry has begun to realize that a greater degree of harmonization in classifying information is now necessary and possible. This harmonization and reuse of information for multiple purposes is at the heart of value and cost savings presented by building information modeling.

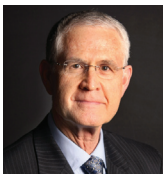
BIM is a significant improvement in the way architects, engineers, and contractors have traditionally worked. BIM allows visualization of a building design along with implementation of methodologies to add scheduling and estimating data to each building element determine conflicts and develop "clash" free installations. As BIM becomes more standard, building products (intelligent tool models) will be inserted directly into a model in electronic form, including hyperlinked references for parts lists, operating and maintenance manuals, and vendor/supplier information. As intelligent models evolve, more sophisticated, even intelligent product specifications will be able to provide information for such tasks as structural analysis, LEED compliance, or installation and operating requirements. Intelligent tool models will become the core information source for construction installation methods, quantities of material, fabrication and ultimately, resource utilization during operation.

Productivity increases for the construction industry will be needed to ensure that capital projects are continued to be provided in a cost effective manner, meeting the needs of owners. Building Information Modeling (BIM) is proving to be such a technology that will have an impact on the delivery process of the architectural, engineering, and construction community. The BIM model is a shared resource that can be used in many different ways and some of those possibilities have not yet been realized. The goals of a better, faster, and more cost effective construction can be achieved, reducing risk, making building information modeling a key tool for the future of project delivery.

References

1. Kymmell, William, *Building Information Modeling: Planning and Managing Construction and Projects with 4D CAD and Simulation,* McGraw Hill, 2008.
2. NIST, *Cost Analysis of Inadequate Interoperability in the U.S. Capital Facilities Industry,* August 2004.
3. SEMI Draft Document 3287 (2002), revision to E6, Guide for Semiconductor Equipment Installation Documentation, August, 2002, Semiconductor Equipment and Materials International, San Jose, CA.
4. SEMI E51 (2000), Guide for Typical Facilities Services and Termination Matrix, Semiconductor Equipment and Materials International, San Jose, CA.

About the Author



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Advances in Vapor Compression Technology for the Production of USP Purified Water and Water For Injection

by George V. Gsell, Chet Nunez, and Michael Smith-Palmer

This article presents the advancements in vapor compression technology and how these advancements affect the efficiency and reliability of the equipment.

Introduction

There are various methods used to produce highly purified water for the pharmaceutical and biotech industry. Vapor Compression (VC) distillation plants have seen widespread use in the production of bulk Purified Water (PW) and Water For Injection (WFI). Two principal reasons for using VC technology are the high thermodynamic efficiency of the process and the opportunity to use a simplified pretreatment system. VC plants utilize a mechanical compressor to drive the distillation process while alternative technologies do not. The compressor has historically been a source of maintenance and reliability concern. In many cases, especially where large volumes of water are required, the concerns surrounding the compressor are outweighed by economics of operation that favor the VC based system. In these cases, maintenance programs are in place to alleviate concerns regarding the compressor. Regardless, there is a need to modernize the existing compressor technology that is more than 50 years old. Improvements in compressor design have increased reliability, decreased maintenance, noise, energy consumption, installation costs, and simplified the operation of the vapor compression process. The integration of variable speed technology to the improved compressor system has increased the ability to synchronize output with production needs.

High Purity Water

The United States Pharmacopeia (USP) is one source of standards for water used in the production of medicinal products. The principal difference between USP Purified Water (PW) and Water For Injection (WFI) relate to the microbial and endotoxin limits. The USP allows WFI to be purified by distillation or an equal or superior process;[1] however, current European regulations permit only distillation. Table A outlines the mandatory requirements of the USP-NF monograph as it applies to conductivity, Total Organic Carbon (TOC), and endotoxins for purified water and water for injection. The microbial limits referenced are non-mandatory, but used for setting of alert and action limits.

Requirement	Purified Water	Water For Injection
Conductivity, ref. 185°F (85°C)	≤ 2.7°S / cm	≤ 2.7µS / cm
Total Organic Carbon (TOC)	< 500 ppb	< 500 ppb
Endotoxin	N / A	< 0.25 EU / mL
Microbial	< 100 CFU / 1 mL	< 10 CFU / 100 mL

Table A. Requirements for PW and WFI according to USP.

Requirement	ME	VC
Chlorine	0 ppm	0 ppm
Ammonia	0.05 ppm	0.05ppm
TDS	5 ppm	500 ppm
Hardness	0 ppm	5 ppm
Silica	0.05 ppm	7.5 - 20 ppm

Table B. Pretreatment requirements for ME and VC stills.

Common Methods of High Purity Water Production

There are various methods used to produce PW and WFI. Reverse osmosis followed by deionization is commonly used to produce PW. Distillation is used to produce WFI. The two most common forms of distillation in considering water to pharmacopeia standards are Vapor Compression (VC) and Multiple Effect (ME). In some cases, where both WFI and PW are required, ME or VC distillation can be used to produce all of the water needs thereby simplifying the installation with only one water generation system. However, given its relatively high efficiency as far as distillation is concerned, and the significant increase in efficiency where ambient temperature water is produced, VC offers advantages when producing all of the water requirements by distillation.

The efficiency of a distillation unit can be defined as Economy (E) and is expressed as the mass of distillate produced per unit of energy input. Early distillation plants used for water purification boiled raw water within a single "effect" or evaporator at atmospheric pressure with separate condensation to generate freshwater. A typical single effect evaporator operating at atmospheric pressure on a feedwater source at 60°F (16°C) will require 1162 BTU to produce 1 pound (2701 kJ/kg) of water. Utilizing 5 effects in a ME plant reduces the energy input to approximately 425 BTU per pound (988 kJ/ kg) of distillate produced. Multiple effect distillation plants use additional effects to improve the economy of the plant by boiling the raw water supply using higher-pressure steam from the preceding effect to generate even more distilled water.2 Hence, these systems are constructed with multiple effects to sequentially boil feed water under pressure and condense the vapor in succeeding effects. A condenser supplied with cooling water is used to condense the vapor from the last effect and preheat the feedwater to the system. There is a practical limit to the number of effects a ME distiller might have given the rising capital cost associated with each additional effect and the diminishing returns associated with efficiency. By contrast, the VC process requires only 130 BTU per lb (302 kJ/kg) of water produced at 180°F (82°C). If ambient temperature water is produced (as is the case most PW systems), more of the heat within the distillate is recovered and the economy of the VC process improves further such that only 51 BTU are required to produce a pound of water (119 kJ/kg).

Vapor compression distillation is a method of evaporation in which a process fluid is boiled on one side of the heat transfer surface and the compressed vapor generated is directed to the other side of the heat transfer surface where it is condensed (giving up its latent heat to the boiling liquid). Compression is normally accomplished via a steam jet ejector or mechanical compressor.[3] The use of a mechanical compressor as opposed to a jet ejector raises the efficiency of the process and is often referred to as mechanical vapor compression. In considering the VC process, energy is input as electrical power to the compressor and a low pressure plant steam supply.

The USP states that distillation or the superior process step must be the final step in the purification process considering the production of WFI. The pretreatment processes upstream of the distillation plants may differ depending upon the feedwater constituents and the user's own preferences or requirements. ME stills require the removal of chlorine, ammonia, hardness, and other scales that may form at the higher operating temperature of a ME plant. Typically, a carbon filter and water softener with a single pass Reverse Osmosis (RO) unit is required. Two-pass RO with DI polishing is also common in the pharmaceutical industry as pretreatment for ME distillation. For a VC unit, a carbon filter and water softener are normally acceptable to achieve the standards outlined in Table A. The exception to this method of pretreatment is typically found where the silica levels in the feedwater exceed the limits provided in Table B. In this event, an RO plant would normally be installed prior to the VC plant

The final pretreatment requirements for the two distillation units can be seen in Table B. The pretreatment requirements for a VC are less stringent than that of ME given the lower pressure and temperature operating conditions of the VC plant relative to that of a ME plant. VC plants operate slightly above atmospheric pressure with an associated feedwater vapor temperature of 215°F (102°C) and a compressed vapor (distillate) temperature of 222°F (106°C). The first effect feedwater vapor temperature in a multiple effect plant is typically referred to as the top temperature. Although the top temperature of a ME plant may vary depending upon the design and plant steam pressure, it is normally found to be approximately 350°F (177°C).

The Multiple Effect Process

The flow diagram as seen in Figure 1 will aid in understanding the description of a typical multiple effect system. The multiple effect process has as its major components a first effect double tube sheet evaporator, succeeding effects of single tube sheet construction, primary distillate and blow

down coolers, a final condenser, valves, instruments, controls, pretreatment systems, and associated piping.

In the design depicted, a typical ME plant for pharmaceutical distillation, pretreated feed water is passed through the final condenser and primary distillate cooler before entering the first effect evaporator where it is evaporated inside a bank of tubes by way of a higher pressure boiler steam supply on the outside of the tubes. The vapor generated is passed through a mist separator to remove entrained water or impurities from the rising vapor. The pure vapor generated within the first effect is passed on to the second effect where it condenses and is removed as distillate. The vapor from the first effect is used to produce vapor within the second effect at a lower pressure and temperature. The process repeats itself for each succeeding effect until the vapor from the last effect and distillate from preceding effects is processed through the final condenser. In order to maintain a temperature difference for heat transfer between the vapor from one effect to the boiling feed water within the next effect, the pressure of each succeeding effect must be lower than its predecessor. The energy input to the first effect is degraded and used within the succeeding effects. A larger number of effects provides for a more efficient ME system. However, the number of effects typically employed is limited considering a fixed top temperature within the first effect, the temperature difference between succeeding effects, and the final condenser temperature.

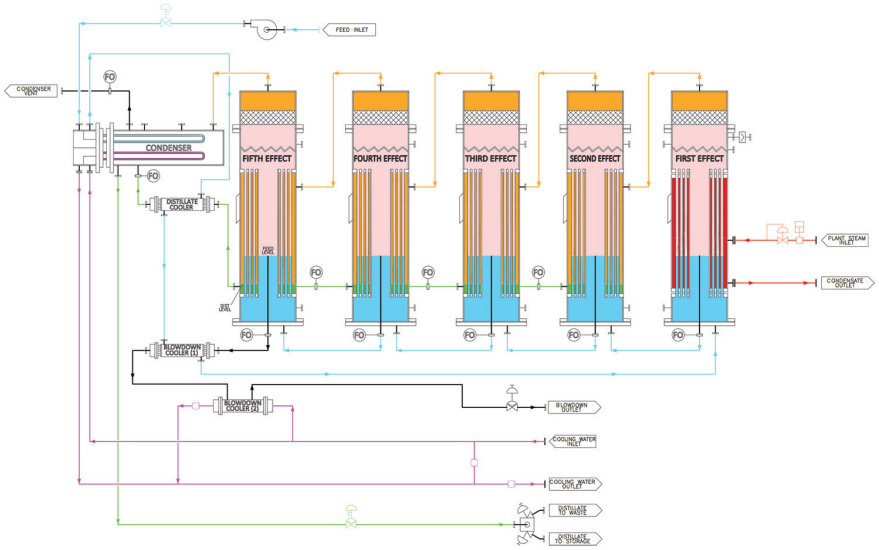


Figure 1. Typical ME process diagram for pharmaceutical distillation.

The Vapor Compression Process

The VC process has a relatively high economy as compared to the ME process. In addition, the feed water pretreatment requirements for a VC plant are typically less than that of ME plants as shown in Table B. As such, in some cases, where feed water pretreatment can be simplified, the overall capital investment for a VC based system may be lower and the operating costs are lower for the water purification process that employs VC. Overall system water recovery rates are sometimes higher for a VC application considering more efficient feed water pretreatment schemes and lower cooling water requirements.[4] Despite these advantages, in comparing alternative methods of distillation, the use of a mechanical compressor is sometimes seen as a disadvantage considering the associated maintenance and implications to reliability relative to the other distillation processes that do not employ a mechanical compressor. As such, there was a need to develop a better alternative for mechanical compressors relative to what has been used historically. The flow diagram in Figure 1 will aid in understanding the description of a typical mechanical vapor compression system.

The mechanical vapor compression process has as its major components, evaporator/condenser, a centrifugal compressor, a deaerator, heat exchangers, pumps, valves,

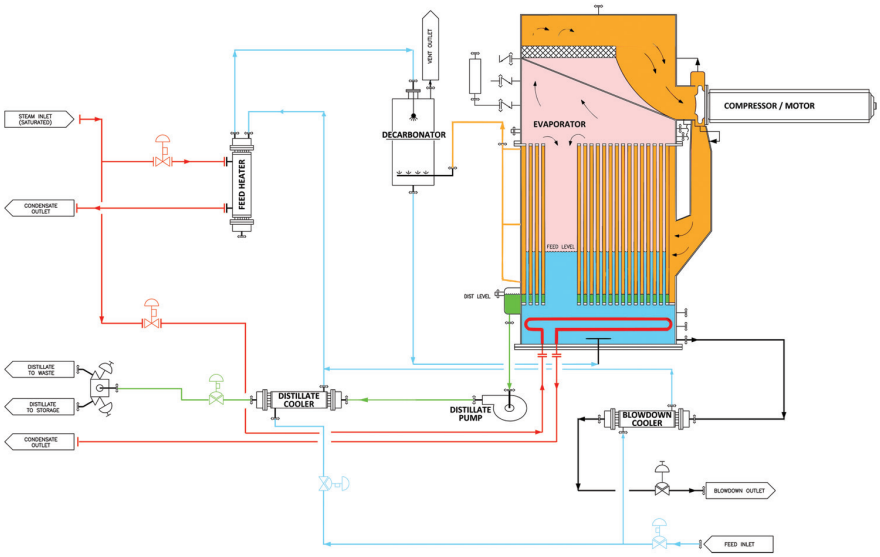


Figure 2. Typical VC process diagram for pharmaceutical distillation.

instruments, controls, pretreatment systems, and associated piping.

In Figure 2, a typical VC unit used for pharmaceutical distillation, softened and dechlorinated water (at a minimum) is boiled inside a bank of tubes. The generated vapor then passes through a mist separator to remove any impurities within the vapor generated from the feedwater supply. The pure vapor enters the compressor, at a controlled saturation pressure (and consequently temperature), where compression takes place resulting in a higher saturation pressure. The higher-pressure (and temperature) compressed steam is discharged into the evaporator onto the outside of the tubes, where it condenses and gives up its latent heat energy to the boiling water inside the tubes. The VC process is very efficient thermodynamically, since only about 10-15 BTU (11-16 kJ) of compressor work is used to recycle approximately 1000 BTU (1056 kJ) of the latent heat contained in the released vapors.

Additional vapor is generated and the process continues. The vapor, which condenses on the outside of the tubes, is collected, and drawn off by the distillate pump and pumped through a heat exchanger. The excess feed water (blow down) is also pumped through a heat exchanger. The distillate and blow down are cooled in the respective heat exchangers while simultaneously preheating the incoming feedwater. The heat exchangers help to minimize energy consumption of the system.

Some make-up heat is required for continuous operation to replace losses within the system, including the terminal temperature difference in the heat exchangers and the heat lost to radiation and venting. This make-up heat is generally provided by an existing steam supply or alternatively by electric immersion heaters.

Compressor Technology

One feature of an efficient VC system utilizes a compressor that generates a low differential pressure (and hence vapor temperature) to drive the distillation process at the optimal heat transfer coefficient. A low differential pressure across the compressor contributes to low electrical energy consumption in the VC cycle. Three principal types of compressors have been used until a new variable speed directly driven centrifugal compressor was most recently developed. A review of the technologies employed follows.

Blowers and Industrial Fans

Blowers and industrial fans are sometimes used in Vapor Compression (VC) applications because of the need to produce a relatively high volume of vapor at low compression ratios. Lobe type positive displacement roots blowers were used on VC plants in the 1940s through the mid 60s and can sometimes still be found in use today. Although the positive displacement blowers are widely used in numerous applications today, they have largely been discontinued in VC applications, especially due to the sanitary restrictions of the pharmaceutical industry.

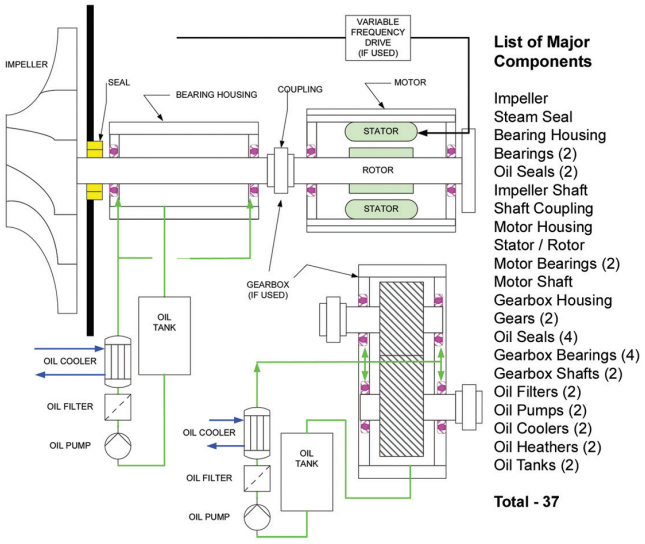


Figure 3. Typical industrial compressor.

Industrial fans are commonly coupled to a standard motor operated at 1750 to 3600 RPM through a monoblock bearing housing. With the addition of a variable frequency drive, the standard motor speed can be increased to 4500 RPM. For a given volumetric flow, the relatively slow rotational speed dictates a large diameter impeller to get sufficient tip velocity for the small differential pressure required. A large impeller results in larger shafting, bearings, and bearing housings to maintain reasonable design loads. The fan itself is often disproportionate to the evaporator size and is not necessarily specifically designed for the application so that it cannot be integrally fitted to the evaporator and external ducting is

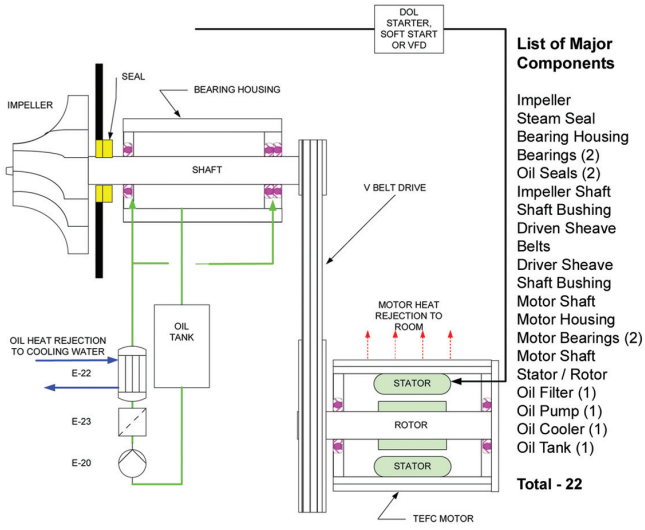


Figure 4. Typical belt-drive compressor.

required. Bearing housings on the industrial fans are fitted with force feed oil lubrication systems to lubricate and cool the bearings. This oil is circulated via a pump, filtered, cooled, monitored, and re-circulated. The standard motor is typically grease lubricated with fan cooling. The use of industrial fans can be costly due to their physical size and external ducting. These costs increase when higher quality materials are used in fabrication. A gearbox is sometimes used to increase the rotational speed and impeller tip velocity, thereby allowing for a smaller fan and casing. Unfortunately, the use of a gearbox adds a layer of complexity in considering additional bearings, oil lubrication, seals, couplings, and gears. The proper operation of the compressor and the motor driver are reliant on the alignment and performance of the intermediate gearbox. While the physical size of the package may be reduced using a gearbox, the costs are not and the maintenance and reliability concerns become more of a consideration given the increased number of components. Maintenance on the industrial fan typically results in downtime on the entire system since its size and configuration make it impractical to change out.

Centrifugal Compressor

Considering the foregoing challenges associated with commercially available units, a compressor specifically designed for the needs of VC evaporators was developed in the late 1960s, such that it could rotate at higher speeds, from 4500 RPM to 22000 RPM. These compressors are physically smaller and integrally mounted to the evaporator by way of a suction adapter and discharge diffuser negating the need for external ducting and slightly reducing power requirements associated with the head losses in ductwork. In comparison to the industrial fan referenced above, greater speeds allow for smaller diameter impellers. In order to achieve the higher rotational speed, these compressors were belt driven from a standard motor. Typically, an across the line or reduced voltage starter is used and the compressor size and speed is selected and fixed for the appropriate evaporator and its required output. The attractiveness of using a belt drive as opposed to gears or other means is a lower cost and relative ease of replacement. The belts operate on a pair of sheaves and require regular replacement every 12 months. Their proper alignment and tensioning is essential for successful long term operation. Over tensioning belts can result in premature belt, seal, and bearing failure. The higher speed machines also used a force feed lube oil system with the associated filters coolers circulating pump, breathers, and controls. Recommended oil changes are every 12 months. Thousands of these systems have been put into use over the last 40 years. The larger industrial fans dictate maintenance and repair "in place," while these smaller units are completely swapped out. The motor and compressor belt drive arrangement as well as the previously referenced industrial fans generate a noise level of 85 to 90 dBA from one meter away.

Considering the smaller size, higher grade materials of construction, such as monel and inconel can be used economically. Despite the attractiveness of a smaller compressor of high quality materials, the belt drive and lube oil system are sources of maintenance. When not properly maintained, they can become sources for reliability concern.

Modern Variable Speed Direct Drive Compressor Technology

As VC technology became more frequently applied in industry, the need for an improved compressor design became apparent. The belt driven approach, while simple and practical is a source of maintenance as is the re-circulating oil system. The physical configuration of the industrial fan with its external ducting, large support base, casing, impeller, intermediate bearing block, and various appurtenances contributes to a high capital cost. The smaller compressor designs had similar albeit different capital expenditures on belts, sheaves, belt guards, and motor stand. The force feed lube oil systems on both designs are a significant subsystem. Compressors associated with the most efficient distillation cycle were developed more than 50 years ago.

The following objectives were considered with the design of a modern variable speed direct-drive compressor - *Figure 5:*

- Reduce maintenance
- Improve reliability
- Simplify operation
- Reduce capital costs

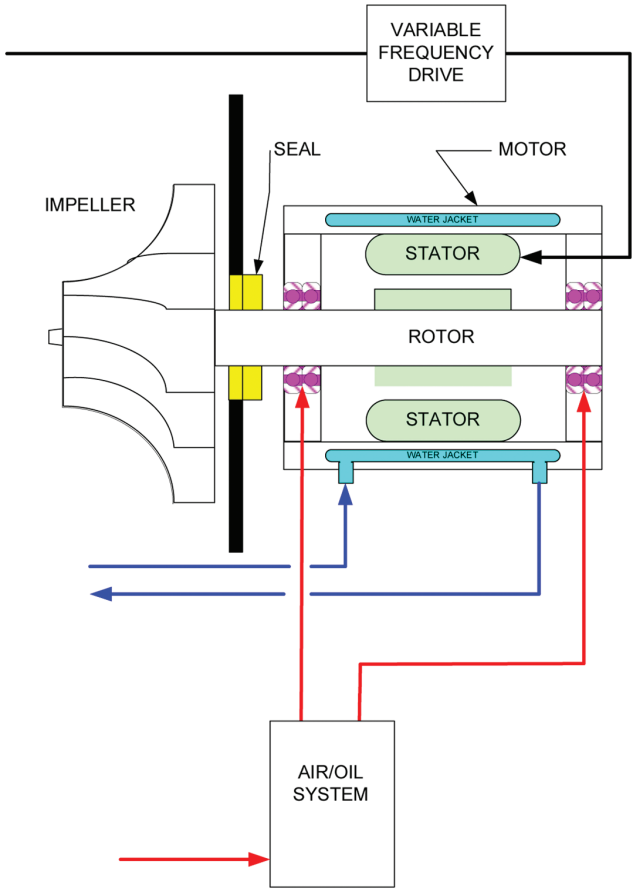
The attributes of the smaller higher speed compressors were desirable, but the use of a transmission system, such as belts or gears to increase the speed was not. Likewise, an alternative to the forced feed oil lubrication systems also would be desirable. It became apparent that a variable speed motor operating at elevated speeds directly coupled to the small compressor fluid end previously described would offer several advantages and design challenges. Since none were found commercially available to suit the required duty, a new system to meet the specific needs was developed.

By coupling the fluid end of the centrifugal compressor with a series of stator and rotor designs, a diverse range of performance characteristics were achieved. These were matched with variable frequency drives suitable for the application. The application of a variable speed motor and drive offers several benefits. Principal among these is the ability to vary the distillate production and the associated power consumption. This becomes important since the operational costs of distilling water are many times the first cost of the plant in considering the life of the equipment. There are additional power savings by eliminating transmission systems, such as belts or gears and intermediate bearing housings.

Motor housings can be designed to accept the thrust load of the impeller directly, thereby eliminating the need for an intermediate bearing block as more commonly found in the industrial fans referenced. The heat generated from the motor windings and the process evaporator necessitates cooling of the motor, which is done through a water jacket machined in the motor housing. Using a jacket of water to cool the compressor motor housing provides the additional benefit of reducing the noise that would otherwise be generated by a cooling fan. Noise levels on the new compressor have been reduced from 85 to 90 dBA to less than 80 dBA at full load and are imperceptible at reduced loads.

An improved lubrication system also was desired. Ideally, one that was greatly simplified in terms of operation and maintenance. Rotational bearing manufacturers typically describe performance in terms of the product *DN* where *D* is the diameter (often in mm) of the bearing and *N* is the rotation rate in revolutions per minute. Today, for DN values greater than 1 million, metered oil or oil jet is recommended. Metered oil systems lower operating bearing temperatures and lubricant shear effects by providing a higher air-to-oil ratio, which also lowers oil consumption.[5] As such, there is no need for a circulating pump, filters, external cooler, or the associated valves and instrumentation. Typical air/oil systems deliver as little as a half drop (0.001 cubic inches) of oil every few minutes per bearing. The majority of the oil is consumed so there is no waste oil to change and no oil filter to change as in traditional re-circulating designs. Most importantly, by eliminating the recirculation of substantial quantities of oil, the issue of oil leaks is essentially eliminated. PLC based control systems provide the opportunity for continuous monitoring of information, such as bearing and winding temperatures as well as vibration data.

The reliability of any system is a function of the number of components and the reliability of those components within the system. In the compressor designs under consideration, many of the components are similar between the designs and serve similar functions (shafts, seals, bearings, impellers, stators, rotors, etc.) Hence, for those similar components in similar service, their reliability can be considered equivalent; however, a review of the complexity of a particular system design as a function of the number of components also can give an indication of the reliability. Figures 3 to 5 provide a listing of major components within each compressor system. By eliminating a number of components within the compressor system, while not introducing new or complex components, the reliability has been improved. In considering only the major components, the modern variable speed direct drive technology has two thirds fewer components than typical industrial fans and half the components of typical belt driven systems.



List of Major Components

Impeller
Steam Seal
Motor / Bearing Housing
Bearings (2)
Oil Seals (2)
Motor Shaft
Stator / Rotor
Air / Oil Solenoid (2)
Oil Tank

Total - 12

Figure 5. Direct drive compressor.

Another factor to consider in evaluating reliability is the L10 bearing life of the rotating machinery. The L10 bearing life is statistically the number of hours that 90 percent of a group of identical bearings will exceed under a given set of circumstances. For a given bearing design, the effect of the load (P) on bearing life is four times that of speed (N). As such, it is a fairly straightforward to design higher speed machines with extended L10 bearing life and high reliability. By removing gearboxes, couplings, belts, and sheaves along with the incorporation of an updated lubrication system, a bearing L10 design life of greater than 60,000 hours can be achieved. The direct coupling of the compressor and motor housing also eliminates the side load associated with belt transmission systems as well as coupling/gearbox induced vibration. These updates prolong both bearing and seal life while eliminating a source of operator

	Industrial Fan	Belt-Drive	Direct Drive
Impeller	Large diameter fan	Small diameter centrifugal	
Compressor Shaft Speed	Slow	High	High
Motor Shaft Speed	= Compressor Shaft	Standard	= Compressor Shaft
Integration Components	Coupling, Gearbox, Ductwork	Motor and Compressor Sheaves, Belts	N / A
System Size	Separate Skid	Separate Motor and Compressor	Compressor with Integral Motor
Compressor Bearing Lubrication Type	Oil Bath		Metered Oil
Lubrication System Maintenance	High		Low

Table C. Comparison of compressor technology and components.

intervention. Table C provides a general comparison of the compressor technology and their components.

Variable Output

Fixed speed systems can be prone to surging if the required suction conditions are not met. Although the same could be said for a variable speed system at any given state, the ability to vary the speed provides one the ability to work with the available suction conditions and hence avoid compressor surging. In designing a complete water system, variable capacity also may enable one to better manage the size of storage and distribution facilities. Variable output on a VC distillation unit is achieved through variation of the compressor speed. Closely matching production with demand minimizes the number of system starts and stops. On startup of a WFI production unit, acceptable WFI is sent to drain to flush the associated piping and hence wasting the water that is produced during this time. Typically, this flush cycle is set between 5 to 20 minutes. Slowing the rate of production during times of low demand in lieu of stopping and starting conserves water. Starting an electric motor exposes it to startup inertia and high currents, which adversely affect the life of the motor.[6] Finally, the friction coefficient between seal faces decreases with speed as wetting takes place. During frequent starts and stops (transient conditions), friction coefficients increase, adversely affecting seal life.7 In addition to the benefits listed above, the efficiency of the WFI unit increases with turndown.

The power consumption varies by the cubicroot of the compressor rotational speed. Consequently, the efficiency of the vapor compression process increases as the production rate for a given evaporator decreases. A turndown of 50% is generally achievable in vapor compression processes. The variable output production of a typical VC distillation plant is displayed in Figure 6. The data of Figure 6 demonstrates that a 25% reduction in capacity yields a 50% reduction in power consumption; a turndown of 50% results in a 80% reduction in power consumption. In order to normalize the data, the production is displayed as a percentage of max output for a given distillation plant.

The directly driven variable speed design provides for flexible operation and disproportionate energy savings at reduced capacity production that was not previously available on fixed output machines. Elimination of direct full voltage (across the line) starting typical of fixed speed designs reduces the inrush current associated with starting as well as the size of installed switchgear.

Summary

The new directly driven variable speed compressor drives have improved the vapor compression distillation process and how it can be used within the pharmaceutical and biotech industries for the production of USP purified water and water for injection. The energy consumption of a given plant is improved by eliminating the inrush current associated with across the line starting and matching the compressor speed to the output demand of the system.

Reductions in maintenance and improvements in reliability are realized through the elimination of numerous components. These components include belts and sheaves or gears and couplings, intermediate bearing blocks, bearings and seals, as well as the re-circulating oil system with its associ-

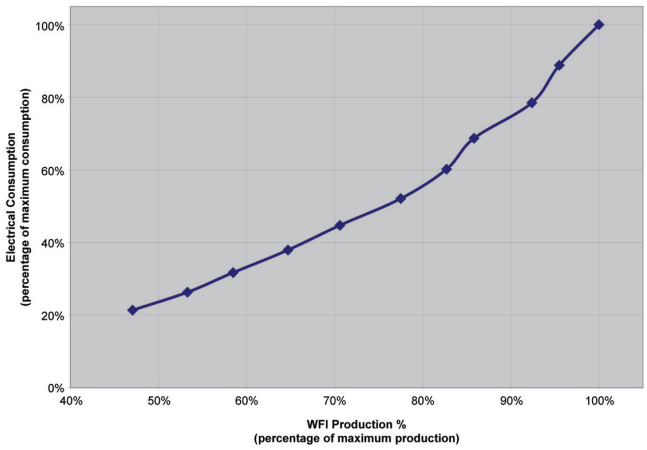


Figure 6. Variable distillate production versus electrical consumption for a VC distillation plant.

ated filters, coolers, pumps, and instrumentation. The direct drive is not dependant upon an operator to properly tension belts or align gears eliminating a possible source of operator induced failure. Eliminating these external transmission systems has reduced the number of bearings and seals within the compressor drive and eliminated the external forces they previously imparted onto the compressor. As a result, the L10 bearing life of a fewer number of smaller bearings has improved to 60,000 hours.

The use of a once through oil mist system in lieu of recirculating large volumes of oil has eliminated the issue of oil leaks. Maintenance is limited to refilling an oil reservoir every six months.

The noise associated with earlier systems has been reduced to less than 80 dBA by eliminating transmission systems and motor fan cooling. This advancement in technology has improved the VC system, such that the economic benefits of the process can be recognized at lower flow rates because the absolute value of operational savings are no longer outweighed by concerns associated with maintenance and reliability.

References

1. United States Pharmacopeia-National Formulary, 36th and 31st editions, US Pharmacopeial Convention, Rockville, MD, 2012.

2. Buros, O.K., CH2M Hill, Office of Engineering, U.S. Agency for Internal Development, Washington, DC, 1980, Chapter 3, p. 1-15.

3. Perry. R.H., and Green, D., *Perry's Chemical Engineering Handbook,* Sixth Edition, McGraw Hill Book Company, New York, 1984, Ch. 11-37.

4. Gsell, G.V., "Water Systems Utilizing Multiple Effect and Vapor Compression Technologies Compared," *Pharmaceutical Engineering*, March/April 2004, Vol 24 No. 2.

5. Torrington Company, *Lubrication*. Fafnir Superprecision Ball Bearings, 2000, p. E38.

6. National Electrical Manufacturers Association, "NEMA Standards Publication No. MG 1," 1993, sec 12.4.3.

7. "How Long Will a Mechanical Seal Last?" *Pumps & Systems Magazine,* March 2007, 75.

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Facility of the Future: Next Generation Biomanufacturing Forum

Part II: Tools for Change – Enabling Technologies and Business and Regulatory Approaches

by Mark Witcher, PhD, Ruben Carbonell, PhD, Jeff Odum, CPIP, Peter Bigelow, Patricia Lewis, and Michael Zivitz

This article is the second of a three-part series focused on defining the facility of the future required for manufacturing biopharmaceuticals in the 21st Century.

Introduction

This is the second of a three part series to define the Facility of the Future (FoF) required for manufacturing biopharmaceuticals in the 21st Century. The articles are the result of discussions and presentations made at the "Next-Gen Facility Forum" held at the North Carolina State University in the Biomanufacturing Training and Education Center (BTEC) on January 31, 2012. The three articles cover the topics discussed at the Forum.

In the first article, Part I: "Why We Cannot Stay Here" – The Challenges, Risks, and Business Drivers for Changing the Paradigm," we elucidate why the biopharmaceutical manufacturing paradigm and the basis of designing and operating manufacturing facilities must change if the industry is to move forward.[1] We reviewed the imperatives, drivers, uncertainty, and risks faced by the industry - *Figure 1*. The patient value and cost risks are impacted by the drivers through various elements of uncertainty.

In this second article, we will review and discuss recent advances in various technologies, and the regulatory and business approaches that provide enabling methods for addressing the drivers and uncertainties identified in the first article.

As shown in Figure 2, drivers and uncertainties are impacted by a number of enablers. These enablers are created or improved by advances in a variety of technologies and the business strategies used to build and operate manufacturing enterprises. In Figure 3, the factors that create or modify the enablers are placed into the following three categories:

- Advances in medical and protein technologies
- Advances in process, facility, and computer technologies
- Advances in approaches and regulatory initiatives

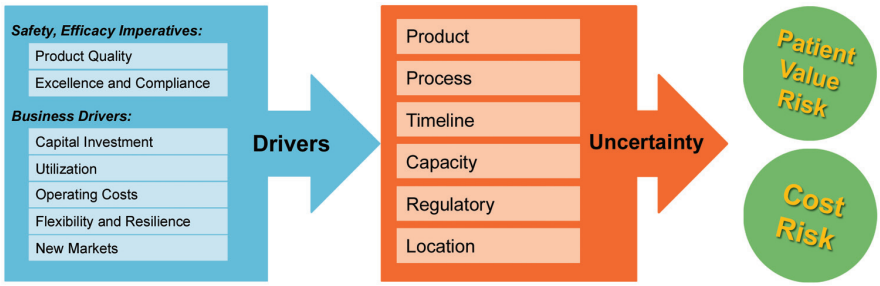

Figure 1. Business drivers, imperatives, and uncertainties.

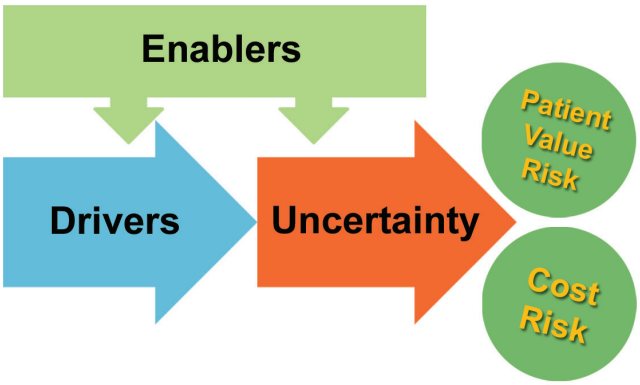

Figure 2. Both the drivers and uncertainties are impacted by enabling technologies and approaches, which in turn impact patient value and cost risks.

Advances in Medical and Protein Technologies

Advances in medical technology are providing a better understanding of both the patient's therapeutic needs and the impact of the therapies they take to satisfy those needs. Significant advances are also being made in protein science and biochemistry related to characterizing the product's Critical Quality Attribute's (CQA's) impact on a diverse patient population. To a large extent, these advances are outside the scope of this article, but they do impact the drivers and uncertainty shown in Figure 1. These advances will result in safer, more effective therapeutic drug products along with improving the industry's ability to develop the required manufacturing processes and production facilities.

Advances in clinical testing methods also fall in this category. Improvements in how biopharmaceuticals are tested and monitored in the patient population are an important set of enablers. All these advances create many opportunities and place more pressure on manufacturing enterprises to be faster and more effectively.

Advances in Process, Facility, and Computer Technology

During the Forum's breakout sessions, a wide variety of advances in processes, facility, and computer technologies were discussed. For organizational purposes, these advances are grouped as shown in Figure 4.

These seven groups are placed in the same broad technology category because they all interact and are used in concert to define, design, and build a biopharmaceutical manufacturing facility.

The following is a summary of these technology advances.

- **Upstream Performance** – significant advances have been made in cell culture yields over the last two decades. Typical yields have increased from fractions of to upward of 10 grams per liter.[2] These increases have come through media optimization and improvements in cell lines. Improvements are expected to continue as systems biology and specialized artificial cell lines with metabolisms modified to achieve specific performance goals are developed. Better harvest and recovery technologies will further improve the performance of upstream processes. In addition, various bioreactor options, such as perfusion, attached, suspension, and micro carrier technologies also are likely to improve upstream performance and efficiency.

- **Downstream Performance** – while improvements in downstream processing lag behind advances in upstream processing, significant improvements in downstream processes are being observed. More selective capture steps using affinity chromatograph are possible along with the use of selective membranes and monolithic structured for Tangential Flow Filtration (TFF) processes. Advances also may be seen in non-chromatographic methods,

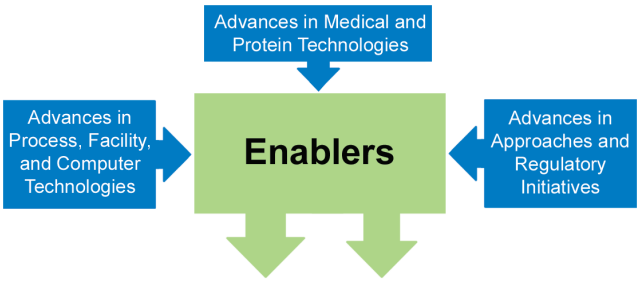

Figure 3. Enablers come from advances in the three categories shown.

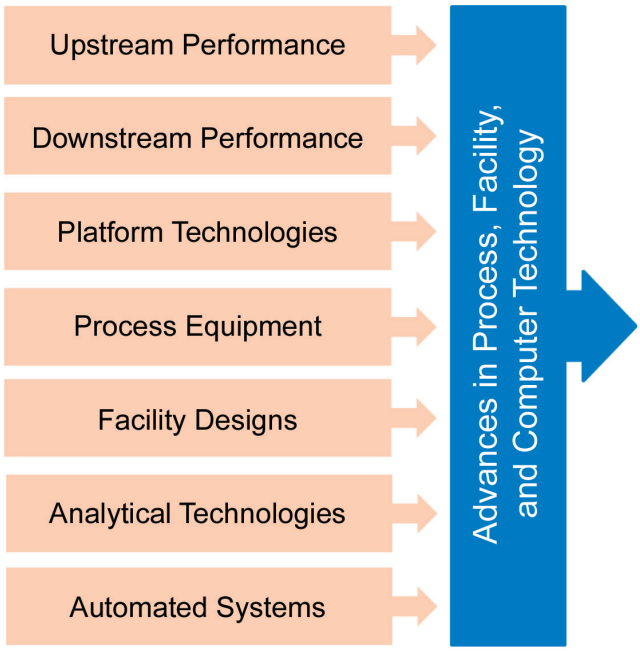

Figure 4. Advances in technology come from a variety of sources.

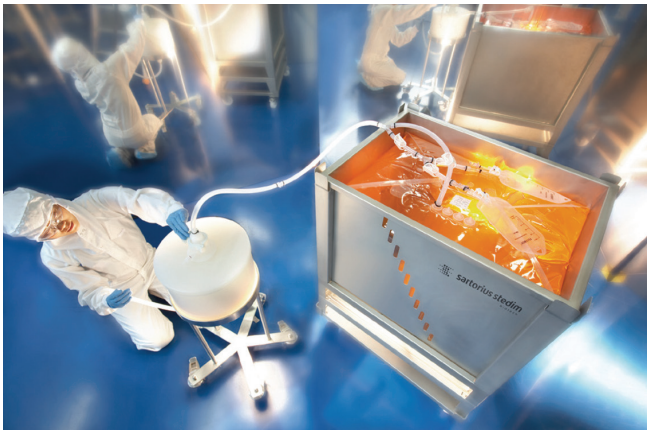

Figure 5. Single Use buffer storage systems provide flexibility for preparing and distributing buffers to a wide variety of unit operations (*photo courtesy of Sartorius).*

Figure 6. Portable Single Use System (SUS) based unit operations can be configured to perform a variety of processing steps (*photo courtesy of Sartorius).*

such as highly selective precipitation of target proteins. Advances also will be seen in automated, multi-batch processes using smaller disposable columns.

- **Platform Technologies** – as the industry's experience with manufacturing processes increases, platform technologies for a number of unit operations are being developed and marketed. These platform technologies, some based on well developed proprietary technology, will provide significant enablers for future improvements. Notable platform technologies are being seen in bioreactor and purification systems.

- **Process Equipment** – advancements are being seen in equipment and equipment components unlike any time in the past decade. In particular, the increase in Single Use Systems (SUS) or disposable components are being developed and implemented in a much broader range than ever before. SUS provide a significant advantage in reducing cleaning, sanitization, and sterilization development and validation requirements. SUS also provides significant opportunities to isolate the process from the surrounding environment enabling a wide variety of process implementations and facility designs. In addition, advances in bioreactor configurations, centrifuges, and TFF units are enabling a variety of process and facility modifications that enhance flexibility and improve utilization.

- **Facility Designs** – a number of facility design options are being discussed in different global industry forums. Facility design and layout options are now possible that improve adaptability and flexibility. These include facility design strategies that range from shared common space in large general operating areas (ballrooms) to highly segregated process steps in many small rooms (matrices).

  In addition, modular construction techniques have been developed for building facility components at contractor factories for assembly at the construction site in "ready to go" modules. These modules contain integrated HVAC systems facilitating a variety of possible combina-

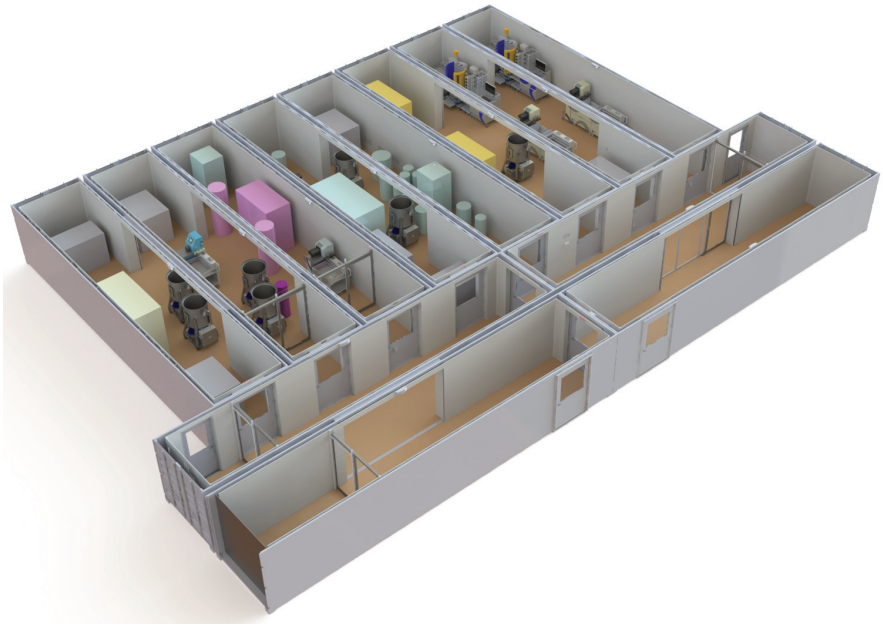

Figure 7. Conceptual layout of one of Biologics Modular's modular manufacturing facilities (*image courtesy of Biologics Modular).*

Figure 8. Manufacturing Execution Systems (MES) support a wide variety of critical information management activities.

tions. Preassembled panels and components can be used to provide easily configurable and reconfigurable cleanrooms to address different process requirements. These different approaches provide opportunities for reducing costs while improving flexibility.

- **Analytical Technologies** – major advances in sensor technologies for measuring specific Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs) are being developed as part of the Process Analytical Technology (PAT) initiative.[5] PAT enables better process performance through improved on-line and off-line process monitoring and control.

- **Automated Systems** – a wide variety of software and support hardware systems are becoming available to implement improvements in infrastructure systems. These include Manufacturing Executions Systems (MES), Electronic Batch Records (EBR), and Laboratory Information Management Systems (LIMS) to name a few. These computer technologies enable many significant improvements to the drivers and uncertainty.

Collectively, these scientific and technical advances provide significant enablers that create many opportunities to build better manufacturing facilities.

Advances in Approaches and Regulatory Initiatives

The third category of advances shown in Figure 9, come from: 1. Evolving regulatory initiatives issued by various global regulatory agencies; 2. Improvement in business practices; and 3. Operational approaches that result in significant manufacturing infrastructure improvements.

- **Regulatory Initiatives** – three regulatory initiatives have provided considerable guidance that enable better strategies for developing manufacturing processes. The primary enabler is the structure for working with the complex technologies and the assistance they provide in aligning the communications between industry and the regulatory agencies during the approval process. These initiatives are:

  - 2011 FDA Process Validation Guidance[3]
  - ICH Q8(R2) Pharmaceutical Development Guidance[4]
  - Process Analytical Technology (PAT)[5]

  The Q8 document defines the key terms: design space, Quality Target Product Profile (QTPP), Quality by Design (QbD), and Real Time Release Testing (RTRT). The design space concept provides a mechanism by which companies can compile process knowledge and understanding into a standard format for review and understanding the product and process information by regulatory agencies. Some suggested examples of design space representations are provided in ICH Q8 (R2). The QTPP provides a comprehensive definition of the product and becomes part of the design space. The use of Quality by Design (QbD) concepts also provides future opportunities if a workable definition of QbD can be identified and put into common practice by industry and the regulatory agencies. RTRT places a higher burden on monitoring and controlling process performance rather than relying on end product testing results for releasing product.

  The 2011 Process Validation Guidance provides a framework for structuring the process development effort from early process definition to operation of the

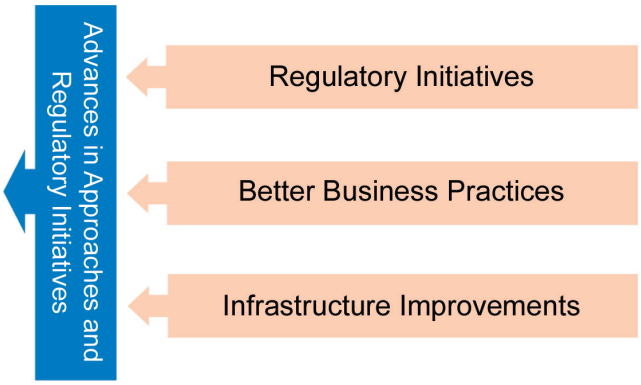

Figure 9. Summary of advances in business practices, approaches, and regulatory initiatives.

commercial manufacturing facility. The PAT initiative stimulates and focuses the pharmaceutical industry's efforts to improve process monitoring and control. These initiatives and guidance when embraced and aggressively used provide significant opportunities to improve the development and licensing of new products.

- **Better Business Practices** – using the regulatory initiatives, companies can apply good engineering and development practices to more efficiently and rapidly build the process's design space using sophisticated experimental tools such as Design of Experiments (DOE) and platform process technologies to develop better performing processes. A more sophisticated approach to current Good Manufacturing Practices (cGMPs) also provides a number of opportunities to run not only multiproduct, but multiphase manufacturing operations within a single facility. If appropriate cGMPs are used to control the facility's operation during production to maintain control of the facility along with the integrity of other ongoing manufacturing operations, the facility will be capable of manufacturing a wider variety of products.

- **Infrastructure Improvements** – advances in computer technology provide a wide variety of opportunities for improving operational infrastructure systems such as Electronic Batch Records (EBR), Manufacturing Execution Systems (MES), Laboratory Information Management (LIMs), Direct Digital Control Systems (DDC), and material and resources planning tools.

All the above advances provide enabling technologies for improving the business drivers and reducing the uncertainties shown in Figure 1. The next challenge is to organize the enabler into groups to better understand how they can be used to create a facility of the future.

Enablers

Taking all of the advances in medical technology, process, facility, and computer related technology along with advances in regulatory initiatives and business methods, the following enablers are defined in Figure 10 along with their relationship to the drivers and uncertainties.

The following discussion briefly summarizes the enablers:

- **Better product characterization** – improvements in characterizing the product come from advances in protein chemistry along with improvements in analytical technologies (PAT). Better understanding the product attributes (CQAs) assists with product characterization and understanding the impact of impurities, contaminants, variant product species, and degradation products on patients.

- **Faster product and process development** – many of the advancements identified contribute opportunities to streamline elements of the product's development timeline. Scientific and engineering experience with platform technologies when combined with improved business practices and a structured regulatory framework provide enablers to rapidly develop better process technology. More rapid process development provides opportunities for reducing facility design and construction timeline pressures.

- **Smaller, portable, flexible processes** – the improvements in the upstream and downstream processes along with the SUS technologies enables a wide variety of facility options. These processes require less facility resources and can be moved and managed within smaller and theoretically, less expensive facilities.

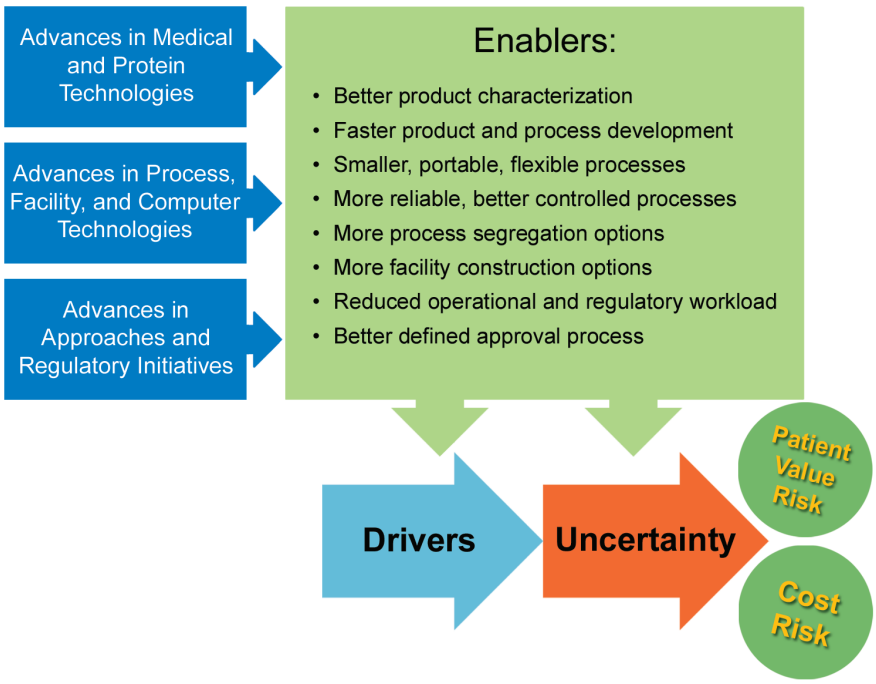

Figure 10. From the advances in medical, protein, process, facility, and computer technology as well as Approaches, and Regulatory Initiatives, the Enablers can be assembled in the groups shown.

- **More reliable, better controlled process** – advancements in using sophisticated development tools described in the regulatory guidance enable significant improvements in the quality of the processes that will be used in the manufacturing facilities. Platform technologies modified and evolved through advanced experimental methods (DOE) to build sophisticated design spaces provide more opportunities.

- **More process segregation options** – the use of skid mounted, portable SU systems provides for a wide variety of options and thus enables solutions to facility design problems that can positively affect the business drivers and uncertainties. Depending on manufacturing and enterprise requirements, process segregation strategies range from a few large common areas to many small highly segregated area layout scenarios.

- **More facility construction options** – design, engineering, and construction options ranging from stick-built to modular approaches become available.

- **Reduced operational and regulatory workload** – several advances provide opportunities to reduce operational and regulatory workloads. SUS technology significantly reduces the cleaning validation required to get a manufacturing operation up and running. Other process and computer advances provide opportunities to automate support processes thus reducing personnel workloads which improving business drivers and reducing uncertainty.

- **Better defined approval process** – regulatory approval for complex biopharmaceuticals is driven by the level of product and process understanding. Many of the advances cited above provide opportunities to enhance understanding and thus enable improvements in the regulatory approval process. With the effective communication tools describe in the guidance, the transmittal of that understanding from industry to regulatory agencies should be enhanced.

Summary

This article identifies a number of technological advances that impact the industry's ability to design and build more flexible and capable manufacturing facilities. In addition, advances in regulatory and business methods enable more efficient approaches to develop and license new products. These advances impact the patient value and cost risks by changing the drivers and uncertainties discussed in the first article. The final article in this series will discuss how these enablers can be used to manage the business drivers and reduce uncertainties for the facility of the future.

References

1. Witcher, M.F., R. Carbonell, J. Odum, P. Bigelow, P. Lewis, and M. Zivitz, "Facility of the Future: Next Generation Biomanufacturing Forum, Part I: "Why We Cannot Stay Here" – The Challenges, Risks, and Business Drivers for Changing the Paradigm," *Pharmaceutical Engineering,* January/February 2013, Vol. 33, No. 1, pp. 22-29, www.pharmaceuticalengineering.org.
2. Langer, E., "A Decade of Biomanufacturing," *BioProcess International,* June 2012, Vol. 10, No. S6, pp. 65-68, http://www.bioprocessintl.com/journal/.
3. FDA, *2011 Process Validation: General Principles and Practices; Guidance for Industry,* Current Good Manufacturing Practices; January 2011, Revision 1, www.fda.gov.
4. *ICH Q8(R2) – Pharmaceutical Development,* November 2009, Revision 2, www.ich.org.
5. FDA, *PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance,* September 2004, www.fda.gov.

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Engineering Practices During Manufacturing Process Development for New Products

by David Rich, Mark Blanchard, Salvatore Giglia, Greg Straeffer, Amy Cazeault, Shannon Cleveland, Rebecca Bartkus, and Matthew Desmarais

This article presents a structure and methodology for designing quality into new manufacturing processes for new filtration products.

Introduction

One of the most important responsibilities undertaken during the development of a new product is designing a robust manufacturing process that consistently meets the needs of the customer. Significant problems can occur during full-scale production when manufacturing processes are poorly conceived. If one is lucky, these problems are caught during product qualifications or during pilot manufacturing; however, this is still not an ideal state. Therefore, it is incumbent upon research and development organizations to employ effective procedures for ensuring sound manufacturing process development.

Project management tools, such as New Product Development Processes (NPDs) and quality tools, such as Lean Six Sigma, Design for Six Sigma (DFSS), and Design for Manufacturability (DFM) provide much value when undertaking the development of new products.[1-5] However, in general these tools do not explicitly instruct how and when to apply scientific and engineering knowledge over the course of process development efforts. In the absence of good science and engineering, quality will always be deficient, regardless of the merits of the tools employed.

The objective of this article is to introduce a novel phase-by-phase approach for ensuring rigorous use of the scientific method and engineering knowledge when developing a manufacturing process for a new product. When this methodology is followed carefully, one can have confidence that scientific understanding has been well-considered in product designs and that engineering choices have been based on a sound methodology. Ultimately, this approach can lead to new manufacturing processes that are more robust and optimized and meet the needs of the customer.

New Product Development Processes

Much attention today is focused upon developing a good New Product Development Process (NPD or PDP). NPD systems control the new product design and development activities of the organization and are designed to meet the requirements of ISO 9001 section 7.3. Typically, NPD projects consist of several stages, each gated by a management

Phase	Activity
1	Project Initiation
2	Concept Investigation/Business Case
3	Development
4	Validation/Implementation
5	Manufacturing Scale-Up/Commercialization

Table A. New product development process.

review.[1] Each gate has required deliverables and represents an overall project decision point. While every organization has its own new product development process tailored to its specific needs, they typically consist of the general activities in Table A.

This article focuses on manufacturing process development, which is only one, but a critical component of new product development. Manufacturing process development is typically accomplished during primarily the "development" stage of NPD projects (though some efforts might be conducted beforehand).

In the earlier stages of an NPD project, the new product, its business case, and its project plan are conceptualized, investigated, and detailed. But once the project team has demonstrated feasibility and has outlined the needs and scope of the project, management must make the critical decision whether to allow the project to move into a development stage. During a development stage, significant resources are utilized to turn the product design into a reduction-to-practice in a manufacturing environment. Engineering practices are an invaluable tool for new manufacturing process development.

The benefits of rigorous scientific and engineering practices during development stages quickly materialize during the subsequent stages of the NPD project. Often, these later stages include a final validation of the product performance claims and the manufacturing process. In addition, there is typically a pilot production stage involving scale-up and the evaluation of the performance and capability of the manufacturing process over time. If the manufacturing process is developed poorly, these stages will prove problematic. Ultimately, sound linkage of the manufacturing process to the appropriate scientific and engineering principles is absolutely critical. The engineering practices approach presented here provides a methodology for achieving this linkage.

Lean Six Sigma and Design for Six Sigma

Quality tools such as Lean Six Sigma and Design for Six Sigma introduce useful approaches to process improvement. Lean Six Sigma is based on the Define, Measure, Analyze, Improve and Control (DMAIC) principle shown in Table B. Design for Six Sigma (DFSS) is based on the Define, Measure, Analyze, Design, and Verify (DMADV) principle shown in Table C. Application of these concepts is essential when considering new processes, and they are incorporated into the Engineering Practices method proposed in this article.[2-3]

Phase	Activity
1	Define
2	Measure
3	Analyze
4	Improve
5	Control

Table B. The DMAIC approach of Lean Six Sigma.

Phase	Activity
1	Define
2	Measure
3	Analyze
4	Design
5	Verify

Table C. The DMADV approach of Design for Six Sigma.

The DMAIC philosophy is particularly valuable when making an improvement to an existing process with an historical baseline; however, from a research and development perspective, more is required when introducing an entirely new manufacturing process. Accordingly, the DMADV approach in DFSS is more geared toward new processes. But unlike Lean Six Sigma and Design for Six Sigma, the engineering practices method stresses the importance of gathering scientific and engineering facts, making engineering hypotheses, and building an engineering model to fundamentally understand the manufacturing process.

The Scientific Method

The phases of the scientific method are familiar from general education and early scientific training.[6-7] The scientific method applies not only to simple experiments, but also to the most complex experimental work involving intricate models. Engineering practices, as will be described later, has six phases that reflect the scientific method. The phases of the scientific method are listed in Table D and are compared to engineering practices.

Engineering Models

Developing manufacturing processes requires use of engineering models. In the simplest terms, we can define a model as a relationship between inputs and outputs. A good model

The Scientific Method	Engineering Practices
"Define your objective"	Objective Statement
"Gather the relevant information"	Engineering Review
"Form a hypothesis"	Preliminary Engineering Model
"Test the hypothesis experimentally"	Engineering Model Evaluation
"Refine and repeat"	Process Model Development
"Confirm"	Process Model Confirmation

Table D. Scientific method vs. engineering practices.

	Factor
1	Machine operators (“man”)
2	Machines/equipment
3	Materials
4	Methods/procedures
5	Measurements
6	Manufacturing environment (“Mother Nature”)

Table E. Six types of input factors, often referred to as the six Ms that can influence ultimate output.

also must include a visualization and/or understanding of what the inputs and outputs mean physically. Models can be empirical or theoretical. They can be as simple as a linear regression or as complex as a supercomputer computation.

The concept of “inputs” and “outputs” as they apply to a manufacturing process are mostly quite familiar, though sometimes quite subtle. Inputs typically include the machine parameters and settings and the raw materials. Yet often there are other factors, sometimes highly unanticipated, and these could require special root-cause analysis problem-solving methods.[8] The body of input factors could involve the factors listed in Table E.

The outputs are the measured characteristics that relate to the customer, product design, process, and performance needs. Just like inputs, we often mistakenly assume that useful and critical outputs are easily measured; frequently they are not. Ultimately, our model is only as good as the inputs and outputs that we can identify and measure.

Engineering practices uses the basic scientific method, applying the concept of a manufacturing process model. Examining Table C again, we can see that each stage of the scientific method has meaning in the context of an input-output manufacturing process model. “Defining the objectives” entails knowing what the outputs are, how to measure them, and what the values must be as required by the customer. “Forming a hypothesis” means making an educated prediction about the relationship between the process inputs and the outputs. “Testing hypotheses experimentally” requires proving the proposed relationships between inputs and outputs. “Refining and repeating” means conducting further experimentation, e.g., using Design of Experiments (DOE) to establish a more intricate relationship between the inputs and outputs.[9-10] “Confirming” includes running a final experiment in order to demonstrate that the model is correct. As will be explained below, engineering practices employs the scientific method in the context of a process model.

> *“Mirroring the scientific method and requiring use of quality and statistical tools, this methodology ensures a good science and engineering approach to the problems at hand.*

Engineering Practices Approach

A methodology called the engineering practices approach is introduced here for developing manufacturing processes for new products. This is a fluid phase-by-phase process with issues to be resolved and activities to be completed at each phase. Mirroring the scientific method and requiring

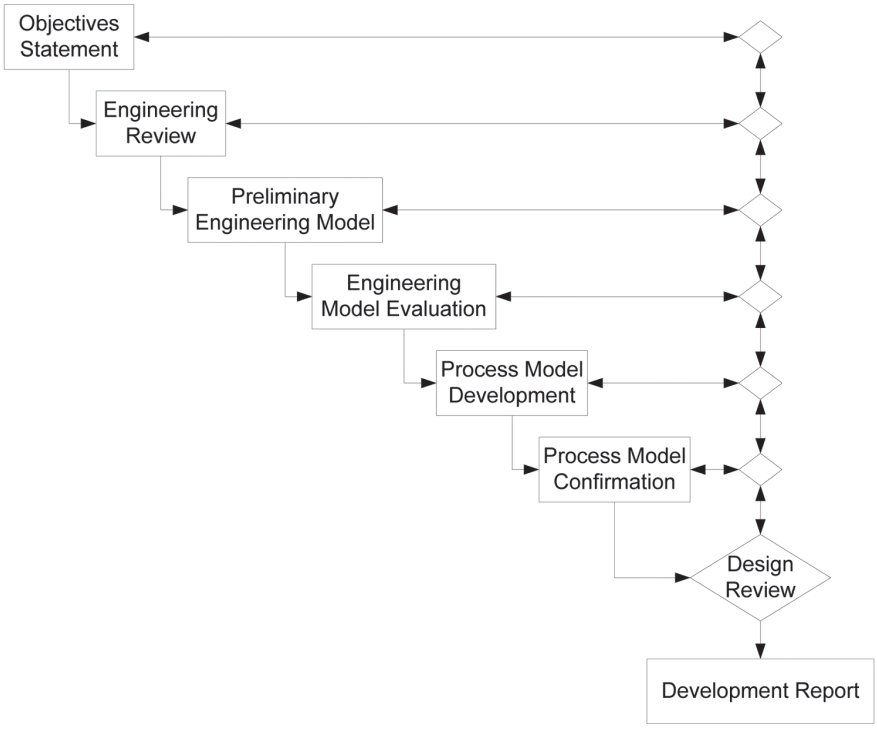

Figure 1. Phases of the engineering practices approach.

use of quality and statistical tools, this methodology ensures a good science and engineering approach to the problems at hand.

The process can be depicted as shown in Figure 1. There are six fluid phases, starting with "Objective Statement," that result in a final process. Each phase represents a stage of the scientific method. The results of the work, usually documented and detailed in a Process Development Technical Report, become an important part of the new product Design and Development Reviews (required for satisfying ISO 9001 part 7.3.4). The next section will review the six phases of engineering practices and the actions that occur in each phase.

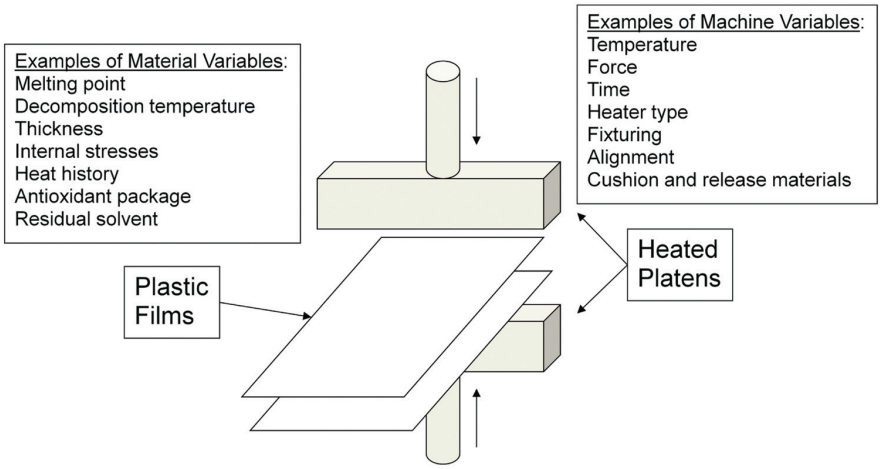

Figure 2. A thermal bonding process in which two plastic films are melted together by heated platens.

This process is not intended to represent a linear series of managed decision gates, but a flow of "semi-linear" activities. The project team proceeds from one phase to the next when the requirements of each phase are completed. There are no stage gate reviews; the decision to move forward can be made more informally, for example, by consensus at a cross-functional team meeting.

Note in Figure 1 that arrows are drawn from each phase back to any previous phase. During the development of a process, any number of new "learning events" could occur that could not have been anticipated. When it is discovered that scientific understanding must be refined, a project team following good engineering practices will step back to an earlier phase and conduct the activities deemed appropriate. Again, the decision point to move backward would be informal, as made in a cross-functional team meeting after the team reviews the data and discusses the technical dilemma.

For example, in the Process Model Development Phase, it could be discovered that there is an additional unknown factor unduly influencing the results. In this instance, the project team might consider revisiting engineering review activities in order to discuss the observations and develop a new model for what may be occurring. After experiments reveal the cause of the problem, the project team may decide to quickly return to the Process Model Development Phase.

Going "backward" may seem like it will introduce significant project delay. This, of course, can be true to a degree; however, forcing the project quickly down a rigid linear timeline rather than permitting a fluid pathway will ultimately incur greater cost. Often, this will take the form of development projects failing, manufacturing quality problems, murky validations, and ultimately longer project delays. Engineering practices, on the other hand, provides an opportunity to solidify understanding of the science and engineering principles and idiosyncrasies of a new product's manufacturing process before validation ever begins.

Stage 1: Objectives Statement

The first phase of engineering practices, the objectives statement, is a list of requirements that are ultimately translated into a set of specific output tests.

Consider the following example depicted in Figure 2. This is a thermal bonding process in which two thermoplastic films of similar composition are squeezed together by heated platens. One output for this process could be the peel strength of the bond which is formed. The project team may want to refer to an appropriate ASTM or international standard for conducting the test. Ideally, there would be a specific target value ensuring the required product performance. Another output could be a functional test of the fabricated final product, the customer-required test result being known.

For most new product development projects, particularly in order to meet the requirements of ISO 9001 section 7.3.3, the customer, design, performance, and process needs are clearly laid out in a negotiated design specification document for the new product. Thus, it is important that a design specification, as much as possible, be completed and finalized when process development begins.

Clearly, it is neither practical nor necessary to perform every single product performance test measurement described in the design specification as the output of each and every designed experiment (DOE). Thus, a key step in this phase is determining which requirements are the most applicable to the process or processes under consideration. The process output tests, or responses, should ultimately reflect the issues of highest risk and the attributes most greatly influenced by the process.

At this point, it is highly appropriate to critically evaluate

the design specifications themselves to determine whether the requirements are reasonable and if there is adequate evidence to support the needs. While much previous work, debate, and negotiation likely went into developing the design specification, it would be quite tragic to optimize a manufacturing process to meet requirements that are incorrect, unrealistic, or for any other reason require significant revision later in the project. As an analogy, when piloting a plane from New York to Las Vegas, we would not want to discover somewhere over Colorado that the destination from the beginning should have been Orlando.

Output tests also should, as best as possible, meet the general requirements of a good response. Ideally, they should be quantitative and readily measured. The needs of an output test also will be taken up in Stage 4: Engineering Model Evaluation.

Stage 2: Engineering Review

The purpose of the engineering review phase is to explore all relevant data and information pertaining to the product, manufacturing process, and the objectives statement. During a good engineering review, the project team will survey all important and relevant sources until able to form a working hypotheses or hypothetical model of how the manufacturing system works.

An important part of the engineering review is to assess whether the task at hand is part of a large previous body of knowledge or a relatively new area. If the new product and fabrication processes have similarities to others that have come before it, the sources of information should be, in most cases, relatively voluminous and easy to find. On the other hand, if the new product is unlike any that has been manufactured before, the search for information will be more difficult.

Sources of information can be internal and/or external to the organization. Common reliable sources of information are shown in Table F.

Internal	• Experts (internal)
	• Process literature from similar products
	• Internal technical literature
	• Internal networking websites
External	• Experts (external)
	• Vendor datasheets/literature
	• Patents
	• Books
	• Journal articles
	• ASTM and international standards

Table F. Common sources of information.

The experience of internal experts is perhaps the most indispensable form of information. Project teams should broadly consider all available expertise in the organization where applicable. Knowledge can be solicited and conveyed directly in conversation and correspondence. Alternatively, experts can be invited to participate in project meetings, such as data presentations, design reviews, brainstorming sessions, and Failure Mode and Effects Analyses (FMEAs).[11]

Internal literature is also a critical source of information. Today, more and more attention is being paid to methods of storing and retrieving organizational knowledge.[12-13] Often, key process information is found in quality documentation, including validation reports, Standard Operating Procedures (SOPs), and lot record forms. Often, written technical reports and memos are housed within searchable corporate database systems. More recently, companies are turning to web-based systems and "social networking" tools to deposit information and foster collaboration.[13]

The World Wide Web is clearly one of the mostly used tools for locating and/or downloading external information (typical sources listed in Table F). However, when using the internet, one should remember that information is only as reliable as its source. Websites are ever-changing and can reflect misconceptions and biases on the part of contributors.

Stage 3: Preliminary Engineering Model

The preliminary engineering model is a qualitative or semi-quantitative hypothesis of how the system operates. Thus, at this phase, we would state the model's inputs, outputs, and expected main effects and interactions.

A key to this is properly identifying all of the critical inputs and outputs. Inputs would typically include key process parameters, but also include other factors, such as raw materials. Outputs could include functional tests on end product, but also could include in-process measurements or examinations. When there are qualitative visual outputs, it is always a good idea to develop a semi-quantitative ranking scale. In this preliminary engineering model phase, tools such as a SIPOC diagram, shown in Figure 3, may be helpful.

Explaining the expected relationships between inputs and outputs is not always straightforward. Clearly, not all relationships are expected to be direct and linear. Typically, there will be relationships and/or interactions between input parameters. And often, there will be curvature and optimum conditions; therefore, these relationships should be understood and detailed before moving forward.

For the plastic thermal bonding example described previously (see Figure 2), inputs could include parameters such as temperature, force, and time. As part of the preliminary engineering model, the team may hypothesize, for example, that if the temperature is not sufficiently above the melting point of the plastic, the bond will not adequately form. Fur-

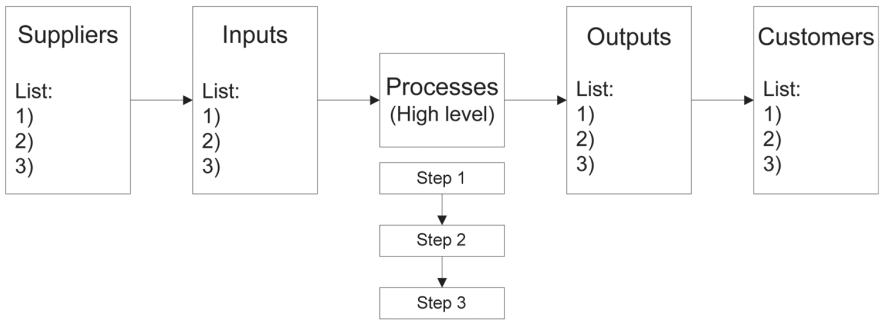

Figure 3. Diagram of SIPOC (Suppliers – Inputs – Processes – Outputs – Customers) Lean Six Sigma tool.

thermore, the team may add that if the temperature is too high, the seal may crack or burn. Regardless, it is important to first foment an engineering understanding of the system, though at this point, the understanding may be hypothesized from experience, but not yet proven for this specific manufacturing process

Also, there will be side effects and limitations. In the simplest case of a limitation, it may be impossible to modify an input parameter beyond a certain point. Alternatively, it may be impossible to produce product when parameters are combined in a certain way. Furthermore, modifying a parameter beyond a certain point may introduce an entirely new set of undesired risks or issues. Thus, all of these considerations must be part of the hypothetical model as they greatly affect the selection of final parameters.

Clearly, it is impractical to investigate every possible parameter. Thus, it is critical to determine what should be included and what should be omitted. This, of course, is helped by a sturdy technical understanding of the process itself. While investigating fewer parameters brings risk, investigating too many parameters dilutes the effort from what is most critical and important.

Often, there may be entire process steps that can be justifiably neglected. This is okay as long as the assumptions can be justified. For example, there may be a long successful history of running that particular process step with the new product in question, introducing nothing new that should reasonably alter it. The ultimate objective is to avoid, on one hand, taking foolish risks, and on the other hand, wasting valuable engineering time on unnecessary activities.

At this point, it would be advisable to review the new product's preliminary Failure Mode and Effects Analysis (FMEA) or initiate one if one does not exist.[10] The preliminary engineering model should speak to the process risks anticipated to be the highest.

Stage 4: Engineering Model Evaluation

Engineering model evaluation is the substantiation of the hypothetical model. That is, it is the generation of data that proves (or disproves) the preliminary engineering model.

This phase actually has multiple steps. The first step is demonstrating that the system is adequate for collecting data. The next step is planning the experiments. Finally, the experiments themselves, typically screening and ranging studies are run.

There are several objectives of showing the system to be ready for experimentation. Essentially, it important to assure that:

- There is sufficient control of the critical input parameters.
- The output measurements have the needed precision.
- The appropriate sample sizes have been calculated.
- The inputs can be varied enough to observe the expected range of performance.

This article is not intended to delve into the tools for accomplishing the above; however, equipment calibration, gage R&R studies, power and sample size calculations are central to this phase. It is also important to ensure that equipment meets the requirements of ISO 9001 section 7.6 for the Control of Monitoring and Measuring Equipment.

Once the system is acceptable for experimentation, the next objective is to prove (or disprove) the preliminary engineering model. This is ordinarily accomplished using screening and ranging studies. Screening studies test all potentially important variables in order to identify those with statistically significant effects. Ranging studies identify the feasible operating range of the process, seeking the edge of failure. In some situations, the edge of failure is never met, and in those cases, the objective is to demonstrate that the feasible operating range is much wider than the anticipated process range. Screening and ranging studies can be considered complete when and only when they successfully prove a complete preliminary engineering model.

At this point, it may be possible to utilize data from screening and ranging experiments to construct a quantitative predictive model. This model can either be theoretical or empirical, but should form the basis for the continued process development work.

At the end of this phase, it should be possible to propose a feasible range of operation of the parameters. This will not necessarily be the optimized range or even a capable range. However, it should address all of the key parameters and provide an approximate window of successful operation from which we can begin to optimize the process.

Stage 5: Process Model Development

During the next phase, process model development, a more

in-depth series of DOEs or other structured experimental studies are conducted. The results are used to generate or further refine the process model. The desired outcome of this stage is an optimized process window and a data-driven predictive model that supports it.

Ideally, a series of overlapping DOEs will be conducted until the process is optimized. There exist various methodologies for designing sequential experiments for the purposes of finding optimum process conditions.[14,15] The series of experiments should not only elucidate the optimum window in which to operate, but also provide the data needed to generate a strong input-output model for the process. In the thermal bonding process example (see Figure 2), a linear regression model might be developed for predicting bond strength as a function of temperature, force, and time (if those are the critical parameters determined).

In this phase, having had a good objectives statement is critical. This is because from the objectives statement comes the definition of the optimized state. Often there will be tradeoffs, and in those cases, reasonable methods must be employed to determine how to weigh them. But without an unambiguous and reasonably fixed desired endpoint, optimization to that endpoint is at best problematic.

Incorporating worst-case input materials into process experiments is highly recommended in this phase. Worst-case inputs could be actual raw materials or semi-finished products from other manufacturing steps. It may be useful to consult the SIPOC diagram. Especially because input materials can be more difficult to control, it is important to generate confidence that the process under development can handle the range of inputs that could arise during production.

Also, the process development team should be considering the eventual transfers of ownership that often occur after the product is approved for manufacturing. Typically, a research and development team may be mainly responsible for the process development stages and manufacturing process engineers subsequently responsible during production. Clearly, these hand-offs only work effectively when there is solid communication, interaction, and teamwork between all functions during development process.

In that regard, it is highly recommended that manufacturing process engineers and equipment operators be highly engaged with the development project at or before this particular phase. It is also important to clearly document process development work (i.e., in reports, process records, laboratory notebooks, etc.) so that all stakeholders have available to them the information they need to know.

Stage 6: Process Model Confirmation

The final phase of the engineering practices approach is process model confirmation. This phase consists principally of a confirmation run. The objective is to demonstrate that manufactured product will meet requirements at worst-case conditions.

Naturally, it is important to consult the process model when defining the optimized process window to be confirmed. From the process model, it should be possible to propose a specific region of operation for the final process. The confirmation run should be an exercise of running the manufacturing process at its final limits that, according to the process model, would produce the worst-case outputs.

Truly understanding what all of the critical inputs are is critical to designing a good confirmation run. As suggested previously, critical inputs will often include a set of machine parameters, but also can involve worst-case raw materials or worst-case inputs from other related processes. All worst-case variables would be included in the ideal confirmation run.

Clearly, a confirmation run should not be a complex DOE requiring many different combinations of inputs. Such experimentation is reserved for the previous two stages. The purpose of the confirmation is not to gain new insights, but simply to confirm that product manufactured at the worst-case limits meets requirements and that the results are consistent with the model.

In that respect, it is important to deal with inputs efficiently and logically. Often, inputs can be grouped together based upon their physical relationships to one another or upon how they impact the key outputs. Some input parameters may be important enough to vary, and some may be held constant. Often, two to four conditions are amply sufficient for a confirmation run. The key is to justify the experimental design with logic and physical reasoning.

Conclusion

This article has described a general approach to process development called engineering practices. The overall purpose of this methodology is to define the phases of effort that lead to a well-designed process. When followed, the engineering practices approach will ensure the use of good science, process modeling, and suitable quality and statistical tools. Ultimately, a research and development program dedicated to good engineering practices will result in fewer problems during product validation, scale-up, and full manufacturing.

The results of the process development work should be documented and assessed in a final report and/or design review. Ideally, these should be organized to reflect the above six phases as outlined below:

- Objectives Statement: state the process requirements. Refer to new product specification where applicable.
- Engineering Review: summarize the relevant technical information used to design the process. Provide references.
- Hypothesized Engineering Model: describe the engineer-

ing model, as best as it is understood, as a system of inputs, outputs, and effects.
- Engineering Model Evaluation: describe the screening/ranging studies that prove the hypothesized model.
- Process Model Development: describe the quantitative process model and how you arrived at the final process window.
- Process Model Confirmation: describe the confirmation run and how it demonstrates that the process will be successful even under worst-case conditions.

The key is to justify the experimental design with logic and physical reasoning.”

One might ask whether it is necessary to rigorously work through each phase of engineering practices for every new product development project. The answer, of course, is that every project is different, and each may require more or less emphasis at certain stages. This all depends on how much previous process knowledge exists[1] and how much risk can be tolerated.[2] These can often be assessed during the engineering review stage.

In thinking about the question above, it is useful to imagine two extremes. The first is a new “line extension” product that is very similar in almost every way to those the manufacturing plant has produced for decades with, let us suppose, stunning success. Furthermore, let us assume that the need for the new product is business-critical and that failure to launch the product quickly will have devastating consequences. Clearly, in this instance, a protracted development process is non-advantageous. Here, it might even be possible to recommend final process parameters during an engineering review and jump quickly to a confirmation run.

The second extreme is a new product unlike any other on the market. Furthermore, the manufacturing process involves new and unique machines and equipment. In this instance, regardless of the urgency of the business need, success is virtually impossible without a rigorous development process. Here, shortcuts based on risky assumption will often result in even longer delays. On the other hand, it is proposed that the engineering practices approach described here provides a strong framework for meeting success.

References

1. Kahn, K.,*The PDMA Handbook of New Product Development,* 2nd ed., Wiley, 2004.
2. George, M., Rowlands, D., and Kastle, B., *What is Lean Six Sigma?,* New York: McGraw-Hill, 2003.
3. Pyzdek, T., *The Six Sigma Handbook,* McGraw-Hill, 2000.
4. Bralla, J., *Design for Manufacturability Handbook,* McGraw Hill, 1998.
5. Yang, Kai and Haik, El, *Design for Six Sigma,* McGraw-Hill, 2003.
6. Hugh G. Gauch, *Scientific Method in Practice,* Cambridge University Press, 2003.
7. Wilson, Jr., E.B., *An Introduction to Scientific Research,* Mc-Graw-Hill, 1952.
8. Okes, D., *Root Cause Analysis: The Core of Problem Solving and Corrective Action,* ASQ Quality Press, 2009.
9. Montgomery, D., *Design and Analysis of Experiments,* 6th ed., Wiley, 2004.
10. Jiju, A., *Design of Experiments for Engineers and Scientists,* Elsevier, 2003.
11. Stamatis, D.H., *Failure Mode and Effect Analysis: FMEA from Theory to Execution,* ASQ Quality Press, 2003.
12. Alavi, M. and Leidner, D., “Review: Knowledge Management and Knowledge Management Systems: Conceptual Foundations and Research Issues,” *MIS Quarterly,* 25(1):107-136, 2001.
13. O’Dell, C. and Hubert, C., *The New Edge in Knowledge: How Knowledge Management Is Changing the Way We Do Business,* Wiley, 2011.
14. Box, G. and Draper, N., *Evolutionary Operation: A Statistical Method for Process Improvement,* Wiley, 1969.
15. Montgomery, D. and Myers, R., *Response Surface Methodology: Process and Product Optimization Using Designed Experiments,* Wiley, 1995.

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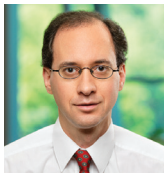

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Index of Refraction as a Quality Control Metric for Liquids in Pharmaceutical Manufacturing

by Brent Schreiber, Christopher Wacinski, and Ron Chiarello, PhD

This article presents a case study comparison of four analysis system technologies: pH, conductivity, osmolality, and refractive index for nine buffer chemical mixtures.

Introduction

The complex processes involved in the discovery and manufacturing of pharmaceutical products require advanced process analytical techniques for even routine applications. This requirement applies to large-scale manufacturing processes in stainless steel and glass vessels as well as single use disposable bag systems. Processes ranging from media and buffer preparation to sterilization and decontamination, require liquid chemical concentration and temperature monitoring and control to ensure peak process performance. Errors at any of these steps can result in the loss of costly product, compromise of product quality, or loss of time and labor. However, while each step in any pharmaceutical manufacturing process does represent a potential source of costly error, most steps also can be used as points of potential quality control. Close monitoring of key steps in manufacturing processes is therefore a critical part of good manufacturing process design.

Meaningful quality control of liquid chemicals requires reliable, easy to use, high precision, and fast response time analytical instrumentation. Current in-line methods that attempt to meet these requirements include pH, conductivity, and osmotic concentration. Briefly, osmotic concentration is the measure of solute concentration, defined as the number of osmoles of solute per liter of solution. All of these available technologies face limitations of dynamic range, linearity, precision, and Limits of Detection (LOD) and Limits of Quantification (LOQ). Furthermore, none of these methods are fundamental measurements of liquid chemical concentration. In the work presented here, a new instrument based on Index of Refraction (IoR) is presented and compared to pH, conductivity, and osmotic concentration. Since conductivity is in especially high use as a concentration monitor, special care is taken to compare IoR and conductivity measurement results.

Index of Refraction measurements offer an advantage over pH and conductivity because IoR is a direct measure of chemical concentration, while pH and conductivity are dependent on the electronic properties of fluids and are therefore by definition an indirect or inferred measurement of chemical concentration. In pharmaceutical manufacturing, IoR may be used in both upstream and downstream applications, while the results presented here are focused on downstream buffer preparation applications. Conventional refractometers operate by shining a single wavelength of visible light onto a prism that is in contact with the fluid under analysis. The IoR of the fluid is determined from the critical angle using Snell's Law. For most liquids, a simple calibration converts IoR values to chemical concentration in either ppm or wt%. A limitation of conventional refractometers is that they operate in a transmission mode, where light travels through the fluid to an optical light detector. This method has the disadvantage that the light signal is affected by diffraction and absorption effects of the fluid. The IoR analyzer used in this study operates in a reflection mode optical

geometry. This means the light reflects off the back side of an optical window (in contact with the fluid under analysis) and up into an optical light detector. In this way, the derogatory fluid effects of turbidity, diffraction, and absorption are completely mitigated, and the concentrations of opaque fluids are conveniently measured.

> *"...while each step in any pharmaceutical manufacturing process does represent a potential source of costly error, most steps also can be used as points of potential quality control.*

To explore the usefulness of IoR as a quality control metric, a set of experiments was performed involving measurement of known concentrations of commonly used buffer constituents and cell culture growth media ingredients dissolved in water. IoR measurements were compared with measurements of pH, conductivity, and osmotic concentration. From these experiments it was determined that measurement by IoR provided data superior to current methods of measurement of conductivity, pH, and osmolality of solutions with respect to accuracy, precision, linearity, Limit of Detectability (LOD), and Limit of Quantification (LOQ). LOD is defined as the lowest concentration of a substance that can be measured compared to a blank value (one sigma). In this study, LOQ is distinguished from LOD as the lowest concentration that can be determined with a reliability of ten sigma.

Experimental Methods

A comparison of pH, conductivity, osmotic concentration, and Index of Refraction (IoR) was made to determine the best method for routine liquid chemical concentration measurements. The measurements were made at the Bristol-Myers Squibb pilot plant in Syracuse, NY. The pH, conductivity, and IoR measurements were all made in-line and in real-time. Osmotic concentration measurements were made off-line using grab samples. Conductivity, pH, and osmotic concentration were selected based on their common use in the industry and as served as benchmarks for the IoR analyzer.

Each technique operates under differing principles of operation. Conductivity is a measurement of the electrical conductance per unit distance in an electrolytic or aqueous solution, and is limited in its ability to measure low or non-conductive liquids. The pH of a solution is a measure of the activity of the solvated hydrogen ion (H+). Osmotic concentration is the number of osmoles per liter of solution. The specific method used here is "freezing point depression" osmotic concentration, where differences in freezing points as a function of solutes added to solvents produces a concentration value of the solution. Freezing point depression osmotic concentration is limited as an off-line laboratory technique with relatively long response times.

Index of refraction is an optical technique that is a direct measure of the concentration of solutions. The IoR instrument used in this study was operated in a reflection geometry; meaning light is reflected off of the backside surface of an optical window in contact with the solution under analysis and into a photo-detector. This geometry offer the advantage that the IoR analyzer monitors the electronic density of the solution without interference from other optical effects, such as turbidity, diffraction, and absorption. Additionally, the IoR instrument includes temperature measurement in a single probe, thereby providing measurement of two key process parameters (concentration and temperature).

IoR, conductivity, and pH measurements were made simultaneously and in series. The pH and conductivity probes were placed in fluidic cells and buffer chemicals were circulated in closed loop. Osmotic concentration measurements were made off-line. Components of buffers that are commonly used in pharmaceutical manufacturing were serially added to various solutions. For each incremental addition of solute, measurements of index of refraction were compared with measurements of conductivity, and the data for the two methods of measurement were compared for accuracy, precision, and linearity. Buffer ingredients used in the studies included serial additions of 1. sodium chloride added to solutions containing fixed concentrations of monosodium phosphates, 2. sodium citrate added to solutions of fixed concentrations of monosodium phosphates, 3. monosodium phosphates added to sodium chlorides, 4. sodium citrate added to monosodium phosphate, 5. HEPES added to sodium chloride, 6. polysorbate 80 added to water, and 7. Triton X-100 added to water. HEPES, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid , is an organic chemical buffering agent widely used in cell culture. These seven buffers were chosen to best represent traditional slat buffers and newer buffers expected to realize increasing use in downstream processes. Limit of Detection (LOD) and Limit of Quantification (LOQ) measurements were made for a solution of 50 mM (mM = milliMolar) HEPES solution of pH 7 into which aliquots of NaCl were incrementally added. In these experiments, IoR was pitted against conductivity, pH, and osmotic concentration. LOD and LOQ values were calculated based on the standard deviation of the response and the slope of each instruments response as a function of concentration

Figure 1. Index of refraction analysis system. The analyzer sensor head contains a miniaturized optical sensor that is in contact with the liquid chemicals under analysis.

change. In a separate set of experiments for media preparation, several chemicals were analyzed in a comparison of the IoR instrument and conductivity. These included HAM F10, Dulbecco MEM, RPMI 1640, yeast extract and other media chemicals.

Results and Analysis

Figure 1 is an image of the IoR analyzer used in these studies. The analyzer consists of two fluidic cells (one fluidic cell is for redundancy), and digital control electronics. The fluid cell contains a miniaturized IoR sensor and thermocouple that is in contact with the liquid chemical under analysis. The digital electronics box performs analysis of the raw optical signal, real-time temperature concentration of the IoR and outputs either IoR or liquid chemical concentration. Figures 2 through 5 are data graphs representative of the results found for all buffer preparation processes studied here. Figure 2 shows an example of typical data acquired in this study for mixing of buffer salt solutions. In the figure, pH, conductivity, and IoR are plotted versus $NaPO_4$ (monosodium phosphate) concentrations. The measurements were performed by adding 20 mM spikes of $NaPO_4$ into 1 Liter of NaCl (sodium solution) 10 times to reach a total concentration of 200 mM of monosodium phosphate in sodium chloride. The pH showed insufficient response to $NaPO_4$ concentration changes. Conductivity and IoR both show excellent response to NaPO4 concentration changes. As was found for other buffer chemicals, IoR showed a higher degree of linearity than conductivity, and has a least squares (R2) fit confidence of 1.00 compared to conductivity's R^2 value of 0.98. The IoR's higher degree of linearity was found for all buffer solutions tested.

Figure 3 shows pH, conductivity, and IoR plotted as a function of HEPES concentration. Neither pH nor conductivity is able to monitor the HEPES concentration effectively. The conductivity data does a linear relationship with HEPES concentration; however, the slope is negative. For an appropriate conductivity response, conductivity should increase with increasing HEPES concentration. The negative slope can be explained by, as the HEPES concentration increases, the solution becomes increasingly less ionic and therefore conductivity decreases. For an appropriate concentration

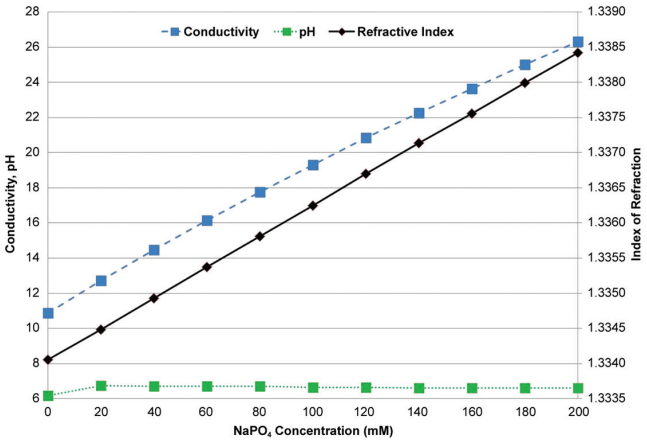

Figure 2. Index of refraction (right hand vertical axis) and conductivity and pH (left hand vertical axis) outputs are shown versus monosodium phosphate concentration in mM. Ten monosodium phosphate concentration spikes of 20 mM were added into a 1 Liter sodium chloride solution.

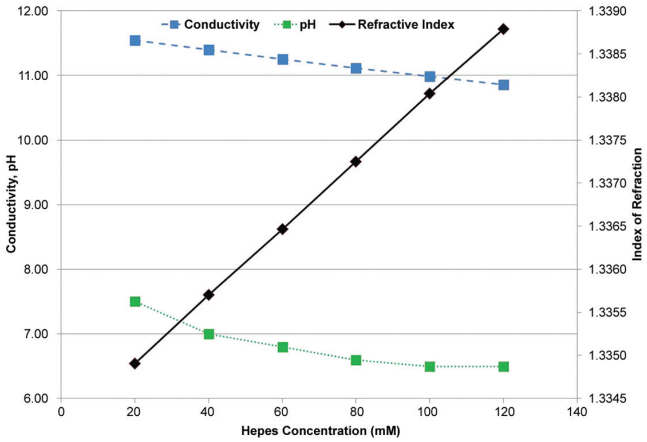

Figure 3. Index of refraction (right hand vertical axis) and conductivity and pH (left hand vertical axis) outputs are shown versus HEPES concentration in mM. Six HEPES concentration spikes of 20 mM were added into the sodium chloride solution for a total HEPES concentration of 120 mM in NaCl.

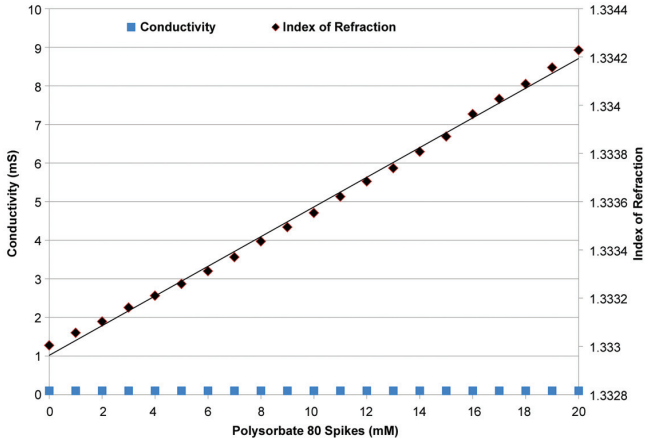

Figure 4. Index of refraction and conductivity are plotted as a function of Polysorbate 80 (P80) concentration spikes added to a 1 Liter NaCl solution. Conductivity shows no response, and is unable to measure P80 concentration.

response, one would expect that as the HEPES concentration increases the conductivity value also will increase, as it does for the salt solution in Figure 2. Therefore, conductivity fails to measure HEPES concentrations because HEPES is a non-ionic solution and the conductivity probe provides false HEPES concentration readings throughout the HEPES concentration range. Conductivity also failed to measure Polysorbate 80 and Triton X-100. IoR measures the HEPES concentration with a high degree of linearity over the entire concentration range studied.

Figure 4 shows IoR and conductivity plotted as a function of Polysorbate 80 (P80) concentration. P80 was added in 1 mL spikes to a 1 Liter NaCl solution. Conductivity fails to measure the P80 concentration. In contrast, IoR shows high linearity over the entire concentration range of Polysorbate

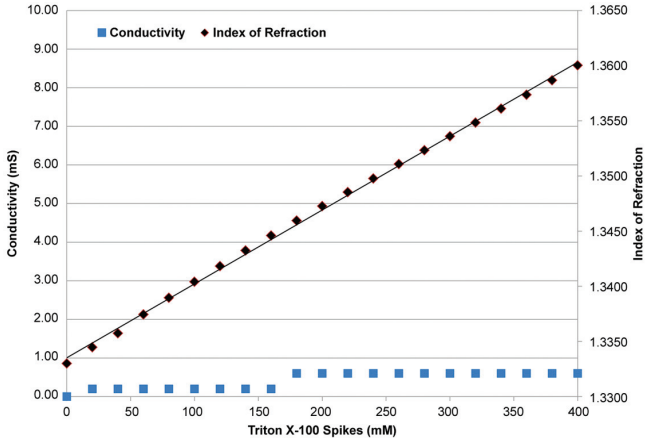

Figure 5. Index of refraction and conductivity are plotted as a function of Triton X-100 concentration spikes added to a 1 Liter NaCl solution. Conductivity shows no response, and is unable to measure Triton X-100 concentration.

Test (Spikes → Base)	Index of Refraction	Conductivity
$NaPO_4$ → NaCl	Yes	Yes
NaCl → $NaPO_4$	Yes	Yes
HEPES → NaCl	Yes	No
NaCitrate → $NaPO_4$	Yes	No
$NaPO_4$ → NaCitrate	Yes	No
P80 → H_20	Yes	No
Triton X-100 → H_20	Yes	No

Table A. Summary of the IoR and conductivity results for concentration measurements of the buffer solutions.

80. Figure 5 shows that IoR performed similarly well for Triton X-100, and that conductivity failed to measure Triton X-100 concentration changes.

Table A, shows a summary of the IoR and conductivity results for concentration measurements of the buffer solutions studied here. Index of refraction showed high linearity and was able to measure the entire dynamic range for all buffer solution tested. Conductivity failed to measure five out of seven buffer processes. Furthermore, the IoR demonstrated concentration measurement accuracies of ±10 ppm compared to ±100 ppm for conductivity.

Figure 6 shows LOD and LOQ for each of the techniques evaluated here. These results show a strong advantage for the IoR analyzer over conductivity, pH and osmotic concentration. For the IOR analyzer, LOD and LOQ were 0.70 and 2.33, respectively. Conductivity LOD and LOQ were more than two times worse than the IoR analyzers with values of 1.76 ad 5.84, respectively.

Figure 7 shows a comparison of the IoR analyzer and conductivity for yeast extract in a media preparation process. The IoR analyzer showed superior linearity to conductivity.

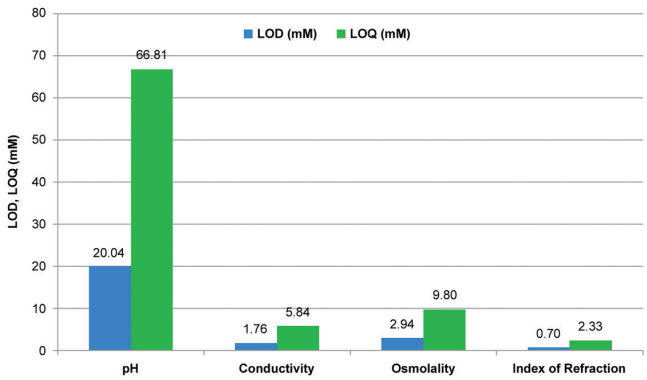

Figure 6. Limit of Detection (LOD) and Limit of Quantification (LOQ) for pH, conductivity, index of refraction, and osmolality concentration measurements.

Similar results were found for all other media preparation processes evaluated here.

For all experiments, solute concentration measurements using the Index of Refraction (IoR) analyzer were superior to those measured by conductivity in terms of linearity (by measured R^2 values of lines generated by the data), precision, accuracy (as determined best least squares linear fit), dynamic range, and reproducibility. In summary:

- For measurement of serial additions of NaCl into a solution of constant [$NaPO_4$], concentration measurement by IoR exhibited superior linearity and precision (as measured by R^2 value).
- For measurement of serial additions of $NaPO_4$ into a solution of constant [NaCl], measurement by IoR exhibited superior linearity and precision (as measured by R^2 value).
- For measurement of serial additions of HEPES into a solution of constant [NaCl], concentration measurement by IOR exhibited superior linearity, precision, and specificity. Since the slope of the line generated by the conductivity of additions of HEPES to solution was mostly flat, and in fact slightly negative, conductivity measurements have little specificity at all for HEPES in a buffered solution.
- For measurement of serial additions of sodium citrate into a solution of constant [$NaPO_4$], concentration measurement by IOR exhibited far superior linearity (conductivity measurement was nonlinear), precision, and range.
- For measurement of serial additions of $NaPO_4$ into a solution of constant [Sodium Citrate], concentration measurement by IOR exhibited superior linearity, precision, and specificity.
- For measurement of serial additions of Polysorbate 80 into water, concentration measurement by IoR exhibited superior linearity, precision, and specificity.
- For measurement of serial additions of Triton X-100 into water concentration measurement by IOR exhibited superior linearity, precision, and specificity.
- For the LOD and LOQ experiments against pH, conductivity, and osmotic concentration, IoR was 2.5 times more sensitive than conductivity, 4.2 times more sensitive than osmotic concentration, and 28.6 times more sensitive than pH for both limits of quantitation and limits of detection.
- For serially increasing concentrations of complex media, measurement by IoR exhibited superior linearity and precision, with higher R^2 values for data generated.

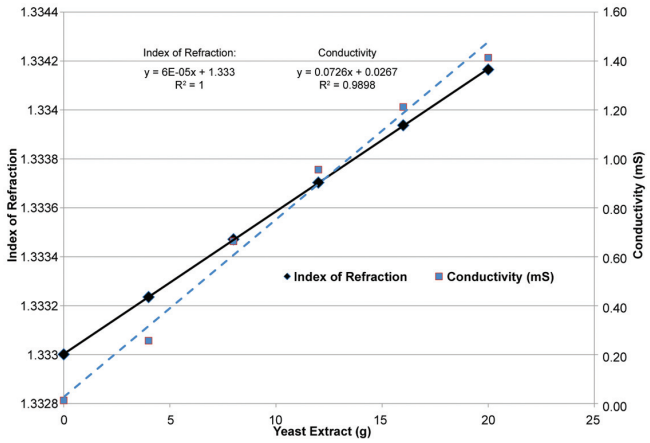

Figure 7. Index of Refraction (IoR) and conductivity plotted as a function of yeast extract (in grams). The IoR analyzer showed superior linearity than conductivity.

Discussion

These experiments demonstrate that metrology of process fluids by measurement of index of refraction is a viable and superior means of real-time, in situ quality control in pharmaceutical manufacturing as compared to pH, conductivity, and osmolality. Furthermore, the experiments demonstrate that a currently available device based on IoR exhibit significantly greater linearity and precision, as well as lower levels of detectability and quantitation than currently available fluid measurement devices which measure other fluid properties, such as conductivity, osmotic concentration, and pH. They also demonstrate that, as compared with conductivity and pH, measurement by index of refraction exhibits greater specificity and relevance for measuring the concentration of anionic solutes in any buffer or growth media containing them. As non-ionic solutes do not affect conductivity or pH, measurement of these properties provides little information when measuring the content of such solutes in prepared solutions. Furthermore, the behavior of solutions containing zwitterions (dipolar ions), such as HEPES is highly unpredictable; therefore, using pH and conductivity to measure the concentration of solution constituents that are zwitterionic is also not optimal. These attributes—superior precision, linearity, and specificity for non-ionic solutions and solutions containing zwitterionic (dipolar ion) ingredients—make measurement by index of refraction appropriate for quality control of many buffers and cell culture media essential for pharmaceutical manufacturing. Furthermore, it is likely that IoR also would be a highly relevant metric for validation of Clean-in-Place (CIP) solutions for fermentation and isolation tanks. The comparison to conductivity especially is based on the need for improved real-time, in situ concentration monitor, and control. In fact, in nearly all cases IoR is a superior method to conductivity for concentration measurements. However, conventional IoR is limited by its inability to speciate a chemical mixture. Therefore, absorption spectroscopy techniques such as Near-infrared (NIR) and Fourier Transform Infrared Spectroscopy (FTIR) are powerful concentration speciation tools for complex chemical mixtures.

Measurement by IoR has additional advantages. Because refractive index measurement only requires a beam of light

reflected off the surface of a process fluid, it is minimally invasive. As a consequence, it effectively eliminates any potential risks of contamination caused by fluid sampling, or potential damage to sensitive media contents due to application of voltage potential or other means of measurement. Furthermore, index of refraction measurement is virtually instantaneous, whereas other methods, such as sampling require more time. Measurement of index of refraction is also more likely to reduce human error as well.

This is not to say that index of refraction measurement has no disadvantages when compared with other quality control metrics. Specifically, conventional IoR measures the average concentration of a multicomponent fluid mixture, and lacks the capability to speciate the concentration of specific components in said mixture. IoR is also temperature dependent, and state-of-the-art IoR analyzers have real-time temperature compensation as a built-in feature. It is not to be inferred that index of refraction measurement should replace measurement by pH, conductivity, or osmotic concentration in all cases. On the contrary, pH, while currently a significantly less accurate measurement metric, is nevertheless a physical property of fluids which in and of itself can have a very direct impact on product quality. A solution's osmotic concentration or conductivity also might have a direct effect on product yield and quality; however, this is not true in all cases. Indeed, given the fact that critical constituents of many buffers and nutrient media are anionic and therefore have no impact at all on conductivity, it could be easily argued that, in such cases, index of refraction would be a metric that is far more directly relevant to overall product quality.

Likewise, equimolar amounts of two very different solutes could yield identical osmotic concentration readings, and the disparity between the two solutes would thus be undetectable by osmotic concentration measurement. It is unlikely that those two different solutes, giving the same osmotic concentration reading, would give the same IoR reading. Thus, for many applications, measurement of index of refraction of process fluids might well be a substitute for other metrics, while for other applications it more appropriately might be an addition to measurement by other physical parameters. In many such cases, the additional metric might be a critical one to safeguard product quality and yield.

Additional applications of IoR as a process quality control metric remain to be investigated, but might hold significant potential. It is likely that index of refraction's superior sensitivity might make it potentially useful in measurement of concentration and/or quality of final product. Less likely might be the ability of index of refraction to detect impurities such as endotoxin. Outside the realm of pharmaceutical manufacturing, IoR is also likely to be a beneficial metric. Additional applications of IoR include related industries such as microchip manufacture, plastics, food processing, brewing, winemaking, and cosmetics. But for all of these applications, IoR would offer the same thing—superior accuracy, precision, and linearity as compared with conductivity measurements.

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Follow-on Biologics: Will the New Biologics Price Competition and Innovation Act Live Up to the Waxman-Hatch 1984 Expectations?

by Michael R. Goodman

This opinion article presents a candid look at the motivations behind the new biosimilar legislation and if it really will be as influential as the Drug Price Competition and Patent Term Restoration Act of 1984.

The Patient Protection and Affordable Care Act (PPACA) has been a polarizing topic since its inception into law on 23 March 2010. Most of the criticism to the act has been on affordable coverage, federal and state funding, and coverage eligibility. The Biologics Price Competition and Innovation Act (as Title VII, Subtitle A of the PPACA) that established legislation for an abbreviated pathway for biological generics is a small section of the several thousand-page PPACA that was seemingly overlooked.

The concept of biosimilars or Follow-on Biologics (FOBs) has been a hot topic of debate in the international biotechnology and pharmaceutical industry for years following the 1984 Drug Price Competition and Patent Term Restoration Act (Waxman-Hatch Act). The Waxman-Hatch Act of 1984 was a bipartisan act that introduced the first abbreviated pathway for rapid regulatory approval of generic, Small Molecular Entity (SME) drugs. In the act, the most important but most inhibitory concept was the word "bioequivalence." The act required generic drugs to have equivalent physical, chemical, pharmacodynamic, and pharmacokinetic traits relative to the first moving branded drug (the standard). As soon as a patent expired for a branded small molecular entity, a generic drug with bioequivalent traits would be filed and assumingly approved via an Abbreviated New Drug Application (ANDA).

In 1984, complex biological drug products sourced from biological systems such as (but not limited to) recombinant proteins and cell lines were not relied on for therapeutic uses like they are today. These complex biological drugs are a fairly recent phenomenon. From complicated recombinant proteins to stem cells, biological therapeutics certainly have the most potential for medicinal therapies; however, biological-sourced therapeutics have been marketed for much of the 20th century. Simple biological drugs like Heparin Sodium have been licensed to market since the late 1910s.[1] The FDA approved the first of the highly technical and innovative biological drugs in 1982 to be marketed as recombinant insulin.[2] Now, many more patents on therapeutic entities are of biological origin and are expiring. Yet, only since the enactment of the PPACA has there been any enacted legislation that tackles the question of "bioequivalence" involving biologically-sourced entities. Unfortunately, the issue of bioequivalence with biologically sourced therapeutics is much more complicated than the SMEs captured in the Waxman-Hatch Act. I believe that there is merit in achieving an objective-based abbreviated pathway for FOBs, but that this pathway requires cautious examination far beyond that of a SME.

So far, innovations for new drug products have been

too slow to meet the demand generated by an increasing United States and European population and the new drugs manufactured are not capable of reaching the entire effected populations. In 2004, the European Medicines Agency (EMA) examined possibilities of a generic biological drug abbreviated pathway and published concept papers on the generic biological entities that showed similar effects to the original biological entity.

In 2005, the European Medicines Agency (EMEA) approved novel FOB (referenced as biosimilars) guidelines to encourage competition between pharmaceutical companies. The European Universal Health Care system was considered for allowing biosimilars to be approved through a fast-track regulatory process. The governments in the European Union (EU) hypothesized that the countries could create competition and spend less without compromising safety and efficacy.[3] The debate on biosimilars in the United States was and is still about "how similar" could a FOB be to a referenced biological entity.

> *"...understanding the true difference between a small molecular entity and a biological helps elucidate the reason why bioequivalence is not an option.*

The other problem with FOBs originates from the proprietary and nonproprietary steps in the respective biologic's manufacturing process. It is given that most biological entities are protected under the United States Patent and Trade Office (USPTO). As part of the numerous intellectual property associated with one biological entity, the process of manufacturing is generally captured in the claims of one or more of the patents. What are not included in the claims are specific characteristics related to the appropriate facilities, utilities, and equipment. These process-specific tangibles are a critical factor in method and process transfer that in many cases, companies send the exact equipment from the original facility to the new facility to maintain process equivalence. This option is not feasible when the patent-holding first mover is in direct competition with a generic manufacturer.

In order to understand the ramifications of this new legislation, it is important to understand the difference between biological and synthetic entities and why reproducing biological entities are highly variable even from process to process at the same facility. Unlike small molecular pharmaceuticals that are organically synthesized in a lab, a biological is an Active Pharmaceutical Ingredient (API) composed of sugars, proteins, nucleic acids, or a complex of them. They are produced from animal, plant, microbiological, or viral crude material. The FDA division that monitors and evaluates biologics is the Center for Biologics Evaluation and Research (CBER). Generally, CBER is responsible for monitoring pharmaceuticals, including vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins.[4] Under normal circumstances, a new biological drug application is filed in the United States under a Biologic License Application (BLA) and approved by CBER.

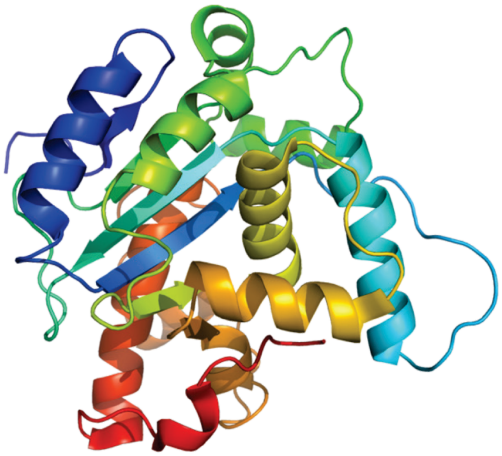
The EMEA did not redefine generic drugs to be similar, but not equivalent. Instead, it made an exception to their accelerated approval process. The EMEA defines a generic medicinal product as having:

- The same qualitative and quantitative composition in active substances as the reference product
- The same pharmaceutical form as the reference medicinal product
- Whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies[5]

The EMEA recognized that current analytical technologies are not able to fully characterize the large and complicated biologics. Biosimilars could not be completely characterized according to the same processes for the EMEA fast-track approval process for small-molecular genetics. In 2004, the EMEA explicitly made an exception to the 2001 directive. The European Directive 2004/27/EC was written to address "biological medicinal products" that are not equivalent, but similar. The directive eased the specification for a biological to be similar. It states that if there are differences in raw materials or manufacturing process between a pioneer biological drug and its follow-on, pre-clinical or clinical trials relating to these conditions must be provided.[6]

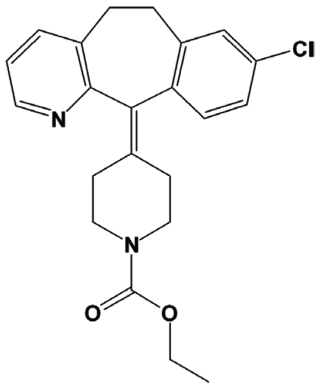
The 2004 European Directive requires comparability studies between the similar biological drugs. They compare physio-chemical, biological, pre-clinical, and clinical comparability. The requirements for clinical trials are based on pharmacovigilance, automatic substitution with the pioneer drug, quality, and efficacy.[3] The EMEA took strides to support biosimilars into the European market; however, the pathway is more similar to a pioneer drug application than that of a generic small molecular entity. Regulatory directives guiding the EMEA on FOBs are more open-ended to allow the agency to structure rigorous pre-clinical and clinical trials on a case-by-case basis. I believe that the EMEA's directives for defining acceptance criteria case-by-case are the best way to approve FOBs, but does not address the main concern for significantly more and cheaper biosimilars

Biological (Protein 3° Structure)



- Genetically engineered
- Expressed by living cells
- Post-translational modification
- Heterogeneous
- Species-specific activity
- Complex biological activity
- MW 5000 to >1,000,000

Small Molecular Entity



- Chemically synthesized
- Activity not species specific
- Well-define mode of action
- MW ± 1000

Figure 1. A visual representation of the tertiary structure of a protein compared to a small molecular entity.

reaching a larger portion of the afflicted European population. However, understanding the true difference between a small molecular entity and a biological helps elucidate the reason why bioequivalence is not an option.

Interchangeability and Analytical and Scientific Considerations

There are fundamental differences between the small-molecule and biological APIs. The FDA has traditionally been conservative in their interpretations of biologics and distinguishing them from small-molecule APIs that are formulated into drug products. However, the Agency correctly did not plan to be constructionists to the FD&C and Waxman-Hatch Acts. The root of the problem between the distinguishable APIs lies in their distinctive characteristics.

The Waxman-Hatch Act of 1984 was generated around small molecules that are synthesized in the lab. These small-molecule APIs start and end by in-lab organic synthesis and purification. Included in the Waxman-Hatch Act was another alternative pathway for modifications to marketed drug products that do not entirely circumvent the need for clinical trials, but on a subjective, case-by-case basis, reduces the length and required participants generally assumed in a full Phase Ito III clinical trial procedure for a new molecular entity. The 505(b)(2) pathway enables drug manufacturers to circumvent some or all of the early phase clinical trials by referencing previously performed applicable nonclinical and clinical trials on safety and efficacy of a marketed drug product.

Crude biological products are not synthesized in the lab. As previously stated, they are sourced from animal, plant, microbial, or viral origins. In contrast to typical non-biological drugs, biologics are 100 to 1,000 fold larger and more complex. The biologicals are also highly susceptible to variations in species, geographical origin, and even dietary activities of the biological source.

The impurity profiles of a synthesized small molecular entity can be determined from picture diagrams that predict and characterize intermediates throughout each step of an organic synthesis process. Likewise, the impure intermediates can be drastically reduced by various chromatography methods. In most cases, the final step in the organic synthesis ends with a purification process that purifies the desired API from what little is left of the impure intermediates that followed through the process.

Impurity profiles for biologics will always vary from one source to another. Porcine material from China will have different impurities than the same material sourced in the United States. Companies cannot reasonably prove that two different sources for the same biological entity can have the same impurity profile, i.e., impurities from food, pesticides, antibiotics, environment, and infections (viral and bacterial). Currently, the Waxman-Hatch Act would be infringed on by approving a FOB based on "bioequivalence." FOBs cannot be defined as equivalent between two manufacturers when there are unknown variables that cannot be assessed without nonclinical and clinical safety and efficacy trials.

The size and stereochemistry of generic small molecules allow for precise analytical characterization and detection when small changes arise in the manufacturing process. A single chemical formula can correctly characterize the molecular structure and composition of a small molecule makeup of tens to hundreds of atoms.[7] Analytical technologies are not yet capable of conclusively detecting small changes and variations to a biological matrix. For example, a Class 1 recall performed in early 2008 found that filler was introduced upstream in the biological purification process. The physical similarities between the filler and the drug substance were astonishing and could not have been detected by the normal analytical procedures used for final product testing. This example of an undetectable impurity is only one example of how critical it is to understand the complexities

and variability of changes to a biological matrix.

There are substantial differences between two biologics that are classified as "similar;" however, viral epidemiology has been a focal point of the FDA. The major concern is the viral load in varying biologics and the potential for those viruses to mutate from non-zoonotic to zoonotic. Complete viral profiles in certain biological sources are not possible. The requirement is to have a means of monitoring viral epidemiology. Different geographical locations have varying epidemics. Hypothetically, if a pioneer drug had an associated FOB, once a new virus emerges, the two drugs would not be equivalent and impose different safety risks.
There can be multiple avenues to take when synthesizing an organic small-molecule. In many cases, patents on synthetic processes for organic intermediates force other API manufacturers to find different routes to synthesize the desired end product. Unless there is a patent on the final product and that patent has not expired, the small molecule can be synthesized by multiple synthesis routes. Additionally, generic development of small molecules should have a more efficient development process than the innovated API. The purpose of a generic drug (and thus enactment of the Waxman-Hatch Act) is to market cheaper, bioequivalent drug products that reach a larger population of the afflicted United States populous.

The development process for biologics can be intrinsic and complicated. Steps for impurity inactivation, protein activation, therapeutic properties, and potencies are all tied into the manufacturing process. For a biologic to be equivalent or even similar to the pioneer drug, the process must be completely known and mastered. Unless the pathway for the biologic has somehow become public, information pertaining to the manufacturing instructions would be proprietary. Unless legislation is passed forcing drug master files to become public knowledge, the feasibility of achieving an equivalent or similar biologic is very low.

Like generic small molecular entities, manufacturers of FOBs are trying to prove that their generic is "interchangeable" with the brand name biologic. According to the FDA, a FOB will be considered interchangeable if:

- It is biosimilar to the reference
- It is expected to have the same clinical result
- It can be switched with the reference during multiple administrations without a risk to safety

In the draft guidance "Guidance for Industry – Scientific Considerations in Demonstrating Biosimilarity to a Reference Product," the FDA recognizes that even a minor difference between a FOB protein to a reference can significantly affect the safety, activity, potency, and purity of that protein. Even examples of purified sugars from animal sources will have different chemical and physical characteristics (such as varying positions of glycosylation on the sugar) dependent on the origin of the source. These variables make proving interchangeability nearly impossible. It is believable and even feasible that FOBs can show the same activity and potency of the reference; however, I believe that even our most capable analytical equipment and techniques do not draw a complete picture of a reference or the FOB. Additionally, the activity of the reference to the FOB may be similar in one pharmacological aspect, yet significantly different in another, unexamined system. To prove interchangeability, even biosimilarity, the FOB must show similarities in pharmacodynamics and pharmacokinetics in the entire system and not just the targeted part of that system. This nonclinical and clinical testing may even require more testing than what the branded drug underwent during the original clinical and nonclinical studies. This testing along with differing viral and microbial adventitious agents and even impurities with the same retention times as a known impurity make it nearly impossible and possibly as costly as developing and characterizing the branded drug product. Yet in the draft guidance "Guidance for Industry – Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product," the considerations for analytical similarities between the reference and the FOB should be based on the "known" quality attributes and performance characteristics of the specific reference product and not more extensive analytical studies on the currently unknown attributes. Unfortunately, it can be argued that the unknown quality attributes may prove vital, but remain unknown as to the overall "biosimilarity" of the reference and the FOB.

Economic Considerations

In 1960, Cutter Laboratories was sued for negligence and liability pertaining to their polio vaccine. The Gottsdanker v. Cutter case opened the floodgates for unreasonable lawsuits against pharmaceutical companies. After in depth litigation, the jury came back with the verdict that introduced "liability without negligence." This judgment has been used for more than 60 years to sue pharmaceutical companies for supposed side effects to their drugs. Even if there were no negligent and unlawful acts performed in the process, the pharmaceutical company still may assume liability.

The distinction between liability and negligence increases administrative costs to the pharmaceutical industry. When a pharmaceutical company loses or settles on a lawsuit, insurance pays the lawsuits. The insurance companies recoup their losses from tort by charging high premiums to the pharmaceutical companies. This causes the pharmaceutical companies to raise the prices of their drugs to cover the costs of the high insurance premiums. For example, in 2002 Merck was liable for supposed side effects from their drug Vioxx costing the company in total $4 to $6 billion. Litigations continued even after a 120-person study of Vioxx

showed post-operation recovery with potential for a decrease in post-operational narcotics. The study showed no complications for using Vioxx.[8] The malpractice attorneys are the only beneficiaries from these class action lawsuits.

Regardless of successful clinical studies and Biologics License Application (BLA), New Drug Application (NDA), or Investigational Device Exemption (IDE) approval, drug and medical device companies have a high insurance premium to protect the company from lawsuits. The newly innovated technologies in the biological field have the highest risk for these lawsuits. The technology is so new and state of the art that there is certainly the potential for liability.

Product liability is only part of the economic disincentive with formulating a FOB. According to the Generic Pharmaceutical Association (GPhA), the average cost of pioneer biological drugs to the consumer is $93.24 a day and even though the GPhA predicts that marketing FOBs will contribute to savings and improve access to health care,[9] the research performed by the Federal Trade Commission (FTC) does not correlate with these predictions. The FTC studied the FOBs competitors in Europe and the US. The studied concluded that the market of FOBs resemble brand-to-brand competition rather than the brand-to-generic drug competition. It is important to realize all the intrinsic parts of manufacturing biological drugs.[9]

Generally, pharmaceutical companies do not only rely on intellectual property to protect years of research and development, pre-clinical, and clinical trials. Tacit and codified knowledge (trade secrets) are commonly relied on in manufacturing instructions. Those secrets must be replicated in order to manipulate the biologic to possess therapeutic equivalence with the pioneer biological entity. Using current analytical techniques, i.e., Nuclear Magnetic Resonance (NMR) spectroscopy and chromatography, enables generic pharmaceutical companies to uncover the molecular structures of small-molecular APIs. Then by retro-synthetic analysis, process development assets can formulate processes to synthesize bioequivalent molecules. The process is anticipated to take three to five years to develop and cost between $1 and $5 million. On the other hand, because of so many "unknowns" in the process, FOB products commonly take eight to ten years to develop at a cost of between $100 and $200 million. This high cost of entry discriminates against small biotechnology companies that may have the analytical capabilities, but not nearly enough capital to market a FOB.[9]

The high requirements to show interchangeability and even biosimilarity of a FOB to the pioneer drug product stunts the price advantage a generic drug would expect to have. Even before the PPACA, the FDA had publically supported legislation for abbreviated drug applications for follow-on biologics. However, Dr. Woodcock described interchangeability as an undefined variable that is impacted at the discretion of the doctors that prescribe the biological therapies.[10] The ideal qualities that lead physicians to prescribe generic small-molecule drugs do not apply to biologics. Small differences in protein folding between two companies, activity, etc. will influence a physician's decision to prescribe a pioneer drug over its FOB. The lack of interchangeability will enable the branded manufacturer to continue charging monopoly prices and still outsell competition.

From a socioeconomic standpoint, when multiple generic competitors enter the small molecule drug market, the cost can decrease up to 80%; however, anticipating more than two or three FOB manufacturers to enter the same market is not realistic. The more realistic competitive structure between FOBs and pioneer drugs would be more brand-to-brand than brand-to-generic. Ultimately, the competition would force the brand drug to charge less than monopoly prices, but would only reduce at a maximum of 30%.[10] The brand manufacturer reaps considerable advantage for being the first mover over second and late movers into the market. The last factor is the risk of unregulated tort stunting companies from entering the biologic drug market. By factoring in these three current issues, the risks of developing and marketing FOBs outweigh the rewards.

The Pathway

The 351(k) application provides the new abbreviated pathway for FOB approval. The pathway in its primitive form is similar in concept to the 505(b)(2) pathway. The 351(k) application currently requires many of the same drug evaluations that a Biological Licensing Application requires except for a subjectively abbreviated human clinical trial.

The FDA intends to consider the "totality of evidence" in a FOB application. This includes comparative studies to a reference biologic (generally the brand drug). The current guidances on how to approach the comparative studies are still in draft; however, some of the major considerations necessary to determine biosimilarity are captured in Figure 2.[12]

The proposed 351(k) pathway takes a conservative approach to FOB approval. Although I agree with the approach, the testing is still somewhat subjective and the extensive analytical testing will inevitably be costly and taxing on the generic developer.

Considerations

There must be a way to accomplish the similar achievements that the Waxman-Hatch Act has over the last 30 years. I do not believe that the current process for FOBs will accomplish what it was set out to do. I also do not believe (as some do) that eliminating Intellectual Property (IP) or even further limiting the scope of patents is the answer. Instead, the legislation should change directions and attack the problem starting with the patent assignees rather than the second

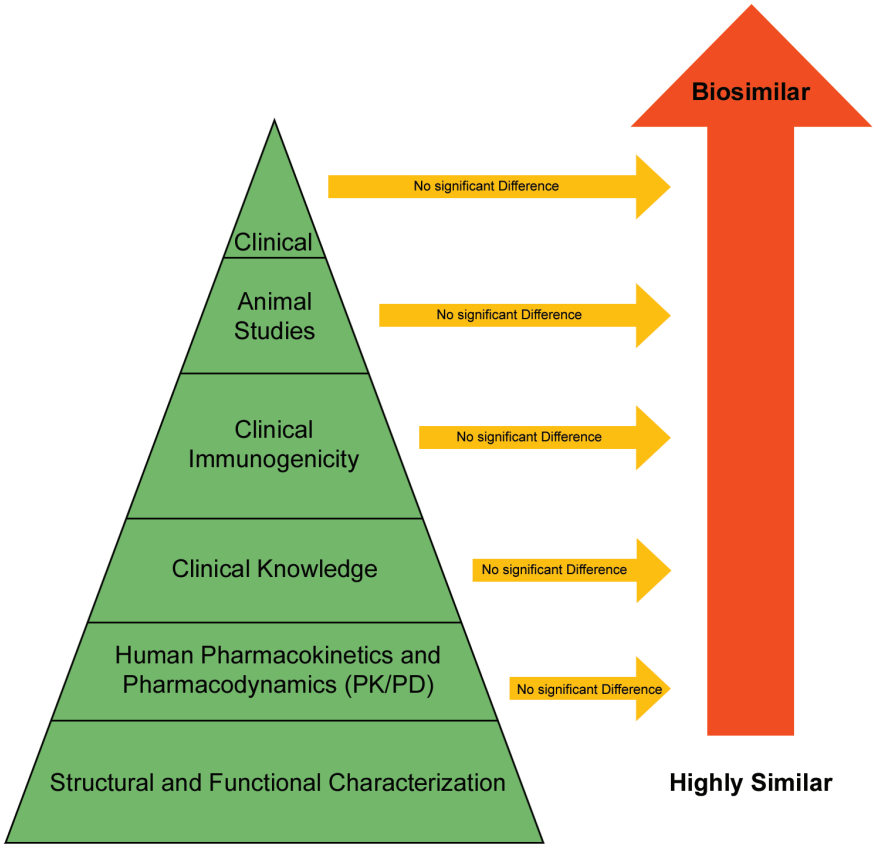


Figure 2. The subjective 351k biosimilars pathway.[12]

and late movers that manufacture the generics. In other words, there must be a renewed focus on the end user safety rather than forced competition between pharmaceutical and biotechnology companies.

I should disclose that I bleed capitalism and subscribe to the United States Patent and Trademark Office's (USPTO's) mission statement; however, the USPTO's purpose inherently discourages mass production of products that need to reach the end users. Patent claims bring enough light to the process to encourage development of similar drug products by late movers. Unfortunately (for the generic manufacturers), those claims do not give enough insight into much of the intrinsic aspects of the process for reverse engineering a biologic capable of interchangeability. Understandably, this was taken into account by acknowledging that a generic biologic is "good enough" as "similar." The current legislation encourages generic manufacturers to fill in the gaps in IP claims by guessing. These gaps will inevitably and significantly raise developmental costs of the potential FOB and these costs will be passed to the patient. All that is left is a high costing FOB that is similar, but not equivalent to the reference.

To mitigate these significant issues, the drafters should have focused on transparency between the branded drug and its FOB. Currently, the United States has groundbreaking biologics that are not available or obtainable by most of the patients that need them. In this case, creating competition was not the right move. Instead, the brand drug manufacturer should have been given incentives to play a role in bringing FOBs to market. This way, FOBs would be "more similar" to the reference by filling in many of the gaps that generic FOB manufacturers are currently facing. With more and "better" FOBs on the market, many more patients can get what they need to mitigate or even remediate the indications they struggle with. It is time we taper back the idea of forced (yet irrelevant) competition and try and achieve a better sense of collaboration in the industry.

Conclusion

The legislation to enable an abbreviated pathway for FOBs was inevitable. I caution the enthusiasts that FOBs will not have the same impact on cost reduction that bioequivalent generic SMEs had following the ratification of the Waxman-Hatch Amendment in 1984. Biologics are too complicated to compare to SMEs.

The procedures used to reverse-engineer synthesized molecules cannot be performed for biological entities with facets that in many cases, are independently affected by intrinsic and even unknown parts in the process. It is naïve to classify a biological entity as similar in chemical (2°) characteristics and structure, but has differences in the tertiary (3°) structure. This alone affects the activity of that biologic and could be arguably a completely different protein structure.

An unmentioned risk in all biological entities is the concern for adventitious agents. Viral and other microbial contamination is a risk that can only be mitigated, but not necessarily eliminated. The microbial loads in the original biologic may be acceptable, but the FOB microbial loads may be too high or even more likely, unknown to even exist in the formulated product. The disparity in possible adventitious agents is another cause for concern with FOBs.

Although this opinion is seemingly pessimistic, there is a need for an increase in supply of many of the new biological entities and I do not see how the legislation will significantly help. The current manufacturing processes for biologics can be slow and expensive. This problem is the underlying source for the need for other manufacturers to be able to manufacture and market similar drugs that act on the same patient indications. Allowing generic biologics to enter the

market (assuming the biosimilarities are acceptable) will add some level of competition, but more importantly, reach a greater number of the populous that a single drug manufacturer could not possibly accommodate.

Another concern with this new pathway is how biosimilarity determined and by whom. Hopefully the takeaway is that determining biosimilarities is subjective and not objective because the analytical, nonclinical, and clinical testing probably is not comprehensive enough to entirely characterize the similarities and differences between the reference and the potential FOB. The answer is that the FDA is largely responsible for deciding if two biologics are similar. Is this a responsibility that the FDA can and is willing to accept? As of September 2012, the FDA had not received a 351(k) application although there were 11 INDs and 30 pre-IND meetings with the FDA pertaining to potential FOB applications.[12]

In general, I believe an abbreviated pathway for FOBs to enter the market was necessary; however, the motivation surrounding the pathway should not have been to reduce the cost by creating competition. In fact, the work required to prove interchangeability and/or biosimilarity is so comprehensive that providing "meaningfully cheaper" alternatives to the branded generic is not feasible. The focus of the legislation should have been to motivate and even incentivize companies with branded biologics going off patent to cheapen their product and collaborate with companies that are willing to manufacture biosimilars. The primary goal should be to manufacture more acceptable product and have a cost reduction be a welcomed byproduct. The new biosimilar abbreviated route of approval will not significantly impact the amount of available therapies to patients nor reduce the drug shortages experienced when a manufacturer cannot produce enough or any of the formulated drug product that many people are now dependent on.

References

1. Linhardt R., "Heparin: An Important Drug Enters its Seventh Decade," *Chemistry & Industry,* Version 2, 1991, pp.45–50.
2. Rubin, Rita, "For Many Biological Drugs, "On the Market" Doesn't Mean Safe," *USA Today,* 2008.
3. Zuñiga, L. and Calvo, B. "Biosimilars Approval Process," *Regulatory Toxicology and Pharmacology,* 2009.
4. CBER Vision & Mission, 2009, http://www.fda.gov/AboutFDA/CentersOffices/CBER/ucm122878.htm.
5 *Directive 2001/83/EC of the European Parliament and the Council of 6 November 2001 on the Community Code Relating to Medicinal Products for Human Use,* Office Journal of the European Communities, 2001.
6. *Directive 2004/27/EC of the European Parliament and the Council of 31 March 2004 on the Community Code Relating to Medicinal Products for Human Use,* Office Journal of the European Communities, 2004.
7. *PhRMA Scientific Comments for Docket #2004N-0355,* Web, Dec. 2009, http://www.fda.gov/OHRMS/dockets/dockets/04n0355/04n-0355-cr00001-01-vol5.pdf.
8. Horattas, M.C., et al., "Does Preoperative Rofecoxib (Vioxx) Decrease Postoperative Pain with Laparoscopic Cholecystectomy?" *The American Journal of Surgery,* 2004, Volume 188. pp. 271-276.
9. GPhA. AARP Press Release: *AARP "Rx Watchdog Report" Highlights Need for Congressional Action to Provide Generic: Competition for Biologics Competition Would Lower Medicare Part D Costs for Life Saving Specialty Drugs,* GPhA Press Release 2008, Web, (Dec. 2009). http://www.gphaonline.org/media/press-releases/2009/02/12/aarp-rx-watchdog-report-highlights-need-congressional-action-provide.
10. Wroblewski, M et al., "Emerging Health Care Issues: Follow-on Biologic Drug Competition," Federal Trade Commission Report, June 2009, © Federal Trade Commission.
11. Woodcock, J. "Interview on Follow-on Protein Products before the House Committee of Oversight and Government Reform 2007," Web, Dec. 2009. http://www.fda.gov/NewsEvents/Testimony/ucm154070.htm.
12. Sherman, Rachel, "Biosimilar Biological Products," 2012, Biosimilar Guidance Webinar.
13. Malkin, Brian, "Biosimilar Reviews 'Under-Resourced' at FDA Woodcock Reports in DIA Meeting", FDA Lawyers Blog – Frommer Lawrence & Haug LLP 13 Sept. 2012.
14. *Follow-On Biologics,* Hearing of the Committee on Health, Education, Labor, and Pensions, 2007.

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Global Regulatory News

International

ANZTPA's Possible Joint Regulatory Scheme for Therapeutic Products[1]

In June 2011, the Australian and New Zealand Governments have agreed to proceed with a joint scheme for regulation of therapeutic products (that is, medicines, medical devices, biological and others) to be administered by the Australia New Zealand Therapeutic Products Agency (ANZTPA).

The Heads of the current regulatory agencies in Australia and New Zealand, TGA and Medsafe are inviting participants to discuss high level aspects of a possible framework for regulation I of therapeutic products under the joint agency. The possible framework has been developed against the background of the Trans-Tasman Mutual Recognition Arrangement that aims to develop a more integrated trans-Tasman economy by removing regulatory impediments between Australia and New Zealand and to enable goods to be traded freely between them. It is also based on the Treaty, an Agreement between the Government of Australia and the Government of New Zealand for the establishment of a joint scheme for the regulation of therapeutic goods, signed by both countries in 2003.

The objective is to develop a responsive and cost-effective regime for regulating therapeutic products that is consistent with international best practice.

ICH E2C(R2) Guideline Reaches Step 4 of the ICH Process[2]

The ICH E2C(R2) Guideline on Periodic Benefit-Risk Evaluation Report reached Step 4 of the ICH Process in November 2012 and now enters the implementation period (Step 5). The purpose of this revised guidance is to ensure that the periodic safety update reports for marketed drugs have the role of being periodic benefit-risk evaluation reports by covering: Safety evaluation, evaluation of all relevant available information accessible to Marketing Authorization Holders (MAHs) and benefit-risk evaluation.

The final Guideline is now available for download under the ICH Efficacy Guideline page at http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html.

ICH S10 Guideline Reaches Step 2 of the ICH Process[3]

The ICH S10 Guideline on Photosafety Evaluation of Pharmaceuticals reached Step 2 of the ICH Process in November 2012 and now enters the consultation period (Step 3). This new Guideline on photosafety testing will be a valuable adjunct to the guidance provided in the M3(R2) Guideline.

The draft Guideline is now available for download under the ICH Safety Guideline page at http://www.ich.org/products/guidelines/safety/article/safety-guidelines.html.

ICH Steering Committee Revises the S1 Strategy[4]

In November 2012, the Steering Committee endorsed the revision of both the S1 Concept Paper and Business Plan to provide clarification concerning how the prospective data gathering period should be integrated in the normal ICH Step process. The revised S1 Concept Paper and Business Plan now describe the S1 strategy which consists of first preparing a draft "Regulatory Notice for Public Input" to be issued by each ICH regulatory health authority to solicit comments from the public to the proposal, the procedure, and the specific weight-of-evidence criteria. A final "Regulatory Notice" is planned to be published in June 2014 and will mark the beginning of the prospective data collection period. After collecting and incorporating results from the prospective analyses, a Step 2 document is planned to be published in November 2016, and a Step 4 document finalized in November 2017.

U.S. and Canada Working Together to Provide Access to Needed Veterinary Drugs[5]

The first simultaneous review and approval of a veterinary drug by the United States and Canada marks a successful start to a collaboration aimed at providing quicker access to needed veterinary medicines. The collaboration is also intended to remove trade barriers and reduce costs for consumers, regulators, and manufacturers.

Chinese SFDA Commissioner and Deputy Commissioner Met with Assistant Deputy Minister of Health Canada[6]

On 10 December 10, 2012, SFDA Commissioner Yin Li and Deputy Commissioner Bian Zhenjia respectively met with the delegation led by Mr. Paul Alfred Maurice Glover, Assistant Deputy Minister of Health Canada Health Products and Food

Branch. Both sides reviewed the cooperation in the field of drug supervision and exchanged opinions on implementation of GMP, monitoring of adverse reactions, experience on joining PIC/S, supervision on traditional Chinese medicines, and supervision system of international drug regulatory agencies. Main directors of SFDAs Department of International Cooperation, Department of Drug Safety and Inspection, and relevant directors of Center for Drug Certification of SFDA attended the meeting.

European Union and Russia Partner for Modernization[7]

Cooperation on medicinal products is specifically considered in the Sub-Group on Pharmaceuticals of the Health dialogue. The current activities of this subgroup are focused on important issues such as:

- Legislation relevant to medicinal products
- Clinical trials
- Pharmacovigilance
- Orphan products and biosimilars
- GMP and details of registration procedures

Asia/Pacific Rim

China

Chinese SFDA Cracks Down on Illegal Internet Pharmacy Sales[8]

In order to ensure drug safety for the public, from February 2012, the State Food and Drug Administration (SFDA) carried out the special operation on strengthening the supervision of drug information service and drug selling over the Internet, stringently cracking down on releasing false drug information and selling drugs illegally over the Internet. Throughout the past year, local drug regulatory authorities carried out the SFDA's overall deployment and worked actively. The special operation has achieved notable results.

Chinese Government Agencies Jointly Promoting the Implementation of Newly Revised GMP[9]

A notice on accelerating the implementation of newly revised GMP and promoting pharmaceutical industry upgrading was recently jointly issued by the State Food and Drug Administration, National Development and Reform Commission, Ministry of Industry and Information Technology and Ministry of Health. Under the original standard and schedule, the four government agencies advanced incentives in merger and reorganization, certification and inspection, examination and approval, contract manufacturing, price adjustment, bid procurement, and technical improvement to encourage and guide drug manufacturing enterprises to meet the requirements of the newly revised GMP.

India

Order Issued Ensuring Rights/ Safety of Clinical Trial Subjects in India[10]

The Directorate of Health Services issued an order that the Ethics Committee review and accord approval to clinical trial protocol in order to ensure that trials are conducted according to GCP guidelines and other guidelines published by CDSCO as well as applicable regulations to safeguard the rights, safety, and well-being of all trial subjects.

India's National Vaccine Regulatory Authority Declared Functional Against WHO Assessment Indicators[11]

As a result of an assessment, WHO assures that the regulatory oversight of National Vaccine Regulatory Authority for vaccines meets international standards.

India Publishes Guidelines for Good Distribution Practices for Pharmaceutical Products[12]

The objective of these guidelines is to ensure the quality and identity of pharmaceutical products during all aspects of the distribution process. These aspects include, but are not limited to procurement, purchasing, storage, distribution, transportation, documentation, and record-keeping practices.

These guidelines are intended to be applicable to all persons and outlets involved in any aspect of the storage and distribution of guidelines on good distribution practices for pharmaceutical products from the premises of the manufacturer of the product to the person dispensing or providing pharmaceutical products directly to a patient or his or her agent. This includes all parties involved in trade and distribution of pharmaceutical, including the manufacturers of bulk, finished products, wholesalers, as well as others such as suppliers, distributors, government institutions, international procurement organization, donor agencies and certifying bodies, logistics providers, traders, transport companies, and forwarding agents and their employees as well as health workers. It also covers biological products in general.

Malaysia

Malaysia Enacts New Drug Registration Guideline[13]

This guideline, which went into effect 1 January 2013, can be downloaded at http://portal.bpfk.gov.my/newsmaster.cfm?&menuid=52&action=view&retrieveid=213.

Europe

European Union

European Medicines Agency Reviews its Operations and Prepares for Reorganization in 2013[14]

The European Medicines Agency has begun a review of its operations and

processes, focused on increasing the efficiency of its scientific activities and information- and communication-technology operations. As part of this process, it will focus on the support provided to the Agency's scientific committees to help them deliver high-quality, consistent opinions. The Agency expects this process to result in a significant reorganisation of its staff during 2013.

European Medicines Agency's Management Board Endorses Work Program 2013[15]

The European Medicines Agency's Management Board, at its meeting on 13 December 2012, adopted the Agency's work program and budget for 2013. The Agency's priorities will be to continue to ensure that assessment activities are conducted to the highest scientific levels, to increase efficiency in its activities, and to develop initiatives for greater transparency and communication with stakeholders. Further specific drivers include the continued implementation of the pharmacovigilance legislation and the new falsified-medicines legislation, and the planned revision of the veterinary medicines legislation.

In 2013, the Agency expects a stable total number of applications for human medicines with 100 applications in 2013. These include some 54 applications for new medicinal products (excluding designated orphan medicines), 20 new orphan medicines, and 20 generic applications (2012: 52, 13 and 39 respectively). Some 10 applications for new veterinary medicines are expected, with three generic applications (2012: nine and three respectively).The work program is accompanied by a budget of €231.6 million ($309 million), an increase of 4.1% over 2012, which includes fee revenue of €179.8 million ($239.9 million) (3.8% increase compared with 2012, this increase is mainly due to inflation) and a European Union (EU) contribution of €39.2 million ($52.3 million).

Public Consultation on the Revision of EU Commission Guidelines on Good Manufacturing Practice Medicinal Products[16]

The EU launched a public consultation of the following revised guidelines on good manufacturing practice: Chapter 3 - Premises and Equipment; Chapter 5 - Production; Chapter 6 - Quality Control; and Chapter 8 - Complaints, Quality Defects, and Product Recalls. Comments are due by 18 July 2013.

Denmark

Danish Health and Medicines Authority Publishes New Guideline: Renewal of Marketing Authorization for Nationally Authorized Medicinal Products[17]

Pursuant to section 27 of the Danish Medicines Act, a marketing authorization must be renewed after five years. The marketing authorization holder must submit a renewal application not later than nine months (human medicinal products) or six months (veterinary medicinal products) before expiry. Once an authorization has been renewed, it is valid for an unlimited period of time. However, if the benefit/risk ratio so dictates, the Danish Health and Medicines Authority may decide that an additional 5-year renewal is required. For more information, see http://laegemiddelstyrelsen.dk/en/topics/authorisation-and-supervision/licensing-of-medicines/renewal-of-marketing-authorisation/guideline-on-application-for-renewal-of---horisation.aspx.

Danish Health and Medicines Authority Publishes Annual Report on Human Tissues and Cells 2011[18]

The annual report for human tissues and cells for 2011 has been prepared pursuant to the Danish Tissue Act and is based on reports submitted by tissue establishments and gynaecology clinics in Denmark in the period January to December 2011. The full report can be found at http://laegemiddelstyrelsen.dk/~/media/3753F2FF5378466387D731260AD3F4E1.ashx.

Great Britain

British MHRA Publishes Medicines Reclassification Guidance[19]

Following the announcement in the Chancellor's Autumn Statement, the Medicines and Healthcare products Regulatory Agency (MHRA) has a new, streamlined procedure to speed the process of moving medicines from prescription-only to over-the-counter medicines.

The new procedure is underpinned by a new guideline on "How to change the legal classification of a medicine in the UK" published on the MHRA website. The new process outlined in the guideline could cut the time from application to decision by three months or more.

North America/South America

Canada

Health Canada Publishes Summary Report of Drug GMP Inspection Program[20]

In this report, Health Canada provides data on the drug GMP Inspection program. Over a five year time frame, the examples of the most common observations cited during GMP inspections include:

- Process validation for critical production processes not conducted or incomplete
- Incomplete manufacturing procedures/batch documents; failure to follow manufacturing procedures
- Incomplete packaging documents or procedures
- Inadequate/lack of quality agreements
- Inadequate/lack of recall system/procedure

- Absence of/ inadequate self inspection program
- Inappropriate procedures for handling storage and shipment of drug products with respect to temperature requirements
- Laboratory operations issues

Summary Report of Inspections of Cells, Tissues, and Organs Establishments Conducted from August 2009 to June 2012[21]

This summary report provides the result and analysis of Cells, Tissues, and Organs (CTO) program inspections conducted by Health Canada from August 2009 to June 2012. This is the first summary report issued since the inspection program was launched in August 2009. The objective of sharing inspection results, anonymously, is to increase awareness of compliance with Canadian regulatory requirements within the CTO community, while maintaining the confidentiality and privacy of those involved in the inspections. The document can be found at http://www.hc-sc.gc.ca/dhp-mps/compli-conform/info-prod/cell/report-rapport_2009-2012_CTO-eng.php.

United States

US Publishes Strategies for More Successful Drug Trials[22]

In recent months, drug developers have succeeded in bringing important drugs to market for cystic fibrosis, cancer, and other conditions by employing strategies for achieving greater clinical trial success. FDA issued a draft guidance that spells out how drug developers can use such strategies, known as clinical trial enrichment, to greatly increase the likelihood that data collected during a clinical trial will demonstrate that an effective drug is effective. These are potentially powerful strategies for the pharmaceutical industry because appropriate use of enrichment could result in smaller studies, shortened drug development times, and lower development costs.

U.S. Court Voids Drug Rep's Conviction, Cites Free Speech[23]

A divided federal appeals court threw out the conviction of a sales representative for promoting off-label use of a prescription drug, a ruling that could make it harder for the government to police how drugs are marketed and sold. The 2nd U.S. Circuit Court of Appeals in New York found that the sales representative's free speech rights under the First Amendment had been violated.

References

1. Australia New Zealand Therapeutic Products Agency, http://www.anztpa.org/consultation/Discussion_paper-ANZTPA_regulatory_scheme-20130107.htm.
2. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, http://www.ich.org/ichnews/newsroom/read/article/ich-e2cr2-guideline-reaches-step-4-of-the-ich-process.html.
3. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, http://www.ich.org/ichnews/newsroom/read/article/ich-s10-guideline-reaches-step-2-of-the-ich-process.html.
4. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, http://www.ich.org/ichnews/newsroom/read/article/steering-committee-revises-the-s1-strategy.html.
5. US Food and Drug Administration, http://blogs.fda.gov/fdavoice/index.php/2012/12/u-s-and-canada-working-together-to-provide-access-to-needed-veterinary-drugs/.
6. Chinese State Food and Drug Administration, http://eng.sfda.gov.cn/WS03/CL0757/76878.html.
7. European Commission, http://ec.europa.eu/health/international-activities/bilateral-relations/index_en.htm#fragment4.
8. Chinese State Food and Drug Administration, http://eng.sfda.gov.cn/WS03/CL0757/77556.html.
9. Chinese State Food and Drug Administration, http://eng.sfda.gov.cn/WS03/CL0757/77555.html.
10. Indian Central Drugs Standard Control Organization, http://www.cdsco.nic.in/Order_ensuring_right_safety_of_ct.pdf.
11. Indian Central Drugs Standard Control Organization, http://www.cdsco.nic.in/who%20nra%202013.pdf.
12. Indian Central Drugs Standard Control Organization, http://www.cdsco.nic.in/GDP%20final%20draft%20for%20pharmaceutical%20products_09012013%20-%20for%20website.pdf.
13. Malaysian National Pharmaceutical Control Bureau, http://portal.bpfk.gov.my/newsmaster.cfm?&menuid=52&action=view&retrieveid=213.
14. European Medicines Agency, http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/12/news_detail_001682.jsp&mid=WC0b01ac058004d5c1.
15. European Medicines Agency, http://www.ema.europa.eu/

ema/index.jsp?curl=pages/news_and_events/news/2012/12/news_detail_001680.jsp&mid=WC0b01ac058004d5c1.

16. European Commission, http://ec.europa.eu/health/human-use/quality/developements/index_en.htm.

17. Danish Health and Medicines Authority, http://laegemiddelstyrelsen.dk/en/topics/authorisation-and-supervision/licensing-of-medicines/renewal-of-marketing-authorisation/guideline-on-application-for-renewal-of---horisation.aspx.

18. Danish Health and Medicines Authority, http://laegemiddelstyrelsen.dk/en/topics/authorisation-and-supervision/company-authorisations/tissue-establishment-activity/news/annual-report-on-human-tissues-and-cells-2011.

19. British Medicines and Healthcare products Regulatory Agency, http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON213182.

20. Health Canada, http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/2011-03-31-report-rapport-eng.php.

21. Health Canada, http://www.hc-sc.gc.ca/dhp-mps/compli-conform/info-prod/cell/report-rapport_2009-2012_CTO-eng.php.

22. US Food and Drug Administration, http://blogs.fda.gov/fdavoice/index.php/2012/12/strategies-for-more-successful-drug-trials/.

23. Reuters, http://www.reuters.com/article/2012/12/04/us-offlabel-conviction-idUSBRE8B21DC20121204.

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Ultrasonic-Assisted Extraction of Berberine in Ionic Liquid

by Yang Chang

This editorial presents a poster presentation from a graduate student at Sichuan University in Chengdu, China.

Abstract

Ionic Liquids (ILs) solutions as green solvents were successfully applied in the Ultrasonic-Assisted Extraction (UAE) of Berberine from *Coptis chinensis*. A series of 1-alkyl-3-methylimidazolium ionic liquids with different cations and anions were evaluated and compared for their extraction efficiency; the results indicated that the structure of ILs has significant influence on the extraction efficiency for target analytes. [PSMIM][H_2PO_4] was finally selected as the optimal IL. In addition, the concentration of the [PSMIM][H_2PO_4]-water solution was optimized. Moreover, the extraction mechanism was discussed.

Keywords

Ionic liquid

Ultrasonic-Assisted Extraction

Berberine

Coptis chinensis

Target Constituent and Original Herbal

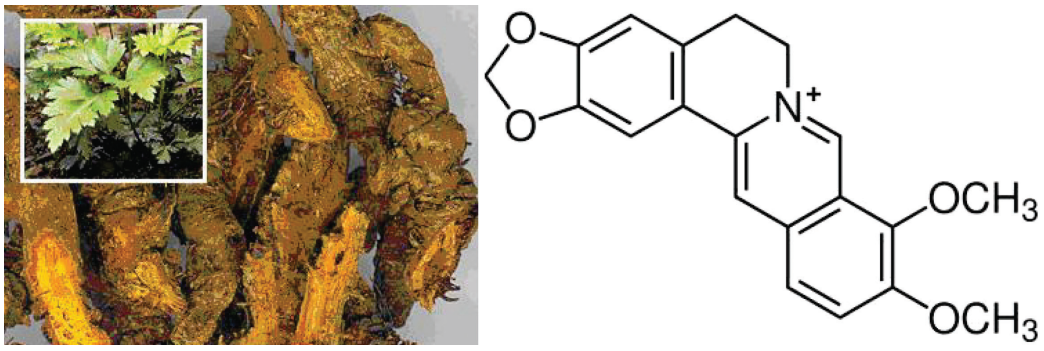


Figure 1. The *Coptis chinensis* branch and the structure of berberine.

Process Route

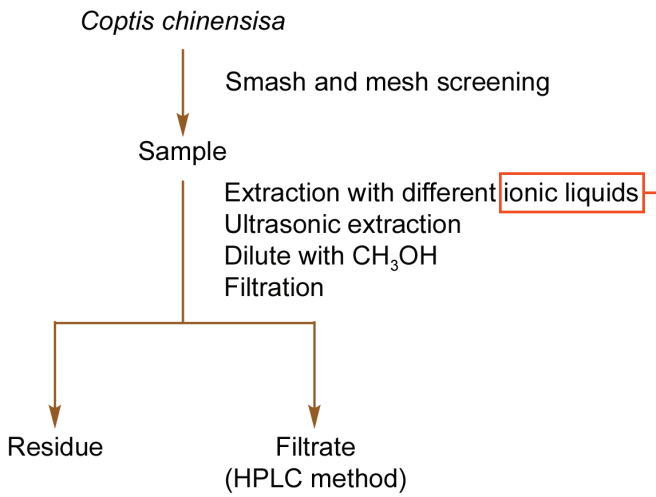


Figure 2. The process route of the extraction of Berberine from *Coptis chinensis*.

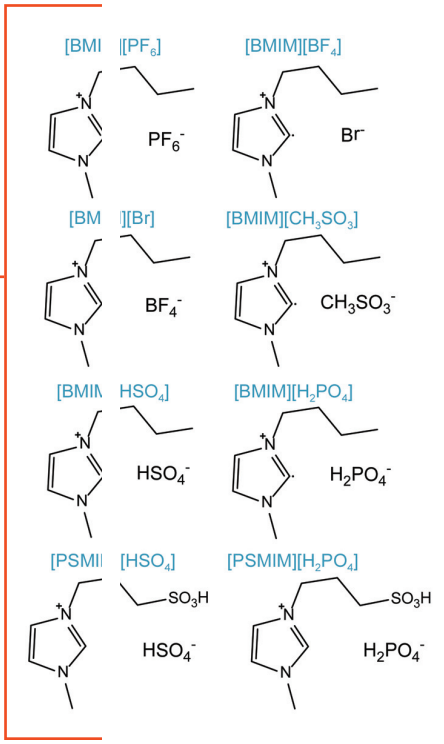


Figure 3. Structures of different ionic liquids.

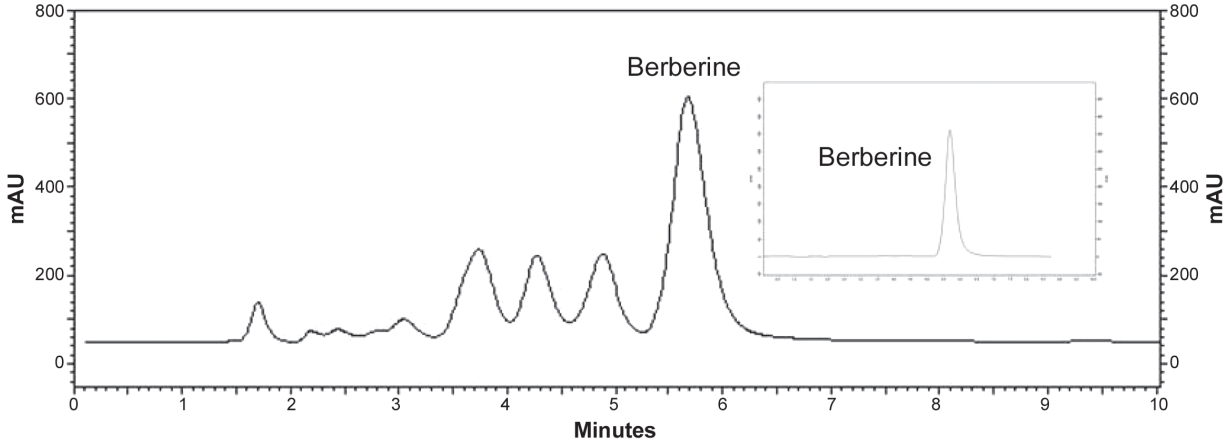


Figure 4. HPLC chromatogram of berberine in the [BMIM][CH_3SO_3] extraction; insert has the HPLC chromatogram of standard berberine solution.

Process Optimization

Screening of ILs

As shown in Figure 5, acidic IL [PSMIM][H_2PO_4] is the most efficient catalyst. Preliminary experiment showed that HSO4- ionic liquid has a stronger acidity than $H_2PO_4^-$ with the same cation, but under the same conditions, $H_2PO_4^-$ ionic liquid solution could extract more target analytes. This result could be interpreted by the fact that $H_2PO_4^-$ anion could afford more protons at the same IL concentration level, which might facilitate the extraction of target alkaloids. Considering the above results, [PSMIM][H_2PO_4] was selected for the subsequent evaluation in this work.

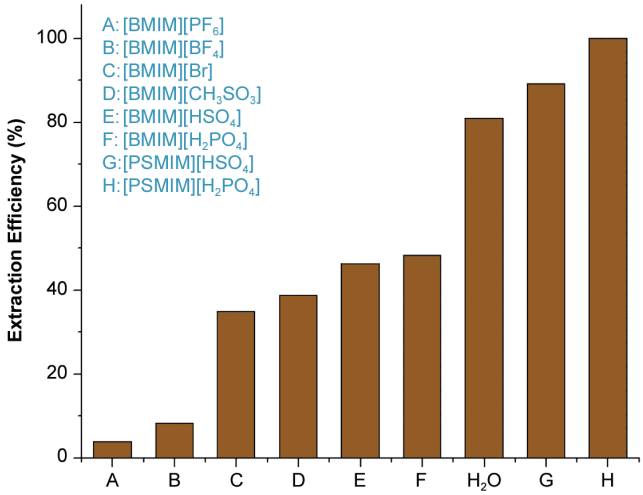


Figure 5. Effect of ILs solution on the extraction efficiency of berberine from rhizome of *Coptis chinensis*.

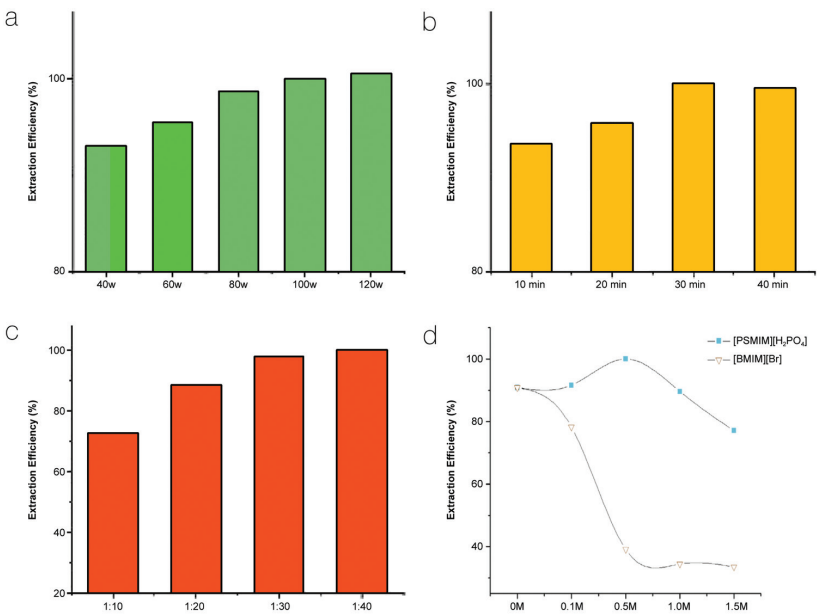


Figure 6. Different effects on the extraction efficiency of berberine with 0.5 M [PSMIM][H_2PO_4] as extracting phase.

Optimization of UAE Conditions

The effect of ultrasonic power (a), extraction time (b), solid-liquid ratio (c), and concentration (d) on the extraction efficiency of berberine with 0.5 M [PSMIM][H_2PO_4] as extracting phase is shown in Figure 6. Sample used is 1.0 g. The extraction efficiency is expressed as the observed values of berberine and the maximum amount in curve was taken to be 100%.

Optimized Results

- Ultrasonic power: 100 w
- Extraction time: 30 min
- Solid-liquid ratio: 1:30
- Concentration of ionic liquid: 0.5 mol/L

Response Surface Method

Figure 7 shows 3D plots between the following two parameters for the extraction of berberine:

a. Time and ultrasonic power

b. Solid-liquid ratio and ultrasonic power

c. Time and solid-liquid ratio

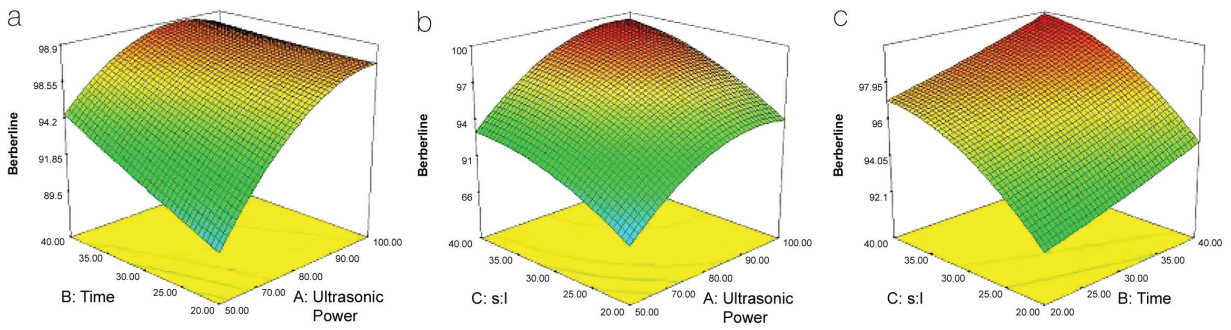


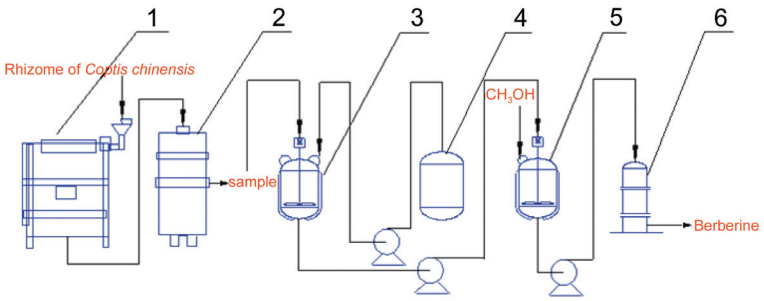
Figure 7. The extraction of berberine between various parameters.

Analysis of Results

- Ultrasonic power: 88.03 w
- Extraction time: 39.81 min
- Solid-liquid ratio: 1:37.05

This model can be used for indicating the optimization of factors: F-value: 44.14, P-value: 0.0001, and the coefficient of variation: 0.94%.

Industry Process



1. Crushing device: Raw materials were crushed in this step
2. Screening machine: Different size of particles were separated
3. Reactor: Ultrasonic-assisted extraction for active ingredients
4. Storage tank: Used for storing ionic liquid
5. Reactor: Used for dilution
6. Concentration tank: Used for concentration of berberine solution

Conclusions

The structure of ILs has significant influence on the extraction efficiency of berberine. The results indicate that if IL is more hydrophilic and could afford more protons, the extraction efficiency of berberine would be better. Based on the advantages of ionic liquids, the UAE method will have great potential and broad space when it is applied in the food and pharmaceutical industry as an environmental friendly approach.

About the Author

Yang Chang is a graduate student at Sichuan University in Chengdu, China, majoring in pharmaceutical engineering. He received a full scholarship for his postgraduate studies. He won the ISPE Student Poster Competition in the China Affiliate (under development) in the graduate category. A last-minute visa issue prevented him from competing in ISPE's International Student Poster Competition in San Francisco, California. Chang recently received the outstanding student award from Sichuan University.

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ISPE is Changing with the Industry

ISPE's President and CEO Nancy S. Berg discusses changes at ISPE to better understand and act on the issues important to Members, their companies, regulators, and patients.

Here in the United States, we have been dealing with more than our share of influenza strains, several of which impacted a number of our Member sites along with our North American Office. During the worst of it, those who were vaccinated against influenza couldn't help but be thankful for the people, science, and technology that drive the development and manufacture of vaccines and other pharmaceutical products. This also brings to mind the role ISPE has in education and training of Members who help to bring new drugs and vaccines to patients faster and the impact of ISPE Members in the treatment, control and even eradication of sickness and diseases that were terminal just a few years ago.

Being a Member of ISPE and working in the pharmaceutical industry carries great responsibility. With this responsibility comes the obligation to be the best our industry can be—to stay ahead of trends and technology, to work collaboratively in advancing technology utilization, to stimulate regulatory harmonization and to sustain a culture of quality that drives thinking beyond what is "acceptable" to what is "possible." ISPE shares these responsibilities. As the global professional society industry depends on to help achieve their goals, ISPE must be dedicated to understanding the needs of Members, their companies, regulators, and patients and be prepared to respond rapidly to opportunities. And, we are doing this. In the last issue, I mentioned that ISPE is leading a survey to better understand the root causes of drug shortages so we are better positioned to bring together industry and regulators to develop a risk-based approach to mitigating drug shortages. You also may have noticed that we have planned a number of *all new* conferences in 2013 that focus on the issues that will help Members develop professionally and be more aware of how industry is changing and how smart practices are driving innovation, process improvements, and higher quality worldwide.

ISPE's new Strategic and Business Plans direct other changes in how we offer benefits to Members and value to industry. I hope you are noticing how ISPE is involving, listening, and focusing its program and publication efforts on those issues that matter most.

I am particularly enthused about our efforts to grow and enhance our *Pharmaceutical Engineering* magazine. We know our Members have many publication and online options and that our advertisers have a choice to run in our magazine or others. That is exactly why we must ensure that our publications remain relevant and world class--and why we must cover the most significant technical, engineering, and regulatory issues you are facing. We hope that over the last few months, you have noticed some subtle changes in the magazine articles and the addition of more regulatory news. Our Editorial Advisory Board is encouraging more Members to get involved and they have done an outstanding job of evolving our magazine. As we move through 2013, we will be building on the strengths of *Pharmaceutical Engineering* magazine and aligning it more specifically to the Society's strategic direction and to industry "hot" topics. We are also planning a minor facelift of the magazine's design and its web site. As we embark on these changes, we will be asking for your input. Watch for upcoming readership and advertiser surveys to arrive in your email. Interested in writing an article or contributing to a team paper? Let us know.

With a new event schedule, new guidance documents in development, an enhanced magazine, new Member groups, and engagement options for Members and their company leadership, ISPE will be the society industry views as relevant--and getting things done. Next month, I will discuss our technical and industry hot topics and how you can get involved in technical, engineering, and regulatory efforts that lead to industry's advancement.

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ISPE Drug Shortage Initiative Supports Global Efforts to Understand Drug Shortages

The prevention of drug shortages is critically important to public health. As a not-for-profit global organization with both industry and regulator Members in 90 countries, ISPE is uniquely positioned to facilitate communication between the different sectors of the pharmaceutical industry and global health authorities as it seeks to understand and address this complex problem.

"Any effort to effectively address the complex and multi-faceted issues contributing to drug shortages requires close technical collaboration and clear communication between the pharmaceutical industry and global health authorities," said Nancy S. Berg, ISPE President and CEO.

Over the past several months, ISPE's Drug Shortage Initiative, led by a task force of industry leaders, has been developing an anonymous survey designed to better understand the underlying issues and possible root causes regarding drug shortages.

By design, the ISPE task force has limited the scope of this unique survey to the technical, scientific, manufacturing, quality and compliance issues associated with a company's supply chain and related to its ability to source, manufacture, and distribute products that have resulted in drug shortages. For example, consider the following areas of concern:

- Insufficient manufacturing capacity, exacerbated by industry consolidation, leading to fewer firms making the product
- Product quality issues that result in temporary or permanent halting of production
- Lack of secure, consistent availability of active ingredients, components, containers, or closures of suitable quality, even reagents for quality control tests, which can be exacerbated by the increasing globalization of the supply chain for ingredients and manufacturing
- Shifts in demand that arise from shortages of another drug – causing a chain reaction of shortages
- Unexpected market outcomes from new approvals, e.g., generic manufacturing capacity does not meet expectations, manufacturer of newly approved entity does not have sufficient capacity to meet market demands

"Better understanding of the root-causes of drug shortages resulting from technical, scientific, manufacturing, quality and compliance issues is a critical step in establishing a strategy for drug shortage prevention," Berg said.

ISPE recognizes that there are many other factors that may impact the supply of drugs, including regional economic factors, differing regulatory requirements, insurance programs, and government procurement procedures. However, given ISPE's technical expertise, the ISPE task force determined that this drug shortage survey was not the appropriate tool to examine these issues.

ISPE's Drug Shortage Survey, distributed in February 2013, includes questions probing the following areas: (1) Underlying Root Causes of Drug Shortages, (2) Company Strategies to Prevent or Alleviate Drug Shortages, and (3) Regulatory Bodies: Ability to Prevent / Help Avoid Drug Shortages. ISPE expects preliminary results to be available in June 2013.

ISPE believes that the anonymous survey data will provide the pharmaceutical industry and global health authorities with much needed scientific data to support the development of different risk-based approaches, using modern quality systems, to mitigate and prevent drug shortages, including potential shortages in breakthrough products approved based on limited development programs.

"While the ultimate goal is to prevent shortages occurring in the first place, we will do all we can to provide strategies and guidance to those with relevant capacity to enable them to produce high quality drugs in response to a potential or actual shortage in a short timeframe," Berg added.

ISPE also will take this critical drug survey data and leverage its international network to lead industry-regulator collaboration regarding drug shortages through meetings and conferences. In addition, ISPE will continue to work with and through the International Leadership Forum, a group of global industry leaders who gather twice a year under the auspices of ISPE to explore issues of importance to industry.

"We are immensely grateful to regulators from Europe and the United States, as well as representatives of the major European Industry Associations, for collaborating with ISPE on this important global initiative. We look forward to learning more about drug shortages through our Drug Shortage Survey and sincerely appreciate your thoughtful participation," said Berg.

A View to Pharma Excellence in US – Japan Affiliate on the Road Again

by Shigeru Nakamura and Michael J. Lucey

The yearly US Plant Tour by Japan Affiliate members was held 5 - 9 November 2012, combined as always with follow-up participation in the ISPE Annual Meeting. During the tour, members visited six plants in five days.

A total of 18 ISPE members traveled to the US, including Plant Tour Organizing Committee Members Shigeru Nakamura as Affiliate Officer/Head of Secretariat, Michael Lucey, Adjunct Director, and two other Committee members who also serve on the Affiliate Board, in addition to the 14 tour registrants. Effective advance support also was provided by Affiliate Executive Director Masayuki Akutagawa and Adjunct Director Mason Waterbury.

The group comprised seven visitors from pharmaceutical companies, five from engineering companies, four from construction companies, and two from equipment-related companies. The following are highlights from each plant visit.

Merck

Merck's Vaccine Bulk Manufacturing Facility (VBF) Program of Projects is the Facility of the Year Award (FOYA) Overall Winner for 2012. Located in Durham, North Carolina, the project addresses a shortage of urgently required vaccines. Planning called for design and construction within four years, adopting an innovative hybrid modular construction method. Engineering and construction work were executed in parallel, dividing into factory buildings and process modules, enabling a greatly shortened construction period. Visitors saw the interstitial modules and HVAC modules for the utility facilities which support production facility operations.

Affiliate members and hosts at the Merck VBF Facility in Durham, North Carolina.

Affiliate members and hosts at GSK in Research Triangle Park, North Carolina.

GlaxoSmithKline (GSK)

The Girolami Research Center located in Research Triangle Park (RTP), North Carolina, combines laboratory and pilot plant functions and is capable of producing up to P2a class of solid medicines, injections, inhalants, vaccines, topical formulations, among others. This impressive GSK facility features seven production lines and 32 process rooms, with a production scale of 10 - 100 kg. Each production room has an independent HVAC system which allows temperature and humidity control. The center adopted QbD two years ago, with significant advances achieved.

Bristol-Myers Squibb (BMS)

The tour group was fortunate to be permitted to visit BMS's R&D Center in New Brunswick, New Jersey, despite the recent adverse impact in the area caused by Hurricane Sandy. The center had been constructed by completely renovating the original building which dated back to 1995. It consists of three facility zones with the concept of promoting technical innovation: process, laboratory, and office. The office zone is ingeniously designed so as to encourage staff communication, with the free atmosphere stimulating staff creativity.

Abbott Laboratories

The tour group visited the investigational solid medicine production facility located in Abbott Park, Illinois. Capable of handling investigational drugs whose pharmacological

...Japan Affiliate on the Road Again

Continued.

activities are in the ranges of OEL 1 - 10 µg/m^3 and OEL ≤ 10 µg/m^3, the plant was constructed under a design concept of human safety, facility safety, and environmental safety. A high level of ISS is achieved by prioritizing maintainability, and corridors for visitor access are laid out around the process room with careful consideration given to visibility.

CMC Biologics

Sited 45 km from the airport in Seattle, Washington, CMC Biologics is a contract manufacturer for R&D and production. The company has fully segregated microbial fermentation and mammalian cell culture suites. Disposable bags are used in the preparation of culture media and buffers. In the biological production facility, the tour group was given a close-up view and detailed explanations throughout. With its clients in Seattle already including a major Japanese manufacturer, it was learned that CMC Biologics' acquisition of facilities in Berkeley, California, would enhance services to industry.

Genentech

Genentech Vacaville facilities are located about 50 miles to the northeast of San Francisco. The major site footprint includes a total of 10 facility buildings. Production, QC, warehouse, utility, and other buildings are laid out along its spine, in axis-like formation. The three-story production facility building was built under a clear design concept featuring unidirectional flow, with discrete and automated upstream and downstream processes, as well as gravity feed. As always, a remarkable and highly informative guided tour characterized the visit.

A highlight of the tour is the yearly opportunity to enjoy a networking reception together with a local Chapter. This year's event was graciously hosted by the Pacific Northwest Chapter. As always, a brief introduction to the Affiliate's activities was given by S. Nakamura, and the food and beverages kindly provided by the Chapter made for a very pleasant evening.

Sightseeing in New York City as well as in Napa Valley, California offered relaxation and enhanced the total US experience. The NYC stay came just one week after Hurricane Sandy struck, but before the Nor'easter which brought further severe weather. Uncollected waste and long lines of cars at gas stations were visible, although a remarkable clean-up operation was under way. This all left a lasting impression on the visitors from Japan as a further reminder of the force of nature. Moreover, because of Election Day, long lines of voters appeared at polling stations.

At the Affiliate's Winter Meeting held in Osaka shortly after return, summary information on the tour was provided to ISPE Members by a poster display, further promoting the tour as a benefit for membership. The Affiliate organizes annual reunion events for its plant tour participants. This year, a joint reunion was attended by a total of 35"alumni" from 2008, 2009, 2010, 2011, and 2012. The tour and follow-up events contribute to further expanding the networking possibilities made possible through ISPE membership.

Finally, the Japan Affiliate wishes to express its gratitude to all of the individuals at host organizations who made a very special effort and helped realize a successful 2012 tour.

ISPE QbD Conference Endorsed by CASSS

The ISPE Conference, "The State of QbD in the BioPharmaceutical Industry: Critical Assessment, Design Space Implementation and Control," has been endorsed by CASSS, an international separation science society.

CASSS, headquartered in Emeryville, California, USA, is a not-for-profit professional society made up of more than 4,000 industry, academic, and public sector professionals who focus on separation science, including the chromatography process used to determine impurities in pharmaceuticals. A mutual interest of ISPE and CASSS is the end quality of pharmaceutical products through Quality by Design efforts.

The ISPE Conference, to be held 10-11 April in San Francisco, California, USA, will present case studies including best practices and documented opportunities and challenges resulting from the implementation of Quality by Design. The event will be global in scope and focused on how smart companies are designing and developing formulations and manufacturing processes to insure pre-designed product quality. Outcomes are intended to build an understanding on how planning and controlling the evolution of a pharmaceutical product will lead to superior quality, better use of resources and more effective business results.

For more information on the conference, visit www.ispe.org/2013qbdconference.

An Interview with Sadayoshi Tomita, CPIP

Sadayoshi Tomita, a regulatory consultant and 16-year ISPE member, recently received his Certified Pharmaceutical Industry Professional (CPIP) credential. This interview discusses his personal experience as a CPIP candidate and awardee.

Tomita's professional experience at Eisai Co. Ltd. pharmaceutical company includes the marketing of pharmaceutical products in Asian countries starting from the initial era of the pharmaceutical products export business from Japan.

With the subsequent expansion of export operations in Asia, Central South America, and the Middle East, registration applications to regulatory authorities came to occupy the major part of Tomita's work. As overseas joint ventures became increasingly organized, Tomita coordinated with medical department staff members to train the staff of overseas offices and plants in the areas of strategy, marketing, and product knowledge of the pharmaceutical products which were being exported or manufactured locally.

After being assigned to the International Development Division, Tomita assisted research personnel on drug safety as well as those involved in the production of clinical materials in reviewing their data and documents prepared in English.

Tomita was then appointed as a member of the QA/RC Department to work for the globalization of Quality Assurance and Regulatory Compliance in order to ensure compliance with global requirements.

In the pharmaceutical industry, Tomita served the Japan Pharmaceutical Manufacturers Association (JPMA) and the Federation of Pharmaceutical Manufacturers' Associations of Japan (FPMAJ) as a GMP committee member of both organizations.

When did you begin studying for your CPIP?

I started studying for the CPIP certification after attending a meeting for CPIP candidates at the ISPE Japan Office in January 2010. We learned at the meeting about the purpose of CPIP, competencies to achieve, application eligibility and procedures, and knowledge elements required at CPIP tests. The group study program using the ISPE online course for CPIP was introduced and monthly schedules for study meetings were confirmed. Our minds were made up to take on the challenge of CPIP.

My interest in pursuing this professional qualification began when I heard Dr. Janet Woodcock's presentation at the ISPE Winter Meeting on Friday, December 5, 2008. Dr. Woodcock, Director, CDER, FDA emphasized, to my understanding, the need for collaboration among nations, as well as collaboration among regulatory authorities and industry to protect the good health of people in an era of accelerated globalization. A single nation alone cannot achieve this, but global cooperation will make it possible, and she added we need industry professionals more than ever. I made up my mind to further contribute to the pharmaceutical industry through obtaining the CPIP credential.

Did the language aspect (working exclusively in English) bring an additional level of challenge?

As the CPIP examination was entirely in English, it posed a kind of tension and anxiety as to how clearly I would understand the questions. Viewing the ISPE online course and answering the questions in a group were very effective measures for getting used to English. I also tried to pick up English technical expressions in the ISPE online course and read FDA guidelines and ICH documents in the original English, and took notes in English.

At the time you began seeking your CPIP, what did you think the benefit(s) would be?

CPIP would objectively qualify me as a professional in the pharmaceutical industry, and make it possible to communicate and cooperate with people of different countries as fellow professionals.

The accreditation would enhance my credibility and would broaden my area of activities as a consultant, auditor, lecturer, and medical association member.

It was my wish that if I could pass CPIP it would encourage industry people to also take on the challenge of CPIP as I would be a good example

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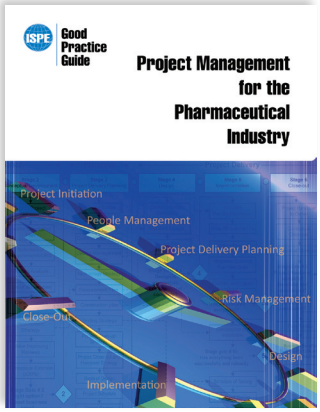
ISPE Approved as a Registered Education Provider by PMI®

The Project Management Institute (PMI), the world's largest project management member association, has named ISPE as a Registered Education Provider (REP). REPs are organizations that have been approved by PMI to help project managers achieve and maintain the Project Management Professional (PMP)®, Program Management Professional (PgMP)® and other PMI professional credentials. These organizations have met PMI's rigorous quality criteria for course content, instructor qualification, and instructional design.

"We are pleased to be identified as a PMI Registered Education Provider for our Facility Project Management in the Regulated Pharmaceutical Industry training course," said ISPE President and CEO Nancy Berg. "Partnering with PMI enhances ISPE's world-class programs and gives us a benchmark distinction that is recognized globally and across industries."



The targeted course includes a complimentary copy of the *ISPE Good Practice Guide: Project Management for the Pharmaceutical Industry,* which is the basis of the training. Upcoming sessions are scheduled 22 - 23 May, 2013 in St. Louis, Missouri as well as Brussels, Belgium.Visit the ISPE Training webpage for details on upcoming training events.

ISPE joins more than 1,500 REPs in more than 80 countries. These organizations include commercial training providers, academic institutions, and corporate training departments within corporations and government agencies.

The ISPE Training Department's mission is to develop high quality, topic-specific, in-depth training products in a variety of delivery methods. This includes the identification, development, delivery and continuous improvement of global classroom and online training products encompassing the pharmaceutical supply chain emphasize new manufacturing science, quality and regulatory compliance, and alignment with the Society's Strategic Plan to meet the needs of global pharmaceutical manufacturing industry professionals.

ISPE's Critical Utility Community to Develop Good Practice Guide on Sampling

Seeking Input and Contributors

Sampling means collecting a small portion of a larger stream that accurately reflects the content of the larger stream. Sounds simple, right? Unfortunately, we all wish it were that simple. Have you ever had issues with sampling? Obtained results that were inconsistent or difficult to explain, or that had more variability than expected? Have you ever seen excursions that mysteriously disappeared the next day? Any trouble identifying the root cause? Regardless of whether sampling closed systems such as pharmaceutical water, steam, or process gas streams, or open systems such as controlled environment systems, the extraction of truly representative samples poses unique challenges in the industry.

As many of us know all too well, sampling is one of the largest sources of variability and inconsistency in the industry. ISPE's Critical Utility Community of Practice is tackling this complicated issue of sampling and is forming a team of experts to develop and publish a Good Practice Guide on Sampling focused on best practices and covering all aspects of sampling.

If you believe you have expertise to offer, we welcome your input and encourage you to get involved with this critically important Good Practice Guide. Please contact team leader Brian Hagopian at brian@clear-water-consulting.com or ISPE at Guides@ispe.org.

An Interview with Sadayoshi Tomita, CPIP

Continued from page 4.

from the standpoint of pointing the way to the process and means of preparation for the final examination.

Once you were finished, what did you see as the benefit of achieving CPIP certification?

A staff member of a well-established company asked me to negotiate for the post of adviser on GMP, quality system and regulatory issues, and proposed a contract draft for mutual agreement on employment.

Chemical plant professionals, for whom I serve as consultant on GMP issues, welcomed my CPIP achievement, and received my GMP training more eagerly than before.

I was invited to participate in this interview on my success in the CPIP examination. I would like to see more Japanese industry people set CPIP as their goal and realize the benefits of enhancing proficiency and contributing to the industry.

How do you hope to apply your CPIP credential in the future?

One of my hopes is to utilize my CPIP credential in assisting the Japan Affiliate CPIP study group in the near future. The study meeting will be organized as follows:

- First stage of study will be general requirements, namely, cGMP, selected parts of FDA Guidance documents, and summaries of ISPE Good Practice Guidance documents.
- Second stage will be the ISPE online course. View the course, try to understand, and answer questions at the end of each unit. A free discussion and Q&A Session will follow.
- Each special field will be explained by an expert volunteer. English technical terms with corresponding Japanese terms will be introduced at the end of each meeting.
- My target is for around seven applicants to participate in the program.
- Meeting place and time are to be discussed sufficiently in advance.

What is your impression of the CPIP certification process?

My impression of the certification process is that it is very well systematized, clear to understand, and sufficiently detailed to lead the candidate in the right direction.

The CPIP Certification Program clarifies the benefits of certification, application process, preparation for the exam, and how to apply for, take, and pass the exam.

Once the candidate is authorized to take the exam, the applicant can choose the month and date marked available on the calendar within the approved time frame. In addition, the country and test center location can be optionally chosen.

Meanwhile, the CPIP Study Guide provides in detail the technical knowledge elements required to pass the exam. The CPIP Practice exam explains how the examination is conducted, and the type and style of questions.

What advice do you have for others who are considering CPIP certification?

I would like to provide anyone considering CPIP the following advice:

- Make up one's mind to take the exam, with an attitude of determination.
- Clarify the requirements and procedures for application, and confirm the technical knowledge elements upon which the exam is performed.
- Set up a study plan preferably by a group of students, along with a separate plan allotting available time for CPIP study in one's daily life.
- Organize and attend a group study meeting, and study through an ISPE online course that will help with adjustment to English as well as the learning of technical knowledge for CPIP.
- Study carefully referenced parts of CGMP and ICH documents.

How was the CPIP information relevant to your everyday work? Were you able to immediately apply any of the principles to your career while you were studying?

CPIP study covers the entire product lifecycle, from pharmaceutical development, technology transfer, commercial manufacturing, to product discontinuation.

This is more clearly explained by the knowledge elements on which candidates are tested: product development, facilities and equipment, information systems, supply chain management, production systems, regulatory compliance, and quality systems.

These elements represent daily operations at a site; therefore, CPIP technical knowledge is applicable to various stages of the product lifecycle.

While studying for CPIP, I audited a fine chemicals plant and reviewed IQ, OQ documents, as well as discussed commissioning and qualification. On another occasion, I gave a presentation on quality systems. I also explained Q7 on material management in accordance with a check list prepared for the purpose.

An Interview with Sadayoshi Tomita, CPIP

Continued.

What impact do you think CPIP certification could have for the pharmaceutical industry as a whole?

The CPIP certification scheme has the great possibility of promoting the following:

- Enhance collaboration between regulatory authorities, industry, and academe
- Contribute to elevation of proficiency in various fields of industry on the basis of integrated technical knowledge
- Promote interaction among industry personnel of different nationalities through technical knowledge and common communication tools for English
- Provide industry people with the capabilities to cope with paradigm changes and take appropriate measures for changes and improvement

Do you have advice for others who may be considering (or hesitating!) pursuit of the CPIP certification? Any practical considerations?

Paradigm changes in the pharmaceutical industry require those people who can perceive global trends in the pharmaceutical industry and can contribute to the company, industry regulatory authorities, and/or academic circles with his proficiency in his field as well as through a broad spectrum view throughout the product lifecycle.

A person entitled as CPIP will meet such need and will contribute to the promotion of good health of people and protection of patients throughout the world. The paradigm changes include, but are not limited to the following:

- Revision, changes, or addition of rules and regulations
- Speedy development of globalization impacting many countries
- Increasingly complicated material flow
- Rapidly advancing innovation in technology
- Further collaboration between regulatory authorities and industry needed, as well as collaboration among nations
- Enhanced communications required for problem-solving and for harmonization of rules and/or standards

My last piece of advice: a program of steadily performed studies will lead you to success!

About CPIP

The CPIP™ credential is the first professional certification program for the pharmaceutical industry covering development through manufacturing, based on an international, knowledge and skills competency standard. The Credential is administered by the ISPE Professional Certification Commission which is an independent board established by ISPE to oversee the credential.

One of the best ways to ensure career growth is by pursuing industry-recognized certifications. As the pharmaceutical industry's only manufacturing-focused certification, CPIPs are recognized as dedicated competent professionals in their fields.

About CPIP Study Groups

ISPE encourages and supports CPIP Study Group formation in the Affiliates and Chapters. A Study Group helps interested professionals pursue the CPIP™ certification, enter the application process and prepare for the examination. The Study Group experience provides candidates with an opportunity to assess their mastery of the seven technical knowledge elements on which the CPIP examination is based, and provide support to each other in filling their knowledge gaps in preparation for the CPIP examination.
The participants:

- Get practical support for achieving eligibility and preparing for the examination
- Have the opportunity to expand their personal network within the industry
- Learn from others, both companies and individuals
- Have a forum for discussions and sharing of study resources
- Have the opportunity to use the Study group for the future
  - Re-certification
  - Problem solving in daily work
  - Inspiration

ISPE has provided some resources that can be used by the Affiliates and Chapters to assist them in sponsoring and conducting CPIP Study Groups. Contact Michael Phelan (mphelan@ispe.org) or Tracey Ryan (tryan@ispe.org) for help in getting started.

2013 Facility of the Year Awards (FOYA) Winners Announced

The Facility of the Year Awards Judging Panel has named six Category Award Winners in the 2013 Facility of the Year Awards (FOYA) program. The winning projects for 2013 were selected from 27 well-qualified entries and are located in Ireland, Switzerland, the United Kingdom and the United States.

Sponsored by ISPE, INTERPHEX, and Pharmaceutical Processing magazine, the Facility of the Year Awards (FOYA) program recognizes state-of-the-art pharmaceutical manufacturing projects that utilize new and innovative technologies to enhance the delivery of a quality project, as well as reduce the cost of producing high-quality medicines. Now entering its 10th year, the awards program effectively spotlights the accomplishments, shared commitment, and dedication of individuals in companies worldwide to innovate and advance pharmaceutical manufacturing technology for the benefit of all global consumers.

"The FOYA program is about recognizing the pharmaceutical industry's innovation and technical advances in facility manufacturing, which ultimately is about helping patients who need and depend upon us for a reliable supply of quality medications," said Chaz Calitri, Vice President of Network Performance at Pfizer and Chair of the 2013 FOYA Judging Panel. "The six facilities honored by this year's awards program embody innovation, exemplified by advances in areas including flu vaccine manufacturing, which is very relevant in parts of the world right now where outbreaks have occurred, threatening public health. All of this year's honorees are to be commended for their important contributions to our industry, and most importantly, to improving people's lives."

The award categories and respective winning companies and project descriptions are:

Category Winner for Facility Integration

Biogen Idec

Flexible Volume Manufacturing (FVM) Facility

The very nature of clinical manufacturing, smaller batch volume requirements, and less predictive outcomes requires an adaptable, flexible manufacturing platform. To fulfill this requirement in a cost effective manner, while reducing time to delivery of clinical material, Biogen Idec constructed the Flexible Volume Manufacturing (FVM) facility, located at Research Triangle Park (RTP), North Carolina, USA. The facility produces treatments for neurodegenerative diseases, hemophilia, and autoimmune disorders.

The FVM facility integrates into the RTP site, utilizing fixed equipment in existing 2K Small Scale Manufacturing and 15K Large Scale Manufacturing facilities without impact to existing manufacturing operations, creating a hybrid network of fixed and single use equipment to accomplish variable product demands. The facility features a 100% single use flow path in a validated closed system.

The manufacturing methods employed at the FVM facility provide for a flexible multi-product environment, with less capital investment, reduced utility demands, and increased speed through the product pipeline as compared to traditional manufacturing methods. Biogen Idec's bold new methods and resulting success earned them the top spot in Facility Integration.

> *"The FOYA program is about recognizing the pharmaceutical industry's innovation and technical advances in facility manufacturing, which ultimately is about helping patients who need and depend upon us for a reliable supply of quality medications…*
>
> **Chaz Calitri, Vice President of Network Performance at Pfizer and Chair of the 2013 FOYA Judging Panel**

Category Winner for Equipment Innovation

MedImmune

UK Automation Upgrade Project

Recognizing that their existing egg-based bulk vaccine manufacturing process would not support a rapid increase in production of its Influenza vaccine Intranasal, MedImmune implemented the UK Automation Upgrade Project, a series of innovations to their existing equipment line in Speke, Liverpool, UK.

Faced with the lack of commercially available equipment

FOYA Winners Announced

Continued.

and the tight timelines for seasonal Influenza vaccine manufacturing, the MedImmune team utilized a system engineering methodology to redesign each discrete processing step into a fully integrated and automated production train. The team made significant innovations to equipment for automated candling, harvesting, isopropyl alcohol (IPA) spray, decap inspection, and isolation. The result was a 15% increase in yield, a 25% reduction in seasonal labor, an 8% reduction in rejects, and a decrease in waste at every stage of the process.

Because of its work to drive a paradigm shift in egg-based vaccine manufacturing, the Facility of the Year Award Judging Panel recognizes the UK Automation Upgrade Project for Equipment Innovation.

Category Winner for Operational Excellence

Merck & Co., Inc.

Vaccine and Biologics Sterile Facility (VBSF)

Merck needed to make a strategic investment in its manufacturing network to support its long range biologics and vaccine pipeline, resulting in the VBSF project in Carlow, Ireland. This was Merck's first green-field sterile processing facility built outside the US and from the beginning, the project team was committed to employing a Lean Six Sigma philosophy as the foundation for every part of the project.

Lean Six Sigma was used by the team to manage the dynamics of the decision process during the early project scoping, design, and integration activities and the formation of a "One Team" culture. In addition, many focused Lean projects were done independently and seamlessly integrated back into the larger program, including design of the syringe filler, eBeam reliability, and media/buffer suite design. Lean Six Sigma also was employed during project execution, where the methodology drove efficiency of decision making and rapid implementation of remediation measures.

Lean Six Sigma was successfully applied in every facet of this project, prompting judges to select the VBSF project as the winner in the Operational Excellence category.

Category Winner for Sustainability

Morphotek, Inc.

Pilot Manufacturing Plant

Morphotek®, Inc., a subsidiary of Eisai Co., Ltd., proved their commitment to sustainable design and environmental stewardship through the building design and construction practices of its Pilot Manufacturing Plant in Exton, Pennsylvania, USA. The plant supports the manufacturing of advanced therapeutic candidates with either cell culture or microbial systems.

Concludes on page 10.

Contribute Your Expertise on Decommissioning

The Document Development Team producing the ISPE Good Practice Guide on Decommissioning would like to hear from ISPE Members willing to assist with writing the Guide. The purpose of this document is to provide basic information required for the decommissioning of equipment and facilities and will provide templates, flowcharts, and example documents currently in use in the US and Europe. Topics include common practices, closure planning, GxP decommissioning, GEP decommissioning, asset disposal, and demolition/remediation.

There are many different roles within the Team and range from Chapter Leaders to Chapter Members/Writers, depending on how much time can be contributed and area of expertise. Chapter Team Members work closely with and are under the direction of their Chapter Leader to produce text for a chapter or section of the document.

If you are interested in participating with the development of this Guide, please email your contact details, a brief description of your experience, and how you would like to volunteer to GPG Leader Nick Haycocks at haycocks@amgen.com.

Pharmaceutical Engineering Expands Technical Focus, Seeks Contributors

Pharmaceutical Engineering is looking for subject matter experts in the global pharmaceutical industry with knowledge of the latest scientific and technical developments, regulatory initiatives, and innovative solutions to real life problems and challenges who can contribute application articles and case studies. Special features and guest editorials will be considered that focus on new technology, contemporary quality management practices, and production innovation. New Departments include: facilities and equipment, information systems, product development, production systems, quality systems, research and development, supply chain management, and regulatory compliance.

For more information, please visit www.pharmaceuticalengineering.org and click on the "Submit Article" tab. There are publishing opportunities still available for 2013. Deadlines for each issue are listed on the website.

FOYA Winners Announced

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Built on a brownfield site, the new plant gives fresh life to a previously contaminated site which involved soil remediation and demolition of antiquated buildings. Sustainable features also include a modular building envelope system with superior insulation; louvered sunshades, a light shelf to maximize daylight exposure while minimizing interior heat gain; and comprehensive water and energy conservation plans including water recycling, a flexible clean steam generation system, and a roof top solar array for onsite renewable energy. The implemented HVAC system was 90% more efficient compared to a traditional building system.

The project team used Building Information Management (BIM) software to integrate the best sustainable decisions into the design process. The company has submitted for LEED Silver Certification to the US Green Building Council. The Facility of the Year Award Judging Panel was impressed by the demonstrated commitment in sustainable design, naming Morphotek winner of the Sustainability category.

Category Winner for Process Innovation

Novartis Vaccines and Diagnostics

United States Flu Cell Culture Facility

Novartis' breakthrough use of innovative technology and development of a large scale manufacturing process to produce seasonal and pandemic influenza vaccines garnered them the award for Process Innovation.

Their United States Flu Cell Culture Facility in Holly Springs, North Carolina, USA, features a process that breaks with the 50-year tradition of utilizing eggs for the method of growing the virus. By developing a process based on robust, deep tank mammalian cell technology, several issues associated with traditional technology have been circumvented and offers potential advantages including: process raw materials are readily available and not threatened by pandemic events; and cell culture process utilizes closed-system bioreactors, reducing required biosafety level for the manufacturing space.

In addition to the breakthrough technology associated with their mammalian cell culture process, the Novartis team used creative solutions to other facility operations, notably their approach to Containment Convertibility, which allows the facility to operate at BSL -1, -2, and even -3 levels to reduce operating costs associated with the need to operate in higher containment modes on demand. The Facility of the Year Award Judging Panel names Novartis as winner of the Process Innovation category for forging a path in a new frontier for vaccine production.

Category Winner for Project Execution

F. Hoffmann La-Roche Ltd.

Technical Research and Development (TR&D) Building 97

The TR&D Building 97 in Basel, Switzerland was initiated to consolidate the Roche research and development groups for oral solid dosage and liquid parenteral dosage forms for clinical studies into once facility.

Embedded in the city of Basel and adjacent to a residential area, the project had to meet stringent approval of the city design council and ensure a good working relationship with the local neighbors during the building lifecycle. The project addressed issues such as compliance with highly active substances; GMP compliance; usage of synergies between TR&D functions; building in a tight urban area environment; and a complex permitting approval. Despite these issues, the project was executed within budget and schedule constraints, while having a superior safety record.

The project team achieved the end result, which is a facility that meets the requirements and expectations of Roche users and the Basel community. Their excellence in overcoming their challenges within budget and schedule earned them the title of winner for Project Execution.

2013 Facility of the Year Events

There will be several opportunities to learn first-hand about the facilities being honored as "best in their class." These opportunities include:

INTERPHEX2013 – attendees will be able to meet the Category Award Winners at the Facility of the Year Awards Display Area 22 - 25 April at the Jacob K. Javits Convention Center in New York City, New York, USA. Team members from winning companies will be on-hand to discuss the success stories associated with these pharmaceutical manufacturing facilities. More information, including registration information, can be found at www.interphex.com.

ISPE 2013 Annual Meeting – category winners will give presentations about their winning projects during ISPE's 2013 Annual Meeting, 3 - 6 November in Washington, D.C., USA. The highly anticipated announcement of the 2013 Facility of the Year Awards Overall Winner also will take place during the Keynote Session of this event. Information and updates on this global event can be found at www.ISPE.org.

Feature Articles – comprehensive coverage will appear in *Pharmaceutical Processing* magazine and *Pharmaceutical Engineering* magazine.

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