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Plant-Centric Integration - A Value Proposition for Pharmaceuticals

by David E. Woll

The business environment of the new millennium will not be a place for the "faint of heart." More than ever before, data, information, and knowledge will need to be timely, accurate, and presented in perspective. This article discusses a proposal for business unification and information empowerment that supports those requirements.

Preface: The author is an analyst at the ARC Advisory Group, a marketing and consulting organization exclusively focussed on manufacturing and business automation. ARC's extensive research both independently and cooperatively with clients is the basis for benefits, costs, and projections in this article. Consistent with the theme of this issue, this article is a statement of ARC's vision of automation's contribution to optimal business performance in the new millennium. Plant-Centric refers to the plant side of Supply Chain Management integration.

Like it or not, we are facing a social and business revolution that will rival anything in history. Sometimes called progress, this revolution is being driven by fundamental changes in the demographics of our society and information technology in our private and business lives. From a business perspective, processes that depend upon hierarchical structures and control of functions will fail. Companies will no longer be measured by their revenues, but by their strategic advantage. If companies do not adapt, their cost structures will get out of line and they will not be able to compete.

Companies need to gain their strategic advantage through knowledge workers and the degree of advantage will depend upon their ability to empower them. Companies need to be smaller, more distributed, and focussed on their core competencies. Collaboration will be critical. Business will not be a place for "the faint of heart." Risk aversion is not an option, decisions need to be made in real-time, management needs to make a lot of bets, some will fail, but failure will spawn success. More than ever before, this new world will require accurate and timely information presented in views that precisely correlate to the decision at hand.

Achieving Optimal Business Performance (OBP) is the key to thriving in the next millennium. The on-going restructuring of business along with the information technology revolution provides the basis for change. This article will discuss the challenges and propose solutions for the pharmaceutical industry.

The Pharmaceutical Industry Challenge

More than any other industry, the pharmaceutical industry finds itself on the horns of this dilemma. The good news is changes in demographics will dramatically expand the pharmaceutical market. The bad news is this demand drives R&D with costs that do not correlate with revenues, product life cycles become shorter, competition intensifies and a shakeout is on the horizon. Clearly, business performance will dictate the winners. We will discuss this objective in terms of OBP. Also, it goes without saying that this industry is burdened with extraordinarily high R&D costs, this article does not address that issue, and OBP

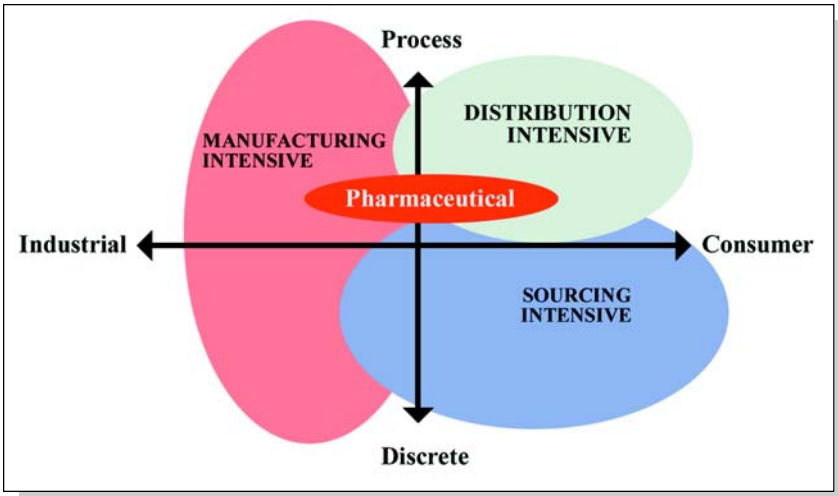

Figure 1. Supply chain positioning.

TOTAL PRODUCTION AND LOGISTICS COST		
ROI BUCKETS	**DESCRIPTION**	**PROJECTED IMPROVEMENT**
Conversion	Cost to convert raw materials to finished goods	5-15%
Asset Utilization	Percentage of time assets are in use	10-20%
Right First Time	Percentage of time what was made was what should have been made	15-20%
Product on Spec Thruput	Percentage of time the required product was produced to the required specifications	10-20%
Adherence to Schedule	Once a schedule is prepared, what percentage of the time is it adhered to?	60-90%
Inventory Turns	Time period measurement from order placement to order payment	5%
SC Cycle Time	Time period measuring the time it takes to convert raw materials into finished goods	40-60%

Figure 2. Typical benefits.

will deal strictly with supply chain issues.

OBP simply means doing more with less. This equates to higher profits and lower costs. The premise of this article is that in the next millennium, OBP can only be achieved when business processes are unified with manufacturing processes. The value proposition is based upon the understanding that a typical pharmaceutical company's manufacturing costs represent 60-70% of total supply chain costs and in today's world since less than 10% of the pharmaceutical companies have even attempted a tight integration of plants there is a real opportunity to improve performance. The value is derived from the fact that: the "value added" in manufacturing is the cornerstone of company performance, manufacturing data is critical for business systems whose primary function is to convert this value added into profit, this data inherently contains relationships that can be used to optimize the process of adding value and optimal supply chain management requires synchronization of business and manufacturing systems.

It is true that in terms of net return on investment, the pharmaceutical industry has done better (36.7%) than the rest of the process industries. However, that also implies that the pharmaceutical industry knows how to use automation tools effectively and could further benefit from them given the opportunity. Figure 1 shows a traditional map of Supply Chain functions. The pharmaceutical industry requirements position it optimally to benefit from Plant-Centric integration. This is partially a result of pharmaceutical manufacturing being a blend of process manufacturing in the bulk plants and discrete manufacturing in the fill/finish plants. In this context, Figure 2 shows the nature and magnitude of the benefits realized in a typical successful Plant-Centric integration project.

At the heart of the Information Revolution is information empowerment and the latest sound bite in this context is e-Business. With this in mind ***we propose that the e in e-Business stands for empowerment, the empowerment of knowledge workers in the Information Revolution.*** In business, information empowerment has a number of benefits. For example, when customers feel in-control, barriers come down and they are more open to purchasing. Suppliers benefit by better targeting prospective clients and having enough information to make their "best offer." Management and their staff benefit through activity based costing, accurate information when they need it in the form they can use, and also by the feedback they receive on performance correlated to business strategy. Finally, investors benefit from enhanced shareholder value from improved performance.

Information empowerment in business has two barriers,

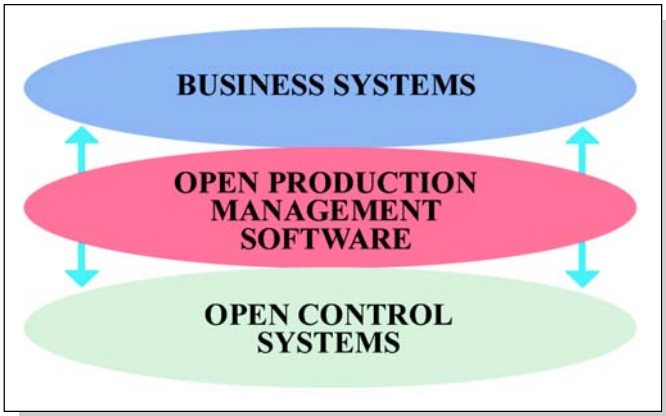

Figure 3. Hierarchy.

the first is between business processes and manufacturing processes (B2M), and the second is between businesses (B2B) in the extended enterprise.

The Business to Manufacturing Barrier

The B2M barrier has both an understanding aspect and a technology aspect. The understanding aspect is a result of how corporate and plant people look at *time*, *information*, *workflow execution*, and their own *culture* differently. Corporate people look at time in terms of months, days, weeks, and hours. Plant people also look at time in terms of seconds and milliseconds. Corporate people look at information on a transaction basis while plant people look at information related to real-time data and events. Workflow at the corporate level is planning and scheduling oriented, but in the plant workflow is control and engineering oriented. Finally, the culture at the corporate level is driven by business processes, but at the plant level it is governed by the physical processes associated with unit operations. The second aspect, the technology aspect, carries with it both accessibility requirements and timeliness requirements. In terms of accessibility, *any* information should be

Figure 4. Common component.

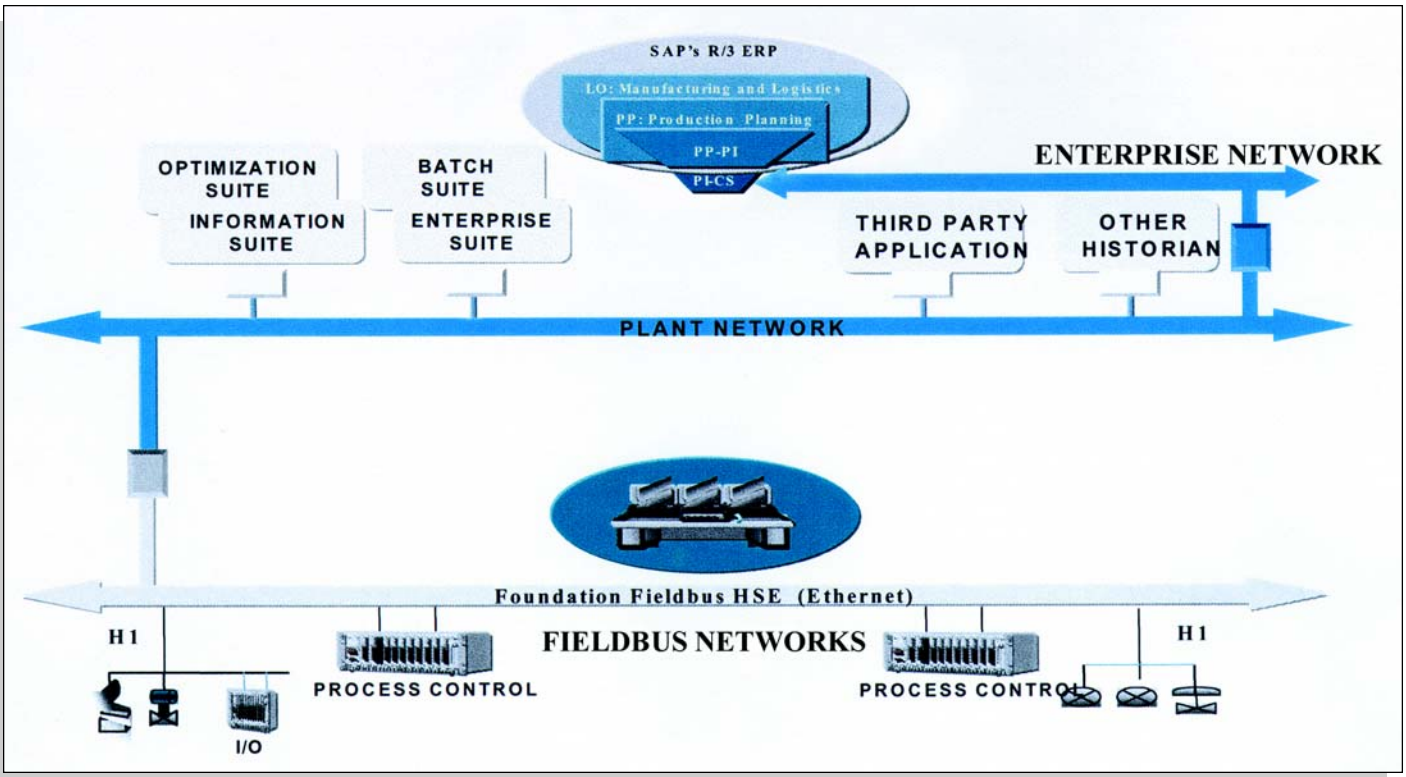

Figure 5. Single environment.

available to *any* valid user from *any* location at *any* time. The access mechanism should be consistent and the presentation should correlate to the information's use. The timeliness requirement deals with the concept of synchronization. Simply stated synchronization does not mean time synchronization. Synchronization is the requirement that a user of information has that information in time to perform his operation and deliver the result in time to satisfy his customer. Synchronization may require a split second, daily or other response, depending upon the application. Actually, synchronization is a more precise term for this topic than integration. The technology discussion is more of a nuts and bolts discussion. The problem with integration both across manufacturing and between manufacturing and business is diversity, a result of having to deal with a large number of disparate devices and point applications with no common mechanism to act as the foundation of this integration. Currently, this is still the case, but emerging and available technology will change the situation. The following discussion is based on the evolving solution.

Looking forward some integration guidelines are appropriate. Networking and connectivity choices should be based upon *standards*. Integration should make minimal use of custom interfaces or "*gateways.*" Application *"bridges,"* if required, should be owned and maintained by the supplier and licensed to the user.

In a typical process plant, an intermediary class of software called Production Management spans the gulf between business systems and process control systems. These applications are actually part of control, but they are supervisory in nature, operate in near real time, and are not deterministic. For these reasons, it makes more sense to make Production Management the touch-point between business and control systems.

Both Production Management and Control have the same functional requirements for horizontal and vertical integration with different criteria. However, the environment and criteria influence how these functional requirements are being addressed. In Production Management, the technology of choice is component technology. This is primarily a result of the supervisory nature of the software and the need to be transparent to the Microsoft Desktop. In Control, the emerging technology with the greatest promise is Foundation Fieldbus. This is driven by the unique timing and security requirements of process control. Both of these technologies are an intermediate step so it is valuable to understand how each of the criteria is addressed in each environment. This understanding will serve as a basis to relate to the more comprehensive solution. In terms of data access, it is common across Production Management and across Control, but not transparent between Production Management and Control. The same situation applies to presentation. In the case of objects, in Production Management, the object normally is COM and the equivalent in Control is the Function Block. An important criterion for users is where each approach stands relative to standards. In the case of Production Management, COM is a Microsoft defacto standard. In the case of Control, the Function Block is a part of the Foundation Fieldbus standard. The difference in how applications are executed is a result of the environment they have to satisfy. In Production Management, the supervisory nature of the application is well served by an instruction driven approach while in control applications require a data driven approach. These approaches satisfy the criteria for horizontal integration across each environment, but it still leaves three environments and does not satisfy our requirement of global data access. We believe that this technology will set the stage for a merging of the Production Management environment and the Control environment as a result of the adoption of a common component model, common messaging,

> *In a typical process plant, an intermediary class of software called Production Management spans the gulf between business systems and process control systems.*

using a common communications backbone, and shared services. Most likely, the common component model will be based upon OLE for Process Control (OPC) to satisfy the MS desktop transparency requirements and the common messaging will be Extensible Mark-up Language (XML) to satisfy enterprise application integration requirements since it is the emerging standard at that level. The result of this level of integration is a single environment that can satisfy our requirements for information access and presentation from control systems through business systems. This configuration is shown in Figure 5.

Many times in a large pharmaceutical facility there is the requirement for a high level of coordination between application running primarily at the Production Management and Enterprise levels. This is typically the case where there are as many as 150 at the plant level, and up to 1500 across the enterprise. In this situation, a Data-Stor is a valuable tool for workflow integration and to serve as a common source of data for applications. The Data-Stor is not necessarily a redundant repository, it can be, but more commonly it serves as a metadata model which either provides data directly or provides a pointer to the primary data source. The Data-Stor also satisfies the requirement of the Production Management and Enterprise level applications to provide a "Dynamic Plant Production Model." This is critical in Supply Chain Management applications where accurate finite capacity, scheduling and loading is required.

The Second Barrier - the Extended Enterprise

The second barrier that needs to be overcome is the information barrier between businesses (B2B). Projections are that B2B will grow from $40 billion in'98 to $1000 in '03. B2B for production goods will ultimately be the largest between production goods and non-production goods, but it is being hindered by the absence of a standard for electronic signatures and contracts. B2B for non-production goods and services along with Material, Repair, and Operations (MRO) is the current opportunity. Keep in mind the extended enterprise is an opportunity for you as both a supplier and a buyer.

As a supplier, it gives you the opportunity to extend your business processes to include your customers, partners, and suppliers giving them the option to use your applications, systems, and data for mutual benefit. For example, a customer can create a transaction without any direct contact with your staff. If your primary supplier sees your inventory is low, they can initiate a proposal for your approval at the same time that

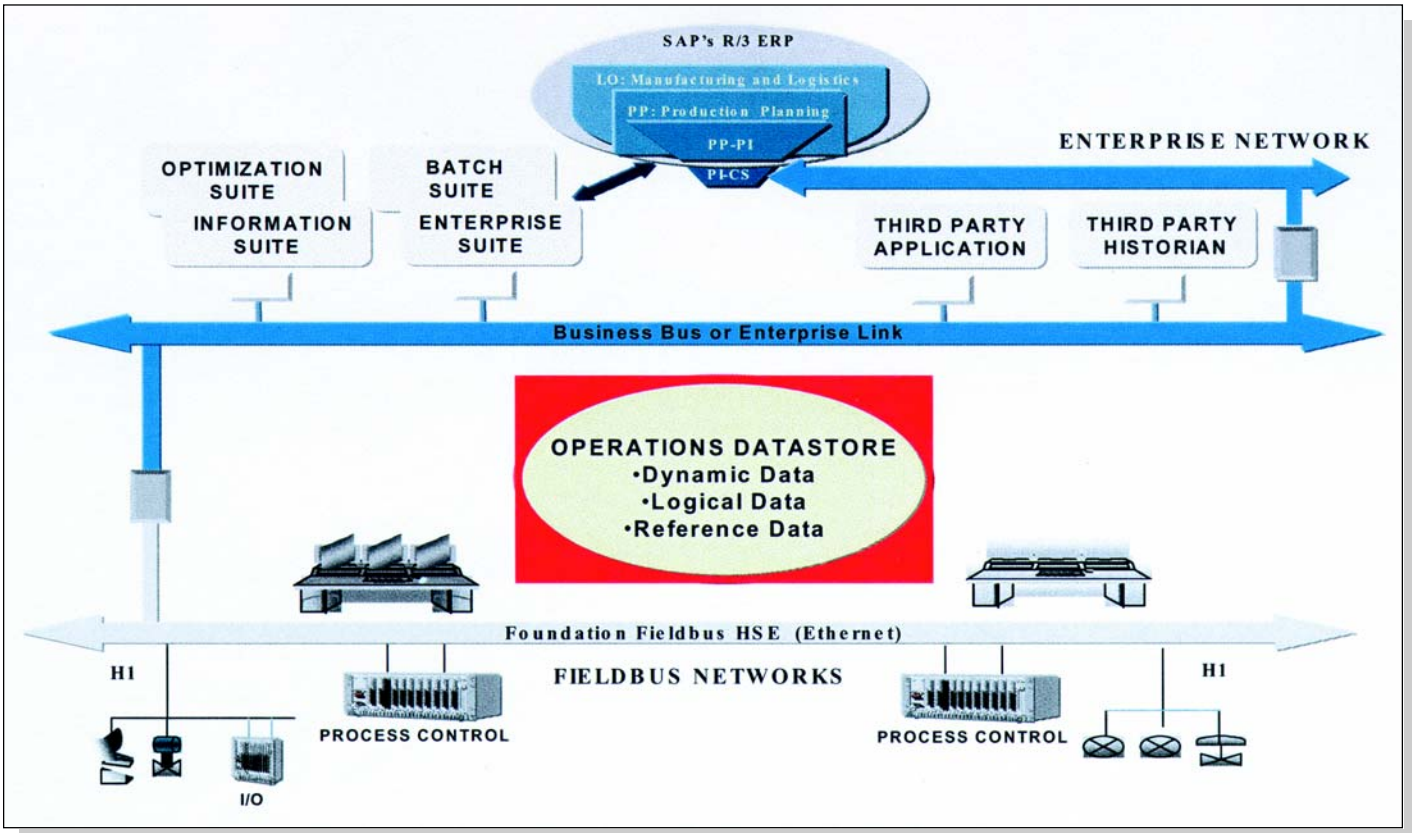

Figure 6. Data-Stor.

FROM	TO
Time-Consuming	Time-Efficient
Paper Based	Web Based
Manual Steps	Workflow Driven
Phone/Fax/Face to Face	Seamless to Supplier
Purchase Department	Employee
Task Focussed	Supplier Management Focussed

Figure 7. Procurement trends.

they prepare the shipment. B2B also will benefit you as a customer, primarily in reducing your procurement costs. Currently overhead costs tend to be the same through several orders of magnitude ($10-$1000) for procurement. The cost to create a purchase order is business specific, but can range from $50-$250. About 40% of procurements are direct and not attributable to a specific project. More than 30% is outside normal channels at an average 25% premium. And, finally up to 70% of procurement cost is paperwork. When a company is the customer rather than the supplier and as both is using e-Business, the benefits are complementary. Time or space will not permit delving into it, but in this future paradigm customers and suppliers will experience different degrees of role reversal for their mutual benefit.

The underlying technology that makes the extended enterprise happen is Internet technology, in particular, XML. XML is an acronym for Extensible Mark-up language. Extensible means that the tag structure is expandable and mark-up means that it is self-describing and in fact it is human readable, which makes it easy to use. It is an evolving standard, precise, secure, and as HTML (Hypertext Mark-up Language) has become a part of the Internet Revolution in our work and private lives XML will become an integral part of our business infrastructure. If you remember in our earlier discussion, we identified XML as a common mechanism to eliminate the B2M barrier. Its use in the B2B solution makes it the extensible solution for B2M/B2B unification. This concept is further enhanced by the emergence of business frameworks based on XML. Frameworks provide an infrastructure for e-Business by fostering business transactions, supporting transaction persistence and representing unique proxies for the transaction that links the customer to the supplier at the transaction level. Simply stated a customer is empowered with as much or as little information about a purchase and the acquisition cycle as desired.

This article proposes the value of business unification and information empowerment in the pharmaceutical industry. We hope you found it valuable.

About the Author

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This article reviews 10 principles that can result in improved project validation, reduced design problems, reduced cost over runs, improved regulatory compliance, and an overall meeting of project and client needs.

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The Problem of over Regulation, over Engineering and over Validation

No Problem, Just Apply Common Sense

by John Tashijan, PE, RCDD

What do we want out of each of our projects? Do we want a project that has problems during planning, engineering, validation, construction, and operation? Do we want a client that is not satisfied? Of course not. We want a customer/client that is happy and satisifed . Generally, this means that for this customer/client the project was within budget, on schedule, and provided better than expected results. Getting there can be a battle. Too many projects today bust the budget, run long, or simply do not accomplish the requested, designed, or perceived objectives. But why is that and what can we do about it? The following discussion highlights some of the causes, and provides a simple process to help avoid these problems or pitfalls.

- Design problems result in delays and cost over runs.
- Validation went on forever.
- Unforeseen regulations caused reengineering and or revalidation.
- Validation and engineering were always fighting.
- Engineering did not design what the client really wanted.
- There were excessive field changes and change orders.
- Production seemed to change their mind when construction was completed.

Are these excuses? What does it take to avoid these and other problems? There is not a simple answer, but application of common sense and following these 10 simple rules will go a long way toward achieving a successful project:

1. Do not design based upon regulations.
2. Understand your process.
3. Understand the real basis for the limits of your process/product.
4. Consider the entire system.
5. Make it stable and robust.
6. Involve Production early in the design.
7. Realize that Production, R&D, and Engineering speak different languages.
8. Allow Validation to be an extension of Engineering and Start-Up.
9. Track construction.
10. Never make emergency field changes.

Do Not Design Based Upon the Regulations

This statement DOES NOT mean do not follow the regulations. It means do not start with them as the basis for your design. On the surface, this may seem to be a contradiction. How can you solve regulatory problems by not designing to them? The problem lies in the fact that regulations are either written to define what can not be done, what is not allowed, or very general guidelines to be considered. For example, the National Electric Code prohibits non-GFI electrical outlets from being within six feet of sources of water. This would be a problem for production areas due to the 480 volt receptacles needed for portable equipment and if it were not for the exceptions identified in the code later on.

The current Good Manufacturing Practices (cGMPs) are general/vague guidelines for production. For example, all critical instruments shall be periodically calibrated. But what are your critical instruments, how should they be calibrated, and exactly how often is periodic.

In general, the FDA and other applicable regulations can be viewed as a road map. They show you an overall view, possible destinations, the roads or highways you can use etc. Once you are on the road, you have your speed limits and road signs that you need to follow. However, you still need to choose the destination, the road, the lane, and speed based upon your needs, wants, and weather conditions. When you start with the regulations as the basis of your design, it would be like building a new highway just

because you want your speed to be 63 miles per hour and not 65 mph. That is why designing to the regulations results in overkill.

Do not misunderstand. You may still need to add specific things to your designs to meet regulations. For example, adding instrumentation and controls to verify an FDA approved steam "sterilized" tank versus knowing that the tank is adequately sanitized with a steam bath. By adding one or two items or devices may make a big difference in covering all bases. This also reduces validation requirements and subsequent production headaches.

In short, temporarily lose your Code of Federal Regulations when you start your design. Apply Good Engineering Practices (GEP), Common Sense, and document what you are doing and why.

Understand Your Process

So, if you are not supposed to base your designs on regulations, what do you base them on? Where do you start? Start by establishing what your process and/or product really is. This may seem easy, but that is only an illusion. Even though you may have been making that product for years, how have you really made it? What size tanks did you use? How did you heat it or cool it? Would you bet your paycheck that it was made exactly the same, every time down to the smallest detail? This may seem extreme, but the next step requires you to know why you are doing each step.

For example, if your product is a vaccine, you start with fermentation of your master cell culture. This may require starting with roller bottles, tray tables, bio-reactors and/or fermenters. Then, you may concentrate filter, di-filter, ultrafilter, and/or inactive; finally, resulting in filling/packaging the product. Each of the above steps may be done in various combinations or under different conditions depending upon the objective, the volumes, and the purity. Will the final product be administered by injection, orally, or inhaled? Understanding the details and basis for each process step and ultimate expectations allows you to make logical choices. For example, if your vaccine is orally administered, then the subsequent requirements for water used by the process does not need to meet Water For Injection (WFI) standards. You may still use WFI because it is easily available within your facility, but not because it is required. This will reduce future quality concerns if you exceeded your water standard for this process and reduced your validation requirements if lesser quality water is used that still meets your process needs.

For existing processes which are being upsized, the design can actually be fun. If you closely evaluate an existing process, there are times in which steps may appear unnecessary. Before you delete them, verify why they were there in the first place. Even better, try to test the affects before making any permanent changes. This is one of the best reasons for change control. Sometimes these steps really are "unnecessary." But, if you are upsizing or making some plant wide changes you need to understand what and how your process will be impacted.

If you know your process and product, it allows you to establish the design using reasonable and appropriate requirements/criteria, process limits, instruments that are "critical," what must have emergency power, what needs an uninterruptible power supply. But most importantly, it allows you to technically defend and justify why you do not need to do certain things. It is not doing or needing to do various things that allows you to save money, improve project efficiency, reduce regulation headaches, and make quality product sooner. In short, improving your knowledge of your process is extremely beneficial. This can only be accomplished with good and valid technically supportable information.

Understand the Basis for Your Process Limits

Knowing the real basis for your process limits is a continuation of knowing your process, but one should specifically address the importance of specific parameters and conditions required to produce the final product. For example, defining process limits such as the maximum or minimum temperature, heat up rate, cool down rate, agitation speed, pH, O_2 concentration, or any other applicable parameter. The basis must be initially driven by the requirements of the process. Other external requirements, such as scheduling, can be used to adjust the process requirements, but not override them.

For example, all too frequently, when scaling-up a process the question will arise, "How fast do I need to heat up to the set point?" The answer will be "Currently, we take three hours, and since that we need to complete the process within a shift, the heat up rate should remain the same." What may appear to be a simple production request can result in several problems. Depending upon how other process limits are explained, you can drastically increase costs or cause the process to fail. For example, increasing the heat-up rate will force changing the surface area or the maximum temperature. Significantly increasing the surface area could require changing a simple jacketed tank into an elaborately internally tubed tank or by adding a re-circulation loop with heat exchanger. Increasing the tank jacket temperatures could cause product damage not because you overheat the bulk material, but you damage the material right at the boundary of the tank jacket. This would be similar to baking a cake at too high a temperature. The outside burns, but the inside is still raw and runny.

Another pit fall of not understanding your limits begins with computers and data logging. We can now monitor almost anything you can think of. But do you really need to? Just because you can or want to, is not a good reason to monitor or control a parameter. Monitoring a point means you must install instrumentation, calibrate it, test it, and live with all resulting alarms. This may be more work than any benefit, especially if you get several nuisance alarms and do not really need the information.

Knowing the limits and making them reasonable allows you to make technical decisions, which can reduce start-up and operational problems.

Consider the Entire System

Now that you understand your process requirements, the next step is to understand the entire system. This means knowing how everything fits together. Take a step back and look at the process as a whole. Start to ask yourself questions about the process:

1. What are the important or critical items to the process?
2. If this step fails or we lose control of a particular process parameter, what happens? Do we lose an entire multi-million dollar batch, or can we simply re-run that particular step?
3. What do you need to do to ensure proper use and ease of maintenance?
4. Did you consider installation cost versus long term maintenance?

5. Is this a long term or short term application?
6. Is power reliability an issue?
7. Is there a simpler way?
8. How big is the skid and how are we going to get it in the room?
9. Has anyone been trained to operate the equipment?
10. Are the existing utilities adequate to support the new loads, electrical, steam, etc.?

All too often, we fail to catch the obvious and frequently critical issues. For example, the doorways to the production rooms are seven feet, and the portable skid used in three different rooms was designed to be one inch under seven feet, but that was before you added the four inch wheels.

The processes we design, develop, test, validate, and use are only as good as the forethought and planning we put into them.

Make it Stable and Robust

It is generally a hard lesson to learn, but theory and reality seem to have very little to do with each other. We engineers can sit at our desks with paper and pencil or computers and calculate to our hearts content the exact pressure drops and heat loads, but to do these calculations we make numerous assumptions for the basis of the calculations which are not necessarily the real world. In the real world, we have pipe runs that are longer than estimated, HVAC systems that use steam reheat in the summer to maintain temperature and humidity, and many other unknowns.

In most cases, that is why we lean on standards, but we need to use good judgement. For example, a common problem with mixers is that they are undersized and have to be upsized in the field. Electrical wiring and Variable Frequency Drives (VFDs) should be sized to allow a reasonable degree of flexibility. Final system pressures and flow rates can be established by appropriately sizing pumps so that triple duty valves or trimming the impeller in the field will provide the necessary configuration.

It may seem that this indicates that everything should be oversized, but that is not true. Oversizing can often be worse. For example, using a 1 1/2" steam control valve where only a 1/2" would be sufficient would result in poor temperature control and high maintenance as one frequently replaces a control valve seat that is eroded due to throttling off its seat. I am advocating a reasonable balance. Provide your design with a reasonable degree of flexibility and allow for final field adjustments. You should not blow your budget on this flexibility, but good common sense judgement will save installation time and provide for quick changes during construction and start-up. Spend the money for the initial installation and it will save you time and money during start-up.

Involve Production Early in the Design

One of the biggest problems in completing the start-up phase of a project is the last minute delays, design changes, and documentation hold ups. The equipment does not work like the operator expects it to. Operators are not sufficiently trained to operate the equipment or the operating procedures are not complete or are incorrect. This is a key completion issue on any project to the Operation/Production Departments. Involving Production early in the design not only helps to make sure the client approves the design, but allows time for the training, procedure development, and operator indoctrination. Although this is not a new notion, one variation is that the same people starting the project should finish it. Changing personnel in the middle can result in changes simply due to personal preference.

Realize that Production, R&D, and Engineering Speak Different Languages

Now, just because we have the Production Department involved in the design does not guarantee that there will be no last minute changes. In fact, a common quote heard is "That's what I understood." You as the engineer know in your heart that you sat there in the meeting explaining the drawings and how it would work; it was clear as day. The problem is that Production personnel think differently than R&D personnel, which is still different than Engineering personnel. None are wrong, but the differences can easily lead to confusion and misunderstanding. Most production people are not trained to read a drawing. Let's be honest, how many of us can look at a drawing of something and actually imagine it working or what it will finally look like? That is not easy. Even with the 3D computer graphics programs available, until you touch it, see it, kick the tires, it is not real.

To help solve this problem, one recommendation is to see it somewhere else or to have mockups, models, or walk-thrus. When it is possible to see the exact system or piece of equipment, there is a big advantage. It is not always possible to see the exact system somewhere else. That is when mockups, models, walk-thrus are an option. I am not necessarily recommending complicated or expensive setups. Modeling a freeze dryer control panel may be nothing more than a scaled cardboard cutout taped to the wall. You then have the operators play act through the process. This also can help when you are trying to determine how some custom portable equipment will be moved from one room to another. Doing this has the added benefit of being able to develop operating procedures prior to equipment arrival.

The language barrier is also different when it comes to tolerances. For example, when R&D is talking about specifications and tolerances you can drive a truck through, the instrumentation/automation engineer is hearing and thinking a Semi-Trailer, but in reality it was really a match box toy truck. This is a common problem resulting from years of dealing with laboratory grade equipment or perceived accuracy of old equipment. For example, one company had been using a simple strip chart recorder to monitor and record time response and valve sequencing of a safety system. The real accuracy of the chart recorder was 0.1 seconds, but because they would use a standard ruler and measure to the 1/32 of an inch, they had a perceived accuracy in the 0.001 seconds. Any replacement equipment was being requested to meet the perceived accuracy and not the actual.

Some of these types of problems will need to be resolved so that a true understanding of the process, process limits, and the entire system can be achieved. The results are improved project completion.

Allow Validation to be an Extension of Engineering and Start-up

In 1986, the Food and Drug Administration (FDA) issued Guidelines on General Principals of Process Validation. In that document, it describes Validation as:

> *"Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes."*

The two word definition is "Prove It." The key to proof is providing the appropriate amount of documentation. Validation is providing sufficient documented information to prove to the FDA that your process works, is repeatable, and will provide indications if it were to become out of control, and not more than that. Validation documentation should be clear and concise. Since validation documentation is provided to a federal agency, the FDA, it must be closely controlled with all "i's" dotted and "t's" crossed; in essence, a legal document.

Engineering start-up and commissioning are the steps that you take to start-up the system or piece of equipment for the first time. It is the initial test drive; a chance to break in the equipment. It is a time for the engineer and operator to make the minor corrections, confirm that it will run as expected, and determine what the actual performance limits are. In general, commissioning may include a start-up procedure, a check list of items to complete, equipment and instrumentation check outs, system functional checks, a list of tests to be performed, and system expectations. In general, commissioning documents should provide guidelines and not restrict the action of the start-up personnel. Good Engineering Practices would indicate that all major systems and pieces of equipment should have some form of formal commissioning or start-up packages even if they do not require validation. For example, the plant chiller, compressed air system, or electrical distribution system would not necessarily require validation, but you do need to be sure that they are working as expected.

Although commissioning does require some documentation, do not make validation personnel the initial start-up engineers or the policemen. Most engineers and operators take pride in making their systems work right. Having validation personnel perform start-ups, forces the engineers and operators to instruct the validation personnel while they are still learning. It also forces ridged documentation standards onto a system before it is completed and operational. This also forces validation into the role of the policeman writing the engineer a ticket for everything that did not work just right or confirming that the engineer is telling the truth in their documentation.

As part of the engineering start-up of a system, you will verify many of the same items that FDA style Validation will do. For example, when installing a Distributed Control System, initial loop checks will verify equipment, wiring, controller points, and function. This is a direct overlap with Installation Qualifications (IQs) and Operational Qualifications (OQs). As long as Validation does not have to act as the policeman, redundancy can be reduced.

For example, a freeze dryer is setup at your site. You would first do a systematic start-up, maybe even under the vendor's tutelage. You would then start with some dry and sample runs of the freeze dryer. Each run may or may not result in complete cycle with complete documentation, but that is what you are testing for or tuning in. All failures are not necessarily documented or require detailed write-ups to justify. It is learning time that is well spent and will make OQs and Performance Qualifications (PQs) run smoother. However, information such as equipment identification and drawing verification are potential duplication of IQs. Instrumentation input/output check sheets and Calibration checks are duplication of information provided in OQs and PQs.

In many cases, if engineering documentation is laid out properly up front, validation work can be reduced. The key is to determine what basic information is needed and what additional information is required to support FDA validation. It is my belief that the FDA did not intend Validation to become the policeman. They simply wanted to ensure that the documentation existed to prove that systems did what they were expected to do.

Track Construction

Taking specifications and drawings and turning them into a real object, is a cold slap of reality. Even the best-laid plans will miss a detail or two. Contractors do not always follow plans exactly. There is only one solution - frequent and periodic walk-throughs.

The appropriate engineers and production personnel must walk-through and inspect the facility or equipment during construction. This is the only way to verify you are getting what you thought. For example, pipe runs during construction have been installed without being sloped to allow drainage. It was clearly shown on the drawings, but it was not being installed that way. This will cost you a lot less time and money to fix it early, than it would during start-up.

There also will be situations that production can help correct because now they see what is being built. It is no longer just lines on a piece of paper. They can see it, touch it, and kick it. The types of problems detected include, but are not limited to, valve orientations or steam condensate drains that could collect water.

Never Make Emergency Field Changes

We have just talked about making walk-throughs to discover potential corrections, but now I say do not make emergency field changes. Field changes will happen. They are a fact of life. The common belief is that all changes have to be completed immediately before the next step can be performed. The problem is that Emergency Field Changes are blank checks which can be cashed in the form of both time and money. The costs are not always direct. An emergency change in one place, pulls manpower from somewhere else. Placing workers back in the same area may now cause two groups of workers on top of each other. This may be unavoidable, but make sure it really is. All to often, everything becomes priority ONE, and every thing is an emergency. This only results in busted budgets, high degrees of frustration, and even longer time tables.

The key is simply to make sure that it really is a priority and realize you will have indirect effects that are adverse as well as beneficial.

Conclusion

The above items are not the 10 Commandments. They are not carved in stone. They are not the cure all for over regulation, over engineering, over validation, or cost over runs. They are a good solid basis for the initial planning, the preliminary and final design steps, validation, and commissioning and start-up of a project. This is true whether the project is a modification, an upgrade or brand new from scratch. These items are a check list, a set of guidelines or rules to go by for the application of common sense engineering, good communication, and involvement of all the needed participants in the ultimate operation of the project. These steps will aid in early discovery of common pitfalls and problem areas. They will allow timely resolution of these items before they are cast in concrete, block walls, piping, conduits that are in the wrong place or the wrong size. These steps will ultimately result in a successful project. A successful project has a happy customer/client, and a happy customer/client is always our goal.

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This article discusses a number of new approaches that should lead to an improved pharmaceutical project model - one that is more attuned to business objectives for the 21st century.

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In Search of a New Project Management Model

by J. Philip Southerland, Jr.

Initiatives focus on shortening delivery schedules for pharmaceutical facilities while maintaining quality and budgets. They prove that innovating and pushing the limits can pay off.

Driven by intense competition, the pharmaceutical industry has changed radically in the last five to ten years. Margins on sales were previously higher than other industries, and the value of facilities' assets in relation to a company's performance was less. The thinking had been that if you could make a quality product, facility costs mattered less. The result was an industry with spiraling facility costs and personnel who by their own admission were risk averse.

Now there is a recognition by the pharmaceutical industry that facilities conducting research, in addition to those manufacturing product, are a component of competition. Thus comes the recognition of the value of delivering facilities more quickly, while still managing their costs and maintaining their quality. Since building faster means assuming some risk, the pharmaceutical industry will need to think differently about the way they bring new facilities on line. Learning to think and act differently about project delivery will be one of the great challenges entering the new millennium.

According to the old construction model, a shortened schedule meant more expense and/or lesser quality. During the course of the last couple of decades, the industry has taken many incremental steps towards achieving better, faster delivery. But now to shape a new project delivery model, pharmaceutical companies and their construction managers, designers, engineers, and trade contractors are collaborating to develop methods that make a quantum leap to achieve a new project management model for delivering facilities without sacrificing cost or quality.

As a result of these changing dynamics, project drivers for the design and construction of a typical pharmaceutical facility are expanding as are the members of the project team. The old model focused on cost, schedule, and quality. The new, expansive model incorporates a broader team focus on issues such as safety and the business strategy which the facility is intended to support - *Figure 1*.

A larger circle of project participants is actively sharing in setting project goals, and defining roles and responsibilities - and taking a stake in the outcome. While there is always risk associated with exploring new ground, these innovative methods have strong potential to deliver on their promises.

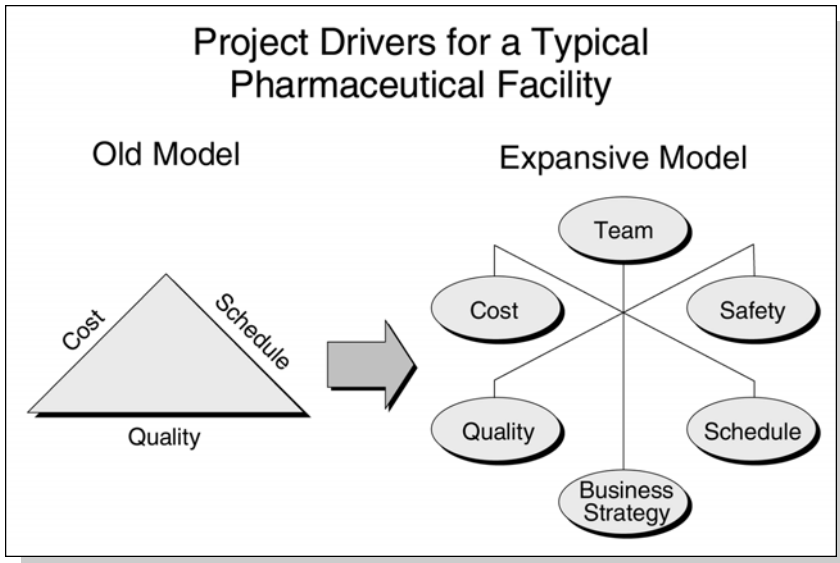

Figure 1.

Searching for Ways to Take More Than Incremental Steps

The topic of how to move beyond taking incremental steps in project delivery and instead make a quantum leap has captured intense interest at Gilbane's annual Pharmaceutical Facilities Executive Forum, attended by facilities executives from major pharmaceu-

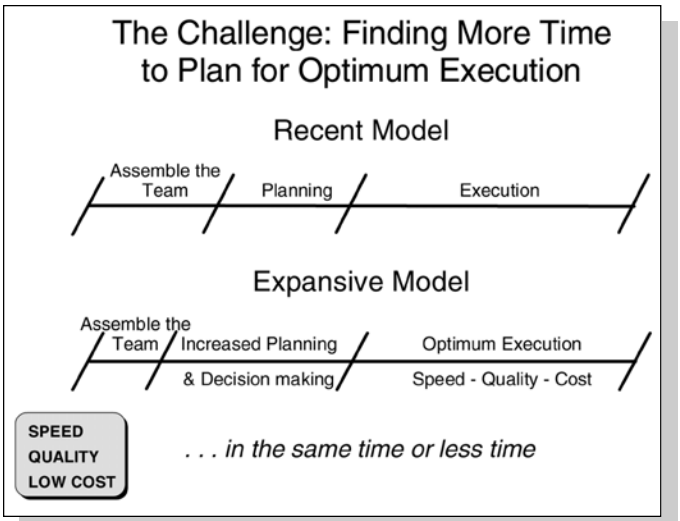

Figure 2.

tical companies and leading architect/engineers. At this year's Forum, following a presentation on this subject by representatives of the pharmaceutical industry, the group formed a task force to focus on the search for a new project management model.

In its initial meeting, the Task Force Steering Committee defined its mission: *to substantially improve project delivery so that owners' business objectives are met or exceeded*. To succeed in this mission, the group will look for a change so dramatic that it will require them to challenge/reinvent the paradigm in which we in the industry currently operate. Even fast track variations of our present paradigm have been incremental. The task force will collaboratively explore delivery systems such as cost, schedule, and quality; means and methods; tools; and technology. This process will include ways to improve the decision process and the design and construction process in a way in which the whole outcome enhances the ability to meet business objectives - both individually and in the ways they interrelate.

A key focus should be on the means and methods - execution of the trades and the materials - by which we deliver a project. Eighty percent of the costs of projects lie in this area. One area the group will investigate is modular or shop fabricated systems. Another area to explore is putting in a foundation without committing to exactly what is going into the building. The hope is this task force will allow participants to look at these broader issues and barriers and find ways to bridge them.

Richard Menke, Project Manager with Eli Lilly and Company and a member of the steering committee, observes that the pharmaceutical industry has lagged behind other industries in developing better ways of delivering projects. "Our industry is made up of 'zero risk' folks," says Menke. "But intense competition and recognition that the cost and time of delivery of our facilities are now significant elements of that competition have changed the scene. Now we know there is value in being fast and taking some risks." He adds, "What we really need to do is, not build faster per se, but start later in the drug development process and then build faster. The longer you can delay the start, the more information you have about your production needs."

Meanwhile, we continue as members of the design and construction community to work with our pharmaceutical clients on many fronts to develop and improve upon practices that move us forward in the way we deliver pharmaceutical facilities.

Building on the Stronger Foundation of Team Relationships

In some instances, building owners are forming ongoing strategic alliances with construction managers, architect/engineers, vendors, and subcontractors to save time and reduce redundancy. With a proven team ready for new projects, bid processes can be eliminated, and, as trust builds, the innovative spirit that leads to improvements can flourish.

Biologically-based drug developer Human Genome Sciences (HGS) believes strongly in the team concept. Joe Morin, Project Manager of a new HGS production facility in Rockville, Maryland, says, "What makes a project work is people. When we sole-source and negotiate with a contractor, for example, we're specifying particular people from that firm." Aside from "chemistry," ongoing relationships allow HGS to eliminate steps and immediately tap a proven resource for future projects.

The in-progress HGS project is ahead of schedule - due in large part to the trust between the owner, the construction manager, and key contractors. With reduced owner focus and time spent on assembling a project team, more time can be allocated to increased planning and decision making. That yields optimum project execution of speed, quality, and cost - *Figure 2*.

Several pharmaceutical companies also are working with a selected small group of architect/engineers, construction managers, and subcontractors over multiple projects, and their facilities executives find that team continuity has real, practical value. They can hit the ground running and know what to expect of one another.

One way of avoiding risk that may be associated with abandoning the project bid process for a strategic alliance is to negotiate up front with the alliance vendor service and rates based upon a large volume of work. By lumping a series of jobs together, the pharmaceutical company can reasonably ask for some benefit. The first purpose of the alliance is service - mainly quicker turnaround. Cost is important, but it may be secondary. Earlier project team assembly through alliances produces earlier project starts - *Figure 3*.

Also, the industry is emphasizing that capital is a resource and time is money. Delivering a facility more quickly means

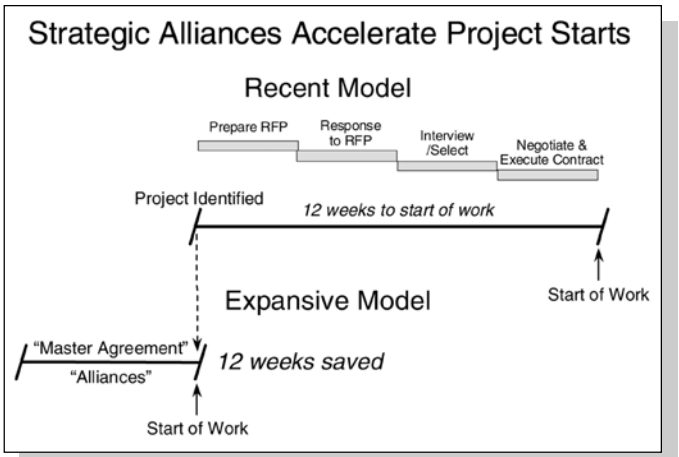

Figure 3.

Many project teams are transforming their environment from static web pages to dynamic, user-driven centers of collaboration.

the facility becomes productive sooner - a value added that mitigates concern about relatively minor cost premiums. Additionally, according to the TRW life cycle analysis on the total investment in a facility, operation accounts for 6%, occupancy and people costs account for 92%, and design and construction represent only 2% of the cost of a facility over its life cycle.

Faster Delivery

Recently, a large biotech firm's construction team employed new methods to achieve aggressive goals. To bring a manufacturing facility on line as soon as possible, the schedule specified constructing the building before final process designs were complete, overlapping construction and system validation, and fostering a team attitude.

The complex systems inside pharmaceutical facilities usually determine the building design. Design and construction of process systems is where all the time is. Rather than wait for process design to be complete, the building shell was constructed based upon educated assumptions about the internal components. So when the internal design was done, the building shell was ready. In the case of the biotech firm in which this approach was used, delivery was shortened by roughly three to four months. Also, turning over each system as it was completed allowed the owner to validate individual systems as they were ready, slicing six to twelve months or 25 - 30% off the schedule. In other words, the biotech firm was able to accelerate the income stream from the products manufactured there by up to a year.

At HGS's new production facility, both schedule and budget were aggressive. The internal fit-out of an additional production line is being managed with strategic alliances with subcontractors. Bringing in key subcontractors to self-design systems or components eliminated redundancy and shortened the entire design phase. The Production Facility Expansion project is at least three months ahead of where it would be with the traditional construction. Using a design-build subcontractor approach frees engineers to move onto other critical needs.

In another speed-efficiency initiative, HGS's Morin says, "We're also sole-sourcing a lot of equipment. Sole-sourcing gets us specialized knowledge - vendors are the ones who know their equipment inside and out. We're having input meetings with the vendor, HGS user groups, and the design firm. The result is a better product. That's added value you don't get in a competitively bid job. And you can take about four weeks off the scheduled delivery date for each piece of equipment."

A uniquely executed distribution center in Virginia took just four instead of nine months, more than a 50% reduction in schedule. The project was managed by developer Craig Davis Properties, who worked closely with the city and the code compliance department as well as the construction team to achieve these remarkable results. Frank Hellmuth, Vice President for Craig Davis Properties says, "Our client needed the building in a short amount of time to meet operational requirements. We had to meet client needs."

In this case, the collaboration of the local economic development team also contributed to better delivery. The city, which owned the site and was competing with other cities for the 1,300 jobs and tax revenues, also was committed to meeting the client's needs. The Codes Compliance Department was set up to approve plans within seven days, and unless they fall outside guidelines, plans don't require review by other municipal boards. The Economic Development Department discussed the building needs with the client and modified the zoning ahead of time to accommodate some of the design characteristics. They were ready to roll before they even got their first permit.

On the construction side, the construction manager created an innovative plan including Craig Davis Properties authorizing funds to be used at the CM's discretion to allow immediate decisions and execution. Efficiency techniques at the site included pre-fabricating joist systems and utilizing design-build for plumbing, electrical, and other trades.

On another pharmaceutical research facility, the pharmaceutical team, designer, and construction manager are working closely to merge design and construction processes into a fluid, dynamic process with construction literally one step behind design, and often based upon schematic-level drawings. Assigning a construction manager to interface with the architect/engineer and pharmaceutical management on constructibility issues has smoothed the process. To speed bidding, major system contracts such as mechanical, electrical, and plumbing were put out to bid using design development documents versus detailed construction documents. Also, recognizing the high levels of construction activity, the team purchased structural steel and selected contractors early to avoid shortages.

These and many other initiatives have helped put the project six to nine months ahead of a conventional schedule.

Harnessing Communications Technology

Rapidly advancing web technology also plays a significant role in accelerating the delivery cycle. Many project teams are transforming their environment from static web pages to dynamic, user-driven centers of collaboration. Instead of just viewing documents and information, authorized users can upload and download financial reports, photos, CAD drawings, and other files as well as participate in real time discussion groups. Now, for example, an architect/engineer can respond to a Request For Information (RFI) electronically, and attach a sketch(s) online for immediate review. This eliminates the need for fax machines or same-day delivery services. The cost savings add up quickly, and the immediacy of communication helps to shorten the design phase and increase the efficiency of field operations.

There is no faster way to interact when drawings and other files are involved. Getting a design detail clarified in the field might have been a one-day process before. Now team members just upload it to the site and notify the subcontractor, who has it immediately. These sites also eliminate the need to buy the application to view a drawing or photo, and can reduce delivery charges by 30 to 40%. Before internet technology, this same

process either required hours of printing, mailing, and distribution, or necessitated saving the changes to disk and mailing them to multiple sites.

Cost Control

A key technique in reducing costs is a balanced schedule. Scheduling work to avoid one intense period of activity saves labor overtime costs or additional hiring to man a second shift (difficult in today's tight labor market).

A new product development facility currently in pre-construction is intensive in its design and internal process systems and equipment. With an optimal manpower density of 400-500 square feet per worker, a typical heavy labor concentration late in the project would exceed the ideal maximum of workers (350), resulting in inefficient work space or a cost premium for overtime. To optimize schedule and budget, the facilities team and the design phase manager have identified key objectives: construction-driven design packages overlap construction with design and even-out peak work activity to avoid cramped conditions and worker inefficiency. By executing these plans and eliminating the standard "crashing wave" of labor in the latter part of the work schedule, the project will achieve an 82% reduction in premium time for craft labor - *Figure 4*.

A plan to use innovative purchasing agreements with vendors that involve them in the initial design process will further the savings and optimize the schedule. Duplication can waste weeks or months, with architect/engineers, trade contractors, and fabricators redrawing each other's detailed work. On some typical pharmaceutical plant projects the solution has been to give selected trade contractors and fabricators just the basic information they need to bid. The construction manager can award to the one with the lowest guaranteed price, and then bring the parties together to work out details and deliver the most economical design. This technique can save the owner both time and money.

Joe Morin is finding that the HGS sole-sourcing initiative has cost benefits, too. "We're getting pricing up front and working from good data from a recent project, plus our vendors are thrilled they don't have to jump through the hoop of the competitive bid process," he says. "The result is better prices and value. Right now, we're running under budget on equipment."

No one professes to have all the answers to making the quantum leap and to achieving the perfect new project model. But through collaboration, exploration, and mutual trust we are making good progress - *Figure 5*. The success of this effort

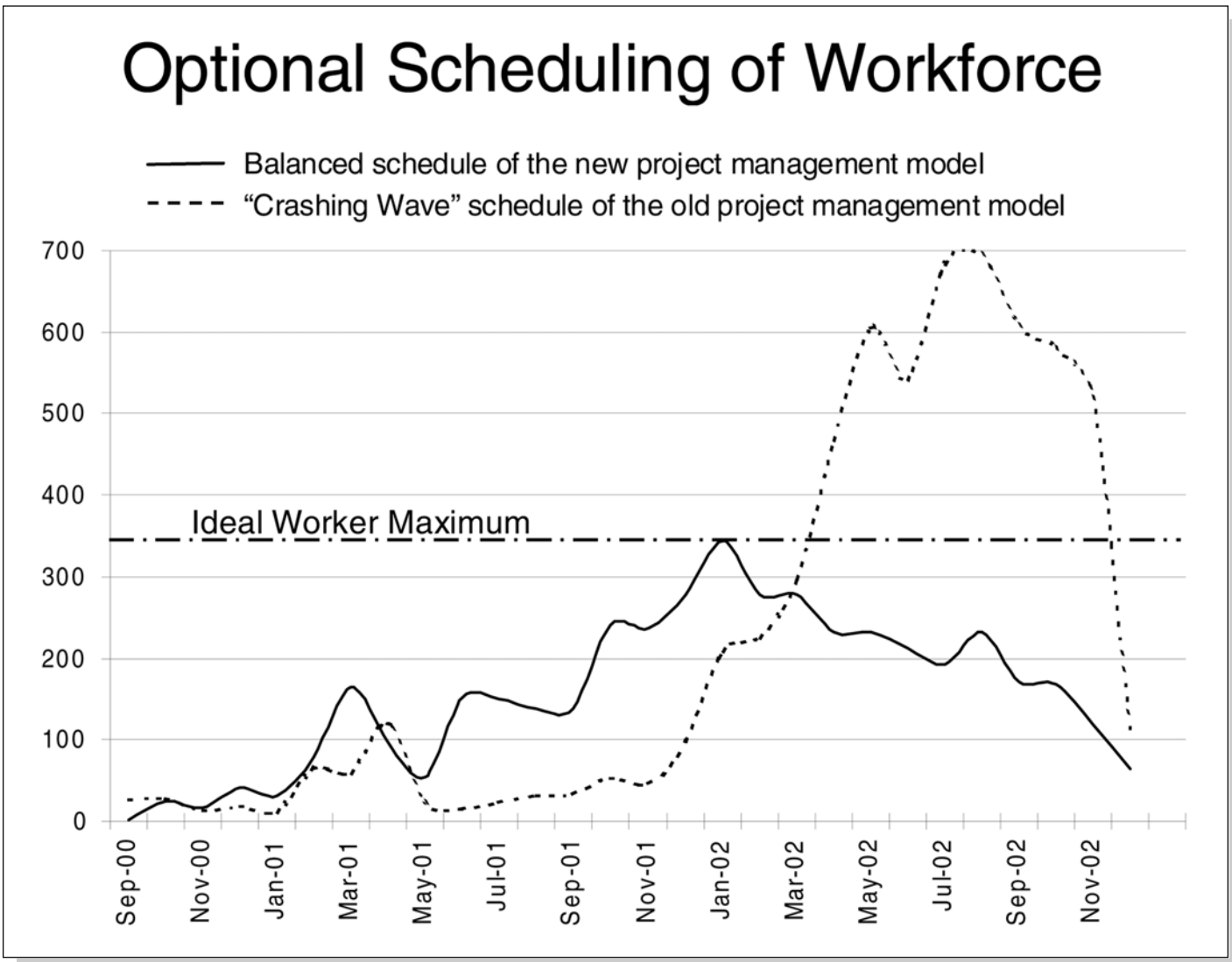

Figure 4.

Methodology	Source of Savings	Potential Time Savings on Typical Process Project (Months 1 2 3 4 5 6)
Strategic alliances with pharmaceutical companies, CMs, A/Es	Elimination of RFP/proposal/selection process Earlier project team assembly with resulting innovation and increased planning time	3 months
Design/build subcontractor and vendor approaches	Elimination of design redundancy Shortened design phase	3 months
Sole sourcing equipment	Specialized vendor knowledge in final design Shortened procurement process	1 month
Project website	Immediate team communications Increased efficiency Reduced RFI response time	1 - 2 months
Phased system turnover	Earlier validation Accelerated product manufacture	6 - 12 months
Building shell completion during process systems design	Construction progress during process design time	3 - 4 months

Figure 5. Typical available schedule savings: new project management methodologies.

will be a key to improving the design and construction process to better meet pharmaceutical companies' business objectives.

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This article has been compiled from a body of knowledge and experience on a variety of pharmaceutical construction projects performed by Gilbane for clients like Human Genome Sciences, Inc., Eli Lilly and Company, Genentech, and other major pharmaceutical and biotechnology firms whose projects are confidential.

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J. Philip Southerland, Jr., Senior Vice President of Gilbane and Manager of the company's Advanced Technologies Sector, is responsible for all of Gilbane's process-related manufacturing and production facilities nationwide. He has more than 25 years of experience in the process-related design and construction industry. Southerland has a BS in construction management from Clemson University, and is a graduate of the Executive Development Program at Johnson Graduate School of Management, Cornell University. He is a member of ISPE and the American Institute of Chemical Engineers.

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This article discusses the benefits of manufacturing automation based upon the industry standards such as S88.01 to optimize the product life cycle cost for the pharmaceutical industry.

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Automation's Evolving Role in the Pharmaceutical Industry

by Baha U. Korkmaz and Velumani A. Pillai

With Y2K projects winding down, many pharmaceutical companies have updated computer systems in both business and manufacturing automation systems. This provides a solid basis for improvements in the new millennium. We believe the improvements in manufacturing automation and information integration into business systems will provide competitive advantages and benefits for the pharmaceutical industry in the new millennium.

Enterprise Resource Planning (ERP) implementations have well advanced during the 1990s, and the new technologies became available for automating the manufacturing plants. Resulting in significant benefits of the real integration of the business systems to process automation systems such as integration of the supply chain and optimization of production cost.

Where and how can improvements be made to derive these benefits? Is automation going to help get these benefits? Why does the pharmaceutical industry need them? First, let's examine the following key drivers for pharmaceutical manufacturing other than regulatory requirements:

1. time to market
2. agility in manufacturing
3. reliable and quality supply
4. optimize product life cycle costs

Time to Market

The pharmaceutical product starts its life cycle as a candidate drug in the research labs. While the product is undergoing clinical trials, drug development activities and plans to build an asset to produce or source the product are made. Getting the product to meet a specific patient need on time means that the asset must be ready before final approval of the product by the regulatory agencies. Pharmaceutical companies must focus on making an asset productive in the shortest possible time yet at an optimal cost - *Figure 1*.

Agility in Manufacturing

Pharmaceutical manufacturing increasingly is focused upon building flexible facilities. In dedicated facilities, productivity can be relatively high as it would be specifically designed and optimized for a product. A decision to build an asset has to be taken early during the process development stage. If a drug fails during clinical trials or if the final process changes considerably, then it could result in an asset that may not be productive. To overcome such risks, increasingly the trend is to build flexible plants that can handle one or more families of products.

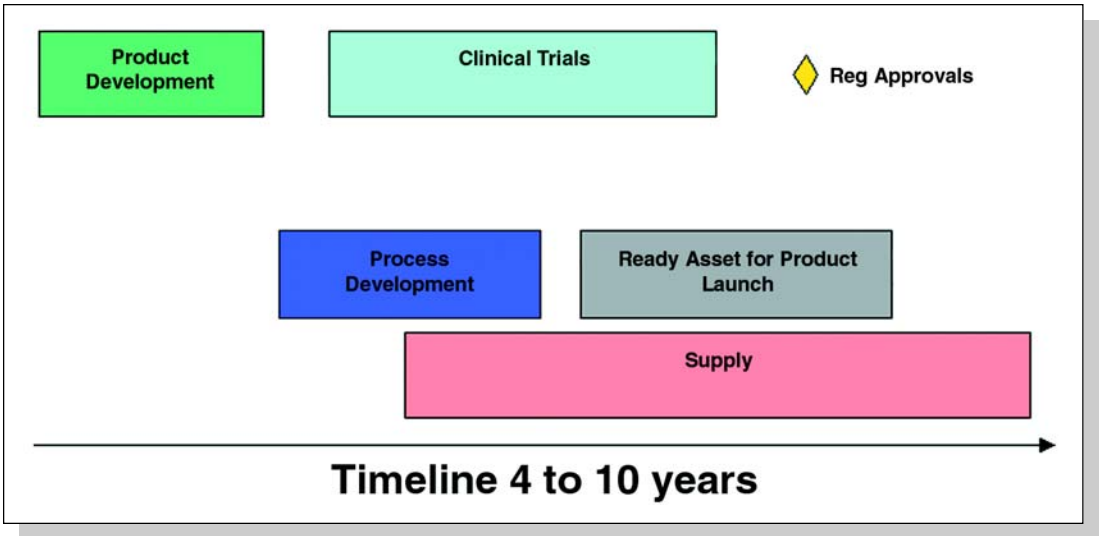

Figure 1a. Product life cycle timeline.

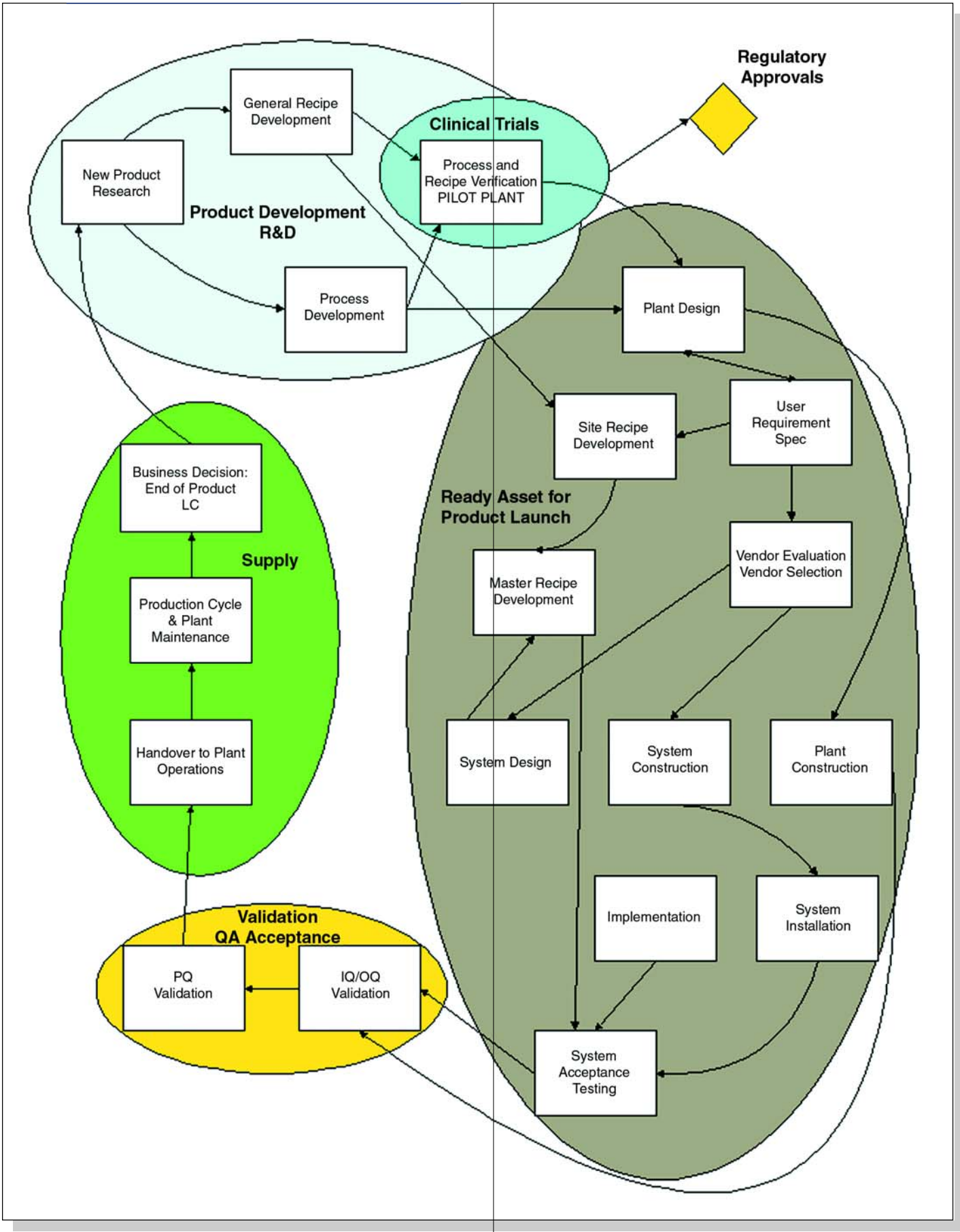

Figure 1b. Product life cycle diagram.

> ***A high level of reliability and consistency in flexible facilities is ensured by process automation systems.***

Pharmaceutical firms are increasingly outsourcing the manufacturing as well. These contract houses need to build flexible (multi-product) plants so they can accommodate more than one client or more than one product for the same client. Applying standards to the automation design helps to increase the agility of the manufacturing plants.

The rate of new product introductions within the pharmaceutical industry is also ramping up. Dedicated facilities for each product family may not optimize the capital.

Flexibility is the ability to change or react with little penalty in time, effort, cost, or performance.[4] To better understand flexibility and characterize it, a framework for analysis has been proposed.[4] The first dimension of this framework is the dimension of change, second time horizon of the change, third being the elements of change.

Any characteristic of flexibility requires adequate design considerations up front. A flexible process introduces inherent complexities. This necessitates proper definition and modular approaches in design. Process automation systems play a key role in ensuring *potential* benefits of flexible assets are fully available when needed, whether to have the capability to handle multiple products or to optimize and improve a single product.[2]

Reliable and Quality Supply

Pharmaceutical manufacturing has to provide a reliable and quality supply of products. Quality is assured by following consistent practices in the manufacturing of the drugs. A high level of reliability and consistency in flexible facilities is ensured by process automation systems. Automatic verification functions, consistent process control, and automatic procedural execution systems help in delivering consistent quality.

Optimize Product Life Cycle Costs

The competition and technological advances in the pharmaceutical industry require that product life cycle costs be optimized. The product life cycle costs include the product development costs (research and clinical trials), process development costs (development, optimization, and process improvement), and supply costs (both fixed and variable). Flexible facilities also cost more to build and maintain. This is especially challenging when products can be fairly complex, and time to develop and deliver is getting shorter.

Can automation really help address some of these drivers? Successful pharmaceutical companies have demonstrated that automation can provide real competitive advantage. **Most companies underutilized their investment in their process automation systems.** Quite often they do not need to buy more equipment, they simply need to better utilize what they have. What they find is they do not have the right resources to optimize their systems.

Pharmaceutical companies also are focusing on product life cycle and optimizing the development, production, and automation of the manufacturing facilities to achieve optimal cost in each and every step of the life cycle. When installing new solutions, companies want to spend less capital and end up with better utilized, more flexible, and easier to use systems.

Here let's focus on how automation can help build a competitive advantage at every step of the product life cycle without increasing the complexities associated with flexibility.

Most pharmaceutical processes can be classified as batch process. Batch process manufacturing involves functions such as recipe management, sequential control, and management of equipment and material resources, synchronization of process activities, more elaborative production information management, and production planning and scheduling. Typically, all these activities require some sort of interaction and coordination. ISA has been working on standardization of batch process control since the late '80s. The first batch control standards were finally approved in October 23, 1995. It is called ANSI/ISA-S88.01- 1995.[1] Briefly it is called the S88 standard.

Today, the S88 standard is widely accepted by batch process manufacturing industries and the process automation suppliers in the world. All the major suppliers have developed products and methodologies that are S88 "aware." This allowed the pharmaceutical processing industries to apply the S88 standard for effectively automating plants and executing the projects.

S88 models and terminology can be applied to all steps of the product life cycle. Let's examine how the concepts can help in optimizing the product life cycle of a product.

Product Development Phase of the Product Life Cycle

A research lab is the starting point for a product. When a product is identified as having potential, a procedure or formulation is developed for the possible new product. This is in the form of a general recipe.[2] A team of development chemists and engineers begins to design the process for the new product by utilizing process simulation software. The general recipe specifies the raw materials, their relative quantities, and required processing to make the product. This recipe and the processing requirements will be tested and verified first at the small scale in the lab, then larger scale at the pilot plant. The result of the pilot plant experiments will identify the equipment requirements and the site recipes for the actual site for the commercial size production. Figure 2 shows the R&D steps and the possible optimization areas for the increased performance of R&D activities.

Pre-Project Engineering Activities of the Product Life Cycle

The pharmaceutical company begins losing revenue and market share opportunity each day after approvals. One of the reasons could be if a project to create an asset takes longer than it is absolutely necessary. Pharmaceutical companies make important decisions such as vendor selection and project engineering team selection (in-house, outsource, or combination of the both) when an asset needs to be created or changed. The pre-project activities play a key role in setting up the right specifications for the design and construction including optimum automation of the asset.

Utilizing industry wide standards and standard methodology helps to shorten this pre-project cycle. For the automation component, this cycle contains the following activities:

> ***When a product is identified to have potential, a procedure or formulation is developed for the possible new product. This is the form of a general recipe.[2]***

- identifying the schedule
- developing the right scope
- automation pre-design involving automation concept, User Requirement Specification (URS) or operational specification development
- development of site recipes
- vendor evaluations and vendor selection

Many of these activities will have to be overlapped with other activities such as process technology selection, process equipment selection to decrease the time before the project detailed design and construction activities can be kicked off. A well-grounded automation strategy saves engineering efforts related to vendor evaluations and vendor selection.[2]

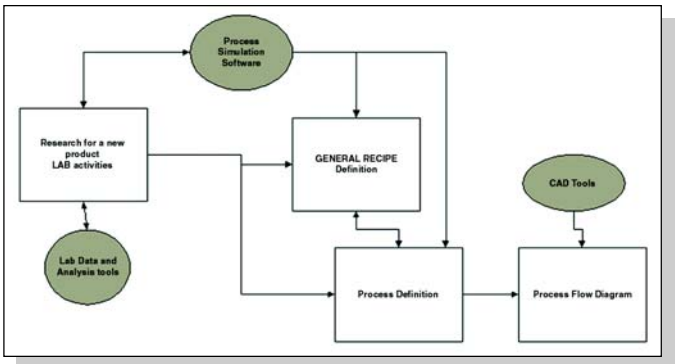

Figure 2. Product development process in R&D from an automation perspective.

To optimize the pre-project and project time, by increasing the quality and decreasing the life cycle cost of the automation is to get the automation project engineering team on board early enough and make sure that the team has sufficient involvement in the automation concept and URS development. It is expected the team understands and applies the S88 based modular batch control standards and applies modular manufacturing principles in design.[2] Figure 3 shows the relationship between the pre-project and project activities on a relative time scale.

The automation project team should have influence on the A&E companies design activities such that the I/O point naming conventions, control loop names, control strategies, finite number of control module, equipment module, and unit specifications can be developed universally. This team activity will help to shorten the engineering time. It also will help to increase reusability, reproducibility, and maintainability of automation elements throughout the plant and across plants within the enterprise. The modularity must be religiously followed and not just the project cost, but the total automation life-cycle cost must be taken into account.

The URS document is a main driving document to define operational requirements, process control requirements to make the products, system architecture requirements, user interface locations and strategies, exception handling, work instructions, equipment phase sequences, product information management requirements, production planning and scheduling requirements, recipe management requirements, and process and safety interlock requirements.

The vendors develop automation project proposals and use URS documents in addition to plant design outputs such as P&IDs and instrument databases. The user company evaluates the vendors and their proposals in parallel, and finally draws a conclusion for final project grant. Increasingly, phar-

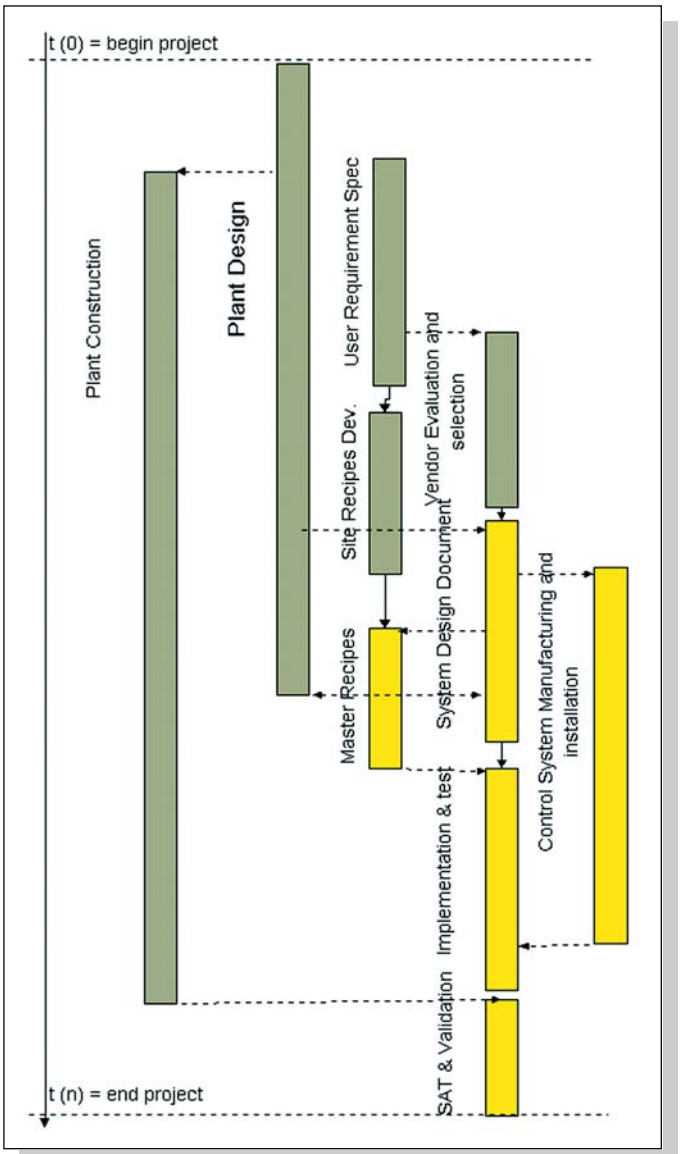

Figure 3. Time relationship of pre-project and project activities.

maceutical companies are working with select vendor partners for the process automation solutions.

This whole pre-project cycle is often a costly and time-consuming effort if no standard templates and/or tools are used. If the tools are not intelligently utilized, it can create many errors throughout the project and the automation project can be perceived as a failure. To avoid quality and efficiency issues, it is extremely important to utilize the standards (e.g. S88 and company internal) and tools to generate and transport information from one project stage to another. However, poor definition or shortcuts in definition leads to problems during the project.

The tools and standard templates also help to implement change management of plant design data. The change management of plant design data should be implemented early enough in the project and must be clearly understood by all project team members. Creation and modification of all P&IDs and instrument and construction design documents by the Architectural & Engineering (A&E) firm must clearly identify the changes in each revision. It is desirable to have tools that propagate changes in design documents automatically. Any change proposed should be evaluated for its impact on all phases of the project before a decision is made.

As part of this activity, the site recipes should be generated from the general recipe. Site recipes will include the site-specific raw material and intermediate material requirements, transportation, and packaging requirements. At this point, equipment requirements are not specified. Master recipes shall include the process cell and equipment specific information in the project cycle.

Project Activities of the Product Life Cycle

As soon as the project is granted to a vendor and the project team is augmented as appropriate by the required skill level of engineers and technicians, the project team develops the Work Breakdown Structure, and the project schedule gets updated.

Utilizing the following tools can optimize project costs for automation:

- project management tools such as project scheduler
- design automation tools to automate development of system design and implementation
- process simulation tool to test and verify the control strategies without affecting the I/O cards and the field instrumentation
- document management tools to control changes and document the automation activities. This helps to shorten the validation cycle as well. It is desirable to generate the IQ and OQ documents as part of the project cycle
- design automation import/export utilities to automate the information exchange between the plant design outputs and the application engineering database
- vendor tool, which can automatically update the control system manufacturing process if necessary during the project (I/O changes, system architectural changes, software licenses, etc.)
- batch management and control package to define and generate the process and physical model including master recipes and tags to integrate batch management to the equipment data and equipment phases

System Design

The System Design activity of the project cycle is probably the most important activity for a successful project. If the design documents are not generated and maintained properly, the price to pay later is very high. The quality of the application and the quality of the test cycle are proportional to the quality of the system design. Inadequate design has a long-term negative effect on the post project cycle as well. The asset management and automation system management cost increases linearly with the poor design up front.

What are the activities to include during system design for an optimized automation life cycle? Process cell (e.g. fermentation plant) data such as P&IDs, instrument index, and phase logic must be reviewed and divided into modules allowing a practical abstraction of control strategies. Units have to be identified and all associated control modules and equipment modules must be identified and classified. Unit, equipment module, control module, equipment phases, material transfer paths, and interlocking of equipment must be designed as a class of modules. Each module must be linked to its class as an object. The naming conventions make a big difference as well as automating the control design development. Each class must have a standard operator interface developed and stored in libraries as part of the design work. It is often desirable to develop prototypes including at least one module from each class. Once the prototype is developed and tested with the end user they become accepted library elements for reproduction. System design documentation should take the validation activities into account and the IQ and OQ document development effort should be automated as much as possible. All exception handling and alarm management activities for each module should be defined as part of the module properties. Once the equipment specific design is finished, the product specific master recipes can be developed and recipe specific exception handling can be designed and documented.

If the project is a large-scale project (multi product, multi path, networked piping), the design, implementation, testing, installation, and start-up activities can be phased in and segregated between process cell trains.

Traditionally, pharmaceutical companies reserved a large budget for the validation of computer systems of these projects. If validation activities are well planned and executed, they do not have to be resource intensive as in the past. Validation of process automation systems must be a part of the automation methodology itself.

Validation activities for computer systems such as Installation Qualification and Operation Qualification must be carefully defined and documented. The validation process is a lengthy, but required process. Any engineering and documentation tool utilized for the project should have a positive impact on the validation process. For example, automatic creation of IQ and OQ documents and linking these documents to the project engineering documents would make executing the test and incorporating the changes based upon the test easier. Utilization of design automation tools and document management packages can optimize and reduce the cost of validation by decreasing required man-power and decreasing the validation time. A&E firms must be aware of the validation process and incorporate all the tools in a timely fashion. At the tail end of the project, each recipe will be validated to complete the

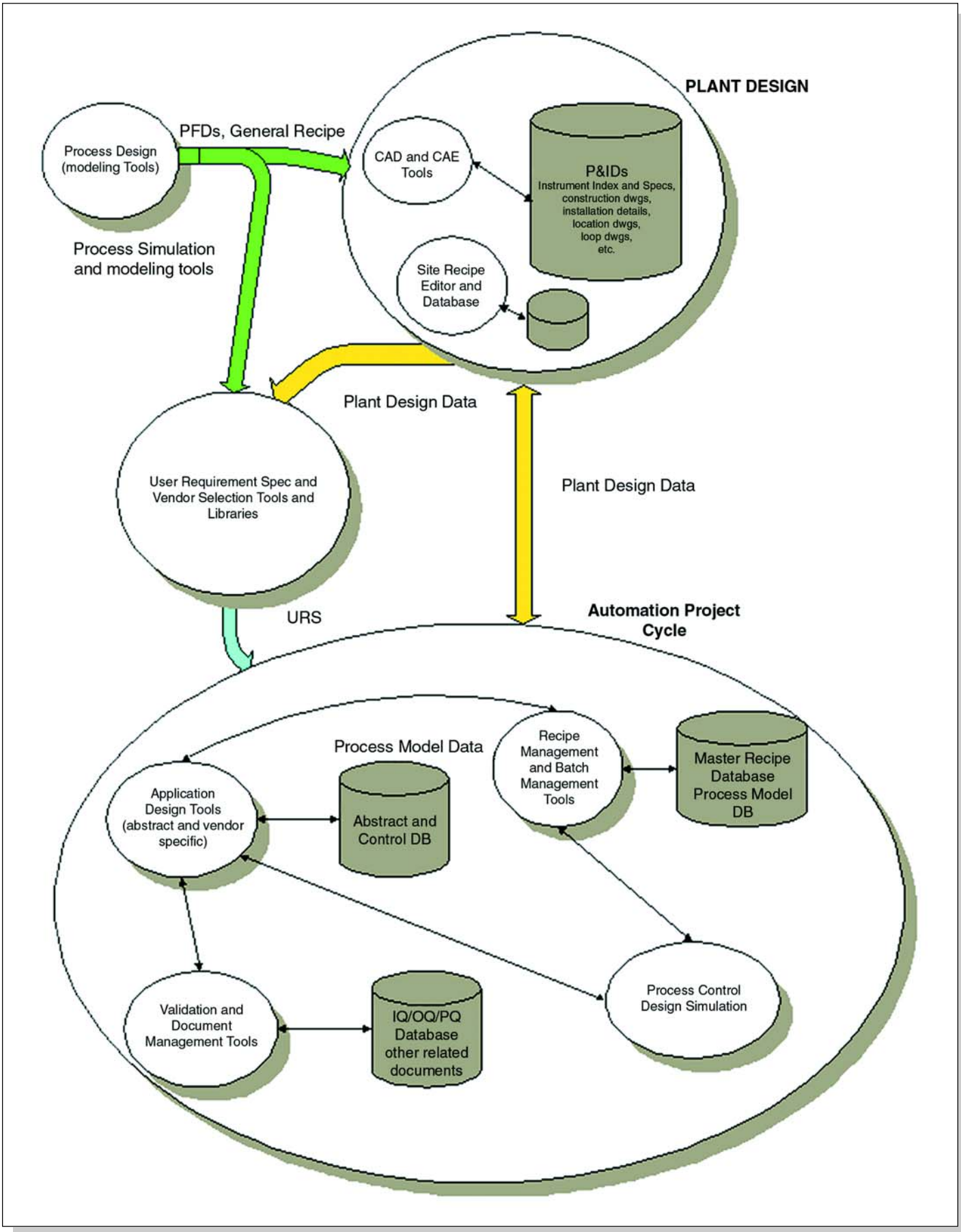

Figure 4. Process, plant design, and automation tool interfaces.

performance qualification. Recipe management packages should have proper revision control, change management, and authorization processes in place to help validation. Prior to the validation stage the automation database change management procedures must be put in place and be effective.

Applying automation standards based upon S88 and modularity of the control design optimize the validation cost. For example, equipment phase logic, recipe phases, and operator interface, and message handling activities can be isolated from each other to minimize the validation requirement if any change occurs. Isolation of product specific logic (control recipe) from the equipment specific logic (equipment phases, equipment module, control module, interlocks) based upon S88 standards helps to decrease validation and later on maintenance cost of systems. This will help to ease the validation once the system is accepted and the plant is in production. Project engineers should always take the impact to the validation efforts when they design a control strategy. Therefore, it is advisable to get the validation engineering involved early in the project instead of waiting for the FAT test and installation at site.

There are multiple technologies and tools available, or are becoming available, to optimize the product development and automation project and plant design and construction cycles as part of the product life cycle. Figure 4 shows the possible interface of these tools.

Now it Works! (Manufacturing Phase of the Product Life Cycle)

Once the validation steps are completed the quality management and the plant operations accept the asset for the full production. At this time, the pharmaceutical company is well in the middle of product marketing and sales. All change management procedures are put in place. Maintenance management and plant asset management tools and procedures are implemented.

Tools and enabling technologies are available today to view the plant status, equipment status, material management, recipe management, production planning and scheduling information, and process management information from anywhere and anytime. Software tools that were utilized to optimize the project cycle are handed over to the plant engineering and maintenance teams to maintain the system and perform necessary updates and changes from time to time.

When a new product starts its life cycle, decisions have to be made on process development and supply of the product. Assessment will be made either to use a flexible plant, retrofit an existing plant, or build a new plant for the product.

Where are we headed in the New Millennium?

Focusing on product life cycle optimization in the new millennium, manufacturing plants have a great deal of room for improvements to cut down time to market for the new products. This is still the relatively untapped area of the enterprise compared to all other business related computerization and optimization. Automation life cycle optimization is the major section of the product life cycle optimization.

Utilization of new technologies and engineering methodologies based upon the standards such as S88 and emerging SP95 will make the automating of manufacturing processes more affordable and necessary to remain competitive. We will see engineering cost and time being decreased by more than 50%. The equipment phase logic and batch management and control function blocks will become commodities just like the PID loops of continuous control in coming generations of DCS and PLC based automation systems.

We will begin seeing new business models implemented based upon e-commerce from process automation suppliers. It won't be surprising to see more and more lease based and bundled services which not only perform engineering, but also maintain the applied systems via web based infrastructure. Once again, existing process automation investments should be better utilized to provide a competitive advantage.

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This article was developed by the ISPE Technical Documents Steering Committee to help explain the rationale behind the development of the ISPE Baseline® Guides, what's in the Guides, and how they relate to one another.

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Introduction to ISPE Baseline® Guides

What are the Baseline® Guides?

The Baseline® Guides are a series of industry publications developed in partnership with the US Food and Drug Administration (FDA). Each volume in the series is a collaborative effort of industry leaders representing a broad cross-section of manufacturers and other industry experts. The Guides document current industry practice for facilities and systems used for production of pharmaceutical products and medical devices. They are intended to:

- establish a baseline approach to new and renovated facility design, construction, commissioning, and qualification, that is based upon clear understanding of the type of product and its manufacturing process
- prioritize facility design features based upon the impact on product and process
- avoid unnecessary spending on facility features that do not contribute to consistent production of quality products

It is important to understand that these guides are not regulatory documents. Where non-engineering issues are covered, the information is included to show engineers the importance of such topics, and the impact they have on facility design. Such non-engineering topics, therefore, are not covered comprehensively, and specific advice from Quality Assurance Departments should be sought where additional information is required.

The Guide principles also may be applied to existing facilities as they are upgraded or modernized.

Baseline® Guides Objectives

- to reduce cost of producing pharmaceutical products and medical devices while maintaining or improving product quality and consistency
- to provide consistent guidance for design and construction of manufacturing facilities regulated by FDA and other health authorities
- to help prevent misinterpretation of regulations which govern manufacturing operations

The Baseline® Approach

The Baseline® approach identifies features of the facility, which may affect the ability to reliably and consistently produce quality pharmaceutical products and medical devices. Features are prioritized to focus on those, which are most critical to the production of safe and reliable products. Investment capital and manpower can then be allocated most productively through intelligent selection of simple and effective systems.

Alternative Designs

The Baseline® Guides address the concept of alternative designs. This aspect of the Guides is critical because it enables the Guides to be adapted to the corporate characteristics of each manufacturer. Where appropriate, Guides identify advantages and disadvantages of design alternatives and provide information to help assess benefits. Alternatives can then be reviewed based upon economics, historical data, and other factors to select an approach consistent with the manufacturer's product and corporate characteristics.

Manufacturers may elect to construct simpler, less capital intensive facilities and utilize procedural controls to maintain quality, or may invest more capital to construct highly automated operations and rely less on operational procedures to assure product quality.

The Guides provide background to accommodate the approach which best fits the specific manufacturer and the needs and economics of a specific product and site location.

How the Baseline® Guides Relate

Current Guides are listed below and the relationship between the Guides is shown in Figure 1.

The Guides are categorized as:

1. **Vertical Guides** which address specific types of product manufacturing operations

2. **Horizontal Guides** which address common support systems and functions such as pharmaceutical water or facility commissioning and qualification

Guides that focus on manufacturing operations include brief sections introducing concepts which are covered in detail in **Horizontal Guides**.

Vertical Guides: Manufacturing Operation Based Guides

Volume 1: Bulk Pharmaceutical Chemical Facilities

The guide covers bulk active, bulk intermediate and bulk excipient facilities, and can be applied to sterile and aseptic bulk manufacturing. It also can be applied to bulk pilot plants and scale-up facilities. It does not apply directly to bulk biological facilities.

The following key concepts are addressed:

- prevalent current design practice for Bulk Pharmaceutical Chemical (BPC) Facilities
- critical process steps
- product characterization and assessment of contamination exposure risks
- level of protection
- critical product and process parameters
- HVAC application for BPCs
- good engineering practice and enhanced documentation

Volume 2: Oral Solid Dosage Forms

This Guide covers facilities which manufacture oral solid dosage forms including tablets, capsules, and powders. It may be applied to clinical supply facilities of these product types. It is not intended to address the manufacture of vitamins, excipients, sterile products, topicals, oral liquids or aerosols.

The following key concepts are addressed:

- prevalent current design practice for Oral Solid Dosage manufacturing facilities
- proper application of facility design *and* procedures to provide GMP compliance
- impact of *non-GMP* technology selections upon facility design and costs
- manufacturer assessment of contamination risk
- product and processing considerations
- flow of people and materials
- selection of materials and finishes
- HVAC applications for oral solid dose facilities

Volume 3: Sterile Manufacturing Facilities

This Guide covers facilities for aseptic processing and terminal sterilization of formulated products, generally for parenteral use. It is applicable to formulations which use active ingredients derived from either conventional chemistry or biopharmaceutical processing. This Guide may also be relevant to sterile bulks, medical devices or other sterile pharmaceutical products.

The following key concepts are addressed:

- prevalent current design practice for Sterile Manufacturing Facilities
- barrier-isolation technology
- integrated facility design
- consistent HVAC terminology
- aseptic processing area operations and process equipment
- flow of people and materials
- selection of materials and finishes
- "in operation" condition for HVAC

Horizontal Guides: System or Function Based Guides (Volume 4 and Volume 5 under preparation)

Volume 4: Water and Steam Systems

This Guide covers water and steam systems for all types of pharmaceutical manufacturing facilities. It covers selection principles for water quality. Generation, storage and distribution systems are addressed. It should be used to complement product specific Guides listed above.

The following key concepts are addressed:

- prevalent current design practice for pharmaceutical water and steam systems
- fundamental criteria for selection of water quality
- water and steam systems programming and basic design approach
- water treatment system pros and cons
- pharmaceutical water distribution system types, advantages, and disadvantages
- control of bio-burden in pharmaceutical water systems

Volume 5: Commissioning and Qualification Guide

This Guide covers principles of commissioning and qualification for manufacturing facilities regulated by FDA and other health authorities. It should be used to complement product specific Guides listed above.

The following key concepts are addressed:

- value added approaches to commissioning and qualifying facilities
- good engineering practices, including master planing and project management considerations
- system impact assessment as a vehicle to optimize the scope of the qualification effort
- the appropriate role for Quality Assurance in the commissioning and qualification of facilities
- using enhanced design review to assure an efficient commissioning and qualification effort
- commissioning practices for effective project execution
- the qualification process and its contribution to the success of facility projects
- assessment of qualification requirements to match product requirements

Revision of Baseline® Guides

The healthcare industry is continually evolving; therefore, the Baseline® Guides also will evolve. Each Guide will be reviewed and updated periodically. The frequency of revision will be based upon the rate of evolution taking place in that sector of industry. Because the Guides continuously evolve, versions of a specific Guide may not be completely integrated with other Guides.

Information regarding latest Guide editions and the status of new or revised Guides is available by calling ISPE or by visiting ISPE's Web site at www.ispe.org. The web site provides other information that may be helpful when using the Guides. Additional Guide updates may be published in ISPE's

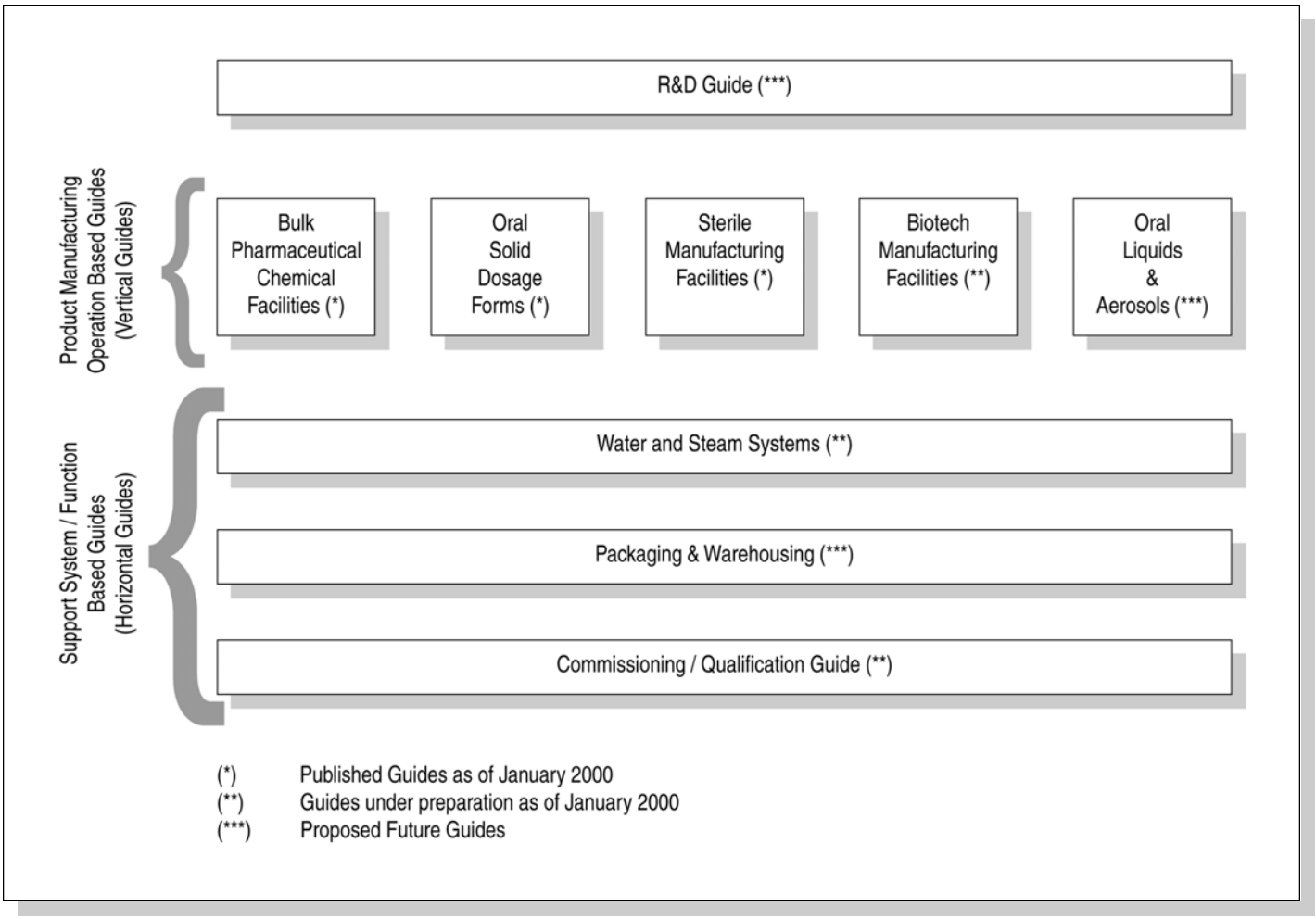

Figure 1. Relationships between guides.

Pharmaceutical Engineering magazine.

Dealing with Guide Interrelationships

The Guides were categorized to communicate information logically and in simple terms. In real life, unit operations interrelate and the interactions within a facility can become complex. Proper application of the Guides requires the user to understand these operational relationships and to apply the Guides accordingly.

In addition to obvious overlaps between support system function and operations based Guides, other overlap is possible or even likely. Many pharmaceutical facilities are comprised of manufacturing operations for multiple products and or multiple phases of pharmaceutical processing. Frequently these facilities have adjacent operations, which fall within the realm of several different Guides.

Economic and practical solutions should be considered with regard to common utilities serving adjacent spaces. This is especially true of modifications to existing facilities. System capacities, available space, reliability and service requirements drive decisions, such as whether to use independent or combined HVAC systems. It may, for example, be more practical and economical to provide WFI quality water when USP grade water is appropriate.

In evaluating common utilities it is always essential to carefully consider how that utility might realistically communicate contaminants from one operation to another.

While each Manufacturing Operations-based Vertical Guide contains sections on HVAC and similar support functions, support systems often serve more than one type of manufacturing operation. Concepts on which system designs are based are fundamentally the same. Where common systems serve multiple areas, the designer should apply these basic principles to define the requirements and identify appropriate solutions. The designer *must* understand the impact of the support function on the product and/or process. Critical attention should be given to systems that affect the ability to consistently and reliably produce quality product.

Each specific manufacturer's situation is different and will require independent analysis to determine best solutions. Often there are several suitable solutions. The alternatives provide flexibility, life cycle cost opportunities and the opportunity to adapt the facility to likely future needs or specific corporate characteristics.

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Using the IDEF as a Facility Planning Tool

by Mary Ellen Champion

The article gives a case study of communication during the preliminary design of a contract manufacturing facility for parenteral and bio products. When we became aware that the client (the user) did not relate well to floor plans and P&IDs, we tried using a communication tool. Our communications were aided by the use of a graphic known as Integrated Definition or IDEF.

The language by which we as architects, engineers, and construction managers communicate is technical drawings. Drawings showing plan views and elevation views are excellent tools for the trained eye of the engineer and construction team, and are universally understood by engineers. However, not everyone in the world is an architect or an engineer. Many of us think that "if we know something, then everyone else should know it and understand it." We believe that everyone can read floor plans and then envision what their lab or manufacturing area will look like. This author's experience managing various projects suggests that these statements and beliefs are just not true.

In order to give a customer what he needs and hopefully what he wants, we must be able to communicate with that customer. The future user, the ultimate customer using the area being designed or renovated, should have a clear understanding of what is being designed. In our quest to communicate, it is important to remember that a picture or a graphic usually conveys information better and faster than the written or spoken word. Our job, as architects and engineers, is to choose the best tool to convey our design requirements to the customer, and to enable the customer to convey their needs to the design team.

One tool that the author has found to be of great assistance is the Integrated Definition or IDEF graphic. In 1973, Douglas T. Ross created the first *Author Guide* used to train analysts in the "Architectural Method" used in the Air Force Computer-Aided Manufacturing (AFCAN) Project. This methodology became known as Structured Analysis.[1] The next step was the graphical approach of the IDEF based upon the Structured Analysis and Design Technique (SADT). In 1981, the US Air Force Program for Integrated Computer-Aided Manufacturing (ICAM) standardized and made public a subset of SADT called IDEF0.[2] FIPS Publication 183 originally described the IDEF0. Since then, the IDEF model has been expanded and adapted for multiple uses. The 7 IDEF standards have been used to build the following:

- IDEF0 Functional Model
- IDEF1 Information Model
- IDEF1X Semantic Model (Databases) also called Entity Relationship Diagrams
- IDEF2 Dynamic Model (simulation)
- IDEF3 Process Description
- IDEF4 Object Oriented Model
- IDEF5 Concept/Ontology Description
- IDEF6 Design Rationale Model[3]

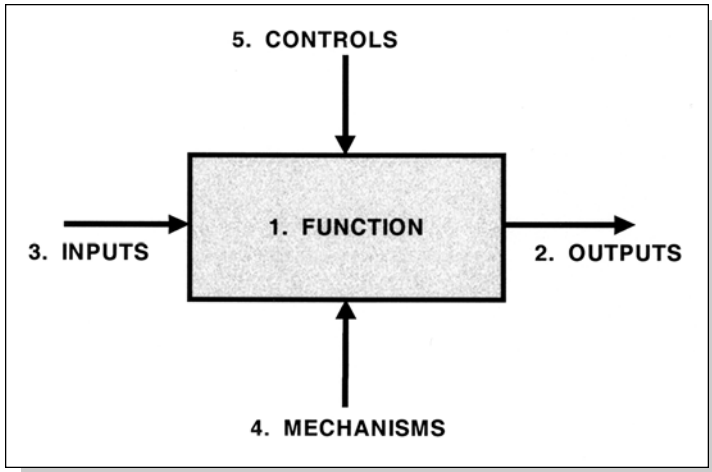

Figure 1. IDEF model.

Note that IDEF3 and IDEF5 are descriptive while the others are used to build a model. Research found the 0 following IDEF to be lowered in some cases and not in others. This article uses the lowered version and is confined to the original IDEF0, Functional Model only. The IDEF0 method results in an organized graphic with a representation of the activities

and the important relations between these activities. The graphic model was designed to define each function in a series of functions and to decompose each function into its systems or subprocesses.

The original tool, the IDEF0, consists of five parts: a central box containing the Function (or Process as used in the following example), and four arrows, one on each side of the box. The arrows represent things, such as information or data, equipment, people, materials, or product. The left arrow points into the box and is labeled "Input,"which represents those things used and transformed by the Function or Process. The right side of the box has an arrow leaving the box labeled "Outputs," which represents the results of the Function or Process. The top of the box has an arrow entering the box labeled "Controls" (or Constraints as used in the following example). The bottom of the box has an arrow pointing into the box labeled "Mechanisms" (or Resources as used in the following example). The IDEF tool should be completed in the order of Function (or Process), Outputs, Inputs, Mechanisms (or Resources), and then Controls (or Constraints). The numbers 1 through 5 shown in Figure 1 show this recommended order of completion.

While working in the United States with scientists and administrators at a College of Pharmacy in the Midwest and a pharmaceutical company on the East Coast, our team became aware that discussions over a floor plan sketch did not elicit the needed information from the users of the space. The task was to design a facility for a Contract Manufacturing Organization (CMO) for sterile fill and biological products. In order to collect data from analytical thinkers that are not architects and engineers, the IDEF was used to document the processes within a parenteral facility. The IDEF was extrapolated further for use as a communication tool to document the design basis for the project.

The following discussion illustrates the use of the IDEF0 to establish the design requirements for a parenteral facility. For the sterile fill project, an overview IDEF was constructed in order to identify the major or mainstream processes in the entire cGMP Parenteral Process Facility. The first step in constructing an IDEF was to complete the "Function or Process" box. The User identified the mainstream processes required for a research facility for parenterals as follows:

A. Receiving
B. Preparation
C. Processing
D. Finishing
E. Shipping.

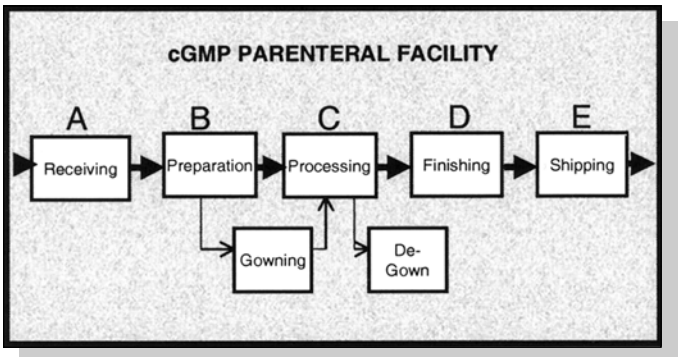

Figure 2. Mainstream processes for parenteral facility.

Note that the IDEF0 tool was designed to define the requirements or needs of a function. It was not designed to develop the process itself. The User must first develop the process sequencing. These processes were placed in the order of occurrence in the "Function" (or Process) Box as shown in Figure 2. Activities that were not in the mainstream process, but were necessary in the facility such as Gowning, were indicated in boxes below the mainstream activities. Arrows connect the boxes and define how the boxes influence each other. Outputs from one activity influence the activity in future boxes.

After the mainstream processes were identified, an IDEF was constructed for each of them, further defining each of the major processes into their component parts. By assigning alpha designations to the major processes and numerical designations to the subprocesses, tracking, and communication was simplified. The IDEF0 tool identifies these numbering sequences as "nodes." The first major process, A. Receiving, was taken to this second level by defining its subprocesses. The subprocesses of A. Receiving were defined as:

1. Receiving
2. Quarantine
3. QC Lab
4. Approved Storage

The subprocesses could be further separated or "decomposed," which is the correct term for the IDEF tool, into systems or unit operations. This expanded A. Receiving Process is shown in Figure 3.

Figure 3 also shows the process with its general Outputs, Inputs, Resources, and Constraints. This data is gathered through interviewing Users, referencing documents and viewing the system or process activity in operation. Outputs shown are Finish Packing Material, Information Systems, Documentation including Receiving Reports and QC Releases, Cleaning Supplies, Sanitizing Material, Biologicals, Actives, Inactives, Equipment, and Waste. Inputs shown are Packing Material, Cleaning Supplies, Sanitizing Material, Biologicals, Actives, Inactives, Equipment, Spare Parts, and Documentation such as Packing Slips. Note that many of these items are "passed through" while others are generated or altered during the process. The general Resources are Personnel, Utilities, and Equipment. The Constraints are Exterior Location, Containment, Storage Space, Temperature, and Humidity. Each individual IDEF diagram is a piece of the larger model.

Using the IDEF as a communication tool on this project was

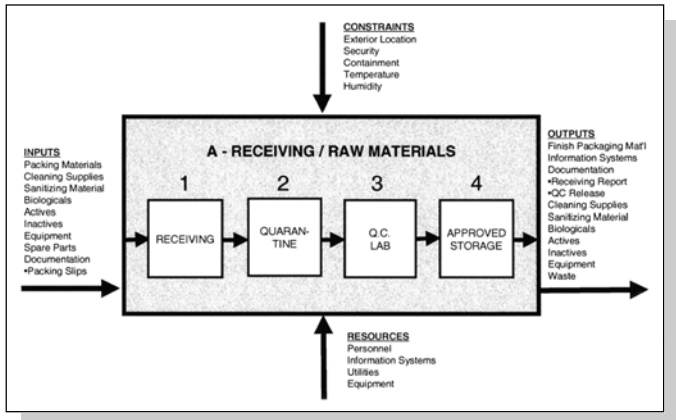

Figure 3. Receiving process.

EQUIPMENT	1	2	3	4
Dock Leveler	X			
Dock Door Seals	X			
Dock Light (bug)	X			
Hand Truck	X			
Fork Lift	X			
Platform Scale	X			
Cool Room		X		X
Freezer		X	X	X
Rack Storage		X		X
Shelving		X	X	X
Plastic Pallets	X	X		X
SS Carts		X	X	X
Lab Casework			X	
Fume Hood			X	
Countertop Equipment			X	
Computer	X		X	

Table A. Equipment list.

an instant success. Everyone involved understood his or her process and the Inputs, Outputs, Resources, and Constraints that related to his or her process.

After an IDEF was developed for each of the main processes, each individual on the team reviewed his or her IDEF. The model must be reviewed, approved and validated - a process well known in the pharmaceutical industry. One review method using a kit is very well explained in a paper written by William D. Waltman and Adrien Presley.[4] After compiling the individual comments, a review meeting was held. The joint team of architects, engineers, scientists, operators, and administrators, surrounded by completed IDEF boards, felt proud of the ease and accuracy of information transfer. Each team member agreed that they understood the data incorporated in the IDEF diagrams. Because the IDEF exercise had proven so successful, the team decided to take great license with the IDEF tool and extrapolate it into two further uses. First, we expanded the completed IDEFs of the mainstream processes to define the specific parameters of the listed Resources and Constraints. Actual personnel were identified for each specific function or process. For example, the QC lab needed a Lab Manager or Supervisor and several Lab Technicians. Equipment such as ovens, hoods, autoclaves, etc. were identified. Constraints such as security and humidity requirements were identified.

Second, we developed tables with these specific parameters and quantified the type and size of each parameter. For

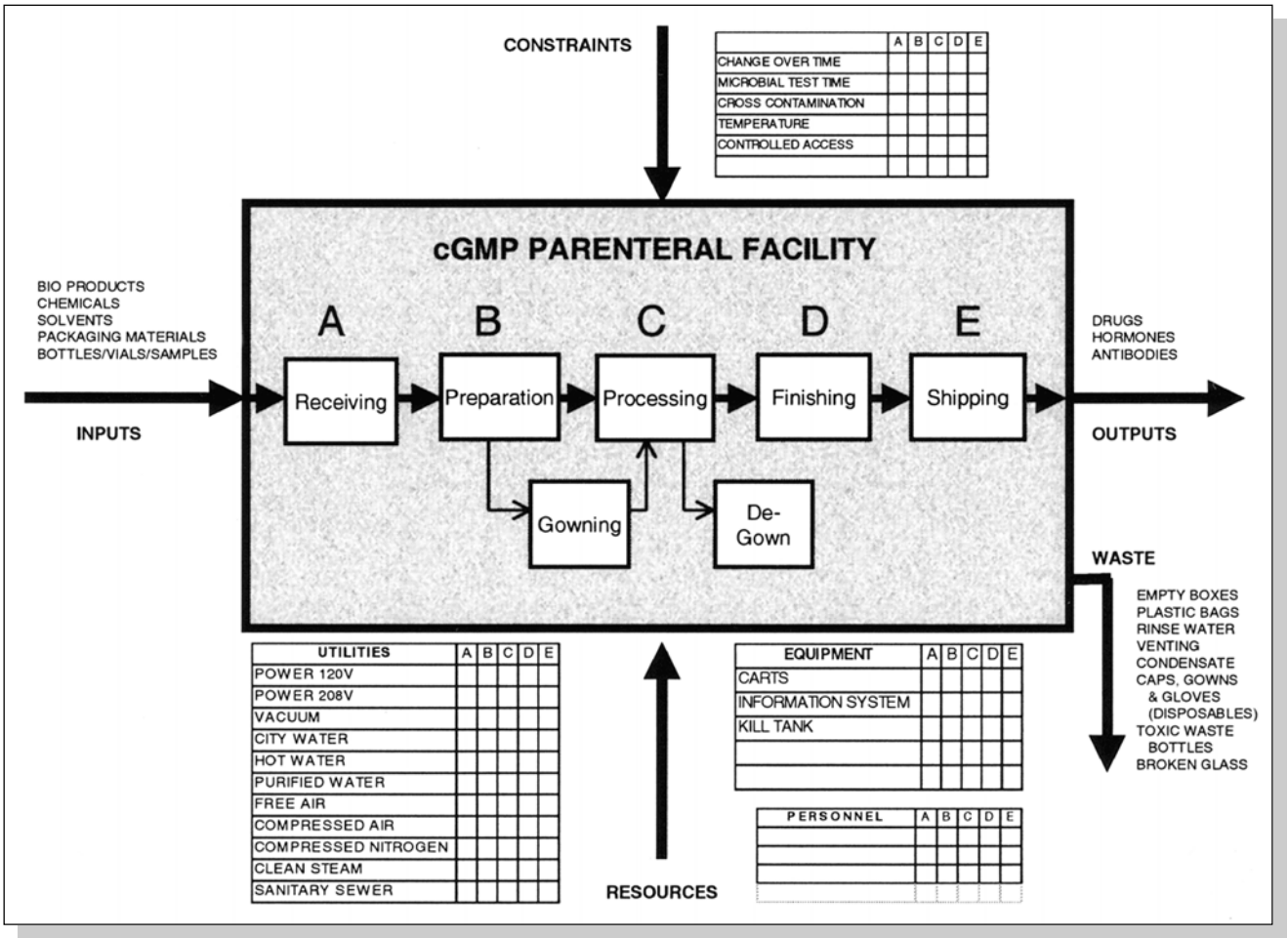

Figure 4. Mainstream parenteral processes.

QC LAB	
80 LF Counter	400 SF
Toxic Hood	40 SF
6 Desks & Chairs	180 SF
7 Computers (6 on desks)	16 SF
Carts	20 SF
2 Incubators	30 SF
1 Freezer	16 SF
Sink & Drainboard	20 SF
Refrigerator	16 SF
Door Swing	20 SF
QC Lab Subtotal	758 SF

MICROBIOLOGY LAB	
40 LF Counter	200 SF
SS Carts	20 SF
Autoclave	10 SF
5 Computers (4 on desks)	16 SF
4 Desks	120 SF
Bio Hood	40 SF
2 Incubators	30 SF
Refrigerator	16 SF
Freezer	12 SF
Door Swing	20 SF
Sink & Drainboard	20 SF
Laminar Flow clearance	40 SF
Micro Lab Subtotal	544 SF

LAB OFFICE	
Desk & Chair	42 SF
4 Chairs	0 SF
Conference Table	120 SF
Computer & Stand	16 SF
File Cabinet	10 SF
Marker Board	12 SF
Door Swing	20 SF
Office Subtotal	220 SF

LAB STORAGE	
Door swing - lock	0 SF
10 SF 12" shelving	50 SF
Storage Subtotal	50 SF

Table B. QC Lab square footage.

example, the QC lab required one QC Manager and four Lab Technicians, etc. The QC lab needed two incubators and one toxic hood, etc. Third, we assigned square footage requirements to each specific parameter. For example, the toxic hood and operator use of the hood needed 40 square feet.

Some of the equipment resources developed for the Mainstream Process of Receiving are illustrated in Table A. The defined square footage requirements of each piece of equipment in the QC lab are shown in Table B. Adding the values from Table B show that the QC Lab area requires a minimum of 1500 square feet. The square footage allowances included aisle space and/or maintenance space needed to operate and service each piece of equipment; however, general circulation area is not included in Table B numbers. This method also helped identify the space or function separations. Note that these separations did not necessarily mean different rooms. The results of the square footage exercise were used as a check against the layouts that were developed from the architect's bubble diagrams. This method also can be used to check industry "rules of thumb," such as CAP standards, which give a minimum of 50 square footage for a lab tech.

Such information can be conveniently summarized using the IDEF tool. Figure 4 illustrates the mainstream processes of the Parenteral Facility with the inserted blank tables. As an exercise, you might try your hand at programming by entering a "x" for each constraint and resource needed in each mainstream process or develop an IDEF diagram tailored to your next project.

It is important to remember that the goal is to communicate in the easiest way possible for the people involved. Each group is different and the individuals have varying knowledge and backgrounds. In order to make our customers happy and meet their expectations, we must all communicate clearly and easily. Try the IDEF tool as one method to aid in your team communication.

One indication that the team liked the IDEF0 is that one of the scientists on the team has since adapted the IDEF0 graphic for educational purposes in his laboratory.

In summary, the IDEF0 technique is useful for gathering and interrupting very complex and sometimes conflicting information. The major benefits derived with this communication tool are scope clarification, efficient programming, promotion of teamwork, and gaining the buy-in of all stakeholders. An added benefit is that the graphics are great for presentations often necessary to secure financial appropriations.

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About the Author

Mary Ellen Champion received both a bachelor of architecture and a bachelor of applied arts, which is a topic major in interior design, art, and architecture from the University of Kentucky. While attending college, Champion participated for five years in the Big Sisters of America Program. She is currently a Project Manager in CH2M Hill Industrial Design Corporation's (IDC's) Fine Chemical/ Pharmaceuticals Group. She has more than 25 years of experience in architectural design and project management. Most of her experience is in the design of facilities and in the development and delivery of technical training for the pharmaceutical industry. Champion also has served on a strategy planning committee for a pharmaceutical manufacturing company and has been a speaker at management meetings for several pharmaceutical manufacturers and a course leader and speaker at both the chapter, regional, and international levels of ISPE. She has served as Secretary, Vice President, and President of the ISPE Great Lakes Chapter and is currently a member of ISPE's Publications/Internet Committee. Champion is a Registered Architect, a certified Project Management Professional (PMP), and a member of the Project Management Institute (PMI).

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Automation, Business, and Operating Advances Align into New Paradigm for Economic Performance Improvement

by Janice Abel and Peter Martin

The next century promises unprecedented market growth for the pharmaceutical industry, but manufacturers will have to fight harder than ever to protect their share. This article describes recent advances in strategic management and process automation that will help companies maintain their competitive edge in the turbulent global economy.

As the pharmaceutical industry enters the new millennium, demand for pharmaceutical products is expected to be at an all-time high, but intensifying competitive pressures and a turbulent global business environment will require manufacturers to align operations more strategically with business objectives than ever before. Fortunately, developments in technology, government regulation, and economic performance management are now converging to bring pharmaceutical manufacturers more control over economic performance. Companies that interpret and apply these developments effectively stand to gain a significant competitive edge in the next century.

Driving the market growth are innovative new medicines, which are finding an aging, financially comfortable marketplace willing to pay for them. By the year 2002, the global market for pharmaceuticals could double or even triple, with sales already surpassing $120 billion - *Figure 1*. In addition, by the year 2006, the total US sales of biotech products could exceed $32 billion. But barriers to market entry for pharmaceutical products are falling as quickly as the demand is rising, creating the most competitive climate this industry has ever known.

Over the next 10 years, more than $46 billion in pharmaceutical products will lose their patent protection, intensifying competition from generic products around the globe. The generic drug industry has already grown from about 21% in 1985 to more than 42% in today's pharmaceutical market and, fueled by continued cost-reduction pressures from managed care, will continue to grow into the next century. In addition, companies are being driven to offer newer more potent specialized drugs that are not only more difficult to manufacture, but also must be made in very small quantities, requiring the production of multiple products on the same equipment. This "genericizing" of the marketplace also means companies must be significantly more agile and much better able to adapt their production lines to leverage demand fluctuations and core competencies.

Such new pressures are adding to - not replacing - traditional market pressures. The Pharmaceutical Research and Manufacturers Association (PhRMA), for example, estimates that the global research-based pharmaceutical industry will invest more than $24 billion this year alone in R&D, which represents 19% investment for research-based pharmaceutical companies, significantly higher than the 4 % average for other industries - *Figure 2*. For biotechnology companies, this percentage is even higher.

The estimated $500 million and more than 12 years

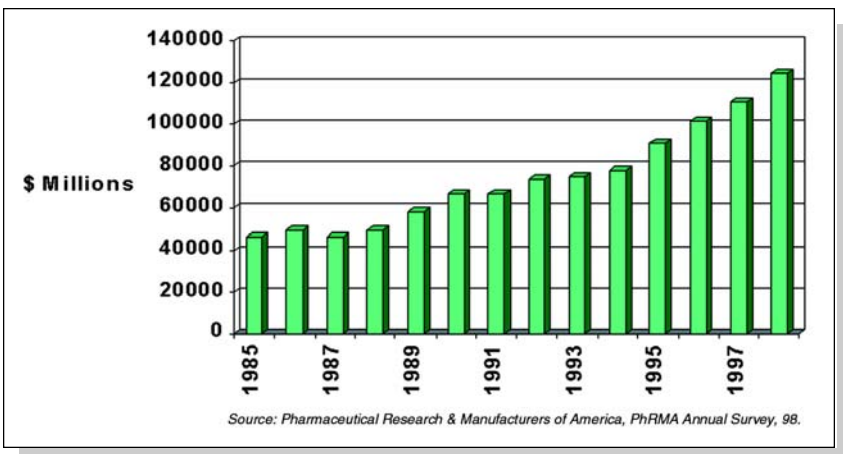

Figure 1. Pharmaceutical sales are at $120 billion and growing.

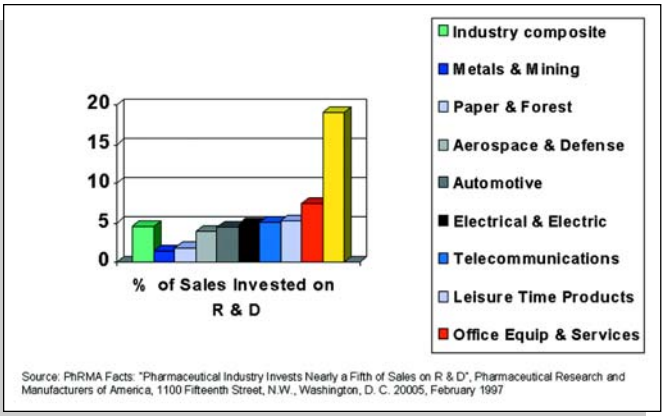

Figure 2. Pharmaceutical industry spends more on R&D than any other industry.

it takes to bring a product to market is not expected to change much, nor will there be much widening of the 5-7 year window to recoup that investment. And although recent FDA regulations enable greater use of electronic signatures and documentation that ease compliance, validation requirements themselves will remain in place and, if anything, intensify.

One symptom of the intensifying business climate is the upswing of mergers and acquisitions, driven in large part by the need to cut costs in marketing, distribution, and manufacturing. By the year 2005, some analysts believe there could be as few as 13 worldwide pharmaceutical giants. While such consolidation looks good on the balance sheets, it often adds a new level of heterogeneity, which must be reconciled as companies seek greater alignment of business strategy and operations.

As pharmaceutical manufacturers face the ever-present R&D and validation pressures with significantly reduced patent protection, survival will require new strategies to improve quality, yield, and speed to market, while keeping costs in control. Such forces have always driven business strategy, but now there is greater urgency to balance the trade-offs between one strategic path over another. The good news is that there are now also more technological and financial advances available to help meet these objectives and ultimately improve the return on investment (ROI).

Business Strategy Revisited

To make the most of emerging technology and management innovations, each company must begin with a clear set of strategic priorities. Performance improvement initiatives to target quality, yield, cost reduction, speed to market, regulatory, safety, or any other area must be undertaken with a clear view of their potential impact on economic performance. Should you improve quality at the risk of reducing yields or changing your validation process? Should you increase speed to market if the cost of doing so prohibits cost reductions? Such decisions cannot be made in isolation throughout an organization, but must be dictated by business strategy set at the highest executive levels.

Pharmaceutical manufacturers, with best selling patented products, are pursuing strategies based more upon quality improvements, and are looking to supply chain management tactics for execution. On the other hand, the generic or commodity pharmaceutical manufacturer needs to improve both throughput and quality while reducing costs at the same time. Overall due to HMOs and other government pressures, most manufacturers are ultimately pursuing ways to produce products more efficiently. Once the manufacturing strategy is set, maximizing economic performance requires enterprisewide alignment of operations.

A helpful technique for modeling this strategic alignment is known as Vollmann Decomposition Analysis. In Vollmann Decomposition Analysis, every operation decomposes into the strategy, action, and measurement criteria that are necessary to complete it. The top of the triangle in Figure 3, for example, represents the strategy that the board of directors or the executive management team set for each year. Each strategy, is supported by actions which are necessary to generate the required success measures, each of which in turn decomposes into another set of supporting strategies, actions, and measures. While only a few people in an organization would be responsible for ensuring corporate-wide alignment of strategy and action, everyone in the company must be responsible for ensuring that their own performance improvement initiatives track to company strategy and that these initiatives are likewise supported by compatible strategies and activities beneath them.

And, while this process of identifying high-level objectives and aligning them throughout the organization may ring similar to the business reengineering rhetoric of the nineties, there are significant differences. Business process reengineering was very much a top down approach that became increasingly impractical for process manufacturers as it closed in on the plant floor. However, technology and standards have advanced to the measurability necessary to complete the model, the visibility that empowers employees at every level of the company to contribute to and actually see the impact on business profitability.

Integrating the Pharmaceutical Enterprise

Figure 4 depicts typical elements of the pharmaceutical enterprise that must be brought into alignment with the business strategy. As we enter the next century, it is feasible to implement information systems that enable managers and operators to visualize how just about any combination of the processes represented by this diagram impact each other. It is now very possible to implement a system that shows in real-time how plant floor initiatives to reduce contamination or operator error, for example, might impact high level business objectives such as improving quality or cutting costs.

As it strives toward implementing the automation systems that will take it in to the next century, the pharmaceutical industry finds itself lagging somewhat behind other industries

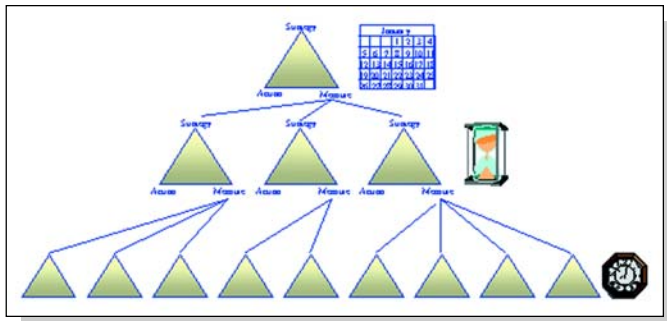

Figure 3. Realizing highest-level economic performance objectives requires alignment of effort at every level of the organization, as illustrated by the Decomposition Analysis developed by Dr. Thomas Vollman.

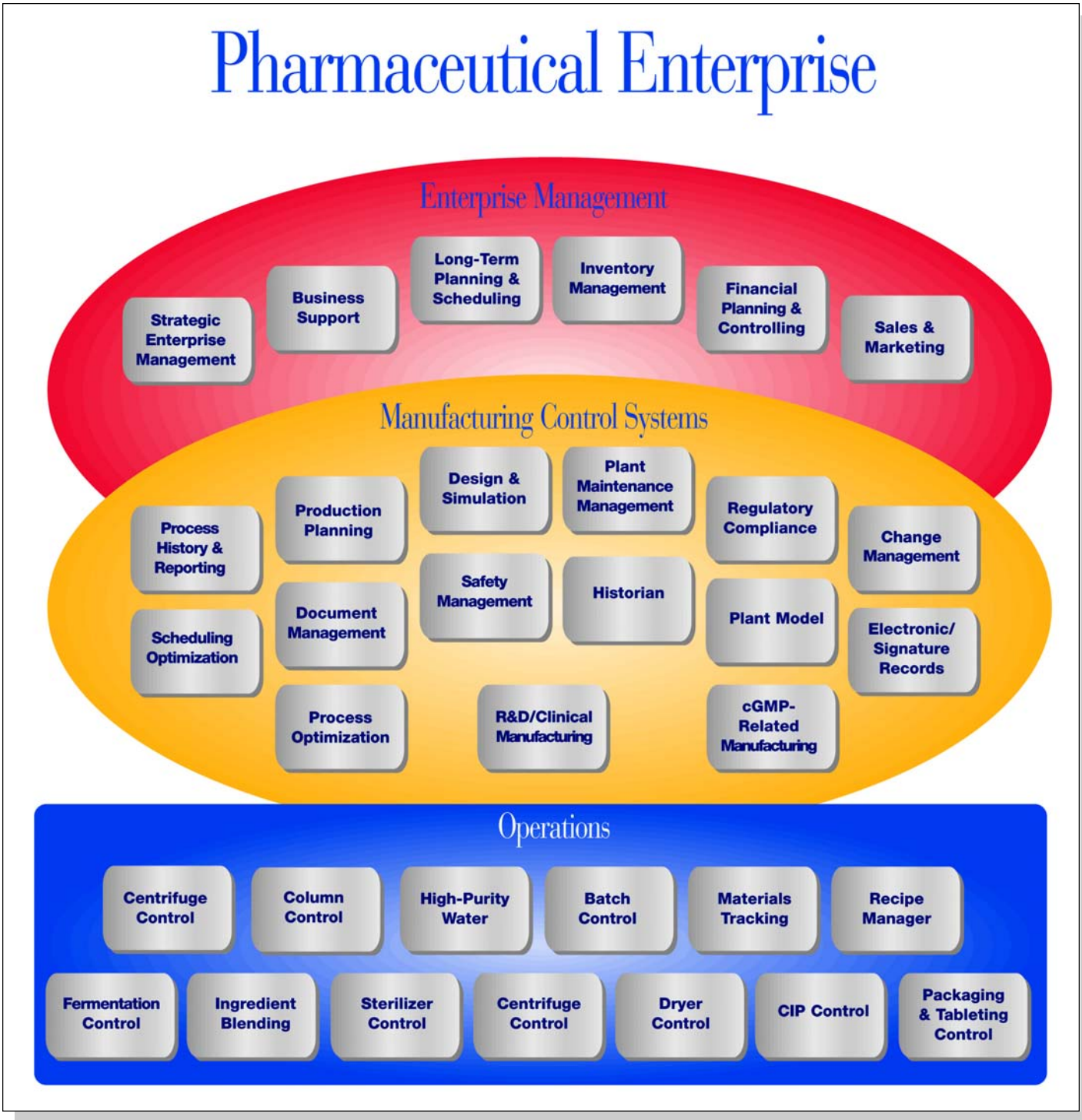

Figure 4. Business success in the next millennium will require strategic alignment enterprise management, manufacturing control and operations technology.

in the deployment of automation. However, this is not for lack of trying. Pharmaceutical processing has always been automation dependent, almost by definition. One cannot, for example, observe temperatures and flows and meet required specifications without using sensing technology of some sort, and cannot do much about what they see without precise controls. In the '70's, the industry showed early leadership in implementing systems to automate such processes. The automation cycle in the pharmaceutical industry began with PLC integration and continued through laboratory automation and operations scheduling, but it was difficult to integrate resulting in the "islands of automation" that are prevalent throughout industry today.

However, in the early '80's, just as industry MIS groups began to evaluate the implications of the PC proliferation that was sweeping the marketplace, hopes were daunted by the FDA restrictions on the use of electronic signatures and electronic documentation in validation. These restrictions perpetuated the use of manual record keeping systems and validation processes that still remain in place today.

Similarly, efforts to streamline operations through batch process automation in the late '80's and early '90's did not pan

out as hoped. Early batch systems were incomplete, proprietary, and often expensive to implement. Many companies concluded that the cost of implementation did not justify the benefit and continued to fall back on tried and true manual or semi-manual systems.

However, in retrospect the caution that industry showed in rushing into technology may prove to have been prudent. They avoided technology for technology's sake-preoccupation that gripped most other market segments. And, now amidst greater urgency to improve performance, quality, and to maximize ROI, they are finding improved techniques and strategies to use state-of-the art technology.

Batch Automation Comes of Age

Many pharmaceutical operations are batch intensive, and they will enjoy the benefit of new technologies that will improve performance, product quality, regulatory compliance, and integrate the plant floor with business systems.

Contributing to the process improvement capability of the new batch control systems are the dual talents of exchanging information with Enterprise Resource Planning (ERP) business information systems, while tracking and controlling plant floor operations. Where business officers once relied on assumptions made during a walk through the plant, they can now obtain real-time data on inventory, unit cost, lot tracking and many other variables from their desktop. Advanced systems also have built-in algorithms to optimize production based upon analysis of historical data and draw on improved traceability to analyze trend information for quality improvement.

These new batch systems owe some of this new versatility to the development and acceptance of computer programming standards by organizations such as the International Society for Measurement and Control (ISA), NAMUR, and International Electrical Commission (IEC). In 1995, the ISA issued its S88.01 standard that enabled creation of interfaces between supervisory control, data acquisition, and Programmable Logic Control (PLC) systems.

The advanced batch control systems also make it easier to comply with current Good Manufacturing Practices (cGMPs) established by the FDA. Poor batch record keeping has in fact been a major source of FDA compliance problems. A recent analysis of FDA warning letter citations, revealed that about 1/3 of the letters concerned batch record keeping.[1] The new batch systems alleviate record keeping problems by tracking events in real-time and enabling a wide variety of FDA compliant reporting options. The FDA has recognized the importance of advanced technology in record keeping and requiring that all companies have plans for replacing outdated legacy systems that do not comply with 21 CFR part 11.

Surely one of the most important developments in the advancement of batch process controls is the 1997 passage of 21 CFR part 11, which defines the guidelines under which the FDA will accept electronic signatures and documentation in meeting validation control requirements. This removes one of the major barriers to process automation and provides a true alternative to manual record-keeping procedures.

Automated batch control systems will reduce operating costs even further by enforcing accuracy and optimizing performance. New batch systems enforce consistency and repeatability in executing recipes so that once a process has been optimized it can be repeated without variation. According to Paul Motise, Consumer Safety Officer for the FDA's Center for Drug Evaluation and Research, the new systems also reduce operator error and sloppy practices. They make it impossible, for example, to engage in "pencil-whipping" type cheating, in which operators sign-off on a process before it is completed. Moreover, the enforcement of automated SOPs, increasing batch-to-batch consistency, decreasing cycle times, and reducing contamination is a key source of quality problems in biotechnology processes.

Back to the Bottom Line

But no matter how well the new technology can improve operations or ease validation pressures, it will not improve economic performance unless related initiatives can be aligned with high-end strategic objectives. The most promising feature of advanced automation that delivers this is the ability to provide real-time measurability. Because these new systems enable on-line, real-time monitoring of just about any batch control operation, it becomes possible for managers to see the impact of their performance improvement initiatives on-line in real-time, as represented by the lower right hand corners of the triangles in Volmann diagrams shown in Figure 3.

To support a yield improvement strategy, for example, a manufacturer may want real-time reporting of off-spec output as a function of process conditions such as temperature and pressure. To increase yield by 10%, plant management may set an off-spec limit and define the pressure and temperature conditions necessary to reach this limit. With real-time measurability and automatic alarming, operators can respond to problems or automatically control the process to meet specifications. At the same time, by viewing a desktop dashboard the process control improvements can be measured and summarized in terms of the real benefits. Using dynamic performance measurements, plant managers can tell at a glance whether the process is operating to specification. They can then examine the data and take immediate steps to optimize their operations.

There are, of course, validation issues which the process engineer must consider prior to making major changes. Depending upon the impact of the change, some such changes can be handled through change control procedures, while others may require some revalidation. However, if the process is designed and validated using standard modules or templates in the process design, the validation process can be minimized.

Eli Lilly is implementing an operator dashboard of the type shown in Figure 5 to increase the efficiency of the incinerators and increase solvent recovery at its Kinsale, Ireland facility. Although the dashboard is not scheduled to go online for several months, Gerard McCarry, leader of Eli Lilly's Kinsale process automation team says that the effort that has gone into mapping out the strategies, actions, and performance measurements has already resulted in productivity improvement and has enabled implementation of advanced optimization and control software which is improving performance further. Even greater benefits are expected once the dashboards begin delivering real-time baseline measurement data to operators, according to McCarry.

McCarry sees this as part of a larger trend toward knowledge management, which he sees as increasingly necessary to handle the complexities of the next generation of pharmaceutical manufacturing. "It's a new paradigm," he said. "The molecules are more complex. The processes are more complex. The global business environment is more dynamic. It seems

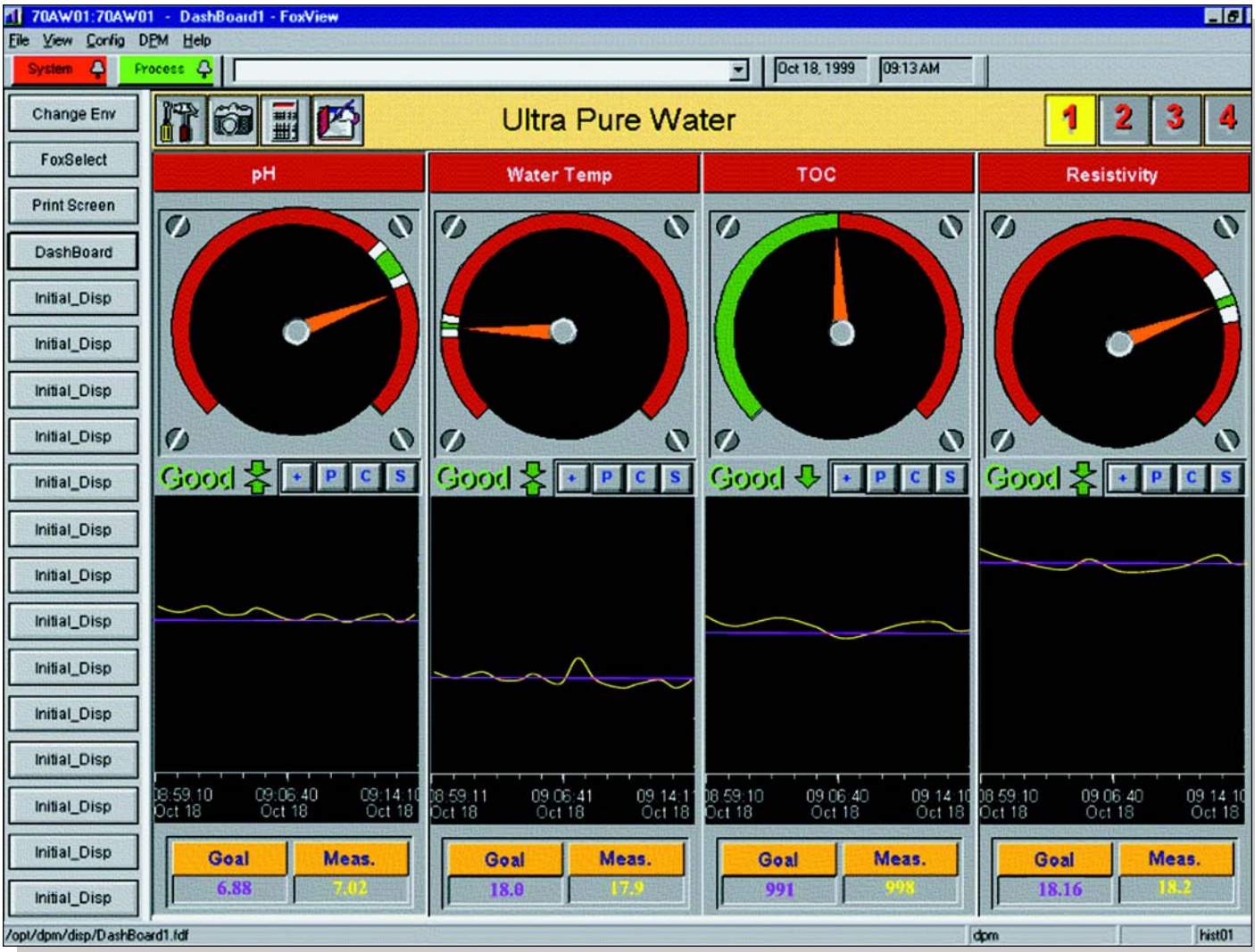

Figure 5. Using a "dashboard" such as this, operators can tell when key performance variables such as pH level, water temperature, and TOC are being maintained at levels necessary to meet profitability requirements, as represented by the purple curves. When the yellow curves drop, operators can see it in real time and make necessary adjustments.

that we are at last getting tools that allow us to store and apply the knowledge we have gained on our production line."

The emerging generation of tools will make it easier for manufacturers to store and apply the knowledge gained on the production line while at the same time freeing operators to make the judgments that will help manage tomorrow's uncertainties. As the pharmaceutical products mature and as everything else in the industry grows more complex – from the molecules to the business environment – a company's knowledge base can become as critical a competitive differentiator as its patents.

Looking at the Lifecycle Benefit

This technology trend toward real-time measurability is converging nicely with a management trend toward lifecycle management. At a recent presentation to investment analysts, for example, Lodewijk J.R. de Vink, Chairman, President and Chief Executive Officer, Warner-Lambert Company, discussed the emphasis that his company is now placing on life cycle management. Likewise, at the 1998 ISPE Annual Meeting, William Smith, III, of Eli Lilly discussed how Eli Lilly uses a lifecycle economic value (EVA) profile to determine the feasibility introducing a new drug to market. A similar kind of lifecycle analysis can be applied to calculating the feasibility of an automation initiative.

A lifecycle economic profile factors in ROI over the lifecycle of the product. As Figure 6 shows, the lifecycle cost of a system is highest at the beginning of an automation project because of purchase, installation, engineering, commissioning, start-up, and other costs. It then drops significantly, but begins to creep up again as the system ages, when training, maintenance, and replacement issues emerge.

To make the most of this information, you must interpret it in the context of its life-cycle economics rather than a pure cost or cost-of-ownership basis. The following equation represents life-cycle economics of a performance improvement initiative for an automation project at its most basic level:

LIFE-CYCLE ECONOMIC PROFILE =
LIFE-CYCLE BENEFIT - LIFE-CYCLE COST.

The LIFE-CYCLE benefit factors the plant cost savings and the value of measured performance resulting from the initiative (e.g. increased yield, reduced contamination,) with any capital value that the initiative might require, such as equipment, hardware, or software. The LIFE-CYCLE COST factors

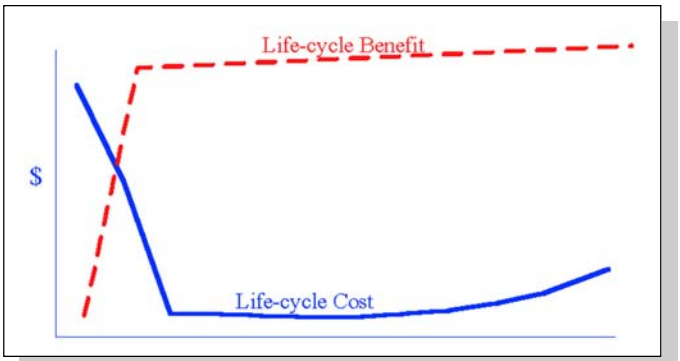

Figure 6. The cost of a system (blue line) is highest at the beginning of an automation project, drops significantly, and then begins to creep up again as the system ages.

in planning, implementation, staffing, and other components of a typical automation cost analysis.

Too often, it is the life-cycle cost factors which weigh heavily in economic calculations, since the cost-information is always much easier to obtain than benefits information, much like the man who lost his keys in the alley, but looked for them in the street where the light was better. Even when decision-makers do consider total cost-of-ownership or operation, they are still applying cost-based evaluation, with little or no factoring of benefits. Once something is pegged a cost – it is difficult for anyone looking at it only on paper to see its true value. Careful attention to measuring and communicating results, however, can provide the data you need to complete the LIFE-CYCLE BENEFIT variable of the equation to ensure viewing of costs in their proper context.

This ability to quantify benefits and map them to high level business strategy, means that we can now take full advantage of technology advances such as the "dashboards" that Eli Lilly is implementing. These enable us to collect and present real-time operations data needed to truly optimize performance in support of strategy.

Such built-in measurability not only provides internal cost justification to pursue business improvement initiatives, it also provides greater leverage in negotiating with vendors when performance improvements involve purchase of products or services. Performance contracts– in which companies pay for efficiency improvements out of related cost-savings – and document the economic performance improvement initiatives, vendors will be more willing to share the risk of implementing solutions.

The Right Ingredients

So, many of the ingredients for success in the new millennium are here. Demand for new and specialized prescription products is rising. New technologies are providing ways to improve productivity, product quality, and comply with validation requirements. New management techniques are guiding us in aligning improved operations with business strategies and sustaining improvements.

And based upon these advances, vendors are adopting business practices that enable companies to pursue economic performance initiatives with little or no risk. We believe that the end of the millennium presents the pharmaceutical manufacturer with unique opportunities and challenges not faced before. While it is not easy to predict the exact nature of the manufacturing environment into the next century, the trend is towards integrated software solutions, process optimization, and economic improvements for the entire supply chain.

It is up to each manufacturer then, to blend these ingredients into the prescription for their own success in this new millennium.

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