This article discusses how optimization and control software can help pharmaceutical companies achieve short-term and long-term energy management goals translating into reduced costs, increased life-span of equipment assets, and the ability to take advantage of market opportunities.

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Reducing Energy Costs in a Central Utility System through Optimization - Impact for a Pharmaceutical Company

by John Havener and Eric Unrau

Introduction

According to the US Department of Energy, energy use accounts for 10% or more of manufacturing companies' operating budgets, the second largest cost next to raw materials. This is significant in mainland US where a fully developed energy market with options for multiple fuel sources exists. Outside mainland US, and particularly in areas where fuels and energy sources are largely imported, such as Puerto Rico, Japan, and Ireland,[1] the increase in energy costs can create a much larger need to focus on reducing energy costs. With the rising costs of energy and increased economic pressures, pharmaceutical companies are seeking solutions that allow them to conserve energy, manage future demand, and reduce the risk of energy supply (price, source, availability). Many major pharmaceutical companies have taken the first step - investing in energy conservation programs that have reduced energy use dramatically. Despite this effort, pharmaceutical companies are still seeking additional solutions. Long used to improve

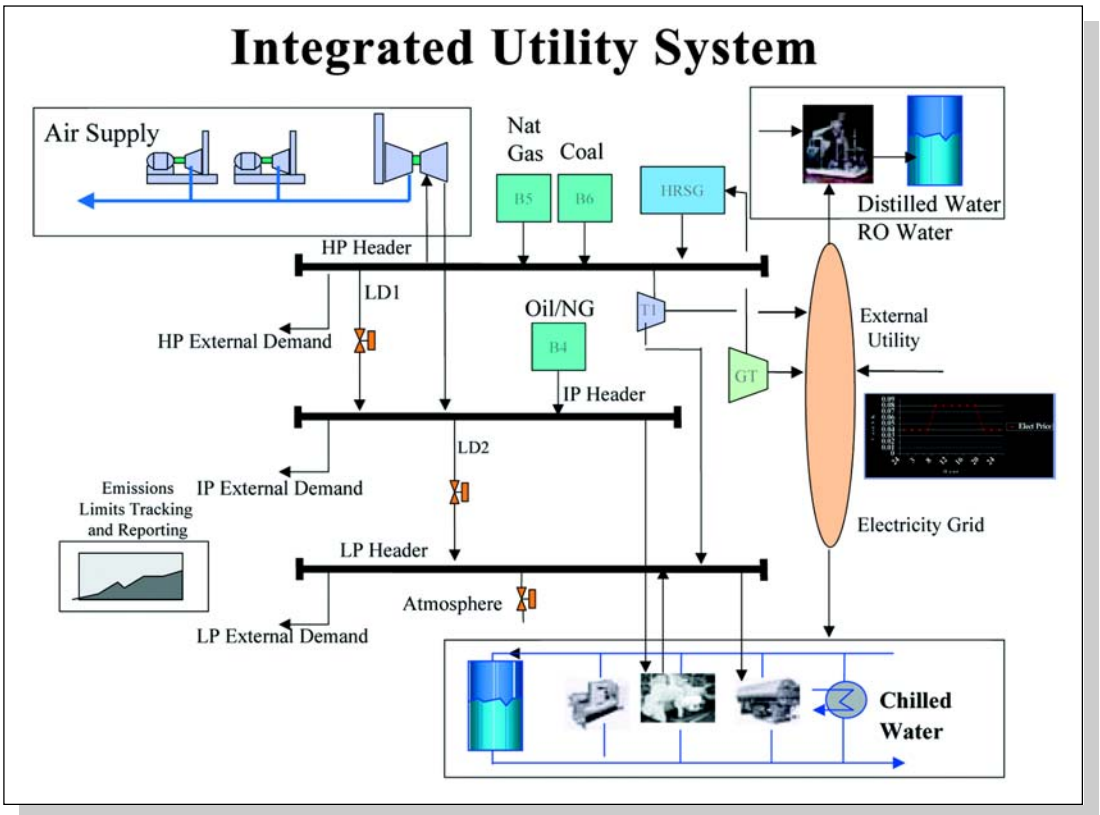

Figure 1. A diagram of a central utility system.

production processes, real-time optimization and control software provides one such solution - allowing pharmaceutical companies to integrate complex economic, operational, and environmental factors to reduce costs, increase reliability, and achieve environmental goals.

Most central utility systems at pharmaceutical manufacturers are critical for plant and facility operations. The central utility system can be extremely complex, encompassing boilers, chilled water systems, distilled water systems, compressed air systems, compressor trains, cooling towers, large building heating, ventilation and cooling systems, and distributed generation systems - *Figure 1*. In addition to a number of equipment capacity constraints, the central utility system operators must incorporate a number of dynamic external factors into their energy management decisions. These factors include fuel price, energy demand, energy prices, energy reliability and availability, emissions limits, and corporate profitability goals. There are also a myriad of options involved in making on-site generation and distribution decisions. One can quickly see how interrelated the factors affecting the central utility system can be.

Options

Historically, operations have relied on operating heuristics, historical data analysis, or single point solutions (instruments, hardware, or software) to increase the efficiency of the central utility system. With the advancement of software (speed and storage capacity) within the last five to ten years, manufacturers now have the ability to capture real-time data about their utility processes to better understand the process and the impact of business decisions. To further leverage this storehouse of data, manufacturers can deploy model-based software solutions that identify patterns in operating data, predict future energy demand, and determine the optimal environment based on real-time information and corporate objectives. Unlike human operators, this control and optimization software can simulate thousands of scenarios in real-time, and determine and execute the optimal decision based on corporate environmental and economic goals. In a complex environment, such as central utility system, for which the optimal decision is based on a number of dynamic internal and external factors - optimization and control software represents an attractive solution.

The cost for generating steam and power changes with time because of demand, fuel mix changes, and external power costs (real-time pricing). Based on the costs at a given time, it may prove beneficial to generate additional steam and increase power production. In addition, there may be additional constraints involving emissions from the boilers. The central utility operator must decide on how much power to generate, sell or purchase; how much steam to generate; how to dispatch the load among the various boilers and turbines. Because there are so many variables and constraints to consider at any given point in time, the operating point that minimizes cost at any given instant may not be obvious to the operators - *Figure 2*.

Optimization Software in Practice

Over the past 25 years, model-based control and optimization has become the standard supervisory control tool in many process industries, and more recently has been applied in the pharmaceutical industry to improve processes and energy management. Model-based software allows the user to utilize mathematical models to represent a physical or non-physical

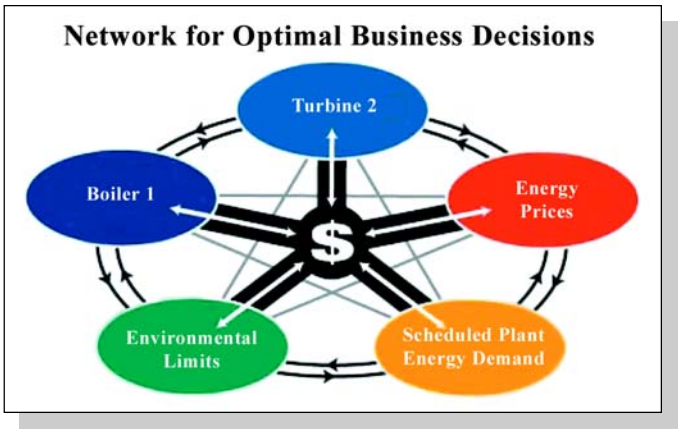

Figure 2. Factors used to determine the optimal central utility system decision.

process. There are different types of model-based software that are available: rules-based, first principles, empirical, and mixed models which are combinations of these types. Rules-based models are used to document the knowledge of best operating practices expressed as rules to define the "optimal environment." Information on existing conditions is fed into these rules and the model outputs actions to control the process. Rules-based logic statements generally cover the establishment or avoidance of known operating conditions. An example would be not allowing a turbine to run in a specific RPM range due to known operational problems in that region.

First principles models are mathematical representations of a process, such as thermodynamics, chemical kinetics, and mass and energy balances, which are utilized in optimization for many different processes. Obviously, the more complex the process, and the more variables and interdependencies that are involved, the more cumbersome rules-based and first principles models become to implement and maintain.

Empirical models use historical data to find patterns in the process and create numerical models that represent the process. Table A shows a qualitative comparison between empirical and rules-based models. Neural networks play on the biological metaphor, and are a type of non-linear empirical model that have been proven to be universal function approximators. The neural network model is trained to reproduce behavior of a process given inputs from historical data. Neural networks allow models to be built quickly and easily from test data, historical data, vendor curves, or any combination of these. Recent developments in empirical modeling techniques and the use of on-line data biasing allow for neural network optimization models to be built with a minimal amount of historical data.Unlike rules-based systems, neural network models are differentiable equations that can be utilized in a control system. To build a neural network-based optimization solution, the engineer does not have to explicitly express the complex mathematics of the process. This allows rapid model development and deployment in comparison to the use of the most rules-based models. Finally, neural networks can calculate the optimal solution orders of magnitude faster than first principle models, allowing complex sets of models to solve control and optimization problems in real-time (seconds to minutes).

Mixed models make use of the features of rules-based, first principles and empirical models. These models allow users to modify empirical models to make explicit the knowledge of the operators about the process. A central utility system is the

perfect example of a mixed model solution. When all potential constraints are considered in a central utility optimization solution (availability of equipment, operating ranges, operating goals, and inoperable ranges), the resulting optimization surface becomes discontinuous, with separate surfaces representing the different options on equipment availability and operating ranges. At any point in time, some assets that are deemed "available" may not actually be activated. Consequently, the optimizer must make binary or mixed-integer (e.g., ON/OFF) decisions regarding available assets based on rules. By utilizing rules-based optimization, the neural network optimizer is able to evaluate multiple combinations of available assets while honoring combined constraints to determine the optimum asset configuration to achieve the business goals.

Figure 3 shows examples of efficiency curves for four different pieces of equipment, which are developed through application of rules-based, first principles and empirical modeling techniques. In order to meet the overall business objective (e.g. low cost, highest system efficiency, etc.) for a central utility system, it is necessary to find the optimum operating point by searching over the entire range for each piece of equipment. In this example, Turbine 1 (third diagram from the left) cannot operate in the middle range of its capacity due to high vibrations in that range. To determine the optimum overall dispatch, the optimizer must search all the remaining curves in combination with the left curve segment of Turbine 1. Then it searches all the remaining curves in combination with the right curve segment of Turbine 1. The solution then compares the two results and returns the optimum dispatch decision. The empirical model is also utilized in searching for the optimum point, but it is constrained by the rules-based model that shows Turbine 1 cannot operate over its full range. The combination of these models results in the mixed model shown in Figure 3 as the multi-unit optimizer.

The Necessity of Multi Unit Optimization

Decision speed is a critical feature of an optimization solution. When one considers the numbers of units to be controlled and the complexity of the optimization analysis required, the ability to simulate multiple scenarios and determine the optimal decision within minutes, if not seconds, becomes a key component of the solution. Currently, a team of operators and engineers make critical decisions about central utility system operations twenty-four hours a day, seven days a week - all year long. The following parameters can affect the ability of a utility system to reliably meet demand under normal and variable operating conditions:

- reliability and flexibility to meet any sudden change in demand
- current and future plant demand for each utility

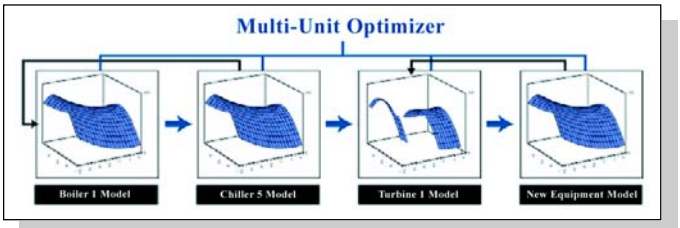

Figure 3. An example: use of mixed models to optimize a central utility system.

Empirical Models	vs.	Rules-Based Systems
• Model of Dynamic Process • Predictive • Accounts for Linear & Non-linear Processes • Numerical with derivatives enabling optimization		• Replication of Operator Actions • Historical • Represents the process as a set of conditional if-then rules • Logical with no derivatives

Table A. Qualitative comparison of empirical and rules based models.

- the day's weather forecast and how it will affect operations
- the real current cost of various energy options, including day/night price variance
- recharging of storable utilities such as chilled water while energy is least expensive
- the current state of repair of each piece of equipment
- planned maintenance and outages
- the operational limitations of each piece of equipment
- the energy efficiency curve of each piece of equipment
- minimization of environmental emissions

The standard response when action is required is for the operator to dispatch decisions independently to each utility system, taking into account as many of the above parameters as possible. However, given the interdependency of many systems, such as chilled water (steam absorber units) and steam systems, this approach is iterative at best when determining the optimal operating point, wasting valuable time and resources. Conversely, within minutes of a detected change a properly constructed optimization software solution can calculate the optimal point of operation, and accurately send out a simultaneous group of actions covering numerous systems. The result is the ability to achieve the new optimum operating point in the minimum amount of time, maximizing savings.

Given the complexity of each decision, the need for quick response, and the profit impact of each decision, the opportunity to use optimization software to improve current utility system management seems natural. The number one goal of most central utility systems is to reliably meet the process demand continuously. In this case, economic optimization becomes secondary to ensuring an uninterrupted process. To maximize benefit to the manufacturer, real-time optimization systems must address each of the parameters listed above. A complete, multi-unit, real-time optimization solution must both provide functionality that allows the operator to interact with the system, and an overview of the current operational situation. Thus, an integrated central utility optimization solution should include for each piece of equipment:

- availability (i.e. down for repair)
- availability for optimization (might be withheld for any number of reasons, the system should optimize around what ever rate the operator picks for this piece of equipment)

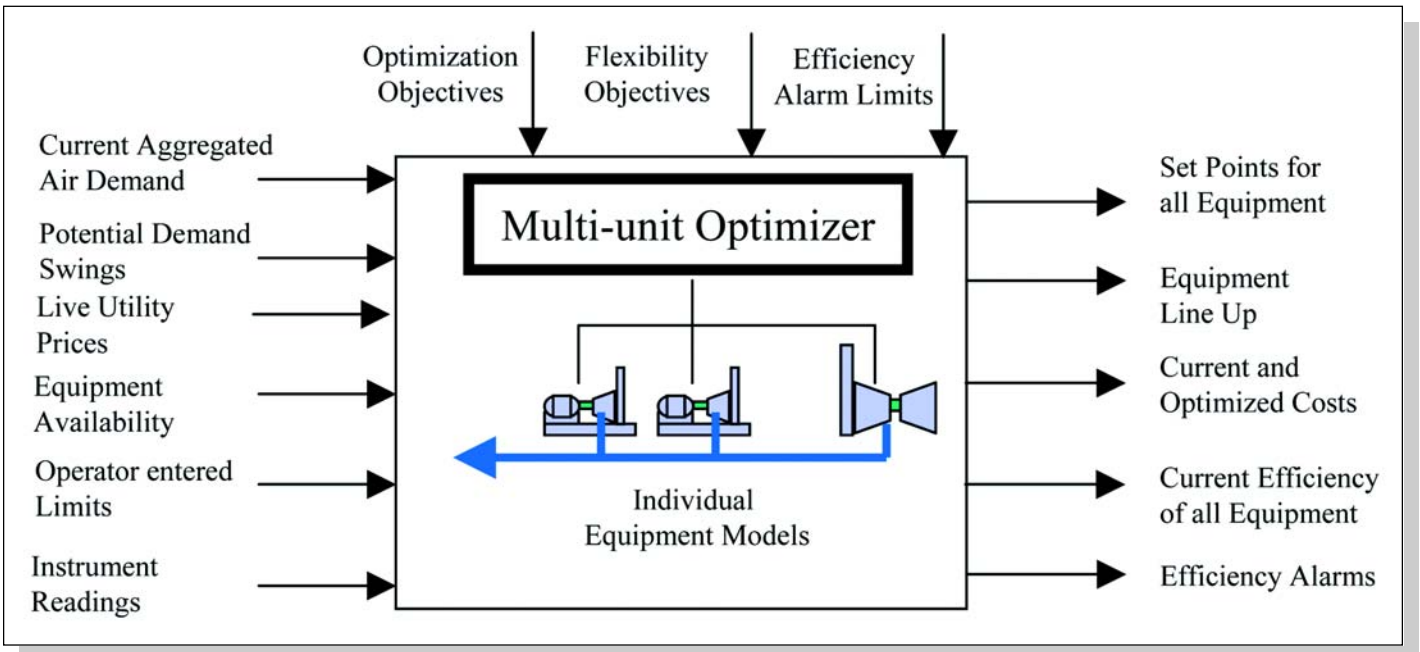

Figure 4. A system model for a central utility system.

- acceptable operating ranges (min, max)
- minimum turndown, maximum ratings, and inoperable ranges

These critical constraints and limitations are factored as "rules" into a global optimization solution, allowing a company to achieve the optimal decision (energy conservation, profits, environmental) based on the unique business requirements.

Energy Optimization in Pharmaceutical Utility Systems

The first step in an optimization project is to individually model the efficiency performance of each piece of equipment. The key challenge is to determine the best modes of operation for each system under varying loads to maximize savings and improve reliability.

In a typical pharmaceutical facility, a central utility system may include the following equipment:

Low Pressure Air Compressors
Steam Turbine Compressors
Electric Motor Compressors
Gas Turbine Driven Compressors
Natural Gas Engine Compressors

Steam System
Coal Fired Boilers
Natural Gas Package Boilers
Oil Fired Boilers
HRSG's

Chilled Water Systems
Electric Centrifugal Chillers
Steam Turbine Chillers
Steam Absorbers
Natural Gas Engine Chillers
Thermal Storage Devices

Co-Generation
Steam Driven Turbines
Single Cycle Turbines
Combined Cycle Turbines
External Dispatch

Many of these systems are linked and therefore require interrelated optimization (i.e. boiler dispatch operations must consider steam absorber and steam turbine chiller dispatch operations). For example, the solution to high vent loss may not optimally lie with reduction of steam production, but might best be solved through reduced use of the steam turbine driven chillers.

Once the individual equipment models are completed, a unifying economic optimization model is designed to reduce costs and achieve profitability goals. The optimizer has an economic objective function that is minimized subject to any number of identified constraints. Depending on the operating constraints and cost structure at any given time, the optimization solution will find the optimal set point for each controller that is commanding the central utility system based on stated goals (e.g. minimizes the operating cost, maximizes the efficiency, etc.). Once the models are complete, the models are placed online and commissioned.

This brings the question of the impact of this type of project on the validated state of a utility system. Noting the differences between critical (product contact) and non-critical (no product contact) utilities can differentiate treatment of these systems. For non-critical utilities, modification, and application of closed-loop control have not been viewed as under a regulatory environment. Generally, justification for these projects has been on standard investment criteria without inclusion of regulatory issues and associated re-validation costs.

However, in pharmaceutical operations, critical utilities have become increasingly under regulatory review in recent years. For these critical systems, or systems where modification will impact the production or distribution of a critical utility system, joint review with the solution provider to

determine any impact to the existing or future system and its state of validation is recommended. This type of approach ensures that validation is incorporated into the solution and its financial justification when required by company policy or regulations.

Even with the addition of an optimization solution for critical utility systems, solutions can be developed to minimize the impact and cost on a validated system. For example, companies can use the solution in advisory control (open-loop) mode and provide the operator with information to make better decisions. This takes the burden off the system and removes most concern regarding validation of such an installation, but gives the operator more intelligence about the complex inter-relationships in the central utility system than available with current systems.

This article will now briefly review each area included in the utility optimization model. The potential savings provided for the equipment and systems below are based on 1999 energy prices which are conservative figures when compared to recent energy prices.

Air Compressors

The typical low-pressure air system is a mix between electric, steam turbine, and gas turbine compressors. From the historical data, efficiency curves are generated for the compressors. One of these examples is shown in Figure 4. The focus for optimization in this area is to shift load to the most efficient units while maintaining reliability. Savings of $5 to $10/yr per installed horsepower are typical. Thus, if a facility has 6000 HP installed, it can expect $30,000 to $60,000/yr savings through dispatch optimization.

Chiller Water Energy Optimization

Virtually every form of energy could be utilized to generate chilled water, and as a result, this is a rich area to exploit swings in fuel prices. Units can be dispatched on a dollars-per-ton metric rather than raw efficiency, resulting in significant savings. The energy optimization project has a side benefit: a new understanding of the full efficiency of units. Today, industry is bogged down in what we call "next chiller mentality" where operations look to fully load chillers before turning on the next unit. Without knowledge of the efficiency curves, this seems the obvious route to save pumping costs. However, the efficiency benefits of partial loading chillers far outweighs pumping costs.

The second area for optimization of chilled water operations is condenser water temperature optimization. Often the benefit of lower condenser water temperature, when achievable though cooling tower operations at lower wet bulb temperatures, can create improved chiller efficiency. Typically, the capability and energy efficiency of cooling tower operations are included in the optimization.

Through dispatch of the most efficient units, partial loading of multiple chillers, and condenser water temperature optimization, most chilled water plants can realize $5 to $14/yr savings in energy per ton of installed capacity. For example, if a facility has 10,000 tons of refrigeration, it can expect to save $50,000 to $140,000/yr on chilled water energy costs though optimization alone. One important note, the potential savings provided above are based on 180 days of operation for the various equipment. If the equipment is operated year-round, the estimated savings could double.

Steam Optimization

Typically, multiple boilers of varying fuels are available for operation depending upon load requirements. In this area more than any other, reliability is key for process operations. Care must be taken to assure the real-time optimization results do not paint the operators into a corner which does not allow enough flexibility to respond to sudden load shifts. It is common practice to dispatch multiple units equally due to ease of operations. However, most boilers are most efficient at high load. Thus, we would like to see "next boiler mentality" developed in industry. The most efficient unit should be dispatched for base maximum capacity. Less efficient units should serve as swing units. The optimizer typically includes savings calculations, which are based on different levels of efficiency and cost of generating steam.

In addition to boiler dispatch, additional optimization savings exist in reduction of steam venting through closer management of steam vent losses due to load balancing. Steam is typically produced at multiple pressure levels, and real-time balance of letdowns versus generation of new steam can cut vent losses dramatically.

Finally, through dynamic real-time closed loop control of steam headers, it is possible to reduce steam pressure variation and degree of saturation variation by more than 50%. These improvements translate directly to smoother plant operations and improved product quality. These savings can dwarf the energy savings, but are usually only counted as a side benefit.

Through optimization of boiler operations through dispatch and smoother steam balance, a facility should see savings of $300 to $500 per year per klb/hr of steam production. As an example, for a facility generating 500 klb/hr of steam this would translate to between $150,000 to $250,000 per year through on-line real-time energy optimization. These savings are based on a typical steam season of 180 days.

Co-Generation

There is much that can be discussed on this subject alone. Certainly, not all manufacturers have co-generation capability. However, almost every plant can utilize the swings in electricity cost from peak to off peak to schedule energy production in ways that minimize their energy bills. Use of a single blended power cost should be avoided in real-time systems. Real-time optimization software can model pricing swings for external sale or model the existing electrical contract for on-line use by the optimizer. Peak savings can be significant.

Description	Potential Annual Savings
Air Compressors	$5 - $10 per installed horsepower
Chiller Condenser Water and Dispatch	$5 - $14 per year savings in energy per ton of capacity
Boiler Dispatch and Steam Vent Control	$300 - $500 per klb/hr of steam production
Increased Life-Span of Assets	Varies depending on equipment
Increased energy reliability	Varies depending on operating swings and energy sources

Table B. Potential savings from a central utility optimization solution.

For those with external power sale capability, the savings can be greater. With the use of the real-time price tracking and dispatch system, power sales opportunities are now exploited to the maximal potential within contracts and operational constraints, creating a significant new revenue stream.

Estimating Savings through On-line Optimization of a Pharmaceutical Utility System

A summary of potential savings metrics for a central utility system are provided - *Table B*. The cost of generating different utilities, such as steam, power, compressed air, distilled water, and chilled water changes with time because of fuel mix changes, demand, and power costs. There may be additional constraints involving system operations, equipment capacities, and emissions (e.g. from the boilers). The utility operator must decide on how much of each utility to generate and how to dispatch the load among the various generators. Because there are so many variables and constraints to consider at any given time, the operating point that minimizes cost at any given instant may not be obvious.[2,3] This problem is addressed through the utilization of real-time optimization software that works with the operator to determine the most reliable and profitable operation.

Projected savings shown in Table B are based on actual savings realized by industrial companies who have installed energy center optimization solutions as discussed in this article.

Conclusion and Benefits

Experts believe the cost implications of the lack of reliable, affordable energy will continue to grow.[4] With energy demands expected to rise significantly in the next 20 years, companies are focused on improving their own utilization, and in some cases, becoming much more self-reliant in energy and utility supply. Optimization and control software may help pharmaceutical companies achieve short-term and long-term energy management goals. Long used to improve production processes and energy efficiency at major utilities, optimization software has proven to achieve 3 - 7% or more in energy savings. These savings have been the basis for financially justified optimization projects to bring solutions to the utility center. Optimization solutions allow operators to:

- easily manage multiple complex systems simultaneously (chiller, boiler, steam)
- achieve energy conservation, economic, and environmental goals
- maximize use of current assets
- predict future operations based on current data and information
- simulate and determine business options based on real-time information (energy prices, environmental limits, energy demand)

This minute-by-minute optimization translates into reduced costs, increased life-span of equipment assets, and the ability to take advantage of market opportunities such as trading, co-generation, and emissions credits. As pharmaceutical companies grapple with the myriad of ways to conserve energy, ensure a reliable source of energy to deliver products on time, and increase profits, optimization software may offer a near-term solution.

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About the Authors

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This article presents performance standards for envelope components, mechanical systems and lighting, and presents potentially significant changes of interest to the designers and operators of pharmaceutical R&D facilities.

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Compliance of Pharmaceutical R&D Facilities with the Updated ASHRAE Energy Standard

by Mark Maguire

Introduction

In 1999, the American Society of Heating, Refrigerating, and Air-Conditioning Engineers, Inc. (ASHRAE) and the Illuminating Engineering Society of North America (IES) revised Standard 90.1, "Energy Standard for Buildings Except Low-Rise Residential Buildings."[1] This Standard was last updated in 1989[2] and mandates performance standards for envelope components, mechanical systems, and lighting. This modified Standard presents potentially significant changes of interest to the designers and operators of pharmaceutical Research and Development (R&D) facilities. This article defines some of the major changes. Table A also summarizes the major impacts.

The Standard covers new and renovation construction projects, and replacements of heating, ventilating, and air-conditioning (HVAC) equipment and lighting equipment. The Standard specifically exempts buildings which house manufacturing and commercial processes, but does include laboratories, offices, and support spaces unless the process needs require consistent space temperature and relative humidity conditions, and this priority overrides the principle of energy efficiency. This would exempt facilities such as data centers, toxicology areas or certain cleanrooms.

The Standard does not have the force of law unless it is adopted within the local governing code, but, as a Standard, it establishes a level of care for the industry so that design professionals will likely start to adopt its principles in the near term.

There are several compliance paths to follow. Buildings smaller than 25,000 ft^2 [2300 m^2] and two stories or smaller fall under a *simplified* path; requirements are captured on two pages of the Standard for these types of buildings.

Buildings which do not qualify for the *simplified* path must comply with certain *mandatory* provisions (related to building envelope performance, minimum mechanical equipment efficiency, domestic hot water generation efficiency, and lighting controls), and then must comply through a *prescriptive* path (in which the Standard defines certain elements which must be incorporated), or an *Energy Cost Budget* path. The *Energy Cost Budget* path is an alternative which simulates the building (using annual energy cost modeling software) using other proposed energy-conserving systems, which essentially substitute for not implementing the *prescriptive* elements. If the simulated building's energy use (employing alternate technologies) is less than the building's energy use (employing the prescriptive technologies), then the Standard is met. The Standard furnishes baseline assumptions to be used in the building simulation process.

Some of the major *mandatory* provisions described in the new Standard are:

Building Envelope

The Standard defines criteria for the installation of wall and roof insulation and building envelope "tightness" to limit outside air infiltration into the conditioned space.

Equipment Efficiency

Minimum energy efficiencies for HVAC equipment have been made more stringent. For example, the efficiency rating for large electric water-cooled chillers has been lowered to 0.58 kW/ton [6.1 COP] from 0.75 kW/ton [4.7 COP] in the 1989 edition. Although market forces have driven chiller efficiencies far below 0.75 kW/ton [4.7 COP] since the 1989 Standard, the 0.58 kW/ton [6.1 COP] threshold represents a challenge that equipment manufacturers will need to meet while still maintaining competitive pricing. This will affect not only new construction projects, but also infrastructure upgrades, such as chiller replacements.

Humidification Jacket Steam

Humidifiers which inject steam directly into the supply airstream are often furnished with an outer tube (or jacket) which preheats the injection steam which runs through an inner

> ***The revised Standard requires a separate control valve on the outer jacket steam which prevents steam from flowing through the outer jacket when humidification is not required.***

tube. This preheating process prevents the humidifier from injecting a cooled, two-phase steam/condensate mixture into the airstream. The outer jacket is upstream of the control valve which modulates steam to the humidifier, so often the jacket steam is continuously energized, even during the summer months since there is no "intelligence" to stop the steam flow. The revised Standard requires a separate control valve on the outer jacket steam which prevents steam from flowing through the outer jacket when humidification is not required. This affects pharmaceutical manufacturers because office and laboratory areas are typically humidified, most often by direct injection of steam provided by a central boiler plant.

Duct and Piping Insulation

The new Standard revises the minimum insulation thicknesses for ductwork and piping. As a result of a lifecycle assessment approach, the duct insulation thickness in the updated Standard is a function of climate.

Commissioning

The revised Standard requires that a commissioning process be specified and executed for buildings larger than 50,000 ft^2 [4600 m^2]. Although the Standard is not specific on the content of the commissioning process, it references ASHRAE Guideline 1[3] in an appendix so the inference is that a procedure complying with that guideline is intended. Commissioning of mechanical systems for pharmaceutical manufacturing areas has long been practiced as a prerequisite to validation and cGMP compliance. This is now being extended to the central utility plant level and other HVAC areas not typically commissioned.

Completion Requirements

The revised Standard strengthens the 1989 requirement to furnish as-built drawings and an Operating and Maintenance (O&M) manual, by identifying items focused on the service and operation of the mechanical equipment which need to be captured in the O&M manual. This item traditionally has been required for pharmaceutical manufacturing areas subject to cGMP compliance, but this is now required for HVAC systems related to labs and offices.

The assumption is that the theory of how energy-conserving equipment is designed to operate and be controlled must be understood by the maintenance group in order to realize the

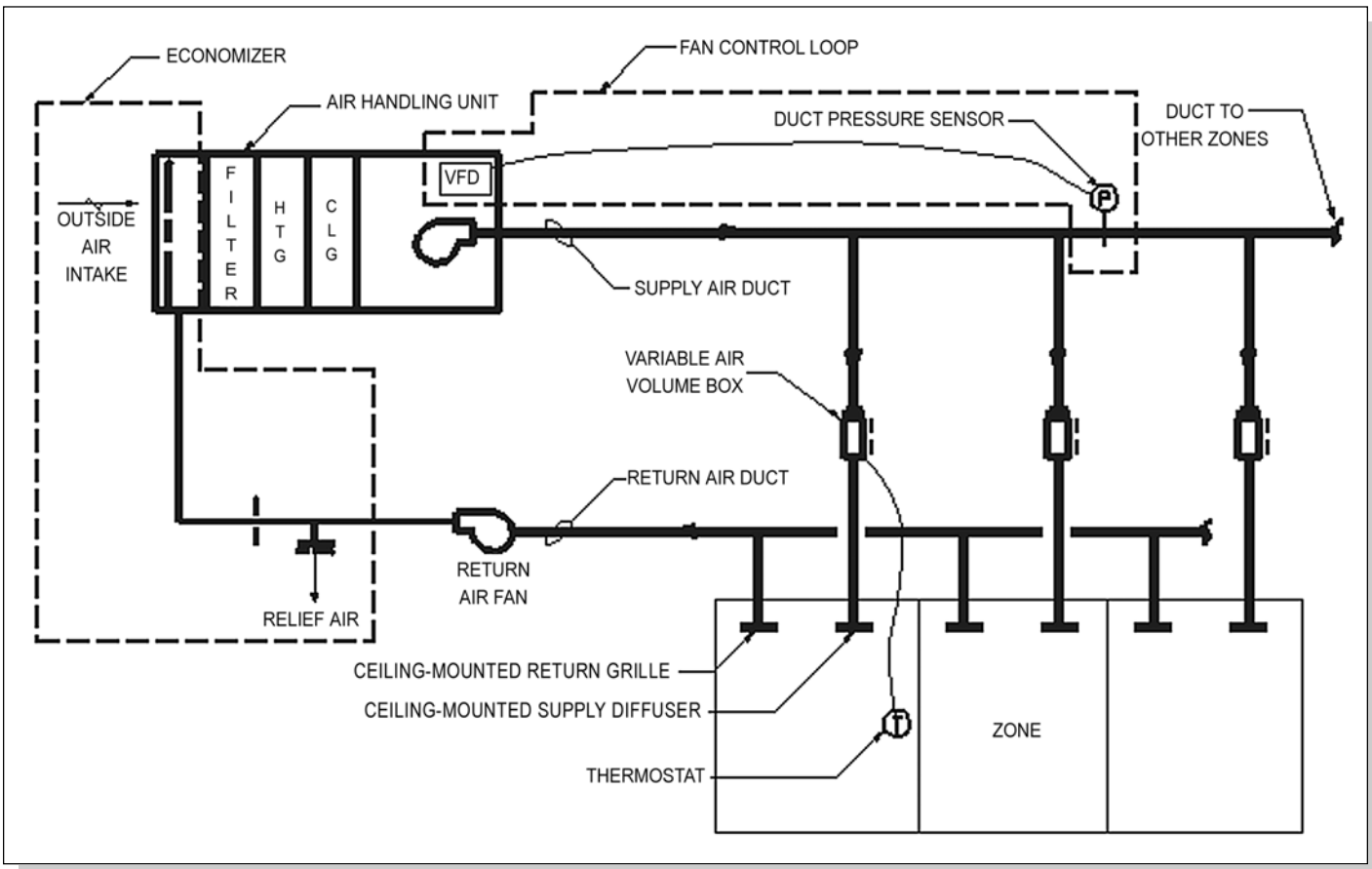

Figure 1. Variable volume airflow design.

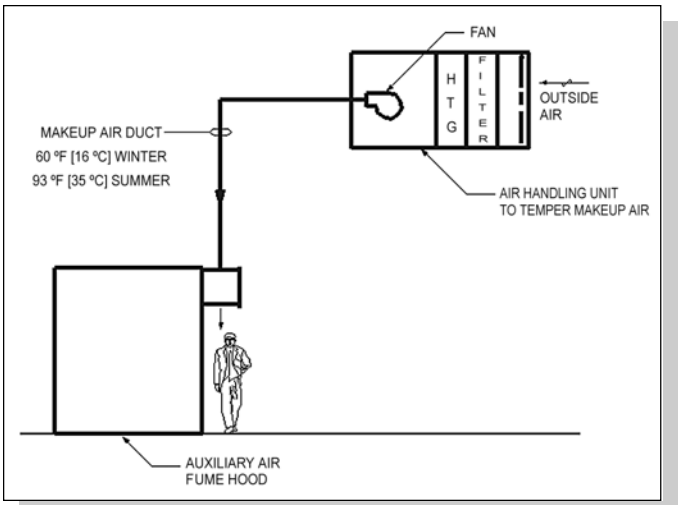

Figure 2. Auxiliary air fume hood arrangement.

energy savings potential. This is an attempt to bridge between the design and maintenance teams: as more information becomes available to the maintenance team, they will be able to operate the mechanical equipment closer to the design intent and therefore be more likely to take advantage of energy-saving strategies embedded in the design.

Electric Power Systems

The 1999 Standard requires feeder conductors and branch circuit conductors to be sized at a maximum of 2% and 3% voltage drop, respectively, at full connected load. A reduction in voltage drop will decrease the amount of power lost as heat. Further, this heat appears as a load to the air-conditioning system, which must use energy to offset this additional heat gain and cool the space.

The requirement for O&M manuals for power systems, including a narrative of design intent, also has been strengthened from the 1989 version.

Lighting Systems

Lighting controls have been made mandatory in more areas, and areas which were exempted from the 1989 Standard have lost their exemption. The Standard addresses lighting systems because they are large consumers of electric power, particularly in office and office support areas.

In addition to the *mandatory* provisions cited above, buildings which do not meet the *simplified* threshold (less than 25,000 ft^2 [2300 m^2] and two stories or less) must take one of two paths: the *prescriptive* path or the *energy cost budget* path. In the *prescriptive* path, the Standard defines certain elements which must be incorporated. In the *energy cost budget* path, the building is mathematically modeled (using annual energy cost simulation software) using other proposed energy-conserving substitutions, which compensate for not implementing prescriptive elements. If the simulated building energy use (employing alternate technologies) is less than the building energy use (employing the *prescriptive* technologies), then the Standard is met.

Some of the major *prescriptive* provisions described in the new Standard are cited in the following paragraphs. Note that if these specific elements are not incorporated into the building design, then a computer simulation of the building will need to demonstrate that other energy-conserving measures have been implemented which essentially save the same amount of energy as the specific element.

Maximum Window Area

The maximum vision glass area is limited to 50% of the gross wall area, unless a building simulation determines that substitutions of other energy-conserving measures *on the envelope* have been taken which offset the additional glass area. For example, if the vision glass area exceeds 50% and causes additional energy consumption due to increased heating and cooling demands, then additional insulation of the roof and wall must decrease the heating and cooling demand by an equivalent amount. Similarly, skylight area may not exceed 5% of the gross roof area without a substitution in other envelope components. The Standard requires that the envelope be judged on its own merits: a more efficient HVAC or lighting system is not allowed to compensate for an envelope that causes a higher heating or cooling demand.

The intent of this clause is the belief that the first step in reducing building energy consumption is to reduce heating and cooling demand.

In the pharmaceutical market, this clause would center most closely on office building projects since the window area of lab buildings is typically limited.

Item	1989 Standard	1999 Standard
HVAC Equipment Efficiency: Large Chiller Example	0.75 kW/ton [4.7 COP]	More efficient 0.58 kW/ton [6.1]
Commissioning		Now required
Duct and Piping Insulation Thickness	Function of fluid temperature and pipe size	Function of fluid temperature, pipe size and climate
Building Envelope	Overall thermal transmission value (OTTV) specified as a composite envelope criteria	Fenestration greater than 50% of wall area requires other envelope-related compensation and a building simulation
Completion Requirements	Operating and maintenance manuals and as-built drawings required	Manuals and as-built drawings still required but language has been strengthened
Airside Economizer	85% of supply air required	Required as a function of climate and system size; 100% of supply air required
Part-Load Control Criteria	Not strongly mandated	Larger fans and pumps to use 30% of power at 50% of flow rate

Table A. The major differences between the 1989 and the current 1999 editions of ASHRAE Standard 90.1 related to energy usage in new and renovated construction projects.

> ***Enthalpy (instead of dry bulb temperature) is often used as an indicator of energy use to capture the effect of both sensible and latent heat transfer at the cooling coil.***

Economizer Cycle

Most commercial office buildings today in moderate climates use an economizer cycle in which more outside air is brought into the building (at the air handling unit) when using more outside air is less energy-intensive, which typically occurs during shoulder seasons. For example, if the supply air temperature setpoint of an air handling unit is 55°F [13°C] and the mixed air (combined return air and outside air) temperature is 81°F [27°C], then mechanical refrigeration is indicated. However, if the outside air falls to 60°F, then the outside air temperature is closer to the supply air temperature setpoint than the return air temperature is so less energy would be used to cool outside air rather than return air. The increased intake of outside air and the relief of air from the building (to maintain a mass air balance) is termed the economizer cycle. Enthalpy (instead of dry bulb temperature) is often used as an indicator of energy use to capture the effect of both sensible and latent heat transfer at the cooling coil. The economizer cycle is an effective energy management tool because in temperate climates such as the northeastern United States, there are statistically a large number of hours when the temperature/relative humidity conditions allow the mechanical refrigeration system to be operated at part load.

An "airside" economizer cycle has been described above. A "waterside" economizer also is available where the outside air cools an intermediate water loop which in turn cools the supply air. This is often used in data centers (where relative humidity fluctuations in the ambient air would disrupt the room relative humidity), and in high-rise construction (where the cost and building area to provide outside and relief air ducts sized for economizer mode are prohibitive).

The 1999 Standard expresses the economizer threshold (i.e., when an economizer cycle is required) as the number of hours between 8 am and 4 pm when the dry bulb temperature is between 55°F [13°C] and 69°F [21°C]. For example, when the 1% cooling design wet bulb temperature is greater than 73°F [23°C], and there are less than 800 hours between 8 am and 4 pm when the dry bulb temperature is between 55°F [13°C] and 69°F [21°C], an economizer cycle is not necessary per the Standard.

The 1999 Standard also requires that 100% of the design supply air quantity be available for the economizer cycle. The 1989 Standard required only 85% of the design supply air quantity be available for the economizer cycle.

For waterside economizer cycles, a maximum waterside pressure drop of 15 feet of water [45 kPa] has been imposed on the precooling coils and any water-to-water heat exchangers in the system. If the pressure drop target is not met, then a

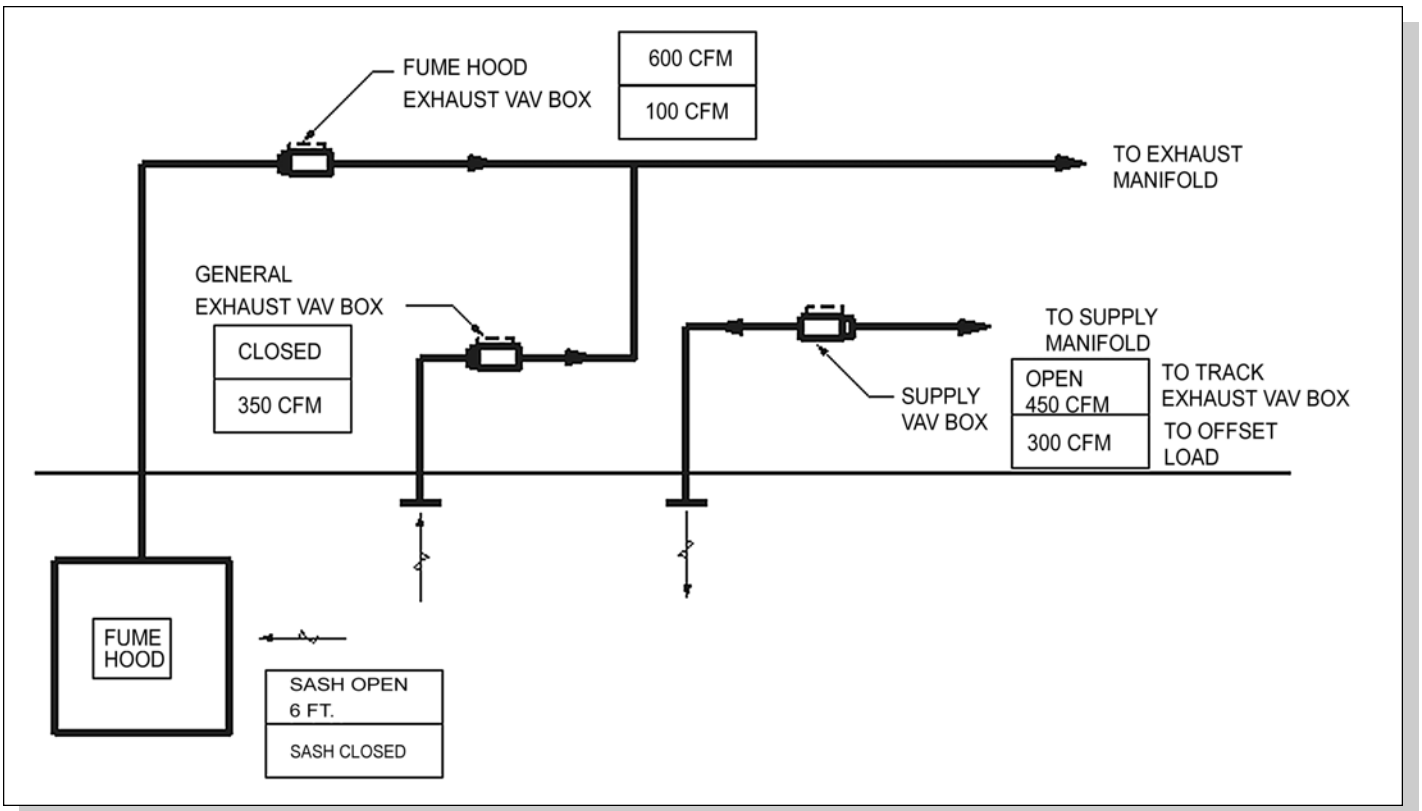

Figure 3. Variable air volume fume hood schematic arrangement.

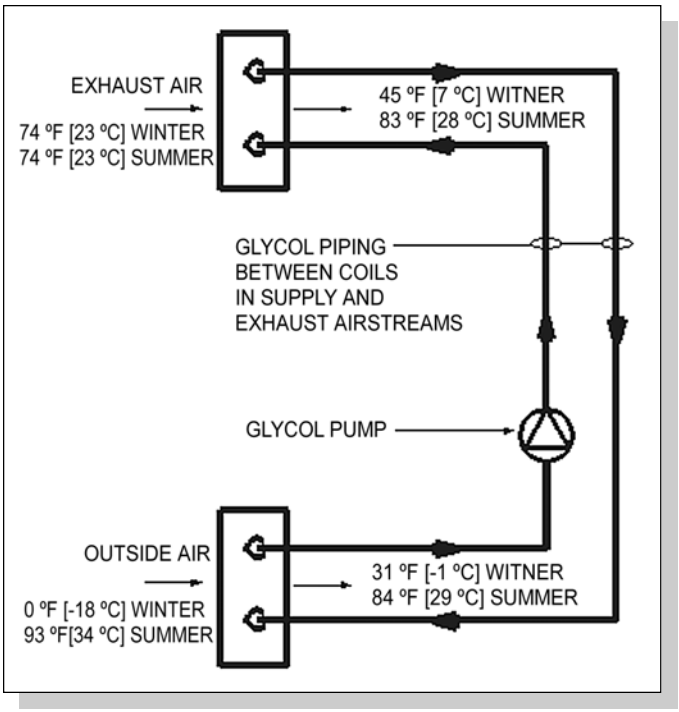

Figure 4. Glycol runaround heat recovery flow diagram.

secondary pumping system is needed so that the main pumping system is not penalized by the additional pressure drop during the times of the year when the economizer mode is not active.

In the pharmaceutical market, this clause would be focused on office buildings because laboratory buildings are usually 100% outside air, driven by exhaust elements within laboratories.

Part-Load Control of Fans and Pumps

A new provision of the Standard is that fans (30 horsepower [20 kW] and larger) serving variable air volume systems must use less than 30% of the design power when delivering 50% of the design air flow rate. This virtually compels Variable Frequency Drive (VFD) control of fan motors since alternative systems such as fan discharge dampers and variable inlet vanes use more than 30% of the design power when delivering 50% of the design air flow rate. Under certain pressure and flow circumstances, selection of a variable pitch vaneaxial fan may meet the Standard's part-load target without VFDs.

Similarly, pumps (50 horsepower [35 kW] and larger) serving variable volume hydronic systems have the same requirement (to use 30% of the design power when delivering 50% of the design water flow rate), which also virtually compels the use of VFDs.

Higher reliability and decreasing costs have been driving more usage of VFDs over the last 10 years, but the 1999 Standard virtually mandates their use in this application.

Part-load control strategies are critical to reducing building energy usage because, statistically, building mechanical systems operate partly-loaded for the vast majority of hours in a year.

Part Load Control of Cooling Towers

Cooling towers (and other heat rejection equipment) that serve non-process loads and have 7½ horsepower [5 kW] fans or larger, must automatically control their fan speed to less than 2/3 of full speed. The intent of this requirement is to reduce cooling tower fan energy consumption since power consumption is a function of the cube of fan speed. This requirement can be met by three types of technology:

- VFDs: VFDs modulate the fan speed to maintain a cooling tower water supply temperature setpoint. One advantage of VFDs is their ability to reduce the sound power level (PWL) emitted by the cooling tower; this is an advantage if the site has residential neighbors which may object to cooling tower noise, particularly at night. If each cell needs individual control, one VFD per cell is required and it is usually more economical to place the VFDs close to the cooling tower to avoid the cost of routing multiple power conductors from the central plant to the cooling tower.

- Two-Speed Fans: Two-speed motors control the fan speed in stepwise fashion (in steps of full-speed, half-speed, and off). Because the cooling tower supply temperature often does not need to be precisely controlled, two-speed fans have historically been used. However, the energy savings and PWL reduction associated with this system are limited.

- One Fan with Two Motors: Certain cooling tower manufacturers offer a fan which is connected to two motors, driven by one at a time. One motor is selected for full speed, full horsepower; the second (pony) motor is selected for 67% of full speed and 33% of full horsepower. Since the smaller load is being operated by a smaller horsepower motor, the motor also is more mechanically efficient.

This requirement will affect pharmaceutical facilities mostly in the generation of chilled water because chillers typically reject heat to cooling towers which must comply with this provision.

Heat Recovery from Chillers for Domestic Hot Water

For facilities that operate continuously (24 hours/day, 7 days/week) even in the winter, the 1999 Standard requires heat recovery from "condensers" larger than about 400 tons [1400 kW].

This recovered heat would be used to preheat Domestic Hot Water (DHW) and is required when the peak DHW load exceeds about 1000 lb/hr steam [293 kW]. This would affect many new or upgraded pharmaceutical R&D campuses with central plant operations because all the thresholds (24x7 operation, 400 tons [1400 kW], 1000 lb/hr [293 kW] DHW demand) are exceeded.

Since the Standard does not differentiate between different types of refrigeration machines with condensers (chillers for comfort conditioning, process chillers, product refrigeration equipment such as walk-in boxes, etc.), the assumption is that chillers for comfort conditioning are included in this category. One often-used utilities arrangement for pharmaceutical sites is a central steam and chilled water plant distributed to buildings on the site. Within each building, steam is routed to manufacturing equipment, autoclaves, and glasswash equipment to heating systems and to domestic hot water heaters. Since each building contains its own domestic hot water generation and the chilled water is centralized at a central plant often remotely located from the buildings it serves, it is unclear how the heat recovery from chillers to preheat domestic hot water can physically be configured.

Air Pressure Control Reset

This will impact pharmaceutical industry office or R&D facilities which have either of two types of popular systems:

- Office Variable Air Volume Systems: VAV boxes modulate in response to a room temperature signal: as the room load increases, the temperature increases and the VAV box receives a signal to increase the flow of 55°F [13°C] supply air to offset the heat gain.

- Laboratory Fume Hood VAV Systems: VAV exhaust boxes modulate to maintain a face velocity setpoint as fume hood sash areas are changed. The fume hood open sash area is calculated and the VAV exhaust box opens to allow enough air through the fume hood to meet the face velocity setpoint (typically 100 feet/minute [0.5 meters/second]. The supply VAV box then tracks the exhaust box to maintain negative pressure in the laboratories relative to adjacent spaces.

For either type of system, duct pressure is typically used as an indicator of airside demand: as the VAV boxes throughout the system close, the duct air pressure increases, and that pressure signal is compared to a setpoint and is used to drive a fan response: change the fan speed through a variable frequency drive, vary the fan blade pitch on vaneaxial fans, or modulate inlet vane dampers. This is illustrated in Figure 1.

The updated Standard requires (for systems with computerized or direct digital controls) that the duct pressure setpoint be dynamically reset: as more boxes close on a decrease in load, the pressure setpoint is indexed lower until, at least theoretically, only one VAV box damper remains fully open.

Fume Hood Exhaust Systems

For fume hood exhaust systems greater than 15,000 cfm [25,000 m^3/hr], the 1999 Standard mandates the use of either auxiliary air fume hoods, VAV exhaust system, or a heat recovery system. Since pharmaceutical discovery facilities typically use 100% outside air due to exhaust elements within the laboratories, their energy use is very high because the facility is continually conditioning hot, humid (or cold) outside air with no recirculation of previously-conditioned air. This requirement is an attempt to reduce the amount of energy consumed by laboratory facilities.

- Auxiliary air fume hood systems deliver "tempered" outside air (typically heated to about 60°F [16°C] in the winter and not preconditioned at all in the summer) directly to the front of the fume hood. This concept is schematically shown in Figure 2. This type of system was an early response to escalating fuel costs in pharmaceutical R&D facilities and resulted in excursions in room temperature and relative humidity conditions, and has largely been abandoned.

- VAV exhaust systems work as described above and in Figure 3, and present several advantages:

  - Combined with a manifolded exhaust system approach, diversity can be applied which downsizes the exhaust and supply fans and main exhaust and supply ductwork.
  - Achievement of a consistent velocity at the fume hood face; legacy "bypass" fume hood systems resulted in high velocities at low sash openings.

There are several types of heat recovery technologies available commercially. The most common are:

- Glycol Runaround: Coils are placed in the exhaust air and outside air intake streams, and an antifreeze glycol/water mixture is pumped between the two coils. During the winter, the glycol is heated by the 74°F [23°C] room air being exhausted, and then the heated glycol preheats the cold (for example, 0°F [-18°C]) outside air. The reverse process occurs during the summer. This is shown in Figure 4.

- Heat Wheel: A dessicant wheel rotates through the exhaust and outside air intake streams and causes both sensible and latent heat transfer between the two airstreams. Although there have been advances in materials used in heat wheels over the past 10 years, their application to air being exhausted from fume hoods is generally discouraged due to the potential for corrosion of the wheel and cross-contamination from the contaminated exhaust airstream into the cleaner outside air stream.

- Heat Pipes: Refrigerant-containing coils are placed in the exhaust air and outside air intake streams and the refrigerant transfers heat sensibly between the two airstreams. For example, in the winter, the refrigerant in the exhaust heat pipe is heated by the 74°F [23°C] exhaust air, then preheats the cold (for example, 0°F [-18°C]) outside air.

Disadvantages to this system are typically large capital cost and the need to place the exhaust and outside air streams close to each other. One goal in the design of laboratory facilities is to prevent the reentrainment of exhaust fumes into the outside air intakes. One way of attaining this goal is to physically separate the two air streams as much as possible; the heat pipe strategy causes the opposite effect (i.e., the two air streams should be as close as possible).

These systems recover the most energy during times of ambient temperature extremes because the Log Mean Temperature Differences (LMTD) at the supply and exhaust coils are at their maximum values at that time. However, during temperate weather conditions of 50 - 70°F [10 - 21°C], the system may be deactivated because the pump energy exceeds the recovered energy.

The exhaust and supply coils cause a resistance to airflow which must be overcome by the fans. The energy to overcome this additional resistance decreases the amount of gross savings caused by the heat recovery system. Further, the resistance to airflow is incurred during all hours of the year, even if the system is deactivated during temperate weather.

Although glycol runaround heat recovery systems save energy, their economic feasibility should be evaluated on a lifecycle cost basis. A Discounted Cash Flow (DCF) analysis is often used because it represents the true cash flow of a project, including the effects of:

- energy savings escalation over the life of the installation

- depreciation and tax effects

- time value of money

Example discounted cash flow analyses for glycol runaround heat recovery system applied to variable volume laboratory

systems for pharmaceutical manufacturers indicates payback periods of 10 to 15 years, and returns on investment of 3-6%. The payback improves if a central plant source of chilled water or steam can be downsized because the peak building demand is reduced due to implementation of a heat recovery system.

Three factors which strongly influence the payback viability of glycol heat recovery systems are:

- Fuel Cost: Many pharmaceutical firms which operate large sites have negotiated relatively low natural gas and fuel oil prices with their suppliers. Low fuel costs have a profoundly negative effect on the payback of heat recovery systems since the gross savings are reduced.

- VAV Systems: Since the maturation of VAV lab exhaust systems in the 1980s, the economics of heat recovery systems have been less favorable because the amount of energy being recovered is less because it is proportional to the airflow.

- Electricity Cost: A lower electricity cost encourages heat recovery because the cost to offset the air resistance and the cost to operate the glycol pump are lower, so the net annual savings becomes greater.

In conclusion, the most recent revision of Standard 90.1 requires designers and operators of pharmaceutical R&D facilities to be particularly attentive to mechanical equipment efficiency, project closeout, window area, and reducing energy consumed by laboratory fume hood exhaust systems.

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About the Author

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Improving Performance and Reducing Cycle Time Using Flow Path Management: A Case Study

by Glenn Gerecke and Tom Knight

This case study summarizes the philosophies, organizational changes, and information systems that DuPont Pharmaceutical Company and SAK Logistics implemented to achieve manufacturing excellence.

Editor's Note: The DuPont Pharmaceutical Company was acquired by Bristol-Myers Squibb Company on October 1, 2001.

Introduction

Pharmaceutical companies are facing increasing pressure to improve the performance of manufacturing operations. Plants must increase shipments, lower costs, and improve profitability while maintaining consistently high quality and delivery performance. The result: manufacturing excellence is a strategic advantage in the pharmaceutical industry.[1]

Traditional methods for improving operating performance are often based on out-dated organizational structures, performance metrics, and information.[2] For example, many pharmaceutical plants still use Enterprise Resource Planning (ERP) or Materials Requirements Planning (MRP) systems for detailed planning and scheduling, despite the numerous limitations of this approach.[3-6] Their performance often plateaus: inventory is too high, shipments take too long, and people are often working on conflicting plans and objectives.

This case study describes how one pharmaceutical plant, the DuPont Pharmaceutical Company's operation in Garden City, New York, broke out of these limitations to reach dramatically better performance. Over the last three years, the men and women at the site, together with some key strategic partners, have reshaped their organization and their systems to pursue

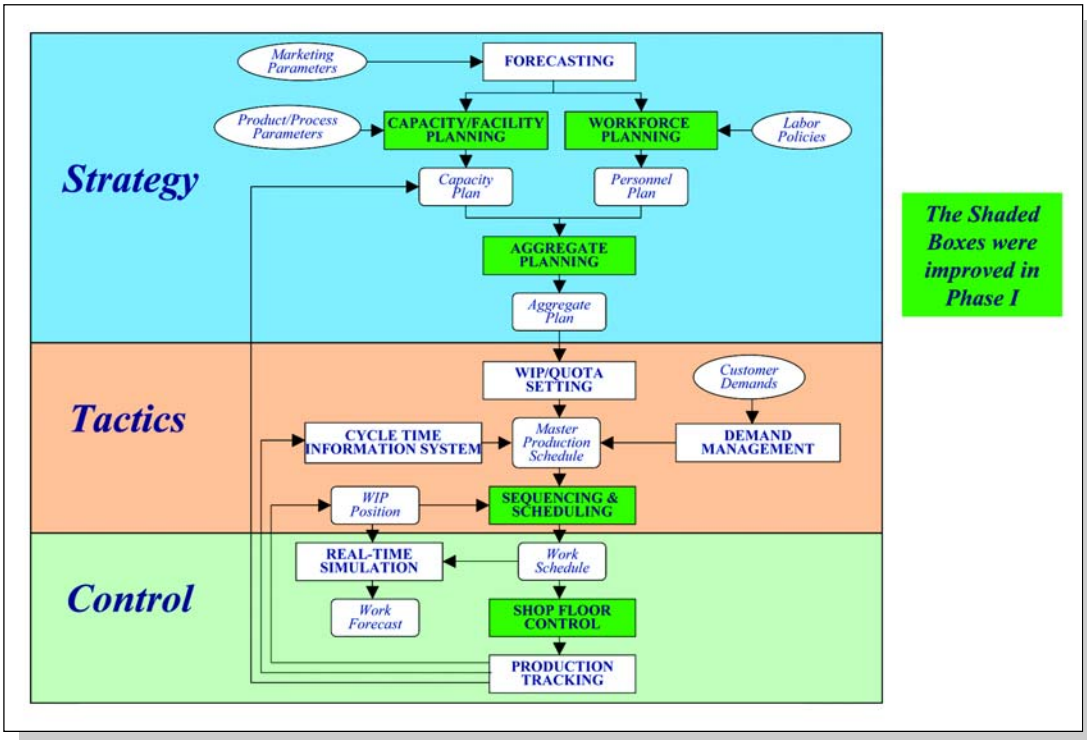

Figure 1. Planning and scheduling system components improved in Phase One. (Reprinted and modified with permission from Spearman & Hopp, 2001).

Factory	Resouce and Equipment Priority	Goal	Detailed Scheduling Method
1. Development, validation, and launch	Top Priority	Speed-to-market for new products	Manual review and control
2. High volume, high cost products	Dedicated equipment where possible, high priority allocation of people and equipment	Low inventory, fast cycle times	Pull Scheduling using CONWIP
3. Low volume, low cost products	Shared equipment, lower priority for resource allocation	No stock-outs	Push ERP/MRP scheduling with generous lead times - use finished product safety stock as a buffer

Table A. Business objectives for each Focused Factory and Flow Path.

manufacturing excellence. The following measurable improvements have taken place throughout the operation without the significant addition of capital assets or human resources:

- Units shipped are up approximately 23% over a two-year period.
- Cycle time has been cut by 50% for high volume, high value products.
- Inventory is $10 million lower for critical materials.
- On-time delivery performance has been dramatically improved and is now nearly perfect.

This article summarizes the philosophies, organizational changes, and information systems that were implemented in order to achieve manufacturing excellence. It concentrates on the planning and scheduling improvements and flow path management techniques that have cut cycle time and streamlined product flow. The article describes the following two phases:

- Phase One: Developing the Planning and Scheduling Infrastructure
- Phase Two: Flow Path Management to Improve Performance and Cut Cycle Time

Plant Mission

DuPont's 370 employees produce a total of 150 product Stock-Keeping Units (SKUs) ranging from tablets and capsules to syrups. A wide variety of processing technology is employed at the plant including direct compression, wet granulation, roller compaction, fluid bed drying, tray drying, tablet compression, aqueous film coating, and encapsulation. The site packages a large number of bottle configurations and also blisters. The facility was built in 1963 and has grown in a series of expansions to a total of 142,000 square feet.

The process flows for oral solids at Garden City are typical for the industry. Raw materials are received, sampled, and tested. The materials are then weighed and blended into powder, which is either compressed into tablets or encapsulated. Most tablets are coated and tested prior to packaging. Finished products are packed and tested prior to final shipment.

The plant has a two-fold mission:

1. Partner with R&D to rapidly scale-up and launch new pharmaceutical products. The plant is involved in 10-12 product development projects per year. Some of these products are later transferred to a sister location in Manati, Puerto Rico.
2. Supply existing products to the market in a high-quality, economical fashion. The plant produces about 40 different commercial products and 150 SKUs.

The business challenges are clearly different for each part of the mission. New products have relatively unpredictable demand curves and require care and feeding as the organization climbs its learning curve. High volume products, on the other hand, must be produced with consistent on-time delivery and efficient operational costs.

Starting Point: The Need for Improvements

Three years ago, the site operated in a fashion that was somewhat typical for the pharmaceutical industry:

- The organizational structure was functionally oriented. Each department used stand-alone systems and performance metrics.
- Individual departments maintained "hot lists" based on their knowledge of required customer ship dates.
- There was limited product flow. Material typically spent 90% or more of the time waiting for the next operation. This resulted in long product cycle times, excessive inventory, and costly material storage and handling.
- Systems were not integrated. The ERP system and the MRP module within ERP was used only to manage inventory and do financial reporting. Inventory transactions were one to three weeks behind.
- Planning and scheduling activities were shortsighted and manual-intensive. The planning horizon was one month at most. Schedules were manually maintained using spreadsheets - hard copies were circulated weekly, often with handwritten notes. Planners tracked work center activities using telephone calls and safety shoe leather. Despite the extra effort, the schedules often had to be re-issued several times each week to track changes. Moreover, several important functions such as Quality Control and Quality Assurance were excluded from the initial scheduling process because of limited planning staff.
- Strategic capacity planning for capital and human resources was not formalized.

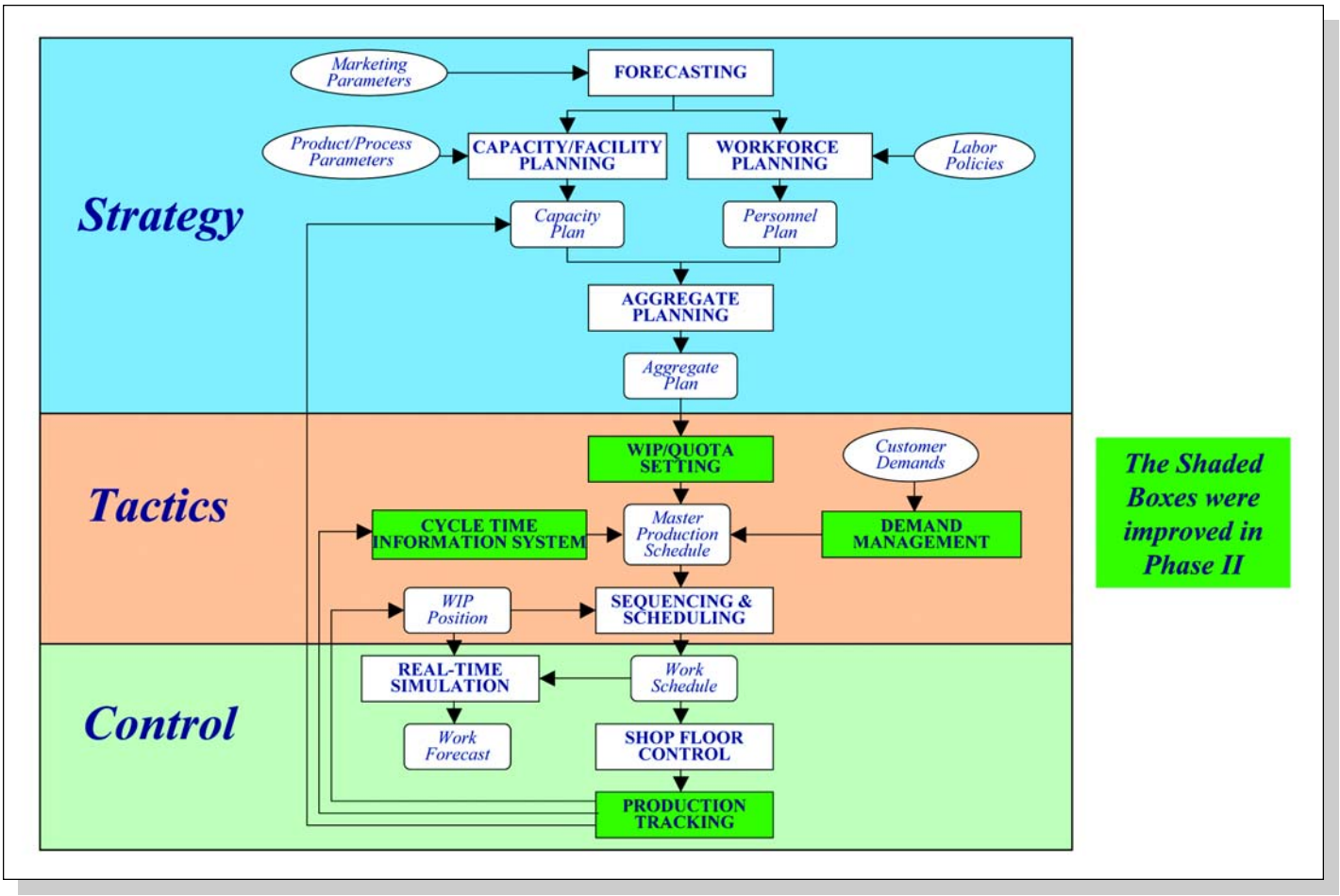

Figure 2. Planning and scheduling system components improved in Phase Two.

To address these shortfalls, the objective was defined to improve planning and manufacturing performance. The improvements were performed in two phases: Phase One built the information systems and planning and scheduling infrastructure to support improved performance. Phase Two built on this foundation by splitting the operation into several distinct product Flow Paths, and then redesigning the organization structure, performance metrics, equipment capabilities, and planning and scheduling tools to meet the needs of each flow path. Detailed performance objectives for the organization also were introduced as part of Phase Two.

The following sections describe each phase in detail.

Phase One of Change: Developing the Planning and Scheduling Infrastructure

The change process began by strengthening the information systems and planning and scheduling tools. This positioned the information systems to function as a true ERP system, rather than just an inventory management and financial reporting system.

An operation management system was built, one piece at a time, starting with the ERP backbone. Figure 1 shows the major planning and scheduling activities improved in Phase One. Figure 2 shows the activities improved in Phase Two.

ERP Data Collection and Analysis

A basic first step was to populate the ERP system with accurate routings and work center data. This involved a joint effort between the site Planning organization and the Manufacturing and Packaging work groups. The pertinent data fields were populated and validated for accuracy over a six-month period. The ERP system was designed with a tremendous amount of detailed data - this investment paid handsomely in Phase Two.

Having the ERP data in place, the goal was to consolidate operating and decision making information within ERP. The goal was to track inventory and production transactions real-time.

Inventory and Production Tracking

Our inventory tracking practices were state of the art *for 1965*: manual keypunching of inventory transactions into the ERP system by a few trained individuals. This caused long delays, large errors, excessive inventory, and, as a result, material shortages and line shutdowns.

How would up to 450 inventory movement, consumption, and production reporting transactions per day be performed while maintaining up-to-the-minute accuracy? Commercially available technology would allow barcode scanning of materials as actual physical activities took place, followed by a database upload to the ERP system from the handheld scanning devices. But this would delay ERP updates by the frequency of uploads. Not wanting to be limited by aged data, a proprietary technology called Radio-frequency Order Picking and Inventory Control System (ROPICS) was selected. This system uses wireless handheld barcode scanning devices to instantly transmit data to and from the ERP system.

Everyone who touches materials was trained to perform

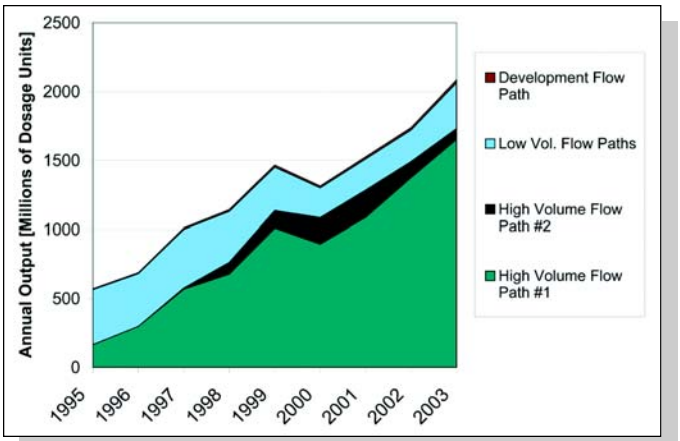

Figure 3. Volumes for each Garden City Flow Path. This graph shows shipments by flow path. It includes historical (prior to 2001) and forecasted (2001 - 2003) volumes.

ROPICS transactions as part of any given operation they perform. As a way to ensure ROPICS transaction discipline, cycle count accuracy was measured and actively managed to be at least 95% on a consistent basis. All "misses" are investigated and corrective actions implemented.

What was the result? Inventory accuracy improved from 70% to 95+% within six months of implementing the new approach. This ensures cGMP compliance when accounting for critical materials. In addition, very significant quantities of raw materials have been removed from inventory, reducing working capital by more than $10 million and cutting cycle times for high volume products by 50%. This is directly related to inventory record accuracy within ERP - when you know exactly what you have at any given point in time, you don't need any "padding."

Our manufacturing and information technology staff has recently leveraged the ROPICS technology for managing the shop floor weigh-up and charge-in processes. This has greatly enhanced the ability to perform these critical operations in an error-free fashion by eliminating manual calculations and by guiding batch formulation real-time using a validated system. New ways will continue to be explored to use this technology for shop floor operations.

Since improving inventory accuracy, the materials requirement plan from ERP has been made much more meaningful by having the rough-cut schedule and real time inventory both resident in ERP. We just don't run out of materials anymore.

Shop Floor Control, Sequencing, and Scheduling

Custom reports were developed to show a weekly rough-cut schedule and equipment capacity utilization for each of the 75 Manufacturing and Packaging work centers - all based on ERP shop orders. These reports replaced the spreadsheets and are now the primary means for communicating the rough-cut schedule.

Quality Control and Quality Assurance were initially left out of the ERP scope. This was a mistake. Since the initial project, a program was launched and completed to add these work centers to the routings so that they are integrated with the Manufacturing and Packaging operations. The addition of QA and QC to the implementation scope was critical for reducing cycle times, since products interface with these work centers up to five times during each cycle.

Capacity/Facility Planning

With the tactical elements in place, we were able to lengthen the planning horizon to the strategic time frame. Equipment capacity utilization can now be predicted for each work center throughout the forecasting horizon (two years in this case).

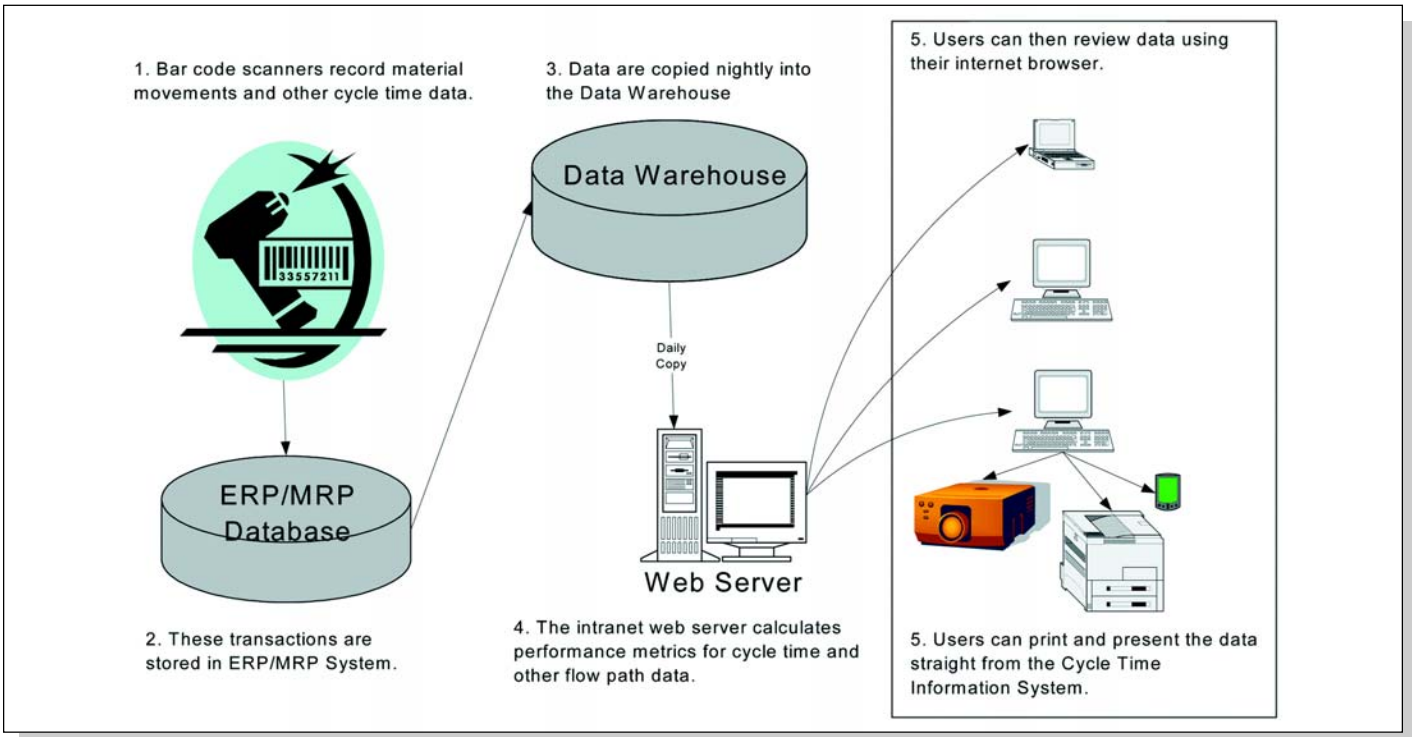

Figure 4. System architecture for flow path management metrics. Bar code scanners feed information into the ERP system and data warehouse. These are displayed for all employees via the company intranet site.

> ***The Cycle Time Information System is used as an early warning system so that bottlenecks are identified and resolved quickly.***

This is done using the ERP capacity planning modules with little customization. The same techniques are used to calculate labor requirements for each work center, knowing only the labor rates and product demand stored in ERP.

The Directors of Engineering, Manufacturing and Packaging, Technical Operations, Human Resources, Finance, Information Resources, and Planning now meet monthly to review the capacity plan for the upcoming two years. All capital equipment and staffing plans are formulated from these meetings and incorporated into the budgetary process. Having sufficient but not excessive equipment capacity and labor available at the proper times makes the best use of the company's cash and provides the necessary conditions for reduced cycle time. The site's financial budgets and long-range operating plan also are developed from the ERP database.

Phase II of Change: Flow Path Management

Defining Flow Paths using Pareto Analysis

Performance soon peaked following these initial successes. Relying on ERP and the traditional performance metrics was reducing efficiency, increasing inventory, and lengthening cycle time.[7]

Given the duality of the plant's mission statement, the complexity of the manufacturing operation, and the limited equipment flexibility, we needed to focus on specific product groups and tailor the management systems for each product group.

Flow Path Management is a management technique that organizes manufacturing systems into process-based flow paths.[8] These flow paths simplify planning and scheduling, support organization structures aligned to process flow, and enable cycle time reductions and other performance improvements. Management can tailor the business processes in each of the following four areas:

1. Performance Metrics
2. Organization Structure and Development
3. Planning and Scheduling
4. Process Control and Equipment Flexibility

To identify the major flow paths, Pareto analysis was used. The analysis showed that the bulk of inventory dollars were invested in two products. We decided to focus on reducing cycle times for these two high volume, high value products. The actual Garden City flow paths along with their associated volumes are shown in Figure 3.

The operation was divided into three distinct factories within the overall operation, called "factories within the factory."[9] Development products were assigned to the first factory. The second factory, for high volume products, held two flow paths: one for each of the two high volume products. The remaining low volume products were assigned to the third factory. The strategy to accomplish the entire mission involved the scheduling rules shown in Table A.

After defining the major flow paths, the business processes were tailored within each flow path to best fit the needs of that business.

Performance Metrics and Feedback Information

To track progress and to motivate and reward improvement, a set of performance measures for each flow path was designed and implemented.

The vision was to automatically generate these metrics on a daily basis and to give individual work center owners the ability to view them on that frequency. To implement this vision, a data warehouse was developed containing all the ERP data and inventory transactions described above. We call this our Cycle Time Information System (CTIS). Using CTIS, work center owners are able to quickly visualize, on a daily basis, their own area's performance for each flow path and make any necessary adjustments. Figure 4 shows how the data is automatically transferred from the ROPICS guns into the data warehouse, and then analyzed on our intranet web server for displaying the performance for a given flow path. Every person at the plant (and in the company at other locations) can view the metrics using the corporate intranet site. Figure 5 shows an example of CTIS output, displaying the location and on-time status of open orders in a flow path.

These metrics are reviewed at the daily operations meeting to make operating decisions and monitor status for each flow path. The purpose of this meeting is to establish a common

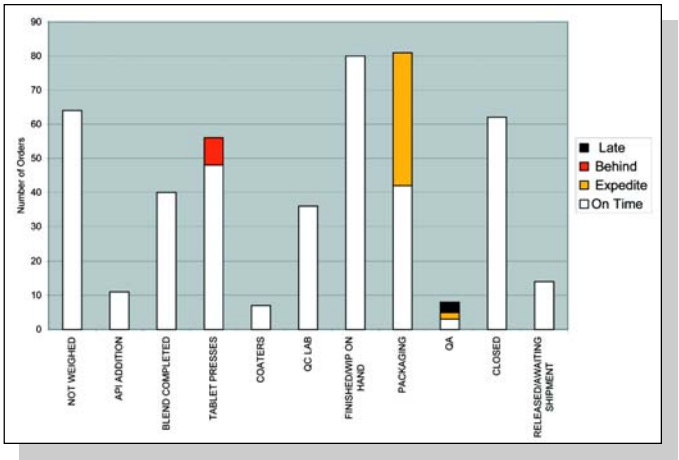

Figure 5. Measuring flow path health to drive operational excellence. This graph shows how many orders are waiting at each operation along the flow path. Employees can see if the orders are on time using the legend on the right, and can double click on the graph to see details for late or behind schedule orders. The graph is automatically updated daily, and is published for all employees on the intranet site. (Similar graphs show cycle time vs. goal and inventory vs. goal).

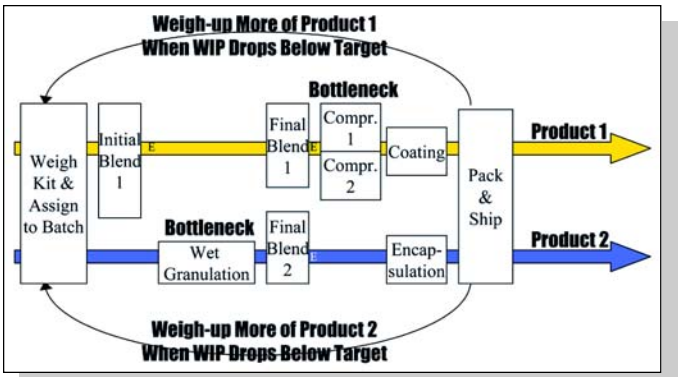

Figure 6. Pull scheduling using Constant Work in Progress (CONWIP). This diagram illustrates how CONWIP signals the first operation to start more Work In Progress inventory (WIP) when inventory levels drop below the target. Note that multiple products can be scheduled, and that equipment can be shared across products.

understanding of the three factories' status each day and to provide a vehicle for communication among the work center owners. Hundreds of active shop orders are managed (by exception) cross-functionally in a daily 15- minute meeting. Issues are identified early and resolved.

CTIS is used as an early warning system so that flow path bottlenecks are identified and resolved quickly. Three Flow Path Metrics are monitored daily:

- Health of the Flow Path: Displays the location of open orders within each flow path (dynamic bottleneck identification) and whether the orders are on time, behind schedule, or late. Figure 5 shows this graph.

- Cycle Time vs. Goal: Measures elapsed time from raw material (active ingredient) receipt to shipping of finished product for each flow path. Provides overall measure of operational effectiveness and motivates cycle time reduction efforts.[10-14]

- Inventory vs. Goal: Determines when to pull work into the flow path. This pull scheduling tool controls work in progress inventory and cycle time.[15]

Distribution of the information through CTIS provides a constant source of performance feedback. Using CTIS, we are able to break flow path cycle time into its individual components and encourage continuous improvement from each work center owner.

Site operating objectives are built around flow path performance for each of the three flow paths. Stretch goals are set with aggressive improvement. Every functional group has its own objectives that are based on the whole organization's objectives. All 370 people in the organization can articulate what role they play in achieving these objectives, since the objectives are an element of each person's performance appraisal.

A portion of each person's compensation is determined by the success of the organization in meeting site operational objectives. The performance management process is carefully monitored at the highest levels of the site organization to ensure that the compensation process is used effectively to drive manufacturing excellence. The site leadership team is responsible to ensure that each objective is approached in a synergistic fashion. This reinforces the site objectives and motivates individual contributions and team performance.[16,17]

Organization Design: Aligning People and Skills

The plant took several steps so that the organization reaches stretch objectives:

- Additional training was offered to help employees expand their skills. The training included an on-site workshop in Factory Physics techniques to expose everyone to the opportunities for cycle time reductions and other improvements. Factory Physics is a systematic description of the underlying behavior of manufacturing systems. These analysis techniques are used to identify opportunities for improvement and target specific improvement projects.[3] The total site training budget has been approximately $250,000 per year over the last three years. In addition, job-specific training is managed as part of the normal course of business.

- Strategic partners were hired to speed implementation and complement the skills of internal staff members. DuPont Pharmaceuticals retained the services of SAK Logistics to support the implementation of the Cycle Time Information System and the cycle time reduction projects.

- Additional people were dedicated to process improvement and cost savings. As part of a corporate Six Sigma process improvement initiative, two DuPont Pharmaceuticals employees were appointed to serve as full-time Six Sigma Black Belts.

- People were assigned to specific flow paths. By focusing on the needs of just one flow path, the employees can customize their work and improve cycle time through their area.

- People within a flow path were cross-trained so that they are able to move to the flow path bottleneck and relieve the congestion. As an example, suppose the tablet coating operation experienced downtime causing uncoated tablet cores to accumulate in front of that operation. The flow path health metrics would quickly highlight the bottleneck. Cross training allows people from the weigh-up operation to move to coating and increase production of coated tablets until the bottleneck is relieved.

- Staff groups were redeployed to support flow path success. Technical and QA resources were made available to the

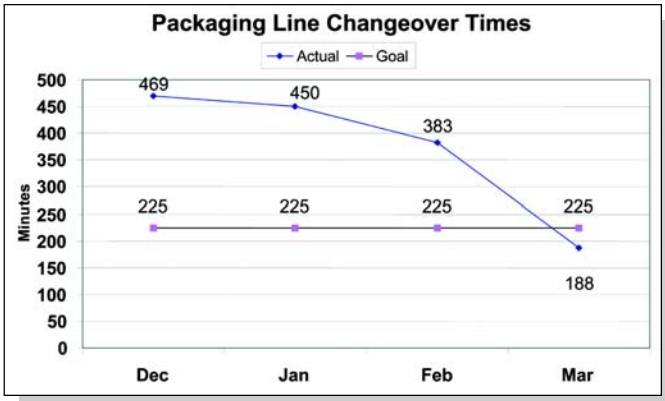

Figure 7. Reducing changeover times using SMED techniques. This graph shows the changeover time reductions achieved at one packaging line using Single Minute Exchange of Dies (SMED) techniques.

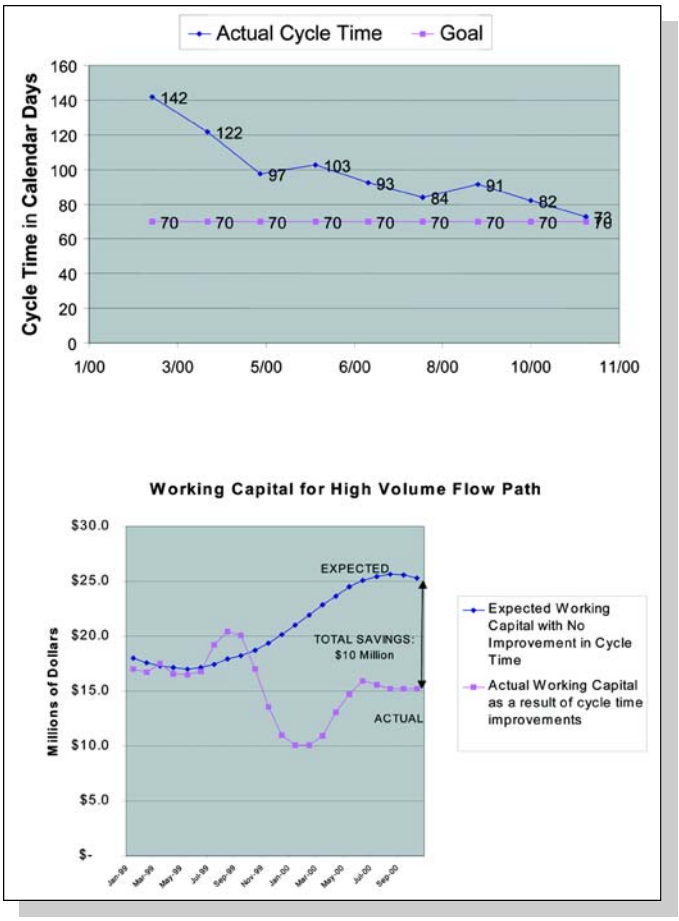

Figure 8. The dollar value of cycle time reductions. This graph shows the cycle time reductions achieved for the high volume flow path. The upper graph shows how cycle times were reduced from 142 days to 70 days. The lower graph calculates how this reduction reduced working capital (inventory dollars on the balance sheet) by roughly $10 million.

operating areas 24/7 for consulting and problem solving. Material is not permitted to move from one operation to the next without complete satisfaction that all work was performed correctly. Focusing on problems as they occur increases visibility, drives more participation in the problem solving process, and creates more ownership for the quality of the product. This minimizes cycle time variability.

Pull Scheduling to Cut Cycle Time and Inventory

With the metrics and organization in place, earlier planning and scheduling improvements were expanded to reach better performance. One primary obstacle to overcome was the weaknesses of Materials Requirements Planning (MRP) as a scheduling tool. While MRP works well in plants with limited complexity and with low utilizations, it begins to fall apart as real-world conditions occur.[18] For example, MRP is not sensitive to capacity constraints. As a result, plants using MRP systems have an incentive to "pad" their lead times just in case variability causes a production problem. These padded lead times increase inventory and cycle times unnecessarily. In addition, since MRP is a "push" system, it will not slow down material releases if there is a production problem in the factory. This causes inventory to build needlessly and increases cycle times further.[3]

To overcome these issues, a pull scheduling system was implemented for high volume flow paths. A Constant Work in Progress (CONWIP) system[15] was adopted - *Figure 6*. CONWIP works by setting an inventory target for each flow path. When inventory drops below the target, the system sends a signal to the first operation to send more work into the flow path. This *pull signal* works to always maintain a constant amount of work in progress in the flow path. Planners and work center owners use the pull signal contemporaneously with flow path health information to schedule each factory flow path and monitor daily performance. Using current, accurate, focused flow path data allows optimum communication and coordination.

The CONWIP system has several advantages over MRP. First, it allows inventory and cycle time targets to be reached. Second, it eliminates the motivation to pad MRP lead times. Finally, it requires significantly less data than MRP since only a single number is needed — the total inventory for the flow path each day.

CONWIP also offers several advantages over other pull scheduling methods such as *Kanban* cards. First, CONWIP works well even if many low volume products are produced on the same flow path; the pull signal authorizes the release of the next order for the flow path, regardless of the specific SKU. Second, CONWIP provides a simple way to move material to the bottleneck for the flow path. As an example, if the tablet coating operation experienced downtime, uncoated tablet cores would accumulate in front of that operation without any changes in the CONWIP target.

Improving Equipment Flexibility and Reliability to Support Faster Cycle Time

With pull scheduling, inventory levels can be lowered to any level. However, care must be taken to avoid setting inventory levels so low that bottleneck equipment starves for work. In short, enough inventory must be maintained to handle expected equipment outages, changeovers, and between-lot cleaning. The more variability in equipment uptime or the longer the changeover times, the more inventory that is required.

As part of the change process, several work centers were identified with long outages and/or long changeover times. Teams were formed to improve this equipment. For example, one team was formed at the high speed packaging line to reduce changeover times. This team included operators, mechanics, QA technicians, and support personnel from all three shifts. As shown in Figure 7, the team was able to cut changeover times by more than 50% in 90 days using Single Minute Exchange of Dies (SMED) techniques.[19] By reducing the changeover times, the equipment utilization dropped, reducing cycle time and facilitating reductions in campaign sizes, operating costs, and inventory.

Results and Lessons Learned

The Garden City organization has validated tens of millions of dollars in working capital reductions by improving the way inventory is managed. Shipments have reached record high levels, and cycle times continue to set new monthly records - *Figure 8*. We are confident that this is just the beginning of the benefits that will be realized.

The key lessons learned include:

- ensure that information systems are timely and accurate
- identify product flow paths based on business needs

- establish flow path performance metrics and metric ownership to motivate improvements
- staff each flow path and train its employees so they work together to reach stretch objectives
- utilize external strategic partners to accelerate implementation and complement internal skills
- use pull scheduling to overcome the weaknesses of MRP
- continued improvement requires faster changeovers and smaller campaign sizes

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This article compares the material of science of the current materials of construction - stainless steel and glass - with that of the increasingly adopted material - fluoropolymers, as well as the biochemical and microbiological impact on such materials.

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Material of Construction for Pharmaceutical and Biotechnology Processing: Moving into the 21st Century

by James R. Fleming, David Kemkes, David W. DeVoe, Lewis Crenshaw, and John F. Imbalzano

Introduction, Problem Statement, and Objectives

The pharmaceutical and biotechnology industries are confronting major chal lenges including increased competition, industry consolidation and globalization, high research and development costs, pervasive government guidelines, and extremely demanding manufacturing and distribution requirements.[1-7]

Faced with such issues, these industries rightfully need to be extremely vigilant in the allocation and expenditure of resources. Contradictory to the careful planning and execution of resource expenditures, the pharmaceutical and biotechnology industries continue to spend untold millions of dollars to compensate for the shortcomings of materials of construction currently used in the production of their products.[a]

The use of an alternative material of construction[8] namely, fluoropolymers, especially PFA fully fluorinated fluoropolymers (Teflon®) affords the pharmaceutical and biotechnology industries a means to redirect these funds to more productive initiatives which impact their business well-being, research and development or profitability. Equipment protected with fluoropolymer linings has been used successfully and with economic benefit in the chemical processing industry for more than a quarter of a century.

One objective of this article is to compare the material science of the current materials of construction - stainless steel and glass - with that of the increasingly adopted material of construction - fluoropolymers. A second objective is to compare biochemical and microbiological impact on such materials.

A third objective is to raise the real potential of reduced regulatory compliance costs through the use of unreactive unchanging fluoropolymers as material of construction for pharmaceutical and biotechnology processing equipment. And finally, a fourth objective is to suggest a redirection, with the aid of fluoropolymer materials of construction, of the untold millions of dollars being spent to compensate for the shortcomings of stainless steel and glass materials of construction to other more productive pharmaceutical and biotechnology industry uses.

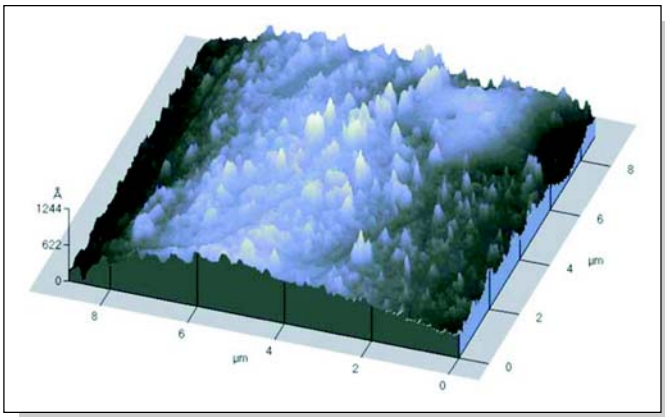

Figure 1. AFM photomicrograph showing spikes from electropolished asperities Ss 316L 15Ra.

Material Science Aspects of Stainless Steel, Glass, and Fluoropolymers

Stainless Steel

Stainless steel has historically been adopted for containment of chemical processing because it is resistant to more chemicals than is iron or mild steel.[9] It is an inorganic chemical combination of essentially iron, chromium, and nickel.[10] Products of stainless steel are strong and their initial cost, though higher than iron or mild steel, are often less than other exotic metallurgical materials of construction.[11] Depending on the amount of the minor ingredients in the metallurgical formulation, the chemical resistance

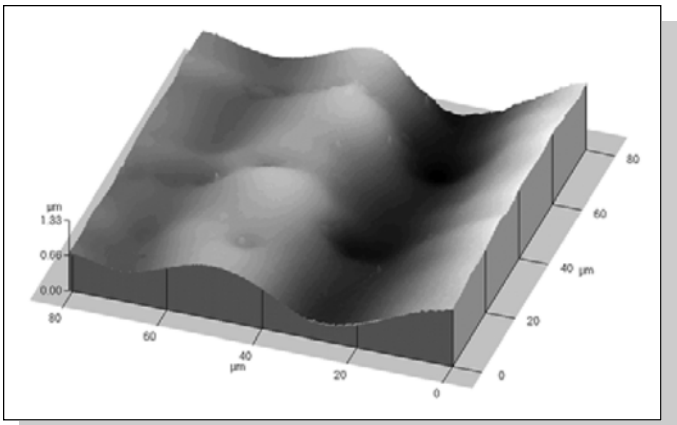

Figure 2. SEM photomicrograph showing pits from electropolishing removal of inclusion Ss 316L 15Ra.

of stainless steel to certain chemicals can be improved.[12] Such improved chemical resistance comes with a corresponding increase in cost. But even such chemical resistance improvement is not sufficient to overcome chemical attack[13] or the corrosive attack of biofilm components.[14] Stainless steels corrode over time as the minor ingredients are lost and as electrochemical potentials arise which promote the oxidation of iron. In stainless steel weldments, for example, iron is made more readily accessible to oxidation in even the "mildest" of chemical conditions,[15] i.e., hot steam and the resulting rust ("rouging") contaminates and compromises the quality of the products being produced in such equipment.

Stainless steel can be further chemically treated to be made less reactive, i.e., passivated,[16] in a time consuming and expensive treatment that must be performed regularly to ensure that the iron in this material doesn't oxidize - i.e., rust. Passivation is costly,[b] is only temporarily durable,[17] and must be repeated if additional weldments are incorporated into the system. Passivated or not, stainless steel is reactive to many harsh chemicals,[18] particularly chloride and other halides, preventing their beneficial use in pharmaceutical and biotechnologic applications.

The surface irregularities of stainless steel - ranging from 180 grit (~25 Ra) to 400 grit (~ 13 Ra) -can be ameliorated although with only temporary beneficial effect, to lower double digit microinches by electropolishing.[19] But, electropolishing also is expensive, non-permanent, and needs to be repeated often to maintain such a surface.[20] Even so, this electrosmoothing only miniaturizes the height of the asperities in the metallurgical surface, but does little to remove the nooks and crannies surrounding the base of the asperities (See Atomic Force Microscopy image in Figure 1).

Worse still, electropolishing can remove inclusions in the metal creating pits, which, in turn, can harbor microorganisms and biofilm components to perfectly shelter them from even the most vigorous cleaning (see Scanning Electron Microscopy image in Figure 2).

Surface physical chemistry of stainless steel is another significant negative for its use in the pharmaceutical and biotechnology industries - it is wettable by aqueous solutions, a characteristic which enhances not only chemical corrosion,[21] but also biofilm adhesion and biofilm resistance to detachment.[22]

Today, the wide availability of components of PFA fully fluorinated fluoropolymers has made them equivalent in installed cost to stainless steel components, and they provide a lower cost of ownership.

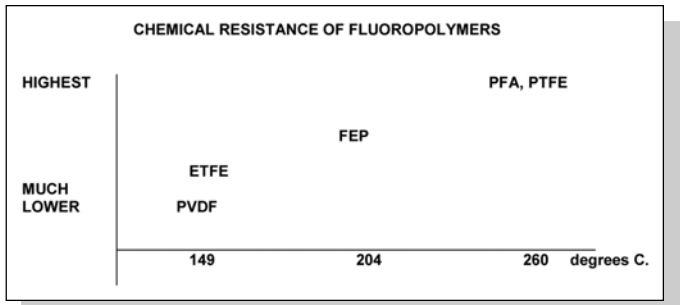

Figure 3. Chemical resistance of fluoropolymers.

Glass

This centuries-old, amorphous inorganic material of construction is readily formed into components and coatings.[23, 24] It is chemically resistant to most organic chemicals and many, but not all inorganic chemicals.[25] It can be formed into many unsupported components and can be further supported by attachment to steel for larger processing components.

By their careful consideration of its shortcomings, the pharmaceutical and biotechnology industries have exploited this material well considering its positives and negatives[26-28] from a material science perspective. If only glass were not brittle. If only it didn't break unexpectedly. If only it could endure thermal cycling. If only glass coatings didn't unpredictably craze and thereby expose the underlying iron substrate to the process fluids. If only it didn't leach elements used to help it overcome its brittle/crazing shortcomings. If only its surface wasn't wetted by aqueous media. If only it didn't tenaciously hold onto biofilms. Feedback indicates that glass surface of most glass-lined vessels in chemical handling industries ends up as a patchwork of perfluoropolymer patches held with tantalum bolts.[29] And, of course, glass is reactive to many harsh chemicals,[30,31] preventing their beneficial use in pharmaceutical and biotechnologic applications.

Fluoropolymers

Because of their outstanding friction reduction, material release, chemical resistance, and thermal stability, fluoropolymers have found increasing applications as materials of construction in the pharmaceutical and biotechnology industries.[32-34] These adoptions showcase its anti-corrosive and non-wetting surface characteristics, enhanced by its reduced surface friction. In combination, these features provide a comparative advantage vis-a-vis biofilm – *Figure 3*.

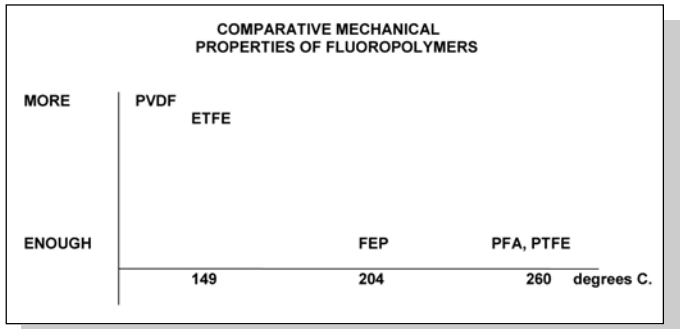

Figure 4. Comparative mechanical properties of fluoropolymers.

PER CENT BIOFILM REMOVAL FROM BIOFILM-COVERED COMMERCIAL SPECIMENS OF 316L STAINLESS STEEL, BOROSILICATE GLASS, SILICON-COATED BOROSILICATE GLASS, and TEFLON PFA IN ESSENTIALLY QUIESCENT, FLOW-PROTECTED EXPOSURE TO 50 PPM SODIUM HYPOCHLORITE SOLUTION

	Per Cent Biofilm Removal		
	K. pneumonia	S. Choleraisuis	E. coli
Stainless Steel	67	25	56
Poly(Propylene)	67	75	75
Borosilicate glass	89	0	0
Silicone-coated glass	89	89	78
Poly(vinylidene fluoride)	89	89	89
TEFLON PFA (machined)	92	92	92
TEFLON PFA (inj.molded)	99	99	98

Source: Hyde, et. al., ibid.

Figure 5. Percent biofilm removal from biofilm-covered commercial specimens of 316L stainless steel, borosilicate glass, silicon-coated borosilicate glass, and Teflon® PFA in essentially quiescent, flow-protected exposure to 50 PPM soduim hypochlorite solution.

Fully fluorinated fluoropolymers are electrochemically, biochemically, enzymatically, and chemically virtually inert. The exceptions chemically are exotic inter-halogen compounds, molten metals, etchants such as sodium metal dissolved in napthalene, and impinging gas plasmas.[35] Such chemical inertness is not the case for partially fluorinated polymers which are subject to varying degrees of reactivity based essentially on their polarity and chemical structure.[36, 37] Figure 3 qualitatively compares the chemical reactivity differences between fully and partially fluorinated fluoropolymers.

Fully fluorinated fluoropolymers can sustain high temperature service, up to 260°C for PFA and PTFE. They can be rapidly thermally cycled below their service temperatures. Although fully fluorinated fluoropolymers do not support combustion, they can be burned as long as the oxidizer and temperature source are present.

Fully fluorinated fluoropolymers are "pure" as polymerized. Many fluoropolymers, but not all (the exception being partially fluorinated polymers), do not require any additives to withstand the harshest of reagents.[38]

Most fully fluorinated fluoropolymer materials of construction are ductile. They are less mechanically strong than partially fluorinated polymers. Systems made from them are widely used. Piping systems up to 2" in diameter, operating up to 150 psi are available as piping systems without steel piping outer support;[39] piping systems of diameters larger than 2" and for pressures higher than 150 psi, are available with steel outer support.[40] Figure 4 qualitatively depicts the mechanical comparison between fully and partially fluorinated fluoropolymers. Both fully and partially fluorinated fluoropolymers can be abraded by high energy, sharp particle slurries which are directed perpendicular to the fluoropolymer surface, e.g., sandblasting; otherwise, they are likely to be unaffected.

Fully fluorinated fluoropolymers have the lowest surface energy of all solid materials rendering them virtually non-wettable by water and by aqueous solutions. The low surface energy, coupled with chemical inertness and a micro-void-free fully fluorinated surface, makes any kind of adhesion very difficult to achieve. The resulting benefit to the pharmaceutical and biotechnology industries is more uptime and ease of cleaning (see Minimized Biofilm Adversity with PFA fully fluorinated fluoropolymers below).

The initial cost of fluoropolymer protected systems, heretofore often higher than stainless steel, is now comparable, [41] while their lifetime cost-of-ownership is considerably less - they do not require electropolishing, having a highly definitive, hydrophobic, smooth surface as a natural outcome of their forming technology. They need no "passivation" - ever. Their non-reactivity opens the potential for more efficient, effective, less-costly cleaning systems which can be more environmentally friendly. This inertness also promises the potential of fewer regulatory compliance issues for manufacturing equipment since the fully fluorinated fluoropolymer is non-corrosive and virtually unchangeable under pharmaceutical and biotechnical conditions.

Biofilm Removal Significantly Expedited by Surface of PFA Fully Fluorinated Fluoropolymers

Biofilm removal studies conducted by the University of Minnesota's Bioprocess Technical Institute and reported by Hyde et. al.,[42] confirm the ease of removal of biofilms of E. coli ATCC 8739, Klebsiela pneumoniae ATCC 12657, and Salmonella choleraisuis biovar typhimurium ATCC 13311 from PFA fully fluorinated fluoropolymers. The data[42] shows that 98% to 99% of area covered by the biofilm on injected molded coupons was removed by exposure of the biofilmed coupons to dilute sodium hypochlorite in a virtually quiescent exposure to the biofilm inactivation protocol with coupons protected from biofilm wash-away fluid flow – *Figure 5*.

The data of Figure 5 show that even surfaces greatly roughened intentionally by machining, showed 92% removal in this virtually quiescent process. In quantitative terms, the data of Figure 5 show that the biofilm release from the conventionally injection-molded surface exceeded that from the conventionally molded surface of partially fluorinated fluoropolymer PVDF by 10% to 11%; exceeded that for conventionally molded surface of the hydrogenated polymer polypropylene by 31% to 48%; exceeded that from the surface of commercial silicone-treated borosilicate glass by 11% to 26%; exceeded that from the surface of commercial borosilicate glass by 11% to 100%, and exceeded that from the surface of conventional electropolished 316L stainless steel by 74% to 296%.

The ease of biofilm release from the surface virtually translates to ease and speed of cleaning components in pharmaceutical and biotechnology industries which have wetted surfaces. The economic benefits for such industries are in increased production "uptime," and lower manufacturing costs.

Non-Wetting Surface of PFA Fully Fluorinated Fluoropolymers is Responsible for Superior Biofilm Release; Wettability of Stainless Steel and Glass Aid Biofilm Retention

It is not possible for a substance to chemically adhere to a surface if the substance is unable to wet that surface.[43] The critical wetting angle of a fluid on a surface is the traditional method adhesion scientists use to establish wettability of a surface by a given reagent. The higher the critical angle of wetting the lower the wettability of that surface by the wetting fluid.[44]

Stainless Steel and Glass vs. PFA Fully Fluorinated Fluoropolymers

The aforementioned studies[42] show the water wettability vs 316L stainless steel and borosilicate glass; these data are tabulated in Figure 6 and are shown schematically in Figure 7.

COMPARISON OF 18 megaOHM PROCESS WATER WETTING CONTACT ANGLE FOR 316L STAINLESS STEEL, BOROSILICATE GLASS, TEFLON PFA FLUOROPOLYMER RESIN

	Stainless Steel*	Glass*	TEFLON PFA*
degrees	41.5	38.5	98.5

source: Hyde, FW et.al. J.Indus.Microb.& Biotech., 19:142-149, 1997

* AFM Rms, nm	41.74	7.42	24.35

Figure 6. Comparison of 18 mega OHM process water wetting contact angle for 316L stainless steel, borosilicate glass, Teflon® PFA fluoropolymer resin.

The data of Figure 6 indicate that the PFA fully fluorinated fluoropolymers are more than 156% less wettable than glass, and more than 137% less wettable than electropolished 316L stainless steel. The depictions of Figure 7 suggest that water molecules roll on the surface much like one would picture solid spheres rolling down a tube (this "rolling" can be readily experienced by observing a drop of water "bead up" on a surface of PFA fully fluorinated fluoropolymer). The differences in wettability between PFA fully fluorinated fluoropolymer, glass, and stainless steel reflect the polarity differences between these materials. Stainless steel and glass are very polar materials whereas PFA fully fluorinated fluoropolymer is a non-polar fluoropolymer. This virtual lack of polarity resists the polar water molecule.

This essential lack of wetting by water of the PFA fully fluorinated fluoropolymer surface can only result in a significantly slower initiation of biofilm on the surface of PFA fully fluorinated fluoropolymer. That result, in turn, will give rise to increased production "uptime" for the pharmaceutical and biotechnology industries manufacturing operations.

PVDF vs. PFA Fully Fluorinated Fluoropolymer

The virtual lack of wetting of the PFA fully fluorinated fluoropolymer is superior not only to that of the inorganic materials of construction such as stainless steel and glass. The surface also is less wettable than are the partially fluorinated polymers such as poly (vinylidene fluoride), PVDF, as shown in Figure 8 and schematized in Figure 9.

The data of Figure 8 shows that the PFA fully fluorinated fluoropolymer is more than 137% less water-wettable than is PVDF. The differences in wettability between PVDF and the PFA fully fluorinated fluoropolymer reflect the polarity differences between these polymers. PVDF is a very polar fluoropolymer, whereas the PFA fully fluorinated fluoropolymer is a non-polar fluoropolymer. This lack of polarity resists the polar water molecule. As was pointed out earlier, the lack of attachment of water to surface of the PFA fully fluorinated fluoropolymer suggests a significantly slower initiation of biofilm on the surface of the PFA fully fluorinated fluoropolymer which, in turn, suggests increased production "uptime" for the pharmaceutical and biotechnology industries manufacturing operations. Conversely, the more wettable PVDF surface would be expected to provide comparatively less manufacturing operation "uptime." Work to confirm this aspect in a dynamic system is planned.

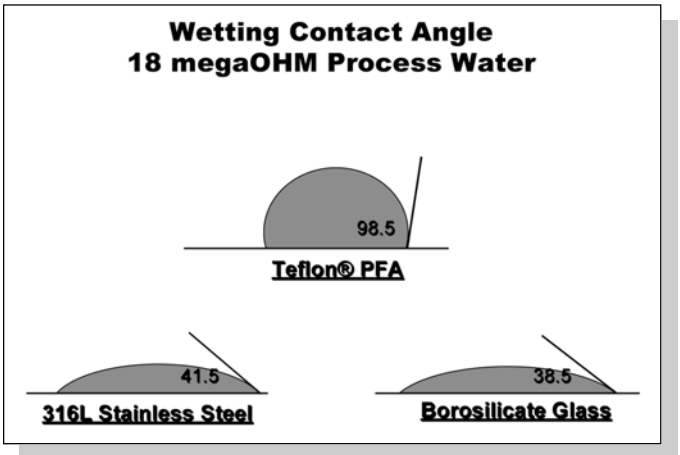

Figure 7. Schematic representations of wetting angles quantified in Figure 6.

Water as Media vs. Nutrient Solution

The wetting data[42] show that when nutrients are added to the water, the wettability comparisons are of the same order.

Reduced Flow Friction

The hydrophobic nature of the PFA fully fluorinated fluoropolymer surface is further complimented by low friction, stick-slip character for fluid flow in piping systems having such a wetted surface. The benefit of this combination of properties to the pharmaceutical and biotechnical industries is that a smaller pipe diameter in PFA fully fluorinated fluoropolymer will provide the same volume throughput, other things being equal, as a larger diameter high-frictional-flow stainless steel piping.[45, 46] In addition, existing stainless steel piping systems can be retrofitted with perfluoropolymer liners to gain all the benefits discussed above without sacrificing any volume throughput.

Asperity of Surface PFA fully fluorinated fluoropolymer is a Non-Factor in its Biofilm Release, but a Significant Factor for Stainless Steel Biofilm Retention

The data of Figure 5 combined with that of surface smoothness measurements made of the coupons also confirm that smoothness of the molded PFA fully fluorinated fluoropolymer surface, as measured by precision Atomic Force Microscopy, bears little significance to biofilm release from this surface – *Figure 10*.

The Ra and Rms data for borosilicate glass and poly(propylene) are significantly lower than those for PFA fully fluorinated fluoropolymer, yet the data of Figure 5 show PFA fully fluorinated fluoropolymer to have significantly greater removal of biofilm. The "Z" data of Figure 8 show that the conventional electropolished stainless steel is 38% lower than that for conventionally molded PFA fully fluorinated fluoropolymer, yet the data of Figure 5 shows significantly more biofilm release for rougher perfluoropolymer surface. This same measure data of Figure 8 show the "roughness"to be highest with the other materials being substantially lower. Yet, the data of Figure 5 confirm the biofilm release from the surface of the PFA fully fluorinated fluoropolymer to be significantly higher than from that of the other materials.

The results of surface asperity and biofilm removal from the related data for injected molded vs. machined coupons of PFA fully fluorinated fluoropolymer demonstrate that although the surface of the machined coupon was 95% to 115% rougher than the injected molded surface, the biofilm release from the machined surface was only 7% poorer than that from the injected molded surface.

The above findings collectively indicate that asperity mea-

COMPARISON OF 18 megaOHM PROCESS WATER WETTING CONTACT ANGLE FOR POLY(VINYLIDENE FLUORIDE) AND TEFLON PFA FLUOROPOLYMER RESIN

	PVDF	TEFLON PFA*
degrees	71.8	98.5

source: Hyde, FW et.al.,J.Indus.Microb.& Biotech., 19:142-149, 1997

* AFM Rms, nm	35.09	24.35

Figure 8. Comparison of 18 mega OHM process water wetting contact angle for poly (vinylidene fluoride) and Teflon® PFA fluoropolymer resin.

surements on the surface of conventionally molded PFA fully fluorinated fluoropolymer are non-indicators of biofilm adhesion on such a surface.

The Non-Corrosive Hydrophobic Inertness of PFA Fully Fluorinated Fluoropolymer Promises More Latitude in Regulatory Aspects of Pharmaceutical and Biotechnology Processing

A great deal of the current regulatory constraints designed for product consistency and quality apparently result from the corrosive and changing nature of the current materials of construction. The non-corrosive inertness of PFA fully fluorinated fluoropolymer removes such concerns, along with associated rouging, passivation, electropolishing, and glass crazing and breakage.

The hydrophobic nature of PFA fully fluorinated fluoropolymer portends a longer time before the inception of biofilm formation, given systems without designed dead volume and with adequate flow velocity. This suggests that the time between production stoppage for biofilm removal can be lengthened. Combined with more speedy and complete removal of biofilm from the surface of PFA fully fluorinated fluoropolymer, this lengthening between cleanings provides additionally improved production uptime.

Government regulatory agencies are forward-looking in their interest in not impeding improvement in pharmaceutical and biotechnical industries' effectiveness and efficiency.[47] For processing systems in which wetted surfaces are PFA fully fluorinated fluoropolymer, this proactive perspective presages regulatory enhancements which improve these industries productivity and effectiveness, all of which translate to more profitable processing.

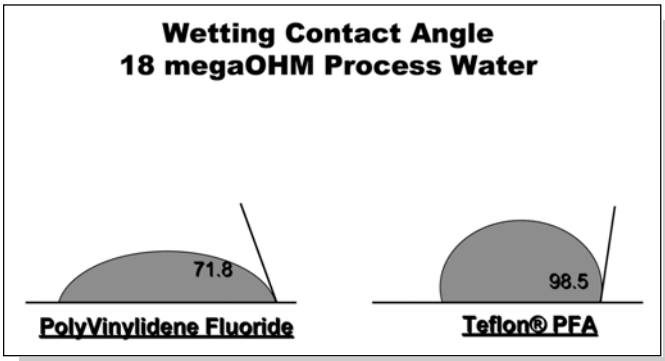

Figure 9. Schematic representation of wetting angles quantified in Figure 8.

Atomic Force Microscopy Surface Analysis

	Nanometers		
	Ra	Rms	Z range
Siliconed Borosilicate Glass	0.84	1.56	35.14
Borosilicate glass	1.11	7.42	78.41
Poly(propylene)	16.19	7.42	78.41
TEFLON PFA (injection molded)	17.17	24.35	438.85
316L Stainless Steel	26.64	41.74	293.09
Poly(vinylidene fluoride)	28.48	35.09	244.24
TEFLON PFA (machined)	36.83	47.47	310.99

Source: Hyde, et.al., ibid.; Ra = arithmetic average of deviations of traced line from center line along trace; Rms = corresponding geometric average; Z = largest perpendicular distance measured along the trace line.

Figure 10. Atomic force microscopy surface analysis.

Conclusion

Published data from experiments conducted by the University of Minnesota Bioprocess Technical Institute confirms that the non-corrosive hydrophobic surface of PFA fully fluorinated fluoropolymer releases biofilm virtually completely in essentially quiescent non-cleaning protocol biofilm inactivation with 50 ppm sodium hypochlorite solution. By comparison, the same biofilms were significantly retained by 316L stainless steel, borosilicate glass, siliconed borosilicate glass, poly(propylene) or poly(vinylidene fluoride). Precision roughness Atomic Force Microscopy measurements on the substrate coupons confirmed that the asperity of the surface of PFA fully fluorinated fluoropolymer is a non-factor in biofilm adhesion whereas the asperity of other substrate surfaces enhanced biofilm retention. The combination of surface roughness and biofilm removal data lead intractably to the conclusion that, other things being equal, the chemical polarity of the surface is the key factor enhancing biofilm retention, and that a non-wetting non-polar surface of the perfluoropolymer maximizes biofilm release. Studies of biofilm onset on, and ease of removal from, the surface of PFA fully fluorinated fluoropolymer are planned.

The non-corrosive non-polar hydrophobic surface of PFA fully fluorinated fluoropolymer promises potential productivity-enhancing easing of regulatory compliance issues brought about by materials of construction.

Using systems in which the wetted surfaces are perfluoropolymer eliminates the cost associated with electropolishing, passivation, roughing, protracted cleaning protocols with their adverse environmental ramifications, unexpected down-time from cracked glass-lined equipment, and product quality contamination. Processing equipment with wetted surfaces of PFA fully fluorinated fluoropolymer offer significant potential for additional productivity "uptime" with its resulting economic benefit. Instead of paying for the shortcomings of stainless steel and glass materials of construction in pharmaceutical and biotechnology processing equipment, these collective savings, measured in millions of dollars, would then be available for more productive initiatives such as the development of new products or enhanced profitability.

The production and product benefits founded by systems manufactured from PFA fully fluorinated fluoropolymer are now available to the pharmaceutical and biotechnology industries to provide enhanced global competitiveness through

lower costs and facilitating continuing advances in process and product development—strengthening our industry for the 21st century.

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b. A conservative estimate of the cost of passivation of a 1000 foot loop is $10K - $12K, i.e., $10-$12/ft.

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A Brief History of the GAMP Forum

by Gail Evans

The regulations governing the use of computers in pharmaceutical manufacture came into existence in 1983.However, they were so inconsistent with IT practices of the time that much argument ensued, and they were not strictly enforced. In 1991, during inspections at Glaxo, ICI Pharmaceuticals (later Zeneca), and Fisons, FDA inspector Ron Tetzlaff issued several 483s and warning letters. All were related to deficiencies in the validation of a range of computer systems and focussed on systems that lacked adequate documentation.

It was the first time that the FDA had so forcefully raised issues concerning computer systems in Europe. In the US, the FDA had been alerted to the potential problems of computer systems by the near disaster of Apollo 13 and the Connecticut blood bank disaster.

The pharmaceutical companies concerned were unsure how to respond so many of them talked to their suppliers. The suppliers, however, did not know what documentation and information they needed to give to the pharmaceutical companies.

At the time David Selby of Glaxo, and Clive Tayler of The Wellcome Foundation discussed the events.

Had it not been for a telephone call some days later from Clive to David, however, what we now know as the GAMP Forum is unlikely to have ever existed and neither would the globally accepted guidance for both suppliers and users of automated systems in pharmaceutical manufacture. Clive's question that ultimately led to the formation of the GAMP Forum was simply "What are we going to do about it then?" This modest query initiated several further telephone conversations that now involved Tony Margetts of Zeneca Pharmaceuticals.

Eventually, a meeting was convened and hosted by Glaxo, at Stockley Park, Middlesex, UK. Those attending this initial meeting represented the UK pharmaceutical industry, and became the Pharmaceutical Industry Computer Systems Validation Forum (PICSVF), with the following members acting as a Steering Committee:

Annis Bratt
SmithKline Beecham

Tony Margetts
Zeneca Pharmaceuticals

David Selby
Glaxo Manufacturing Services

Clive Tayler
The Wellcome Foundation

During the initial meeting the group agreed to the following set of objectives:

- to share information and experience about the interpretations of the regulations and guidelines concerning CSV
- to publish and promote guidance for suppliers to the UK pharmaceutical industry
- to promote discussions with regulators and opinion leaders
- to produce training program to help suppliers understand the needs of the industry
- to maintain a dialogue with other interested professional groups and organizations

The group met on a regular basis to share details of FDA inspections and made it a priority to establish guidelines for suppliers for the validation of automated systems in the pharmaceutical industry.

A sub-group, led by Dr. Tony Margetts, was established to devise a draft set of guidelines. These would take account of the requirements of both the European and North American regulatory bodies, making use of existing internationally recognized standards, where appropriate. Their first draft guideline was derived from an existing Zeneca Pharmaceuticals document entitled VMAN (Validation Management). This document was revised and supplemented by the members of PICSVF to create the initial draft guidance. The content of the guidance was di-

rected by a Steering Committee with following members:
Tony Margetts
Zeneca Pharmaceuticals (Chair)

Rob Almond
Glaxo Manufacturing Services

Malcolm Clarke
Bristol-Myers Squibb Pharmaceuticals

Chris Jones
SmithKline Beecham plc

Stuart King
The Wellcome Foundation Limited

Nicky Tasker
Zeneca plc

Tony Trill
Medicines Control Agency

Malcolm Wright
Zeneca Pharmaceuticals

This draft was aimed specifically at suppliers of automated systems to the pharmaceutical industry and shared with PICSVF in December 1993. Following approval by the PICSVF, the draft was launched in March 1994 in London with the assistance of Logica and the Management Forum, and made available for comment from the suppliers of automated systems and other interested parties. Very valuable comment and input was received at that time from US leaders in the field, including Ken Chapman and Mike Wyrick with the following companies represented in the review of this first draft document:

Abbott Laboratories
The Boots Company
Bristol-Myers Squibb Pharmaceuticals
Eli Lilly
Fisons Pharmaceuticals
Glaxo Manufacturing Services Ltd
Organon
RP Scherer
Rhone Poulenc Rorer
Roche Products
Roussel
SmithKline Beecham plc
The Wellcome Foundation Ltd
Zeneca Pharmaceuticals

Concurrent with the PICSVF's realization that it was important to be independent from IT suppliers and other IT groups, Bob Del Ciello and Harry Dowling initiated the link with ISPE. Following the release of the first draft, Anthony J. Trill of the MCA suggested a new name for the PICSVF. His suggestion, the GAMP (Good Automated Manufacturing Practice) Forum, is the name by which this innovative group is now recognized across the globe.

Following suggestions to improve and extend the first draft guidance document, production of the second draft was supported by ISPE and published in January 1995. In addition to approval from the members of the GAMP Forum, this second draft was endorsed by the Association of the British Pharmaceutical Industry and by the Pharmaceutical Quality Group of the Institute of Quality Assurance.

Version 1.0 of the GAMP Forum Supplier Guide was launched in Amsterdam at an ISPE seminar in March 1995. Based on the second draft, this version also incorporated the APV Interpretation of the EC (European Commission) GMP Annex 11.

Following the introduction of Version 1.0, the GAMP Forum expanded further into Europe with the involvement of the German group APV, led by Heinrich Hambloch and the engineering society GMA/Namur, led by Hartmut Hensel. The Steering Committee by now had members from the UK and Europe, including Hartmut Hensel, Heinrich Hambloch, and Gert Moelgaard of Novo Nordisk Engineering A/S.

As the guidance produced by the GAMP Forum grew, it needed someone to watch over its production, and in preparation for the next release Sion Wyn, then of FJ Systems Limited, became its official editor.

Version 2.0, also known as GAMP 96, of the Guide incorporated comments and additions from a number of companies and was launched in Basle in May 1996. Later that same year the GAMP Forum made its first expedition to the US, at a joint ISPE/PDA conference in Baltimore, MD.

Supplier Forum

Although the original group, PICSVF, published a 'Supplier Guide', they did not in fact have any members who were suppliers. Several 'ad hoc' attempts to involve suppliers had not come to fruition until in 1996, when Guy Wingate of ICIEutech and David Selby discussed a more formal method to link suppliers with the Forum. This discussion led in 1997 to Guy Wingate's proposal to the UK DTI (Department of Trade and Industry) for funding from the 'Sector Challenge Initiative'. The GAMP Forum, including Tony Trill (MCA), supported the submission.

In 1998, following the success of the Sector Challenge proposal, The Supplier Forum came into being, initially with 15 members. From the beginning, the Supplier Forum reflected the structure and model of the GAMP Forum and likewise, they had a Steering Committee. This initially included:

Guy Wingate
ICIEutech (Chair)

Peter Coady
Coady Associates

Craig Gatford
US Filter

Kate Samways
Raytheon

David Stokes
ABB

Tony Trill
MCA

In addition, Paul Hargreaves the Department of Health representative, assisted in monitoring the progress of the Supplier Forum under the Government Sector Challenge Initiative.

The Supplier Forum supports manufacturers of equipment, embedded systems, laboratory systems, SAP, and process control systems. The membership also includes software programmers, integrators, and application/technology consultants. The DTI provided funding for 2 years, following which the Supplier Forum had to become self-sustaining. Early in 1998 the very successful launch of this Forum was attended by 60 participants. Regular meetings every quarter year followed at which the Supplier Forum acted as a 'self help' group for suppliers and a forum for collective dialogue with the GAMP Forum. Suppliers have developed their own guidance on testing, specifications, and preparation for customer audits.

The aims of the Supplier Forum are:

1. to understand the GAMP (Supplier) Guide and other guidance on the regulations

2. provide a forum to discuss problems and exchange best practice

3. influence the development of the industry practice guidelines and pro-

vide feedback on practical implementation experience to the authors

The objectives of the Supplier Forum are:

1. add value to supplier products by improving their GxP (GMP, GLP, GDP, etc.) compliance capability, passing this on to their customers as a competitive advantage

2. ensure that suppliers support their customer's requirements, minimizing product costs without compromising quality

3. maintain public/market confidence in the standard of manufactured drug products and health supplements

Initially, in accordance the DTI funding; the Supplier Forum was solely UK based. Once this expired, the Supplier Forum opened its doors to Europe. Guy Wingate ceased to be the chair of the Supplier Forum in 1998, when he moved to GlaxoWellcome. Chris Evans became chair until mid-2000, when he too moved to GlaxoWellcome, at which point Sam Brooks of ABB (Eutech) took over.

The following companies have adopted leading roles within the Supplier Forum:

ABB
Aitken Scientific Ltd
Aston Dane
Coady Associates
Dickinson Controls
Fisher Rosemount
Foxboro
ICI Eutech
KAS Associates
Logica
Map 80 Systems
Motherwell Information Systems
Perkin-Elmer
Raytheon
Rotork
SAP AG
Siemens
Smart Tech
US Filter
Washington Consultants
Yokogawa

The Supplier Forum has participation from the FDA evident by David Pulham speaking in the second Supplier Forum.

The GAMP Forum and the Supplier Forum have co-existed for several years, with Kate Samways (KAS Associates) as a liaison on the Steering Committee of the GAMP Forum. Today, the Supplier Forum has joined with the GAMP Forum as a Special Interest Group (SIG), and will co-exist with its American counterpart, the Suppliers SIG of GAMP Americas Forum.

GAMP 3

With the continued support of ISPE, the GAMP Forum was able to revise and update the GAMP Guidance and published GAMP 3 in 1998. This is widely accepted as the definitive guidance for suppliers of automated systems to the pharmaceutical manufacturing industry. It enables suppliers to produce their systems according to good practice and assists them in supplying the required documentation to the pharmaceutical industry.

GAMP 3 achieves many of the original PICSVF objectives for guidance for suppliers, but in addition, GAMP 3 also has separate guidance for the users of automated systems. GAMP 3 also saw the introduction of a second volume containing good practice examples and GMA/Namur guidance. Originally produced in German, the GMA/Namur guidance was translated into English specifically for publication in GAMP 3. The remaining components of GAMP 3 were, in turn, translated into German. The German edition of GAMP 3 was available in print, with the English edition published both in print and electronically. The development of an electronic version has allowed companies to distribute GAMP 3 across their company networks and assisted them to standardize validation practices globally. It is also much lighter to carry than the paper version!

Formation of GAMP Americas

The GAMP Forum held its inaugural meeting on September 12, 2000 in Somerset, NJ, hosted by GAMP Industry Board Member Paul D'Eramo of Johnson & Johnson. GAMP Industry Board Chairman Dr. Guy Wingate of Glaxo Wellcome opened the meeting with a discussion of the history and role of GAMP.

GAMP Americas affords professionals in the Americas the opportunity to participate in the creation and sharing of computer validation guidance, recommendations, and example practices. This first meeting was attended by approximately 140 people and focused on establishing the GAMP Americas organization and forming Special Interest Groups (SIGs). GAMP Americas has formed its own Steering Committee, which is chaired by Rory Budihandojo of GlaxoSmithKline.

GAMP Americas' SIGs interact in meetings and by e-mail providing an opportunity to develop a common understanding of particular topics by discussing issues and practical solutions. Topics of interest include Analytical Laboratory Systems, Manufacturing Execution Systems, and Medical Devices. The Review Group for the next edition of the GAMP Guide, GAMP 4, led by Randy Perez of Novartis, has been kept busy throughout 2001 both contributing and reviewing material to make the publication a more global document. The JETT (Joint Equipment Transition Team) Consortium, led by Jim John of Rockwell Automation, which focuses on skid-mounted equipment/embedded control systems, became a SIG concurrent with the formation of the GAMP Americas Forum.

Joining ISPE

On January 31, 2001, the GAMP Forum became a technical subcommittee of ISPE and continues to be supported by, and benefit from the resources offered by ISPE.

Celebrating 10 Years

In June 2001, the GAMP Forum celebrated the resounding success of its first decade. The GAMP Forum is a unique partnership between computer users, suppliers, and regulators serving the pharmaceutical industry.

The anniversary was held in Basingstoke, and hosted by Eli Lilly. Special guests were Bob Best, President of ISPE, and Gordon Munro, Head of Inspection and Enforcement at the MCA, both of whom have provided substantial support for the GAMP Forum. Approximately 30 guests attended a celebratory dinner and were presented with commemorative plaques.

A GAMP Forum meeting followed, attended by over 60 of the Forum's members from throughout Europe and the US, including chairs of the Industry Board, GAMP Forum, GAMP Americas and leaders of many of the SIGs.

Many of those who attended have been involved with GAMP since its inception as PICSVF and continue to contribute significant effort to ensure its continued success and significance to the day-to-day practices of the pharmaceutical industry.

GAMP 4 and the Future

GAMP Guidance is now well known throughout Europe and is ever increas-

ing in its popularity within the US and throughout the globe. This summer GAMP Seminars were held in Singapore, Japan, and Australia. GAMP 4 aims to cover the additional healthcare requirements for automated system validation and compliance including, GCP (Good Clinical Practice), GLP (Good Laboratory Practice) and GDP (Good Distribution Practice). A brief synopsis of GAMP 4 is provided in a separate article in this publication. In its most recent meeting the Steering Committee of the GAMP Forum finalized the agenda for the two-day conference that will launch GAMP 4. This launch will be held in Amsterdam in December 2001 and again in Puerto Rice in February 2002.

To compliment the main body of the GAMP 4 Guide there will be a number of supporting publications providing examples of good practice for particular systems. Planned examples include a publication on process control systems incorporating the work of GAMP's Process Control SIG, the North American JETT Consortium on embedded control systems, and the German GMA-Namur work on the standalone control systems. The discussion document on compliance requirements for IT infrastructure published in 1999 has been updated and will be published as a supplement to GAMP 4. Other SIGs are working on clinical and regulatory systems, web based applications, laboratory systems, manufacturing execution systems, medical devices, and global systems (e.g., ERP, MRPII, LIMS).

Additionally, the GAMP Forum, as a technical subcommittee of the ISPE, has published a Guide to 'Complying with 21 CFR Part 11, Electronic Signatures and Electronic Records', jointly with the PDA. This is the first in a series of three such Guides.

Several regulatory authorities, such as the UK MCA, have benefited from training given by the GAMP Forum.

Acknowledgements

The GAMP Forum would like to thank the literally hundreds of people – technical professionals all – for their technical input both written and oral who have contributed and supported GAMP over the past 10 years.

In particular, the GAMP Forum would like to extend its gratitude to ISPE for providing the financial and administrative support to publish guidance and maintain the GAMP Forum in it present and future forms.

This article has been written with the assistance of Dr Guy Wingate, GSK (Chair of the GAMP forum Industry Board) Dr David Selby, Selby Hope International (Chair of the GAMP Forum Steering Committee) and Dr Tony Margetts, AstraZeneca.

Further Information

For further information about current activities and to join the GAMP Forum visit http://www.gamp.org.

About the Author

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Business Considerations in Building a Computer System Validation Quality Assurance Infrastructure

This article presents guidance regarding considerations and approaches relevant to building a computerized systems validation infrastructure tailored to a start-up company engaging in GMP-compliant pharmaceutical compound manufacture.

by Bob Carrier

Introduction

Start-up contract manufacturing organizations undertaking GMP-compliant operations are faced with meeting regulatory requirements applicable to computer related systems. Succeeding in the business of GMP manufacturing hinges in part on meeting these regulatory requirements, which with the enforcement of 21 CFR Part 11, have become more stringent and subject to local interpretation or misinterpretation.

Money and personnel are typically less than plentiful in a start-up situation, making critical each business decision as to how the Computer System Validation (CSV) program will be built using limited available funds. The strategy presented in this article is to implement those elements of the CSV infrastructure sufficient to position the company as a GMP-compliant manufacturer without investment that results in an unnecessary QA edifice. Restated, the strategy is to build only what is needed without funding those elements of the CSV program that can be deferred until more favorable financial conditions prevail.

CSV infrastructures in practice are customized to the individual company, yet all share a common organization and many common elements. The CSV infrastructure is typically a hierarchy of program-level Standard Operating Procedures (SOPs) and underlying system-level procedures.[1] A program-level SOP applies globally to the company, states policies, and is general in nature so as to be applicable to all computer related systems. In contrast, the system-level SOP applies to only one model of

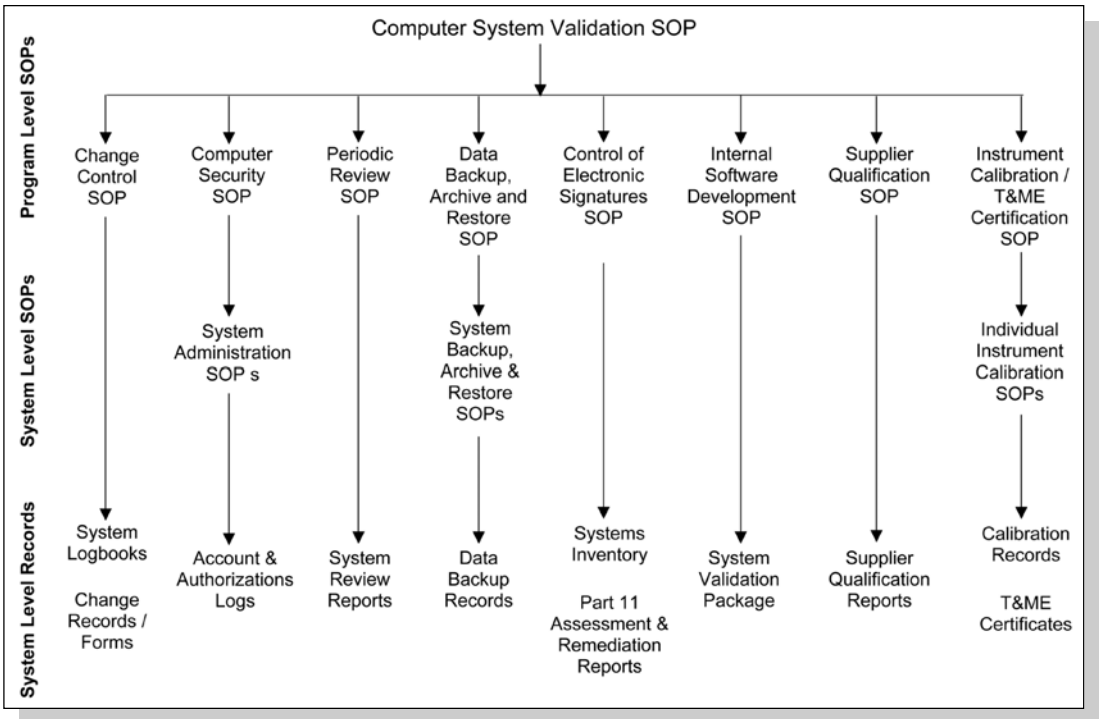

Figure 1. The fully-developed CSV infrastructure.

system, and presents the detailed instructions to be followed for daily operation of the individual system.

Figure 1 depicts a version of the fully built CSV hierarchy. This article will elaborate on Figure 1 and, more importantly, it will provide guidance as to finding the lowest-cost approach to computer validation.

Building A CSV Infrastructure

When a company commits to creation of a GMP-compliant CSV infrastructure, a chicken-and-egg scenario arises. One must decide whether the program level, which provides procedures for all company wide computer related systems, or the system

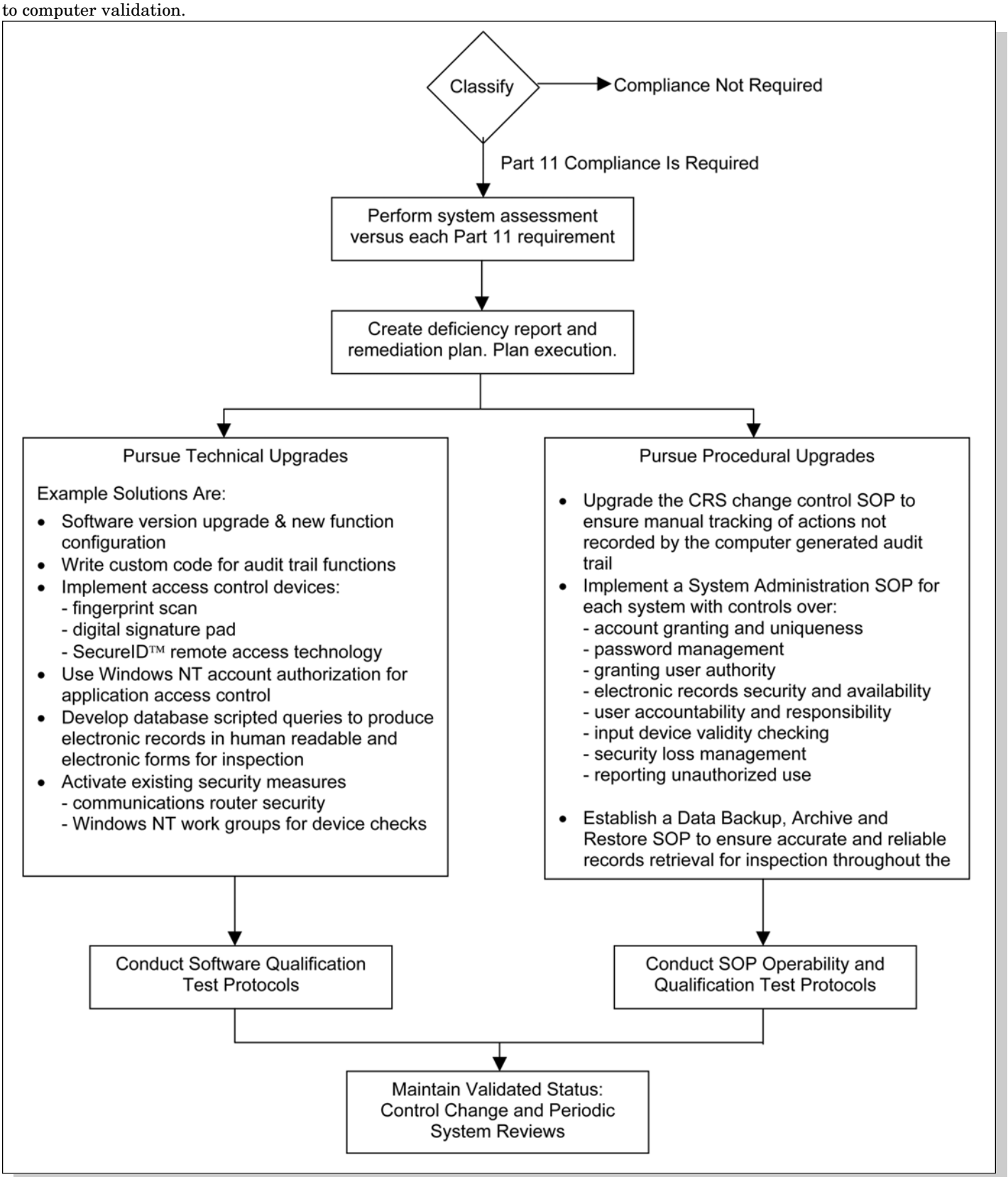

Figure 2. Flowchart of the 21 CFR Part 11 compliance process.

level comes first. The possibilities revolve around the question of "Should we develop high-level guidance first, then build out the details in a top-down approach, or do we start at the system-level reserving development of a comprehensive program for the future?" Intrinsic to this decision is the question "To what level of completeness should the CSV infrastructure be grown?" The result is a program within the spectrum of fully developed, down to a very sparse implementation of selected key computer validation practices.

The significance of this decision is that it will determine the funds and personnel that must be allocated to the CSV program. There are some quantifiable factors to consider when arriving at a decision as to how and to what degree of sophistication the CSV infrastructure will be built. Each of these factors should be cognitively addressed in order to make a well-considered, defensible decision. Factors to consider are:

- scope of computer systems requiring validation
- progress toward drug substance(s) approval for manufacture
- funding available to support CSV-related costs
- availability of technical resources and skill levels
- availability of time to complete the CSV infrastructure
- accuracy and completeness of existing CSV-related SOPs
- QA resources available to implement and administer SOPs
- degree of regulatory risk-aversion

Increase in each of these factors moves the decision toward implementation of a CSV infrastructure that is fully developed. When each of the above factors is strongly present, especially time and money, the company could readily proceed with building the CSV infrastructure in a well-organized, top-to-bottom fashion. However, opposite acting forces such as time-to-market pressure for a new compound, an immediate need to begin generating revenue through manufacturing, or perhaps an imminent FDA inspection can overshadow all other factors, encouraging a minimalist approach to CSV in the short-term. In this situation, the author would direct the company's resources toward initial validation of each critical system, then maintaining the system validated status through controls specified in system-level SOPs. A "build it as you need it" approach enables implementation of a CSV infrastructure that is adapted to the moment, and that can be expanded to satisfy future regulatory compliance needs.

Typically, a start-up company has few computer-related systems supporting GMP operations. For example, the scope of systems requiring validation may be confined to a plant computerized control system and an analytical lab data acquisition/integration system. For this scenario, the author believes a company receives greatest return on investment by implementing system-level SOPs for the individual systems, as compared to spending on development of CSV procedures, guidelines, and master plans. In addition, and as is true for all GMP-regulated companies, there should be a high priority placed on conducting internal audits of each system to ensure the CSV package is complete, accurate, effective, and presentable to an investigator.[1] A current trend in facility inspections is to focus on individual systems,[2] making it a good choice to be fully-prepared for inspection at the system-level.

Solving the Part 11 Puzzle

A major consideration in successful CSV given today's regulatory climate is to fully meet all regulatory requirements

THE CSV SOP

PURPOSE - The purpose of this procedure is to provide a comprehensive definition of CSV program objectives and related quality assurance infrastructure. This SOP describes an overview of the CSV quality assurance infrastructure in terms of related program-level SOPs and system-level SOPs.

SCOPE - This SOP specifies the procedures for development, testing, qualification, change and maintenance of any and all validated computer related systems used to monitor, control, report or to make decisions about a manufactured drug substance.

RESPONSIBILITY - Quality Assurance, Senior management, System Administrator and Supplier

CSV QA - A summary of all procedures comprising this quality management system, i.e. a summary review of all the SOPs described in this article.

INFRASTRUCTURE - summary review of all the SOPs described in this article.

CSV PROCEDURE -

a. **Determination Of Need To Validate A System**
The first step in computer system validation is determination of the need to validate an individual system. This determination should be made cooperatively by QA and the designated system administrator/owner. While there is no set procedure for making this determination, provide tests to apply when deciding on the need to validate a system.

b. **Computer System Validation Procedure - New Purchased Systems**
Validation of a new purchased computer related system is an effort that spans the entire system lifecycle from project inception to use and maintenance of the validated system. The prescribed CSV methodology for initial validation of a new purchased system is presented in this section, with activities arranged in chronological order.

c. **Computer System Validation Procedure - Internally-Developed Systems**
Requirements for validation of internally-developed computer related systems are substantially the same as those for new purchased systems. For internally-developed systems, follow the purchased system validation approach with the exceptions identified in this section.

d. **Computer System Validation Procedure - Retrospective Validation Of Existing Systems**
Validation of an existing computer related system, whether it be purchased or internally developed, is called retrospective validation. Retrospective validation is employed when a system not previously validated is allocated to GMP manufacturing, or when a system that was validated has lapsed to a non-validated status. The prescribed CSV methodology for retrospective validation is presented in this section, with activities arranged in chronological order. This same procedure can also be used for re-validation of an existing system.

e. **Validation of Spreadsheets and Stand alone Calculation Routines**
Spreadsheets and calculation routines used in support of GMP-compliant activities are validated through processing a data set for which the result(s) has been independently verified by hand-calculation or other means. Version control and user documentation are required.

f. **Validated System Acceptance Checklist**
Use a checklist to determine if the computer system is validated the initial time. To declare a computer related system validated, all the checklist questions must be answered in the affirmative.

g. **Validation Documentation Retention**

RELATED DOCUMENTS

REFERENCES

HISTORY OF CHANGES

DEFINITIONS

Figure 3. Outline for the computer related system validation SOP.

SYSTEM ADMINISTRATION SOP

PURPOSE - The purpose of this procedure is to establish the methods used for administration of a computer related system in a manner that is consistent with regulatory requirements stated in 21 CFR Part 11.

SCOPE - The procedural scope covers access control, user authority checking, user account management, device checking, security intrusion reporting, security loss management, control of system documentation and periodic security review.

RESPONSIBILITY - Quality Assurance, System Administrator, Senior Management and Supplier

PROCEDURE -

a. Logical Security for Access Control
- Operating system and application access control by ID code/password pair
- User identity and qualifications verification
- Account uniqueness
- Password controls
- User responsibility notification

b. User Authority Checks
- Table specifying authority to perform actions for each job role
- Procedure for System Administrator to use when granting authority

c. User Account Management
- Procedure for System Administrator to use when adding, modifying or deactivating an account

d. Device Checking
- Use of Windows NT domains and security groups
- Procedure to secure functional area separation
- Procedure to establish control of remote access input devices

e. Intrusion Reporting
- Procedure for filing a report
- Procedure for investigation of potential impact on the system

f. Loss Management
- Reporting procedure
- Procedure for issue of replacement access (temporary or permanent)

g. Control of System Documentation

h. Periodic Security Review
- Accounts and passwords integrity
- System intrusion reports
- System performance reliability, accuracy and consistency

RELATED DOCUMENTS

REFERENCES

HISTORY OF CHANGES

DEFINITIONS

Figure 4. Outline for the system administration SOP.

promulgated in 21 CFR Part 11, Electronic Records; Electronic Signatures (The Rule).[3] Complying with this regulation starts with assessing each existing system and its supporting procedures to identify compliance deficiencies. The puzzle can then be solved by selecting and implementing a combination of technological and procedural upgrades to give full coverage of Part 11 requirements. As an example, the company may choose to upgrade the application software to a newer version that offers audit trail functionality, or choose to meet this Part 11 requirement with manual audit trails (change control records) controlled by procedures. A start-up company with highly constrained capital spending may initially find the procedural solution to be the most cost-effective. Of course, any system upgrade, whether technical or procedural in nature, must be fully qualified by documented testing. An approach to achieving Part 11 compliance is depicted in Figure 2 as a flowchart of the process along with some practical solutions. Most every computer related system offers some software functionality useful in meeting some of the Part 11 requirements. These are the technological solutions for access control, authority level checking, input device validity checking, and audit trail recording. To maximize the committed investment in each system, the company should thoroughly use all software functionality presently available to address Part 11 compliance. It is often the case that not all available security controls have not been activated. For example, password security in a network router to control remote access, use of Windows NT™ user authentication to control application access, or configuration of multiple user levels to restrict authority by job role may presently be inactive.

However, technological solutions may be unavailable (not yet developed by the system supplier), incomplete in functional scope, or considered too costly for purchase. In this situation, the company has no choice except to institute procedural controls. An example of incomplete functionality is the audit trail software that tracks most operator actions, but does not track changes to custom software, software upgrades, and deletion of electronic records through Windows NT file system commands. In this case, the computer generated audit trail must be augmented with a manual log to record those changes left untracked by the software.

Part 11 And Your Supplier

The first Part control stated in The Rule, Sec. 11.10(a) requires "System validation to ensure accuracy, reliability, consistent intended performance …". A practical way to achieve system initial validation, and in the author's opinion, the most viable strategy when resources are limited, is to enlist the system supplier as a partner. The supplier can often assist by delivering a high-quality commissioning turnover package, as well as by preparing initial validation protocols with guidance from the user as to document format, discrepancy reporting, and approvals.

A current trend is that many suppliers of computer related systems and software are making significant investment in understanding The Rule. Suppliers are using their understanding of The Rule to direct development of software functionality in their system in an effort to enable the user to more readily become compliant with this regulation. Suppliers do this to obtain a competitive advantage through product differentiation over competitors. This produces a nice opportunity to leverage the supplier's investment in The Rule for the user company's benefit. The system supplier is a primary resource to successful implementation of the technological solutions available in their application software.

The key here is to select for purchase only systems provided by suppliers moving toward Part 11-supportive software functionality. This is a critical point in avoiding a costly mistake of purchasing and implementing a non-compliant system. Careful supplier selection positions the company to partner with a supplier able to knowledgeably discuss The Rule, explain their product's capabilities/limitations, and generally assist in solidifying the user's compliance position. Since no supplier wants to have an adverse observation (i.e. 483) traced to their product, they are highly motivated to work with you on system validation and procedural controls.

When developing the system-specific SOPs discussed later in this article, consider your supplier as a resource. The supplier can provide many technical details about the procedures that must be specified in the system administration SOP

SYSTEM BACKUP, ARCHIVE AND RESTORE SOP

PURPOSE - The purpose of this procedure is to establish the methods used to backup, archive and restore electronic records managed by the computer related system. This procedure is established to comply with regulatory requirements stated in 21 CFR Part 11.

SCOPE - The procedural scope covers electronic records created and maintained by the CRS. These electronic records, along with the computer system required to retrieve them (operating system software, application software and workstation hardware), must be protected to enable accurate and reliable retrieval throughout the records retention period. The scope of electronic records may include original records produced during system operation, database tables, configurations, meta-data (data about data) and audit trail records.

RESPONSIBILITY - Quality Assurance, System Administrator, Senior Management, and Supplier

PROCEDURE -

a. **Creation of A Rotating Daily Data Backup of Electronic Records**
   - Identification of target files
   - Detailed command procedure and media type used
   - Media labeling
   - Backup record keeping

b. **Rotating Data Backup Frequency**
   - Daily, weekly or other
   - Rules for reuse of media

c. **Creation of A Permanent Data Archive**
   - Specify when performed
   - Media labeled "do not erase"
   - Archive catalog documentation

d. **Media Storage**
   - Physically secure, environmentally controlled location
   - Permitted access by whom

e. **Retention of Commercial Off-The-Shelf Software**
   - Operating system
   - Purchased applications

f. **Backup of Custom Programs and Configurations**
   - Specify when performed
   - Identification of target files
   - Version identification on media label

g. **Data Archive Restoration**
   - Detailed command procedure
   - Identification of media to be used

h. **Retention of Computer Hardware**
   - Procedure to retire a system
   - Method to retain access to obsolete hardware as required to generate records for compliance inspection
   - Procedure to transfer archived data on obsolete media to current type if obsolete hardware will not be retained

RELATED DOCUMENTS

REFERENCES

HISTORY OF CHANGES

DEFINITIONS

Figure 5. Outline for the system data backup, archive, and restore SOP.

and in the electronic records backup, archive, restore SOP. Finally, it should not be overlooked that the supplier plays a role in managing revision history and distribution of documentation as to how the system is administered and operated. Control of this documentation is a Part 11 requirement stated in Sec. 11.10(k).

Make a Plan

While it is not a regulatory requirement, it makes good business-sense to prepare a written plan prior to conducting work to produce the CSV infrastructure. Planning is good business as it can prevent unnecessary development, reduce rework, lessen confusion, and best of all, help control costs. This plan, which could be titled "CSV Infrastructure Implementation Plan," is used to clearly define the selected approach and provide supporting rationale as to why this approach is appropriate from a regulatory compliance perspective. When resources are constrained, consider adopting a phased approach, supported by a proposed schedule, to deliver the desired final CSV infrastructure.

In the author's experience, it has become industry general practice to have a validation plan written for each new system implementation or software upgrade project.[4] This second type of plan defines the validation approach, roles, and responsibilities. It also provides statements of need for a supplier qualification audit, specific criteria for system acceptance as validated, and requirements for a final validation report. A comprehensive description of the validation approach includes development phase documentation requirements, release testing method, site commissioning activities, required qualification protocols, sequence of protocol execution and identifies the test environment, consisting of test data cases, automated software test tools, and computer hardware. The validation approach is tailored to the system. For example, not every system requires execution of a factory acceptance test, a site acceptance test, and/or a performance qualification.

Program Level

The goal of CSV is to provide documented evidence to a high degree of assurance that a system performs accurately and consistently as intended. The program level of the CSV infrastructure contains procedures designed to meet this goal for any validated computer system. SOPs at the program level are written to focus on specific regulatory requirements and to define company procedures appropriate to meet those requirements. A company uses the program level to ensure knowledgeable, consistent, and accurate application of the CSV methodology for all purchased and internally developed computer systems or software.

The remainder of this article presents a brief description of each SOP shown in Figure 1, along with the author's priority for implementation as ranked from a return on investment viewpoint.

The CSV SOP

Occupying the highest position within the CSV infrastructure is the CSV SOP. The purpose of the CSV SOP is to provide definition of program objectives, policies, and procedural details of the company's approved validation methodology. This SOP provides an overview of the CSV infrastructure in terms of underlying SOPs and their purpose. Further, this SOP makes a statement of scope regarding software and computer related systems within the CSV program, as well as identifying those systems excluded from validation. Figure 3 presents an example document outline the reader can reference when preparing a CSV SOP.

While validation is a central issue in Part 11 compliance and this SOP enables consistent and complete CSV projects, the author has found that companies often delay its implementation without incurring adverse regulatory findings. Delaying rollout of this SOP until practical experience is gained on individual systems may yield the advantage of reducing procedure rework and result in a program that can be smoothly implemented by the organization. In the interim, a company can document the CSV methodology in a system validation plan.

Author's ranking: Medium priority.

System Level

Working from the premise that a start-up company receives greatest return on investment by first implementing system-specific SOPs, let's discuss the system-level of the CSV infrastructure. Procedures at this level provide detailed instructions as the daily care and feeding of the system.[5] The system-level SOPs are concerned primarily with system security, electronic records availability, and instrument calibration.

System Administration SOP

This SOP is used to establish the controls required by 21 CFR 11.10(d)(g) and 11.300. Most computer operating systems and application programs provide configurable security measures to control user access. In addition, many application programs offer authority-check functionality to control level of user access to database content and program functionality. Access and authority security measures, which are typically accomplished using ID code/password pairs, need specification as to how they will be configured and maintained. This SOP also specifies the procedure to document system account names, user authorization levels, and the cumulative history of security related modifications. Figure 4 provides an example document outline for the reader to reference in preparing a System Administration SOP.

The likelihood of a facility inspection scrutinizing an individual validated system[2] makes a strong business case for implementing without delay this SOP.

Author's ranking: High priority.

Backup, Archive, and Restore SOP

This SOP establishes the controls required by 21 CFR 11.10(b)(c). Each computer system is unique when it comes to the files that must be backed up to enable retrieval of data and electronic records. The target backup data is a mixture of source (raw) data, configuration data or meta-data, electronic records, and audit trail records. The detailed procedure for creating and managing the backup data is contained in this SOP. It specifies the exact directory structure that must be archived, the frequency of backup, permissible media type, media labeling, and the rules for media rotation. It also defines documentation requirements for recording of data backup activities. Figure 5 presents an example document outline for the reader to reference in writing this SOP.

Once again, the likelihood of a facility inspection placing scrutiny on an individual validated system makes a strong business case for implementing without delay this SOP.

Author's ranking: High priority.

Instrument Calibration SOP

Each analytical instrument and process instrument type is unique when it comes to calibration check and adjustment procedures. This SOP specifies the exact procedure and work instructions to use when conducting calibration work, the permissible service intervals (min/max), and the acceptable tolerances for the calibration results. It is also used to define documentation requirements for recording calibration results as well as the identity of test equipment and reference standards used in performing the work.

21 CFR 211.160.b[6] makes it very clear this is a GMP requirement that needs to be addressed in order to conduct GMP operations. Individual instrument calibration procedures should be established in an urgent manner. The most expedient and probably lowest cost approach is to start with the supplier's published calibration method when preparing each procedure.

Author's ranking: High priority.

Other Program-Level SOPs

Now, let's return to the program-level of the infrastructure with a brief tour of the other SOPs typically established, each of which is described in terms of purpose, some key issues to address, and priority for SOP implementation.

Change Control SOP

This SOP addresses 21 CFR 211.68(b) (6) and provides some measure of protection against unauthorized changes that can have negative impact on regulatory compliance and/or manufacturing operations. It defines procedures for management of changes made to validated computer related systems. The scope of this SOP encompasses computer system hardware, software (operating system, configuration data, commercial off-the-shelf software, and custom programs), and documentation. It is just as important to identify those changes to a validated computer system that do not require change control. For example, it may not be required to control changes to the format of non-GMP reports, user account preferences, and user created database views. For controlled changes, a standard form should be available and used to document the change, assess the potential risk of the change, and record requisite approvals.

It is significant to note that a manually documented record of change serves as a supplemental audit trail for operator actions not recorded by the computer-generated audit trail. Maintenance of system validated status requires managing change in a well-controlled, thoroughly documented manner. This SOP is an essential element of the company's CSV program.

Author's ranking: High priority.

Computer Security SOP

Defines requirements and standards to ensure that adequate physical and logical security measures are uniformly applied to and are functioning properly for each validated computer system. To ensure that a computer related system can reliably and consistently carry out its intended function, as required by 21 CFR 11.10(d), it is necessary to secure it from damage and restrict access to authorized individuals.

From a practical standpoint, implementation of computer system security happens on a system-by-system basis. The System Administration SOP for an individual system specifies configuration and use of security provisions in a more useful way than the generalities typically presented in the program-level SOP.

Author's ranking: Low priority.

Periodic Review SOP

The regulatory requirement met by this SOP is similar in nature to the one for drug product review required by 21 CFR 211.180(e). It defines requirements and procedures for periodic review of performance history of each validated computer system. The purpose of such review is to assess system reliabil-

ity, accuracy, and consistency during GMP operations. This review also assess effectiveness of procedures used for change control, security, data backup, document control, user training, and if applicable, calibration certification.

Documenting system reliability, accuracy and consistency of performance is important to maintaining system validated status. Accomplishing this review requires that detailed performance records, such as a logbook, be maintained for each system - this record keeping should be the immediate priority. The SOP seems less urgent as a review can be done in a free-format way and documented in a memorandum to the system's validation file.

Author's ranking: Low priority.

Data Backup, Archive, and Restore SOP

This SOP defines requirements for developing, then demonstrating computer data backup, archive, and recovery procedures specific to each system. Availability of source data and electronic records, as required by 21 CFR 11.10(b)(c), is maintained through routine backups suitable for accurate, complete retrieval for compliance inspections. This SOP specifies that custom software and configuration data must be stored on durable backup media to ensure the ability to use the electronic records throughout the retention period. Similarly, this SOP specifies a procedure to follow when retiring hardware to ensure a continued ability to run the operating system and application software required to access the electronic records.

From a practical standpoint, ensuring access to source data and electronic records is accomplished on a system-by-system basis. The system-specific data security SOP specifies backup and restore procedures in a more meaningful way than the generalities available in the program-level SOP.

Author's ranking: Low priority.

Control of Electronic Signatures SOP

This SOP specifically addresses electronic signature controls required by 21 CFR 11.100, 11.200 and 11.300. It establishes company procedures for managing identification/password pairs used for system security. It also establishes how this non-biometric method of user identification is to be used in various signing scenarios. Statements appear in this SOP to inform each user of accountability and responsibility for actions executed under his/her account name or electronic signature that impact electronic records.

With heightened investigational focus in this area, it probably makes best business sense to implement this SOP early in the company's GMP history. Otherwise the exposure to an adverse finding is potentially high regarding this critical compliance issue.

Author's ranking: High priority.

Internal Software Development SOP

Internally-developed software should be delivered in conformance with a well-controlled SDLC enforcing the same high quality standard as expected for purchased software.[1] This SOP establishes procedures to follow during software development, identifies related development standards, and specifies acceptance criteria that must be met before approval for use in GMP operations. Within the scope of this SOP are custom programs, spreadsheets, and other computational facilities that will be validated.

Commercial off-the-shelf software (COTS) known to be in use at other GMP-regulated companies is probably the lowest risk approach to bringing software into a GMP setting. Selection of COTS that is configurable is a simple and effective alternative to internally developed custom programs. The author considers in-house software development to be a risky endeavor for a start-up company and one that should be avoided if possible.

Author's ranking: Low priority, unless absolutely necessary to conduct business.

Supplier Qualification SOP

Requirements for administering a qualification program for suppliers of computer systems that will be validated are specified in this SOP. Also specified are the procedural details as to how a computer related system supplier qualification audit is to be conducted and documented. An audit checklist is typically attached to this SOP. Acceptance criteria are established to use in determining if a supplier should receive an approved status.

Following a business strategy of selecting COTS that is widely employed in the industry can obviate the immediate need to conduct a computer system qualification audit. If an audit is determined to be necessary, a company can use outside expertise and procedures to get the job done.

Author's ranking: Low priority.

Instrument Calibration/T&ME Certification SOP

The company-wide instrument calibration program is established by this SOP. The scope includes analytical instrumentation and process measurement instruments used to make decisions about the identity, purity, quality, efficacy, and safety of a drug substance. This SOP requires that each instrument type within the scope have a related calibration SOP to define the procedure as to how the instrument is calibrated and results are documented. The program for test and measurement equipment (T&ME) certification also is established by this SOP. The T&ME program specifies requirements regarding establishment of acceptance criteria (tolerances), equipment labeling, traceability to certified reference standards, and certification records.

As stated earlier, the immediate need for instrument calibration can be met at a low cost by establishing calibration procedures for individual instruments based on supplier recommendations. This point makes a program-level SOP appear less urgent although it remains important in regards to maintaining certified test equipment and calibration standards.

Author's ranking: Medium priority.

Conclusion

Our tour of CSV related procedures has concluded, and it is apparent that a return on investment analysis can be applied in determining the order of SOP implementation. CSV infrastructures come in different configurations and compositions that are tailored to a company's current regulatory needs, types of computer systems, and business direction. All share a common organization typically arranged in a hierarchy of program-level procedures and underlying system-level procedures. Testing the business case for each possible element of a CSV infrastructure is a sound approach to implementing a cost-efficient program suitable to govern validation of com-

puter related systems. Examples of cost-reducing approaches to CSV include placing higher reliance on the supplier during system initial validation, use of supplier technical knowledge in preparing system-level SOPs such as instrument calibration procedures, and favoring procedural controls over software solutions to keep comprehensive audit trail records. Using a "build it as you need it" approach enables a company to implement a CSV infrastructure that is adapted to the moment and that can be expanded to satisfy future regulatory compliance needs.

Glossary of Terms

COTS - commercial off-the-shelf software.
CSV - computer system validation, a.k.a. computer related system validation.
GMP - good manufacturing practice.
ID - identification code.
QA - quality assurance.
SDLC - software development lifecycle.
SOPs - standard operating procedures.
T&ME - test and measurement equipment.

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This article uses a series of different statistical methods to analyze content uniformity results during solid dose blending and compression.

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Statistical Methods for Analysis of Content Uniformity Results During Process Development

by Ed Carey, Joe Leonard, and James Reilly

Introduction

Before beginning process validation, it is recommended that a structured Product Development Report is used as the reference source for writing the validation protocols. The report will probably be divided into three main sections:[1]

- Formulation Development
- Manufacturing of the Biobatch
- Scale-Up to Full Production Size

This article will concentrate on the statistical methods that can be used to determine if a solid dose manufacturing process in development is suitable to proceed to full-scale production. The statistical models that are used will play a crucial role is deciding whether a full-scale production batch can meet its predetermined specifications and begin validation trials. Using incorrect or flawed statistical methods during the development phase could result in validation failure, creating an out of control production process. Part of a solid dose development program should be to give a high degree of assurance that all ***individual tablets*** produced should, as a minimum requirement, meet the specifications for the content uniformity of the relevant pharmacopoeia. Individual companies may also use in-house specifications that are tighter than the pharmacopoeia values. The regulatory authorities expect that appropriate statistical methods will be used during product development and for the validation study. Unfortunately, the regulations do not specify what type of statistical methods to use, and the methods used are at the discretion of the company.

This has of course led to a variety of different approaches being used. To maintain consistency, there should be similar statistical methods applied at both the development and full-scale validation trials. This article will illustrate the use of a selection of different statistical methods on real data generated in our pilot plant for the content uniformity results during both the blending and compression steps. The purpose is to discuss and interpret both the strengths and weaknesses of different statistical methods and to help to choose the most appropriate method during a solid dose scale-up and validation study.

Table A. Analytical results for content uniformity of the blend (expressed as a percent of the target concentration).

Sample	Top	Middle	Bottom
1	102.08	105.78	97.89
2	104.63	106.44	98.03
3	104.45	104.87	97.40
4	104.18	106.66	96.37
5	104.73	104.78	97.53
6	101.01	106.20	97.78
7	105.05	103.44	96.77
8	104.36	107.13	97.49
9	104.97	105.10	98.28
10	101.94	105.74	99.43
Mean	103.74	105.61	97.70
Std Dev	1.47	1.09	0.835
RSD	1.42	1.03	0.85
Specification Min 90% : Max 110%			

Samples	Top	Middle	Bottom	All Samples
Sample size (n)	10	10	10	30
% Mean	103.74	105.61	97.70	102.35
RSD	1.42	1.03	0.85	3.53
USP Criteria	85% - 115% mean ≤ 6% RSD	85% - 115% mean ≤ 6% RSD	85% - 115% mean ≤ 6% RSD	85% - 115% mean ≤ 7% RSD
Pass / Fail	Pass	Pass	Pass	Pass

Table B. Mean and relative standard deviation calculations for blend uniformity using FDA/USP criteria.

An obvious starting point for choosing a statistical model is to check references such as the pharmacopeia and regulatory sources such as the USP, FDA guidelines,[1,2] and a PDA technical report.[3] This article also will use extra statistical techniques such as Analysis of Variance (ANOVA), normality checks and process capability calculations.[4,5]

Blend Uniformity Content Results

The data used for this study are contained in Table A from a pilot plant development process. The content uniformity results were analyzed to decide if the process was suitable for full-scale manufacturing and validation. Ten samples were taken from the top, middle, and bottom of the blender after the mixing process had been completed. All samples were unit dose size and were tested in full by a validated chemical analytical method.

FDA/USP Criteria

The US pharmacopeia specifies for part of their content uniformity test that a sample of 10 tablets from a batch must give a mean between 85%-115% of the label claim and a relative standard deviation (RSD) of less than 6%. These limits only apply to the finished tablets. The solid blend specifications prior to compression are not subject to any pharmacopeia specifications. The FDA has issued guidelines for blend validation that are different and tighter than the USP values. The logic behind this policy is to make the blend more robust and improve the quality of future tablet products. The FDA blend criteria[1] require that a minimum of 10 samples be taken from the worst case positions in the blender and that the mean must be between 90%-110% of the label claim with an RSD of less than 5%.

The mean and RSD were calculated individually for the top, middle, and bottom of the blender, together with using all the sample values. The results in Table B for the 30 samples gave a mean of 102.35% and RSD of 3.53%. Both these values are well within the both the USP/FDA criteria, together with the results for the top, middle, and bottom of the blender.

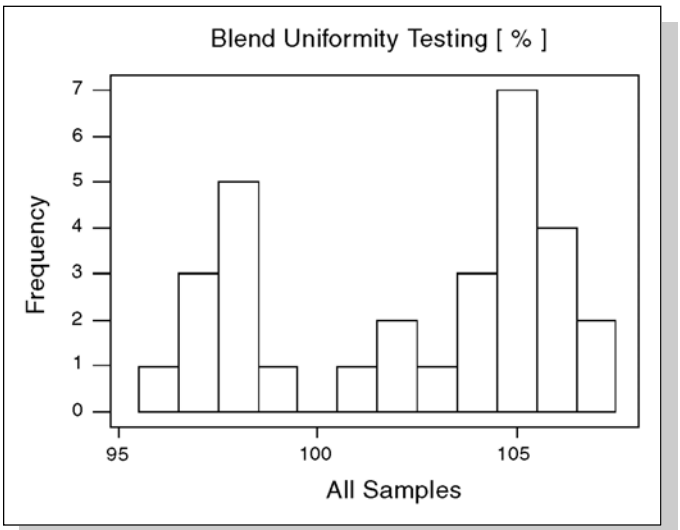


Figure 1. Histogram graph of the blend content uniformity results (from data in Table A).[6]

	SDPI	USP CU Test
Std Dev	4.403% (30 samples)	7% or less
Std Dev	3.841% (10 samples)	6% or less

Table C. Comparison of SDPI and USP content uniformity specifications.[3]

Of course another sample of 30 units would give different mean and RSD values. It would therefore be preferential if it were possible to predict with a high degree of assurance that future samples also would meet the USP and the FDA criteria.

It is possible by using confidence intervals to estimate the mean and RSD of the population. The 95% confidence interval using the 30 results for the mean[6] is 101.0 % - 103.7% and for the Standard Deviation[6] is 2.87- 4.83 [This corresponds to a confidence interval for the RSD of 2.81 - 4.74]. The above calculation gives added assurance that this blend meets the USP and FDA specifications.

PDA-SDPI Method

In 1997, a technical report was produced by PDA on blend uniformity analysis for tablet validation and in-process blend testing. This technical report was produced to illustrate different statistical methods that could be used for different blend conditions. The PDA also considered the sample size that should be taken when analyzing a blend, again a controversial issue since the landmark ruling made in the United States against Barr Laboratories.[7]

One suggested method for blend validation ignores the "mean" of the blend uniformity results and concentrates on the sample standard deviation. The assumption is that a large sample standard deviation indicates a non-uniform blend. The mean is not used due to the assumption that systematic errors due to sampling problems could affect the mean result. The Sample Deviation Prediction Interval (SDPI) allows one to predict, with a specified level of assurance, the standard deviation of a future sample from the same population.

This criterion is more stringent than the USP Content Uniformity specification as there is a need to build a high

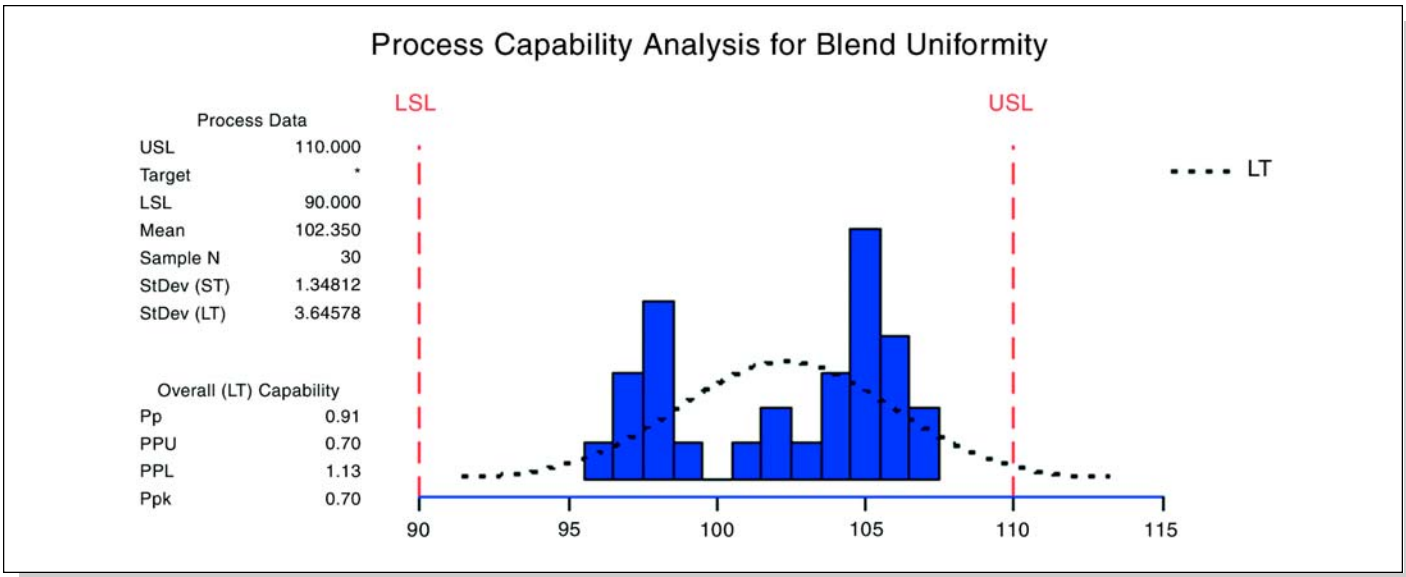


Figure 2. Long-term process capability analysis for content uniformity of the blend.[6]

degree of assurance that further samples will meet the USP criteria - *Table C*.

Conversely, as we move to larger sample sizes, the criterion is less stringent as we obtain more information about the underlying population.

An obvious concern is that this criterion does not use a measure of central tendency such as the mean. It also can be argued that this is one of the strengths of the method as it removes uncertainty due to sampling errors. The active drug distribution in the blend is the primary measure of the effectiveness of the blending operation. Standard deviation is an obvious choice to measure this distribution.[3]

Our data was then analyzed by the SDPI method suggested by PDA - *Table D*. The maximum allowable sample deviation is 4.403[3] (for sample size = 30) which is well above the 3.61 calculated from the blend results. Another variation on this method is to calculate the results from the top, middle, and bottom separately. Again, all results meet the SDPI criteria as shown in Table D.

The above results indicate that the validation has been successful. At a 95% assurance level, a future sample of 10 or 30 units from the blend will have an RSD of less than 6% and will meet the USP criteria.

Analysis of Variance (ANOVA)

Another statistical analysis that can be used is a one way ANOVA, which compares the means from the top, bottom, and middle of the blender. A uniform blend with no sampling errors should have all locations with similar mean values. The results of such a calculation are shown in Table E using the data from Table A. There is a significant difference between the top, middle, and bottom locations indicated by the ***p - value*** of 0.000[6] (a ***p - value*** equal to or greater than 0.05 indicates no significant difference). Since a significant difference has been found between the locations, the data must be analyzed further.

It is worth noting that the error variance in Table E (MS Error = 1.35) includes two components, namely variance due to the analytical method and variance due to the inherent inhomogeneity of the blend even at one particular location. This first component is assumed to be small because the analytical method has been validated. But in any case, the conclusions from these analyses are not challenged by the presence of the analytical variance because this makes it more difficult to detect differences between the blender locations. Despite the inclusion of the analytical variance, differences can still be detected between the blender locations.

In this case, a histogram of the data collected was constructed for all three sample locations to visually check if they are from a ***Normal*** population - *Figure 1*, which is one of the assumptions made for using an ANOVA analysis. The results plotted in Figure 1 suggest there are three populations present, shown by the three modes. A normality test gave a ***p - value*** of 0.000 indicating that the population is not normal.

The results in Table F show that the samples from the top of the blend are not normal as shown by the ***p - value*** of 0.008. The middle of the blender gave a ***p - value*** of 0.801 and the bottom, 0.524, indicating both are from Normal populations.

So far with this analysis, a difference has been shown in the uniformity between the locations tested. Now, the data must be analyzed to see if this will lead to out of specification results throughout the blend.

Sample	Top	Middle	Bottom	All Samples
Mean	103.74	105.61	97.70	102.35
Std Dev	1.47	1.09	0.835	3.61
Max Std Dev[3]	3.841	3.841	3.841	4.403
Pass/Fail	**Pass**	**Pass**	**Pass**	**Pass**

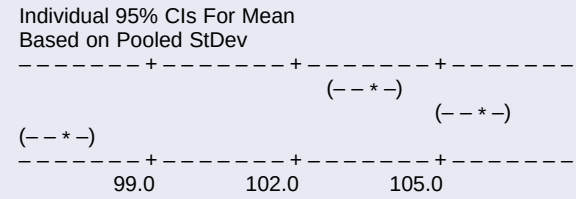
Table D. SDPI calculations for blend content uniformity.

Continued on page 58.

Analysis of Variance for Blend Uniformity

Source	DF	SS	MS	F	P
position	2	342.36	171.18	126.59	0.000
Error	27	36.51	1.35		
Total	29	378.87			

Level	N	Mean	StDev
Top	10	103.74	1.47
Middle	10	105.61	1.09
Bottom	10	97.70	0.84
Pooled StDev =		1.16	



N = Sample Size, StDev = Standard Deviation, SE Mean = Standard error of the Mean, CI = Confidence Interval
DF = Degrees of Freedom, SS = Sum of squares, Mean Square, F = *F - value*, P = *P - value*

Table E. ANOVA analysis of blend content uniformity results (from data in Table A).

Process Capability

A process capability index[6] was calculated using the data for the three blend locations. The results for the three locations will be the short-term capability indices as there are no sources of variation within the blend locations.

The results shown in Table G indicate that based on the variation within the samples from each of the three locations tested all the locations can produce products with the desired uniformity. Again, the result of the top of the blend is from a non-normal population so the result calculated may not be valid.

If this analysis is repeated on the blend samples as a whole, the long-term process capability can be determined[6]. In this case, we are looking at the variation between the three sample locations as well as within each location. The capability result shown in Figure 2 was calculated using the 30 blend sample results. The upper and lower specification limits are the in-house values of 90-110%. It is normally recommended to use about 150 results to get a reliable result for Process Capability analysis. This number of analytical results is not normal practice for pharmaceutical blend analysis. For this reason, the following result can be seen only as an approximation. The fact that we have shown a non-normal population in one of the sample locations will add further uncertainty.

The crucial value for the long-term capability analysis is the P_p value of 0.91 which is well below the 1.33 minimum acceptable value for a process. This means there is a high possibility of the blend producing out of specification results. The risk is that the blend results suggest a high probability of producing content uniformity values greater than the maximum specification.

Tablet Content Uniformity Testing

Content uniformity analysis also was carried out on the tablet batch after compression. Ten samples were taken at the beginning, middle, and end of the compression process. All the samples were analyzed and the results are recorded in Table H.

Sample location	Top	Middle	End
p-value	0.008	0.801	0.524
Result	Non-Normal	Normal	Normal

Table F. Normality calculations for the content uniformity results for the three blend locations.

USP Criteria

The results from the 30 samples in Table H gave a mean of 97.89% and a RSD = 2.20 - *Table I*. Both these values are well within the USP criteria of 7% for 30 tablets. These results also gave 95% confidence intervals for the mean and standard deviation of future samples. The interval for the mean is between 97.08%-98.68% and the standard deviation 1.70 - 2.88. [This corresponds to a confidence interval for the RSD of 1.74 - 2.94]. Using these confidence intervals gives a 95% assurance that future samples from this blend will meet both the USP mean and RSD criteria. The content uniformity results for the beginning, middle, and end of the batch also meet the USP criteria when analyzed separately.

PDA/Bergum's Method[3]

Bergum published a sampling table that could be used to give an assurance that a batch would meet the USP specifications based on a small sample. The method first requires a probability level be established for passing the content uniformity test, e.g. 95%.

The acceptance region for the sample will then be dependent upon the following:

- the probability level
- confidence level
- sample size

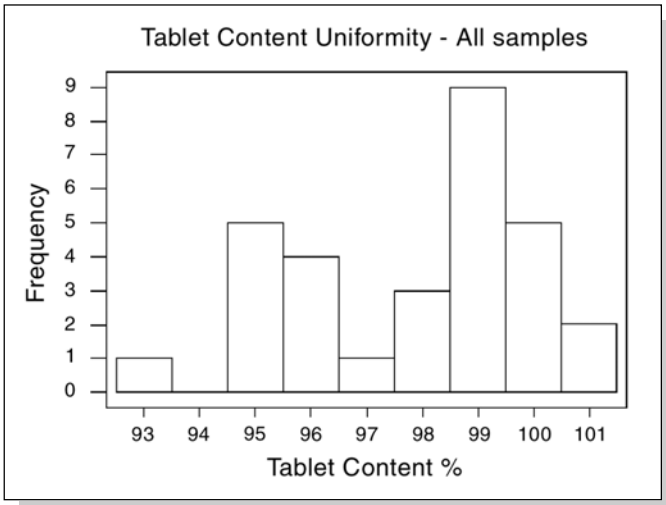


Figure 3. Histogram plot of the content uniformity results (using data from table H).

	Top	Middle	Bottom
Cp (short term)	1.83	2.26	5.81
Minimum Acceptable value	1.33	1.33	1.33
Result	Capable process	Capable process	Capable process

Table G. Process capability analysis for the blend content uniformity results (Short term).

Bergum's system is used by first calculating the mean and RSD for the content uniformity analytical results. The calculated RSD is then compared to a maximum allowable RSD as calculated by Bergum.

The content uniformity results for the batch were analyzed by Bergum's method. The maximum RSD allowed for a sample mean of 97.89% was 3.93%. The blend uniformity results were found to have a RSD value of 2.20% which is within the acceptance criteria. Another alternative is to analyze the beginning, middle, and end separately and all the results in Table J comply with Bergum's criteria.

ANOVA Analysis

A one way ANOVA analysis was then calculated comparing the means from the beginning, middle, and end of the batch. A well-behaved and uniform batch should have all locations with a similar mean. The results of such a calculation are shown in Table K, and there are significant differences for the samples tested at different times during the process as shown by the ***p - value*** of 0.035.

Both the USP and Bergum's methods indicate that the batch is acceptable. But the ANOVA shows there is a difference in the population means. This difference depends on the normality assumption as shown in Table L.

A ***p - value*** of 0.026 was found from the normality test indicating that the sample content uniformity results were not normal. Figure 3 clearly shows this, indicating at least two

Sample	Beginning	Middle	End
1	95.52	95.05	95.24
2	95.89	94.99	96.21
3	97.85	94.86	97.09
4	99.80	95.34	98.91
5	101.31	93.34	99.39
6	99.01	95.84	98.42
7	101.03	98.57	98.50
8	99.91	99.19	100.22
9	100.43	99.54	99.40
10	99.08	99.14	97.53
Mean	98.98	96.59	98.09
St Dev	2.00	2.27	1.56
RSD	2.02	2.35	1.59
Specification Min 90% : Max 110%			

Table H. Analytical results for content uniformity after compression (expressed as a Percent of the Target Concentration).

modes. This result casts serious doubt over whether Bergum's method or the USP criteria of using a mean and sample standard deviation can be used to validate this process. Further normality analysis showed that the middle of the batch displayed non-normal behavior with a ***p - value*** of 0.048 while the other two pass the normality test as shown in Table L. It could be argued that when carrying out so many tests, the 1% or 0.1% level should be used in preference to the 5% in order to avoid inviting Type I errors, hence the middle of the batch could be deemed normal.

A similar pattern can be seen between the blend sample results and those of the Tablet Content uniformity analysis, that is, the presence of possibly two or three populations and

Samples	Beginning	Middle	End	All Samples
Sample size (n)	**10**	**10**	**10**	**30**
% Mean	98.98	96.59	98.09	97.89
Std Dev	2.00	2.27	1.56	2.15
RSD	2.02	2.35	1.59	2.20
USP Criteria	**85% - 115% mean ≤ 6% RSD**	**85% - 115% mean ≤ 6% RSD**	**85% - 115% mean ≤ 6% RSD**	**85% - 115% mean ≤ 7% RSD**
Pass / Fail	**Pass**	**Pass**	**Pass**	**Pass**

Table I. Mean and standard deviation calculations for tablet content uniformity.

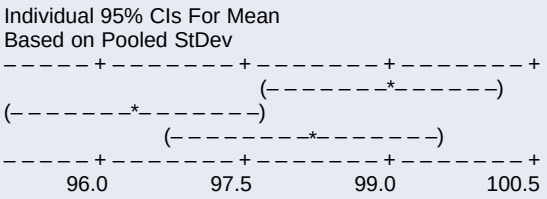
	Beginning	Middle	End	All
% Mean	98.98	96.59	98.09	97.89
Measured RSD	2.02	2.35	1.59	2.20
Max Allowable RSD	2.97 [n=10]	2.55 [n=10]	2.83 [n=10]	3.93 [n=30]
Pass / Fail	**Pass**	**Pass**	**Pass**	**Pass**

Table J. Tablet content uniformity analysis using Bergum's method for finished tablets.[3]

Analysis of Variance for Tablet Content Uniformity

Source	DF	SS	MS	F	P
position	2	29.35	14.68	3.79	0.035
Error	27	104.44	3.87		
Total	29	133.79			

Level	N	Mean	StDev
Begin	10	98.98	2.00
Middle	10	96.59	2.27
End	10	98.09	1.56
Pooled StDev =		1.16	



N = Sample Size, StDev = Standard Deviation, SE Mean = Standard error of the Mean, CI = Confidence Interval
DF = Degrees of Freedom, SS = Sum of squares, Mean Square, F = *F - value*, P = *P - value*

Table K. ANOVA analysis results - tablet content uniformity.

non-normal behavior in one of them. The process capability based on these samples, shown in Table M, is satisfactory for each of the three separate locations, but the long term value of 1.21 warns that out of specification product may be present at some time in the process.

Conclusion/Summary

The most important statistical test that should be performed on all validation content uniformity values is a normality check. Failure to satisfy normal behavior invalidates any conclusions that are made using the standard statistical techniques discussed in this article. Our recommendation is that all data must be tested for normal behavior before proceeding with any interpretation of the data concerning the state of the process.

Validation analysis demands a high degree of assurance and one of the most important statistical techniques that should be used is a "process capability" study. This involves plotting the individual data and non-normal behavior can be detected visually. There is a cost and resource implication as such a study requires taking at least 150 samples from a process.

Using both the USP and FDA statistical criteria alone for process development statistics is not recommended. Their mean and RSD values are sample statistics only. Both methods could be made more reliable by using confidence intervals to make assertions about the properties of the entire batch.

Bergum's method is to sample the batch and estimate whether future samples will meet the USP criteria. It is not as straight forward to use as the confidence interval method and is used primarily to see if future samples will meet the USP criteria. It does not predict that all future individual units in the batch will meet the specification.

The SDPI method gave results that showed future blend samples would meet the USP deviation criteria. This method did not take into consideration the mean value which is still a USP requirement. This method is applied assuming the mean of the blend content uniformity results could be affected by sampling problems, and therefore does not need to be calculated during blend validation. There is a risk that future tablet batches could fail the mean criteria and be rejected. This is a high-risk assumption to make for a validation study which must give a high degree of assurance that all batches will meet the predetermined specifications.

The ANOVA gave valuable information concerning the means at the different locations within the blend and during the compression step. The differences between the means during compression cannot be explained by sampling problems and indicate a non-uniform process.

Sample location	Beginning	Middle	End
p-value	0.263	0.048	0.693
Result	Normal	Non-Normal	Normal

Table L. Normality test calculations for different sample locations.

List of Abbreviations

ANOVA - Analysis of Variance
Cp - Short Term Capability Index
Cpk - One Sided Short Term Capability Index
FDA - Food and Drug Administration
LSL - Lower Specification Limit
PDA - Parenteral Drug Association
Pp - Long Term Capability Index
Ppk - One Sided Long Term Capability Index
RSD - Relative Standard Deviation
SDPI - Sample Deviation Prediction Interval
TYPE I Errors - Rejecting a Good Batch
USL - Upper Specification Limit
USP - United States Pharmacopeia

	Beginning	Middle	End	All
	Cpk = 2.38 (Short-term)	Cpk = 2.49 (Short-term)	Cpk = 2.38 (Short-term)	P_{pk} = 1.21 (Long-term)
Minimum Acceptable Value	1.33	1.33	1.33	1.33
Result	Capable process	Capable process	Capable process	Incapable process

Table M. Process capability analysis for the content uniformity results after compression.

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This article describes common practices related to the design of storage and distribution systems for USP Purified Water and Water for Injection. Special attention is given to the issue of microbial control in such systems.

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Pharmaceutical Purified Water Storage and Distribution Systems - an Engineering Perspective

by Leonid Shnayder, PhD, PE

Introduction

Purified water is one of the key components in most pharmaceutical manufacturing facilities. It is natural that water purification systems and systems used to store and distribute purified water throughout these facilities draw a lot of attention from engineers, regulators, and operating personnel. Many engineering and manufacturing practices have been developed over the years to improve and maintain the quality of the water.[1-3] However, there are still many misconceptions among industry professionals about those practices, mainly about relative importance of various factors affecting system design and performance. The purpose of this article is to shed some light on the underlying principles for the design of purified water storage and distribution systems and to take as much mysticism out of the design as possible. Since the requirements and design practices for USP Purified Water and for Water for Injection are quite similar, we will discuss purified water systems in general, and point out the differences between the grades where applicable.

USP Purified Water and WFI Quality Requirements

The current edition of US Pharmacopeia[4] establishes the following requirements for the USP Purified Water:

- purified water is prepared from water complying with the standard for drinking water.
- contains no added substance
- is obtained by a suitable process
- conductivity does not exceed set level
- Total Organic Carbon (TOC) does not exceed set level.

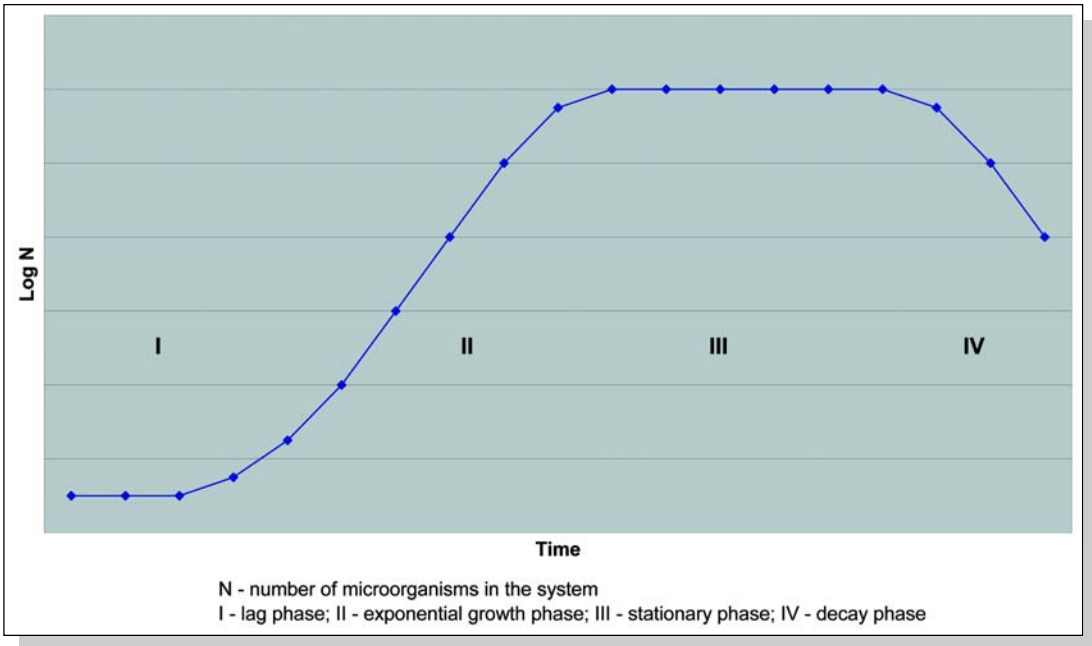

Figure 1. Typical microbial growth curve.

The requirements for Water For Injection (WFI) are:

- meets all the requirements for "Purified Water"
- is obtained by distillation or reverse osmosis
- contains not more than 0.25 USP endotoxin units per ml
- is prepared using suitable means to minimize microbial growth

USP does not specify allowable concentration of microorganisms in the official monograph, but recommends action limits of 100 colony-forming units per ml (CFU/ml) for purified water and 0.1CFU/ml for WFI. USP also does not address non-ionic, non-organic contaminants such as silica that have impact on the overall water quality, and are usually removed in the purification process.

Putting aside the items related to the source water and treatment procedures, the requirements for Purified Water itself can be summarized as follows:

1. Low conductivity (high resistivity). Water shall contain a minimal amount of ions other than H^+ and OH^-. The inherent presence of those two ions determines the theoretical limit of purified water conductivity: approximately 0.05 µS/cm (resistivity18 megohm-cm) at a pH of 7.0. The practical limits specified in the USP are in the range of 1 to 5 µS/cm depending on pH and temperature.

2. Low TOC (less than 500 ppb). Water shall contain minimal amount of organic compounds. Such compounds are undesirable for two main reasons: they may be toxic and/or may serve as sources of nutrition for microorganisms.

3. Low microbial count. Water shall contain minimal amount of viable microorganisms, including spores.

4. Low endotoxin level (required for WFI only). The term "endotoxin" applies to organic compounds that cause harmful effect when injected in the bloodstream of laboratory animals. Such compounds can be produced as a result of microbial growth or microbial destruction ("dead bodies" of bacteria).

Factors Affecting Water Quality in Storage and Distribution Systems

Further discussion assumes that water leaving the purification system and entering the storage tank meets all of the above requirements either for USP Purified Water or WFI. The goal when designing and operating the storage and distribution system is to keep the water at these purity levels, preventing any of the four parameters listed above from exceeding allowable limits during storage. Some of the engineering practices used to achieve this goal are presented below.

a) Prevention of ionic contamination (increase in water conductivity)

Storage tank, piping, pumps, and other components of the system in contact with the purified water shall be made out of materials that are chemically resistant to such water and would not introduce metal ions or other contaminants. The most common material used in the pharmaceutical industry is 316L stainless steel although in the last few years, such plastics as polyvinylidene fluoride (PVDF) and polypropylene also have gained wide acceptance. Material selection will be discussed in more detail later in this article.

b) Prevention of physical entry of foreign particles and microorganisms

The typical steps taken to prevent foreign particles and microorganisms from entering the purified water in the storage and distribution system are:

- provide a sterilizing grade (0.22 micron) vent filter on the storage tank
- maintain positive pressure in the distribution piping (and sometimes in the storage tank as well)
- provide double mechanical seals for the system's pumps, using purified water as a seal flush fluid
- utilize heat exchangers of sanitary design with double tube sheets

c) Prevention of microbial growth

Since above mentioned measures are not 100% effective in avoiding microbial entry, it is necessary to design a system that will not allow microorganisms to grow and multiply once they are in the purified water. It is important to understand that one or two or even ten microorganisms found in a thousand gallons of purified water do not in any way compromise its quality - unless you allow them to grow and to become too numerous. This issue of microbial growth prevention presents probably the biggest challenge to engineers and operating personnel, and causes most concerns and arguments about the acceptable ways to design the system. Various aspects related to microbial growth will be reviewed in the following sections.

Factors Affecting Microbial Growth

Microorganisms, like any other living organisms, can grow and multiply only if they have enough food and the environment is comfortable for them to live. In fermentation processes and other cases where growth of microorganisms is the goal, system designers try to create conditions favorable for microbial growth. That typically involves having media containing sources of all main nutritional components (organic carbon, nitrogen, phosphorus, microelements etc.), sufficient supply of oxygen (for aerobic organisms), temperature, and pH optimal for the particular type of microorganisms (usually in the range of 25 to 37°C and pH 4 to 8). Under such optimal conditions, many microorganisms can grow quite rapidly: the fastest growing bacteria can double the number of cells or biomass concentration in 10 to 20 minutes. However, when conditions are not optimal, the microbial growth slows down dramatically or stops altogether. Growth of microbial culture also stops when available source of food is used up, or when media contains growth inhibitors or disinfectants. A typical growth curve (Figure 1) includes a lag phase (when microbes do not multiply, but adjust to the new environment), exponential growth phase, stationary phase (when rate of new growth is offset by the rate of microbial death), and the decay phase (when the rate of cell death is higher than the rate of growth).

In dealing with the purified water systems, the goal is to create the conditions least favorable for microbial growth so that organisms that managed to enter the storage system will not survive or at least will not multiply to unacceptable levels. One of the factors affecting the growth rate - food availability - works against the growth because pharmaceutical grade water contains very little organic carbon, nitrogen, or other nutritional components. Other factors, however, may favor microbial growth: pH of purified water is usually close to neutral, and there are no growth inhibitors or disinfectants (such as chlorine) in the water. That might allow some organisms to grow if left unchecked for a long period of time.

Microorganisms in purified water systems usually form a biofilm on the internal surfaces of the storage tank and piping.[5] This creates additional difficulties in detecting and controlling microbial growth.

There are several ways to approach microbial control in purified water systems:

- maintain water at an elevated (65 to 85°C) or reduced (4 to 10°C) temperature to suppress microbial growth
- periodically sanitize the system by hot water, steam, ozone, or by other means
- utilize an UV light installed in the distribution loop to continuously sanitize the water stream.

Two of the most common types of the purified water systems are hot (65 to 85°C) and ambient systems. Let's consider them in more detail.

Hot Purified Water Systems

One of the common types of storage and distribution systems for purified water, mostly used for Water for Injection, is the hot system - *Figure 2*. Water in the tank and in the distribution piping is maintained at an elevated temperature, usually about 80°C. No microorganisms can grow at such temperature even if there are enough nutrients in the water. All vegetative forms of microbes are killed at such temperature. Some heat-resistant spores may survive for a long time, but spores do not grow: they need to get into a favorable growth environment and develop into a vegetative form before the organism can grow and multiply. Therefore, as long as we can assure the absence of "cold spots" (anything below 60 - 65°C), the system is safe from a microbial perspective. Here are some commonly used design features intended to achieve this goal:

- Water in the distribution piping should be constantly flowing to stay hot.
- There should be no "dead legs" (stagnant zones such as branch lines) in the piping long enough to allow standing water to cool below 60 - 65°C.

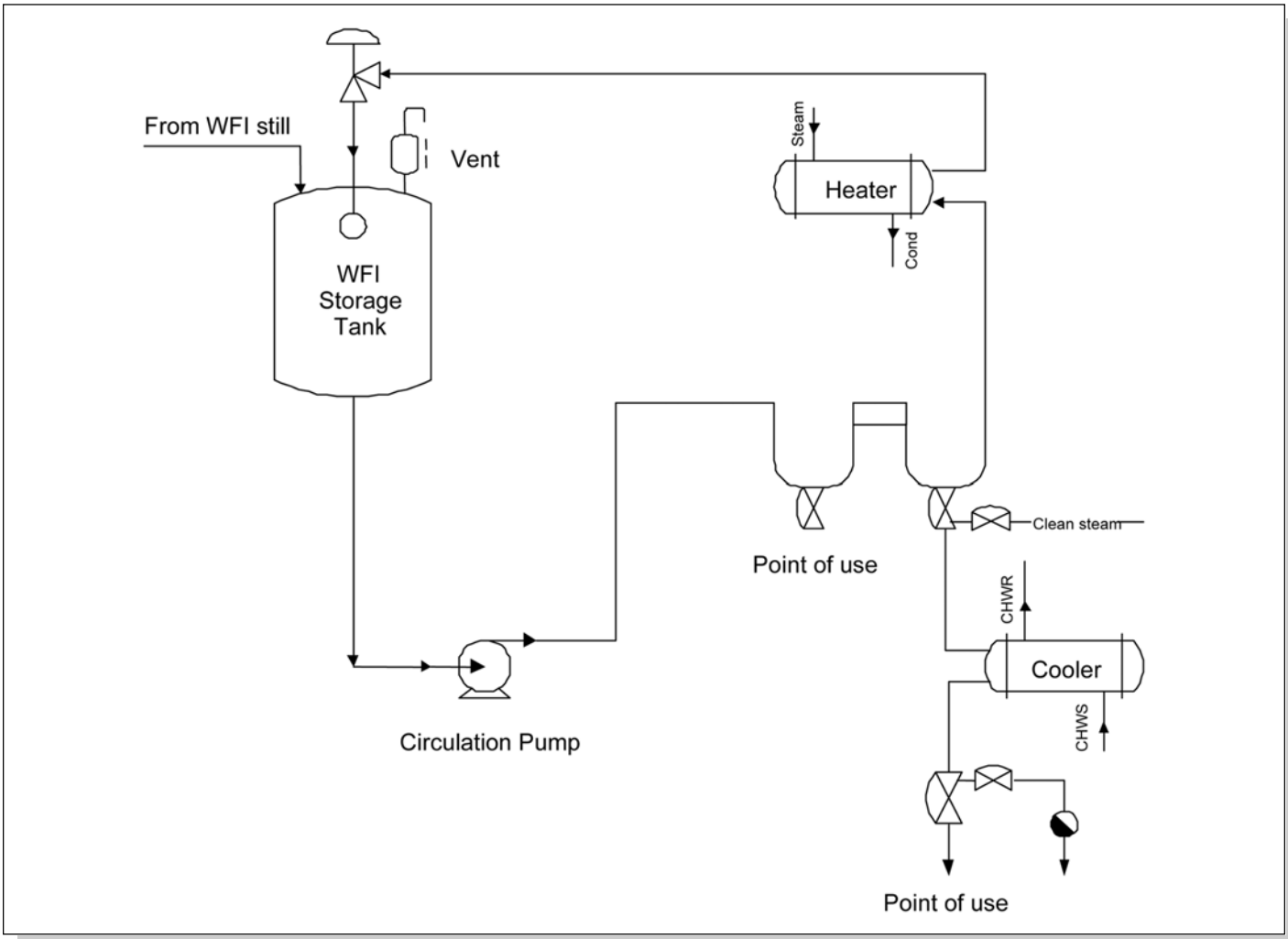

Figure 2. Hot storage and distribution system with point of use cooler.

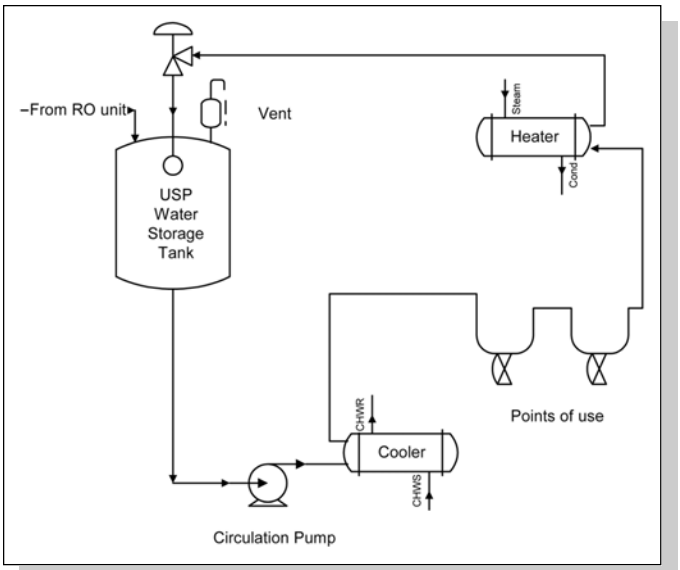

Figure 3. Ambient storage and distribution system.

- Circulation pumps should be designed so that all parts in contact with water remain hot. A stand-by pump (if installed) should be isolated when not in service.

- The vent filter on the storage tank should be heat traced to stay hot - this is necessary both for microbial control and to prevent moisture condensation.

- The top head and walls of the storage tank should be continuously flushed with circulating hot water to remain hot and clean. Special attention should be given to nozzles on the tank's top head.

- The storage tank should be insulated.

If the storage and distribution system has one or more zones that remain "cool" for extended periods of time (days or weeks, not minutes or hours), it is likely that some microorganisms will find their way there and start growing, producing endotoxins as a by-product. These endotoxins as well as some of the microbes will then migrate into the main water stream and get distributed throughout the system. The microbes that get into the hot water will be killed, releasing more endotoxins as a result.

Ambient Purified Water Systems

As the name suggests, the purified water in the ambient storage system is maintained at room temperature. The growth of microorganisms and accumulation of endotoxins is prevented by periodic sanitization of the system, most commonly by heat (Figure 3) or by chemical sanitizer such as ozone - *Figure 4*. In order to understand how and why this approach works, a case will be reviewed in which a limited number of microorganisms had penetrated into the system. Once a group of microorganisms is introduced in a new environment, it experiences a lag phase of no growth from 10 minutes to 10 hours or longer. Microbes use this time to adjust to a new environment, and to produce enzymes necessary for metabolizing available food sources. Microbial culture then moves into an exponential growth phase where the number and/or mass of microbial cells increases at a constant specific growth rate. For commercial microbial cultures, such a rate varies from less than $0.01 hr^{-1}$ to $2 hr^{-1}$ - that corresponds to a duplication time of 0.3 hr to 70 hrs. These numbers are typical for processes where microbial growth is a goal, and the media contains all necessary nutrients added to support it. Naturally, in purified water systems, both lag phase and duplication time for any contaminating microorganisms are likely to be much longer because nutrients are very scarce, initial cell concentration is very low, and temperature is not optimal for growth of most microorganisms.

Based on the above, if contaminating microorganisms are introduced into ambient purified water storage systems and left alone for several hours, no detectable growth would occur. They will need enough time to go through the lag phase and then through multiple generations of the exponential phase before growth or endotoxins accumulation can be detected. Such time is likely to be measured in days or weeks. This permits effective operation of purified water systems at ambient temperatures, as long as the systems are periodically sanitized. Sanitization frequency depends on the water quality requirements (i.e. WFI versus USP Purified Water) and the degree of the system's "closeness." Sanitizing a system once in 24 hours is more than satisfactory for most cases, and experience has shown that sanitizing once a week is often sufficient.

The main criterion for the design of ambient purified water systems is therefore, the system's ability to be completely sanitized either with heat or ozone. One approach is to design the system exactly the same as a hot system, but keep the heater off most of the time. Once the heater is turned on for periodic sanitization the same "no cool zones" requirement as for the hot systems shall apply.

Other Design Features

In addition to the design characteristics listed above, there are many other features typically found in the pharmaceutical water storage and distribution systems. Among them are:

- use of highly polished sanitary tubing

- orbital welding for tubing and most fittings

- piping sloped a minimum of 1/8" per foot (10 mm/m) to assure complete draining of the system

- liquid velocity of 5 ft/sec (1.5 m/sec) or higher in the circulation loop; 3 ft/sec (0.9 m/sec) or higher in the return section of the circulation loop during peak usage

- It is fairly standard to limit piping "dead legs" at the water use points to four to six pipe diameters of the branch line. Point of use drops are often configured with "zero-static" or similar valves.

While these features have become commonplace in the pharmaceutical industry, it is important to understand that there is nothing sacred about them. Unlike the characteristics necessary to prevent microbial contamination and growth as discussed earlier, these features often belong to the "nice to have" category. For instance, the use of highly polished distribution tubing has minimal if any effect on the water quality and is not absolutely necessary here. As strange as it might seem, this is particularly true for the most critical WFI storage and distribution systems operating at elevated temperature

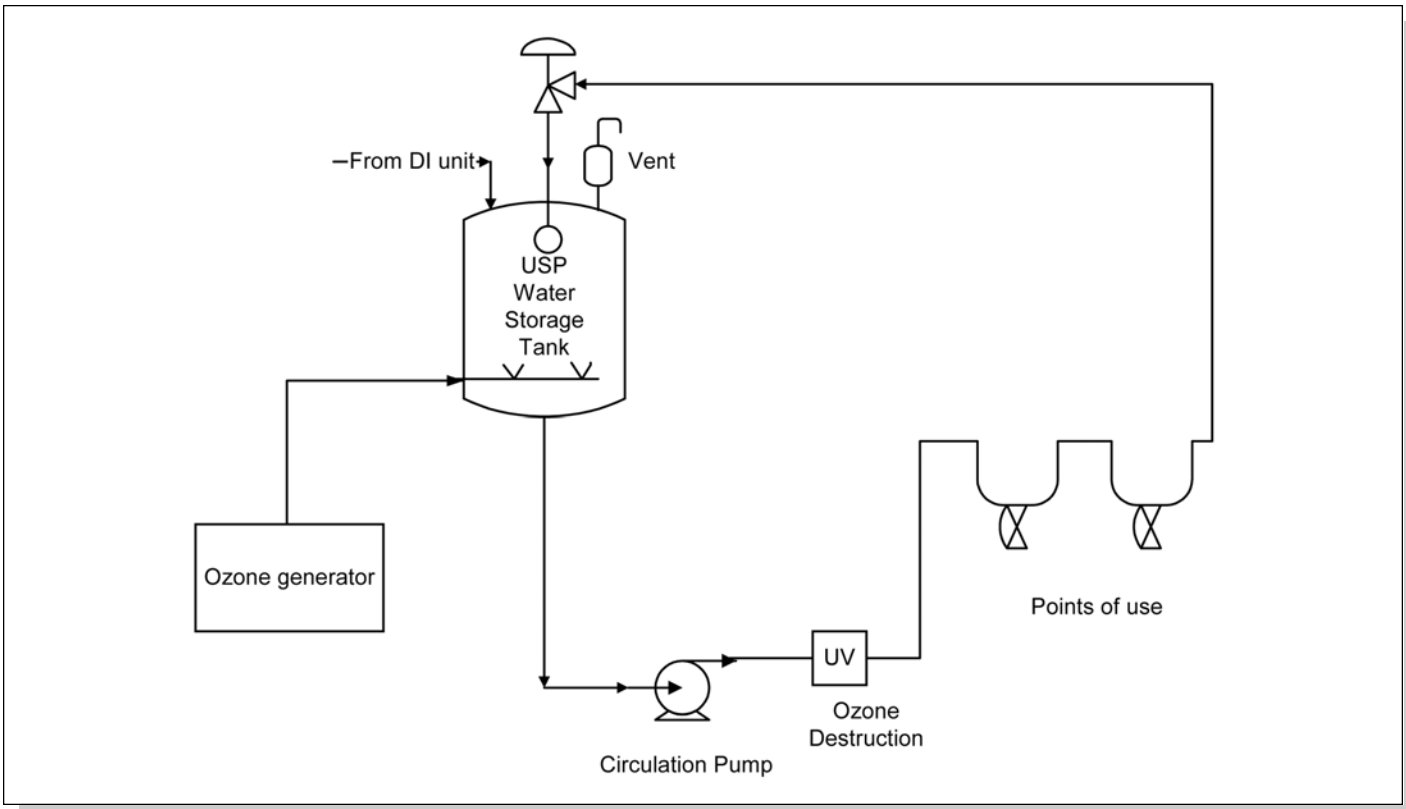

Figure 4. Ambient storage and distribution system with ozone sanitization.

(80°C). There is certainly nothing wrong with high polish, and it has better appearance, but if the project budget is limited, this is one place where lower cost options (such as mechanically polished tubing with 25 - 30 microinch roughness average) may be selected without negative effect on the product quality. The same can be said about the circulation velocity. Although engineers and designers normally use 5 ft/sec (1.5 m/sec) velocity as a "rule of thumb," do not assume that a circulation loop designed for 4 ft/sec (1.2 m/sec) velocity is "non-GMP" or "non-validatable."

Good Manufacturing Practice guidelines do not specify liquid velocities or surface finishes. They require that equipment, piping and facilities be designed and operated in a way that assures clean conditions appropriate for the pharmaceutical product. It is up to the engineer to select specific design parameters and features while staying within these broad guidelines. In particular, when deciding on the design liquid velocity for a purified water loop, engineers should be concerned primarily with the system's ability to prevent microbial growth by maintaining high water temperature throughout the loop (either constantly or during periodic sanitization). For systems designed with relatively long "dead legs" at the points of use (up to 6 pipe diameters), it may very well require 5 ft/sec (1.5 m/sec) velocity to create enough turbulence in those branches so that "cool spots" are avoided. If however "zero-static" type point-of-use valves are specified, then 1 ft/sec (0.3 m/sec) line velocity will most likely be enough to keep them hot.

Some designers believe that maintaining 5 ft/sec (1.5 m/sec) or higher velocity helps control the biofouling by physically shearing the microorganisms from the piping wall. This notion, however, is not supported by experimental results or analysis of the fluid dynamics.[6,7]

Material Selection

Selection of proper materials of construction for purified water system components deserves special attention. The two major groups of materials used in such applications are austenitic stainless steels (typically 316L) and thermoplastics such as polypropylene and PVDF. While plastic materials are prevalent in purified water systems for semiconductor manufacturers, common practice in the pharmaceutical industry still reflects predominant use of stainless steel. The main advantages of the stainless steel systems are mechanical strength within a wide temperature range, and a low coefficient of thermal expansion. This simplifies equipment and piping design and allows sanitizing of the system with hot water or steam. The disadvantages are the high cost of sanitary stainless steel equipment, components and tubing, susceptibility to rouging in high purity water, and the need for periodic chemical passivation to restore the oxide film that provides stainless steel with its corrosion resistance.

On the other hand, thermoplastic systems are lower in initial cost, and because of their light weight, less expensive to ship and install. They offer complete resistance to corrosion, no potential for metallic contamination of fluids, elimination of the equipment, labor and chemicals required for passivation, and extremely smooth internal surfaces without polishing. The concerns about leachout of contaminants from the plastic pipe have been alleviated by extensive testing conducted by the major suppliers of virgin unpigmented thermoplastics recommended for sanitary applications.

In terms of installed cost, typical piping systems in polypropylene run about 50% less than those in stainless steel, and PVDF systems about 25% less than the metal systems. However, the cost differential becomes much greater when we factor in the overall system costs due to less expensive thermo-

plastic pumps, valves, and other engineered components. In addition, plastic systems do not require the passivation operations and other costs associated with the storage, transfer, processing, and handling of the hazardous chemicals and waste materials. Due to these and other advantages, thermoplastic materials of construction are gaining acceptance in the pharmaceutical industry for purified water applications.

Both polypropylene and PVDF can technically meet the service conditions discussed above. It shall be noted however, that the fluoropolymer PVDF is the preferred material for use in the hot (80°C) purified water systems, or in the systems that are sanitized by the hot water. Although polypropylene has an upper temperature rating of 85°C, designers are naturally reluctant to specify this material so close to its upper limit. The higher temperature rating of PVDF (135°C), and its suitability for use in both hot and cold systems as well as its broad chemical inertness gives it an edge despite its higher cost. The use of polypropylene piping and components is therefore typically relegated to those systems that operate at ambient temperature and are sanitized by chemical sanitizers. Some companies use ozone to sanitize plastic piping systems although its strong oxidizing action tends to make plastics brittle over time.

Conclusion

There are many types of purified water storage and distribution systems used in pharmaceutical facilities. While most of them share common features, each system is custom designed for a specific application. Developing the proper design requires good understanding of system operation and careful attention to details. Simply following common "rules of thumb" does not necessarily guarantee a reliable system - no matter how much money is spent. On the other hand, with good understanding, it is often possible to design, install, and validate a functional and reliable purified water storage and distribution system with less capital investment, lower operating costs, and improved workplace conditions.

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