This article discusses key economic considerations when negotiating the terms and conditions of a contract with an engineering company to design, procure, build, and assist with validation of a pharmaceutical facility.

Reprinted from
PHARMACEUTICAL ENGINEERING
The Official Journal of ISPE
July/August 2000, Vol. 20 No. 4

Efficient Allocation of Construction Risk in Engineering, Procurement, Construction, and Validation (EPCV) Contracts

by Richard W. Pearse, Esq.

What is the best and most efficient way to coordinate the EPCV process of major pharmaceutical and biotechnical facilities? Many times, the process is complex, perplexing, and unpredictable. And, at the same time, it often is labor-intensive, expensive, and can involve a learning curve that many companies cannot support. Consequently, a growing number of pharmaceutical companies are requesting that one or more independent engineering or construction firms take over different aspects of the process. As a result of this trend, the owner of the facility must either spend a great deal of upfront time and money haggling over each party's rights, expectations, and obligations with respect to these unpredictable factors, or risk having to administer or enforce ambiguous "letters of intent" or contract provisions after the project has passed the point of no return.

Perhaps the key reason why it is difficult to settle such complex contracts is that the owner and the engineer/contractor often base their understanding of the contract price upon different presumptions about who should bear different aspects of design and construction risk. These presumptions relate to factors that often cannot be clearly determined when the "deal" is struck and contract is initially drafted. This article examines the nature of these differing presumptions, and the contribution of the law and contracting process in allocating such risk between the owner, the engineer/contractor, and third parties.

Contract Performance and Construction Risk

Contract "performance" generally refers to a blend of cost, schedule, quality, and safety. The owner expects the plant to be completed, commissioned, and validated on schedule and within budget, and the engineer/contractor expects to deliver the same and earn a reasonable profit. However, during the course of designing and building the project, events or conditions inevitably surface that either increase the cost of completing the project; delay the scheduled commissioning, IQ, OQ, or PQ validation of the facility; or affect the quality of the facility.

"Construction risk" then, generally refers to the probability that the project will not achieve the expected quality, for the expected cost, within the expected schedule, and without serious injury or other safety or environmental problems. Typical examples of construction risk, include:

- acts of God (such as flood, earthquake, and fire), physical damage, or injury to person or property
- financial risk (such as an unanticipated increase in the cost of the specified lyophilizers due to a sub-vendor bankruptcy, or an unanticipated increase in import duties or sales taxes, or late payments)
- political and environmental risk (such as changes in FDA regulations, or embargoes of certain material or equipment)
- design risk (such as differing site conditions or errors and omissions leading to the failure to satisfy net output, or meet necessary requirements for clean utilities)
- construction-related risk (such as weather delays, labor disputes, productivity, defective work, equipment failures, and design changes)
- a combination of the foregoing (as in the case of a shortage of specified emergency generators, which necessitates a substitute that does not perform with the same efficiency and requires time-consuming and costly re-engineering)

Managing Construction Risk

Like any other type of risk, construction risk can be managed by the owner or the engineer/contractor by one of the following methods:

a. **Avoid or reduce the risk**. For example, the engineer/contractor walks away or refuses to bid on a contract that requires it to assume liability for the owner's lost profits, or avoids doing business in certain states or countries without a joint venture partner. Or, the owner expands its in-house engineering capabilities to monitor the detailed design process.
b. **Assume or retain the risk.** For example, the engineer/contractor acknowledges its obligations to re-perform negligent services at no additional cost to the owner. Or, the owner agrees to reimburse the engineer/contractor for increased costs caused by *force majeure* delays.
c. **Transfer or share the risk.** For example, the engineer/contractor insists on provisions in the general terms and conditions of the contract that release it from "consequential" damages (e.g., the owner's lost profits) or other liability that it would otherwise be answerable for under the law. Or, the owner requires the contractor to provide worker's compensation, employer's liability insurance, and rigorously drafted indemnification clauses, to protect the owner against claims from the engineer/contractor's injured employees.

It should be emphasized that such risk invariably zeroes in on the cost component since delays in the schedule, reductions in quality (or increases in operating costs), or injuries to person or property, all result in either one party paying money or the other party suffering loss or expense, and the bickering during negotiations generally involves who will bear or pay for the unanticipated costs. Consequently, in order for either party to systematically determine whether or not it can profitably assume or share the risk while managing construction risk, it must first estimate the costs of assuming the risk and then compare it against the costs of avoiding the risk. There are several options for performing this species of risk analysis, but the following steps are typical:

1. estimating the probability of certain risky events or conditions occurring that are not specifically known or knowable at the time the contract is signed or the "deal" is made
2. estimating the cost consequences of such events
3. assessing the cost of reducing the likelihood that the event will occur
4. weighing the expected long-term profits from engaging in the activity, against the probable cost from the risk.

Although there have been many attempts at making such assessments more scientific (such as the use of "fuzzy sets" or multiple regression analyses), in the final analysis, each party must ultimately rely upon historical data and upon the relevant skill and subjective judgment of its experienced "experts" in determining what level of risk it is profitable to assume, and which should be shared, transferred, or avoided at all costs.

"Efficient" Allocation of Construction Risk in EPCV Contracts

"Efficient" Contracts

Structuring and negotiating the legal terms and conditions for an EPCV contract can be characterized to some extent as the process of exchanging certain construction risk and the resultant costs (assumed by or transferred to the owner) for decreases to the contract price agreed to by the engineer/contractor. Owners who are shocked by the lack of response to an RFP or by the magnitude of the lowest responsible bid should look first to the construction risk imposed upon the engineer/contractor by the terms of the contract. The overall cost of the project can often be reduced by altering the amount of construction risk assumed by the engineer/contractor, without jeopardizing the schedule, quality, and safety goals of the project.

Recent studies in the economics of contract remedies have proposed the concept of an "efficient" contract to explain the inevitable haggling over which party bears the cost of construction risk. The contract is "efficient" if its terms maximize the value to both the engineer/contractor and the owner that can be created by the contemplated exchange. The contract is "inefficient" if revising the terms can increase the value it creates. A benefit is created for the engineer/contractor if the engineer/contractor values the reduced threat of damages and liability (and attendant cost of taking precautions against damages and liability) more than the decrease in price for trading for it. Similarly, a benefit is created for the owner if the owner values the decrease in price more than the cost of assuming the construction risk. For example, an owner may require in a request for proposal that the engineer/contractor assume responsibility to the owner against any damage to the owner's existing property at the site (i.e., property other than the new facility) to the extent such damage arises out of the work. An experienced engineer/contractor who accepts such liability will increase the purchase price to cover such risk, probably by the cost of a premium for liability insurance to cover the engineer/contractor's responsibility for such damage. If no damage ever occurs, the owner still has to pay for the additional insurance, even if the owner's property insurance already covered any such damage to the existing property. Under such circumstances, the owner may be willing to release the engineer/contractor from any legal liability for damage to the existing property, provided that the contractor/engineer reduces the contract price by an amount at least equal to the value of the additional liability policy.

Some of the tactics displayed by engineer/contractors during negotiations can be explained by this concept of "efficient" contracts. An engineer/contractor can stay in business only by managing construction risk in a way that permits it to pass along its costs to its customers, including the cost of providing its investors with a profit. Based upon the nature of the engineering and construction business, engineers/contractors learn very quickly which legal terms and conditions significantly affect the probability of reducing or eliminating profits (or worse!), and which terms and conditions are necessary to safeguard earnings from the project. Essential to this is knowing how contracts should be structured so that all risks that the engineer/contractor cannot profitably assume will either be avoided or transferred to the owner, either by obtaining the owner's release from certain legal liabilities, or by requiring reimbursement for the cost of any such events or conditions that reduce expected profits.

Before providing examples of different types of contract structures and how they may be more or less "efficient" in different contexts, it is important to describe the three most significant factors by which construction risks are allocated: (a) the formula by which the engineer/contractor is compen-

sated; (b) the method of "project delivery;" and (c) the general terms and conditions of the contract.

Method of Compensation

The method by which the engineer/contractor will be compensated has the single greatest impact upon allocating construction risk. Although there are innumerable permutations, most engineers and engineers/contractors are either paid a stipulated sum for a defined scope of work, or are reimbursed for the cost of the project materials and labor, plus a fee that is fixed or based upon the total cost of the work, or some hybrid with elements of both. In general, a stipulated sum contract allocates most of the risk for cost, schedule, quality, and safety to the engineer/contractor, but tends to require more monitoring of quality, more interpretation and clarification of terms relating to changes, costs, and scope, and generally results in more disputes. By contrast, a cost-reimbursable contract allocates most of the construction risk to the owner since the engineer/contractor will be reimbursed for costs and paid its fee, regardless of errors and omissions. The cost-reimbursable contract places a greater administrative burden on the owner and does not provide an incentive to the engineer/contractor to be productive, efficient, or cost-effective. It does, in general, tend to be less adversarial, more flexible with respect to enforcing quality and changing the design, and easier for phasing of design and construction activities when time is as important or more important than certainty of cost. In an effort to preserve some of the benefits and eliminate some of the problems with these major methods of compensation, the construction industry has evolved familiar derivatives of these two methods such as a cost reimbursable method subject to a stipulated maximum price (so-called "G-Max"), and a target price method, in which the engineer/contractor is provided with certain incentives and penalties for meeting or beating agreed targets for cost, schedule, quality, or safety.

Method of "Project Delivery"

The so-called method of "project delivery" has the second greatest impact on allocating construction risk between the owner and the engineer/contractor. "Project delivery" refers to the method of allocating the roles, responsibilities, risks, and rewards among the parties involved in the technology, basic engineering, detailed engineering, procurement, construction management, construction, commissioning, and validation of the project. If a single engineer/contractor under a single contract is legally responsible to finance the project and perform all basic engineering, detailed engineering, procurement, installation, commissioning, performance testing, and validation for a "lump sum turnkey" price, then, at least in theory, the owner can seek damages if the facility does not perform as required (including cost, schedule, quality, and safety), even if the performance levels promised were beyond the "state of the arts." At the other extreme, the owner can enter into multiple separate contracts with various engineers/contractors to license the basic design, perform the detailed engineering, perform procurement services, perform the installation, perform the commissioning and performance testing, and perform or assist in the validation. In that instance, it will be difficult to isolate any single engineer's/contractor's fault from the owner's fault or any other separate engineer's/contractor's fault if the project fails to perform as required. The general rule, then, is that the owner can hold an engineer/contractor accountable for failures in performance only to the extent the engineer/contractor is in control of the means necessary to achieve success.

General Terms and Conditions

The general terms and conditions of the contract have the third greatest impact upon allocating construction risk between the owner and the engineer/contractor. Many owners rely upon their legal staffs to generate a form protecting their exposure to the crucial areas comprising performance: cost, schedule, quality, and safety. By contrast, an engineer/contractor seeks to transfer all or a part of such risks to the owner, and this is why fixed price contracts tend to be so contentious, and why the majority of construction disputes relate to definitions of the scope of the contractor's work and the change order process. However, not every contingency will be negotiated since the significance of a contingency depends primarily upon the contractor's subjective valuation of cost of performance, and the likelihood that the monetary consequences will result from the assumption of construction risk. The following is a list, based upon my experience with hundreds of contracts with engineers/contractors of the most hotly negotiated items in the legal terms and conditions for an EPCV contract:

Limitations on the engineer's/contractor's legal liability.

- Overall Liability. Sophisticated engineers/contractors will attempt to limit their overall liability to the owner from any cause whatsoever, including the complete failure of the facility to operate, products liability, or any other liability. The limit insisted upon by the engineer/contractor usually ranges from five to 30 percent of the contract price, though in some instances it may equal 100 percent of the contract price. The small probability of a huge loss can equal the moderate probability of a moderate loss.

- Consequential Damages. In addition to limiting the overall liability, the engineer/contractor will insist upon being released from liability for any consequential damages incurred by the owner, including lost income from the failure of the completed facility to perform as specified. Without such a limitation in the terms and conditions, the engineer/contractor could be liable for hundreds of millions of dollars of lost profits suffered by the owner — not a very favorable proposition to a firm which expects if everything goes perfectly to earn a five to 20 percent return on investment. This is why consequential damages can be a deal-breaker for engineers/contractors. In order to induce an engineer/contractor to assume even a portion of such liability beyond the overall limit, the engineer/contractor would either set up a "shell" corporation to shield it from "betting the company" or would have to be given an equity position in the project or be provided with the opportunity to earn substantial bonus payments if things go better than expected.

- Limited Warranties. Warranties will be limited to those expressly agreed to in the contract and otherwise limited as to duration, usually to about a year after the facility is ready for commissioning. In addition, the engineer/contractor does not want to guarantee damages outside its control, including the work of owner or other equipment vendors who are often themselves sophisticated design/build firms. Often the engineer/contractor will attempt to "pass through" to the owner the warranties for any equipment not manufactured by the engineer/contractor or its subsidiaries.

- Limitations on the Engineer/Contractor's Liability for Insurable Risk. Construction is by its very nature a hazardous activity, and injury to person and property is generally unavoidable even with the most sophisticated construction and safety procedures. A very sophisticated international insurance market has developed in response to the particular needs of the construction industry. Not surprisingly, large international engineering firms know how to buy such insurance to cover the cost of replacing any damage to the project itself, damage or theft in transit to the site, damage caused by the engineer's/contractor's own negligence, or damage that results from the engineer's/contractor's attempts to correct defective work. If the engineer/contractor can control the insurance coverage for the project, the engineer/contractor is more likely to agree to assume contractual liability for claims made against the owner or damage to the owner's property to the extent it is covered by the insurance. However, if the owner controls the insurance coverage, the engineer/contractor may insist upon being released from all such liability, since the owner will often use its global insurance policy, sometimes with a huge deductible, or otherwise buy insurance that does not provide the protection that the engineer/contractor requires.

- "Cash-Neutral" Payments. The engineer/contractor incurs costs from the moment the engineering starts. Costs related to payroll, overhead, and equipment down payments, among others, are incurred while the engineer/contractor is waiting to be paid. Not surprisingly, the engineer/contractor will factor the cost of borrowing or using its own funds into the contract price. To avoid paying the engineer/contractor for the cost of such funds, the owner should consider a variety of cash-neutral payment methods, including "just-in-time" payments and the advance of one or more payments prior to the time that costs are incurred.

Examples of "Efficient" Contracts

Variables Influencing "Efficiency" for the Owner

As noted above, an EPCV contract is "efficient" if its terms maximize the value to both the engineer/contractor and the owner that can be created by the contemplated exchange, and "inefficient" if revising the terms can increase the value it creates to one or both parties. As such, "efficient" and "inefficient" are relative terms based upon the subjective valuation of construction of the parties, and must be grounded in the concrete program or requirements of the owner if they are to be useful in structuring contracts. Based upon my experience, the following variables determine the value that different contract structures have for the owner:

- The Value of "**Certainty**" of Contract Price and Date of Completion. Where certainty of final price and often of completion date are of extreme importance, owners may require engineers/contractors to assume significantly more construction risk, and owners might be willing to pay more - often considerably more - for their project if they can be more certain that the agreed final price will not be exceeded. Among such projects can be found many projects financed by private funds using a "project finance" method (repayment guaranteed primarily by revenue from the project), where the lenders require greater certainty about a project's costs than is allowed for under the allocation of risks provided for by traditional forms of contracting. Often the EPCV contract is only one part of a complicated commercial venture, and financial or other failure of this construction project will jeopardize the whole venture. However, if engineers/contractors assume such risk, they must be afforded sufficient time and resources to conduct the preliminary surveys and tests necessary to ascertain to the extent possible, the nature and extent of such items.

- Professional Expertise of the **Owner's Staff**. If the owner's in-house engineering, procurement, construction, and validation staff have considerable experience with developing and validating new facilities, then the owner might be more willing to assume more construction risk (in exchange for a lower contract price charged by the engineer/contractor) since, under such circumstances, the owner's personnel would be more adept at monitoring the process, anticipating problems, and controlling and reducing construction risk

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- **Uniqueness** of Technology and Facility. If the pharmaceutical or biotechnical facility is an expansion or duplication of an existing facility, using the same Fermentors, Water System, Autoclaves, Washer/Dryers, Heat Exchangers, Agitators, Lyophilizers, Cooling Towers, Chillers, Boiler Systems etc., as have been used on other projects, then the owner might be more willing to assume construction risk (which has been automatically reduced by the previous experience with the equipment and facilities). Conversely, if the facility or some crucial items of equipment have not previously been tried and found true, then the owner will be motivated to keep the responsibility for construction risk squarely on the shoulders of the engineers/contractors who recommend, design, and manage the construction and validation of such untried material and equipment.

- "Fast Track" or "Hyper-Track" **Completion Deadline**. It stands to reason, that the owner's schedule also will have a huge impact upon how much construction risk the owner is willing to assume. If an owner is anxious to expand its capacity to produce a "blockbuster" drug, then the owner may wish to proceed with an experienced engineer/contractor to develop the project before the design details have been completed. It is difficult if not impossible to find an engineer/contractor to agree to a fixed price and assume the risk for an incomplete design. Conversely, a project that is not needed on-line for two years can benefit by the savings to be gained by completion of detailed engineering and a thorough bidding process to select the highest quality engineer with the best fixed price.

Two Examples

Based upon these four variables, we can make a recommendation to owners about the circumstances under which the owner is more likely to benefit from more construction risk (for a lower contract price), or less construction risk (for a higher contract price). An owner is more likely to benefit from assuming more construction risk, and attempting to save fixed costs, when:

1. certainty of the overall price is not as important, such as when the owner is self-financing the expansion of a "blockbuster" drug production facility

CONTRACT VARIABLE	TURNKEY PROFILE	COST-PLUS PROFILE
1. Owner's Requirements	High Need for Certainty	Low Need for Certainty
	Low Level of In-house Expertise	High Level of In-house Expertise
	Unique Technology	"Tried and True" Technology
	Normal Schedule	"Fast-Track" Schedule
2. Owner's Risk Preference	Owner avoids, transfers Variable Costs	Owner assumes, shares, reduces Variable Costs
3. Fixed Cost Component	Increased to Cover Transfer of Variable Costs	Decreased, since Owner retains Variable Costs
4. Contract Structure		
(a) Price	Lump Sum	Cost-Plus (G-Max, Target Price with Incentives)
(b) Project Delivery	Turnkey	Construction Manager as Agent
(c) Terms and Conditions		
(i) Liability	Broad Liability	Narrow Liability
(ii) Insurable Risk	Assumed by Contractor	Assumed by Owner
(iii) Timing of Payment	Payment in Arrears	"cash-neutral" payments

Table A. Owner's decision process for efficient EPCV contracts.

tion staff who have worked on many similar projects and understand the details of the process
3. the facility is a "carbon copy" of an operating facility already completed by the owner
4. it is essential to the owner's financial projections that the facility is completed as soon as possible

In this scenario where the owner benefits by assuming construction risk and controlling fixed costs, the owner should consider the following contract structure: the **method of payment** is made on a cost-plus a fee basis, subject to a guaranteed maximum price or a "target price" (with incentives to keep overall costs down); the **method of "project delivery"** requires the engineer/contractor to act as an "agent," while procuring vendors and subcontractors on behalf of the owner; and, subject to **general terms and conditions** that limit the engineer's/contractor's liability to re-performance of services and the sacrifice of its projected fee as its maximum liability, that release the engineer/contractor from legal liability for lost profits, that release the engineer/contractor from liability that can be covered by insurance, and that provide for "cash-neutral" payments, with payments being made in advance of the month for which work is performed.

Conversely, an owner will be more deliberate and calculating about the level of construction risk it is willing to assume and the level it will require the engineer/contractor to assume, to the extent that:

1. certainty about cost is of extreme importance (as with a project finance)

2. the owner has a limited staff with the requisite amount of experience in administering such projects

3. the equipment or applications are atypical or newly invented

4. the owner has the luxury of time to search for the best price

In this second case where the owner benefits by transferring substantial construction risk to the engineers/contractor, the owner should consider issuing a request for proposal to be bid by several qualified engineer/contractors, in which the **method of payment** is a fixed lump sum; the **method of project delivery** is a single contract with a single EPCV contractor who is responsible for errors and omissions of all subcontractors for the entire project; and subject to **general terms and conditions** that hold the engineer/contractor responsible to repair and replace all vendor equipment and defective workmanship by subcontractors with a much higher overall limit of liability (say, 30% to 100% of the fixed lump sum contract price); that hold the contractor responsible for damage to existing property, and that provide for payments to be made on a so-called "after the fact" basis, in which applications are made in the month following the month in which work is performed with payments being made 30 days after the applications are submitted.

Obviously, the fixed costs in this second form of contract are likely to be significantly higher than in the first example, but it is arguable that the increased cost to the owner has value for the owner, equal to (1) the added comfort created by certainty of price, (2) the comfort from being able to transfer risks to an experienced contractor when the owner's staff lacks the necessary seasoning, (3) the more comprehensive warranties for novel or untried items of major equipment, and (4) the comfort of the relative luxury of additional time to be used to evaluate alternative offers from different firms.

The foregoing procedures are suggested as an aid to owners in selecting an "efficient" contract structure based upon the owner's requirements for the project, and are summarized in Table A. Table A traces the general stages that an owner follows in determining the appropriate "efficient" contract structure for an EPCV contract.

Conclusion

The length, expense, and contentiousness of contract negotiations between an owner and an engineer/contractor for an EPCV contract can be significantly improved if the parties can

stay focused upon each other's underlying economic assumptions and constraints. Both the owner and the engineer/contractor will be better off under a contract that approximates an "efficient" allocation of construction risk, trading the threat of damages for a reduced contract price for the project. With these principles in mind, an owner can generally remove any mystery from the contracting process in arriving at the true value of the contract.

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This article discusses the importance of cycle time in achieving manufacturing excellence, contributors to overall cycle time, a methodology of how to reduce cycle time, and a summary.

Reprinted from
PHARMACEUTICAL ENGINEERING
The Official Journal of ISPE
July/August 2000, Vol. 20 No. 4

Creating Manufacturing Excellence Through Cycle Time Reduction

by Rafi Maslaton

The global manufacturing trends in the pharmaceutical industry are toward lower cost, higher quality, and greater added value to provide a competitive advantage to the enterprise. Cycle time reduction and overall responsiveness to marketplace demands are becoming a higher priority than they were in the past. Creating manufacturing excellence, managing the supply chain, and managing overall resources are key in providing the competitive advantage. Cycle time reduction relates to almost every aspect of manufacturing excellence from reducing inventory, improving span of control, increasing staffing efficiency, and bettering general resource utilization.

Today's environment is demanding of cycle time performance, and forces almost every industry to improve its cycle time performance and reduce its response time. The pharmaceutical industry is no longer immune to cycle time performance, despite the long product life. Today's manufacturing organization must add more value and provide a competitive advantage to the enterprise. Achieving manufacturing excellence highlights the importance of cycle time performance to enterprises.

Introduction

Why Cycle Time?

- High Cycle Time (CT) introduces inefficiency and elongates the span of control loss.
- Improvements in CT can be converted to increases in throughput.
- Reduction in CT throughout the supply chain can reduce time-to-market for new and existing products.
- Cycle time influences yield, determines length of feedback loops (i.e., process, out of spec), and determines the time consumed before product testing can be assessed. A longer cycle time increases the delays in process problem identification - placing more Work in Process (WIP) at risk.
- CT reduction can allow reduction in Finished Goods (FG) or enable a faster responsiveness to market changes.
- Reduction in CT directly affects the WIP levels, which translates into lower holding costs.

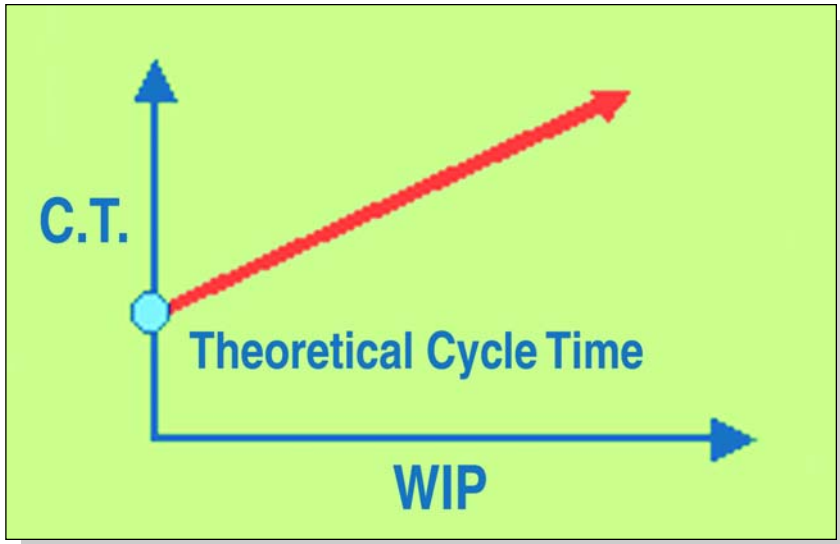


Figure 1. Cycle time as a function of WIP level based upon Little's Law.

- In a low WIP environment, staffing levels and over-time costs are decreased. A more predictable manufacturing environment is created.
- In a dynamic market where projections are uncertain, lowering CT minimizes the effect of introducing changes.

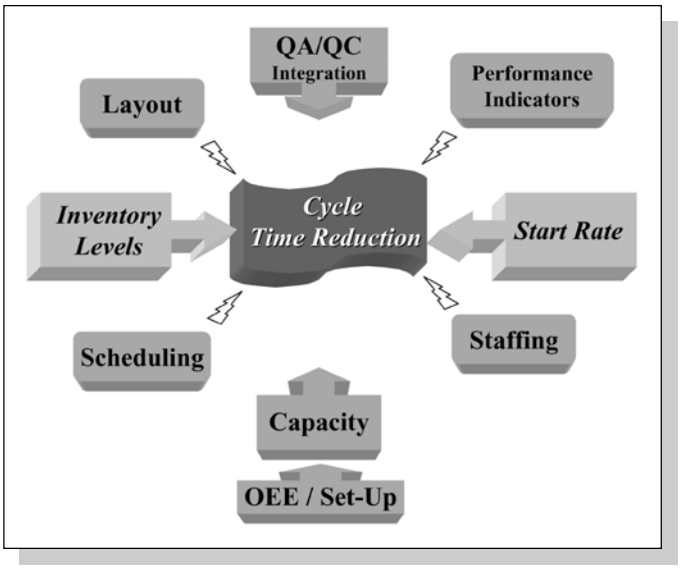


Figure 2. Cycle time contributors.

Little's Law

Little's Law defines the relation between inventory, start rate, and cycle time in a steady-state environment. Figure 1 illustrates cycle time as a function of WIP level based upon Little's Law.

Little's Law:

$$L = \lambda \bullet \omega \qquad \text{or} \qquad \omega = \frac{L}{\lambda}$$

Where
L = average inventory
λ = Start rate
ω = Cycle time

Also
L = average # in queue+average # in process

Example

Steady State
L = 30 Batches in process
λ = 10 Batches per week
ω = 30/10 = 3 weeks

As this equation illustrates, where the rate of production is steady (X batches every week) in order to reduce cycle time, the key parameter is inventory level. However, there are multiple components and contributors that affect the reduction and control of inventory. For example, capacity, scheduling, and business processes are major contributors. The next paragraph will detail and elaborate on the contributors and their effects.

Cycle Time Components and Contributors

As previously mentioned, Little's Law indicates the significance of inventory management. Yet, cycle time is affected by many components as illustrated in Figure 2.

Cycle time is affected by almost all elements involved in the manufacturing environment.

Scheduling - determines the release to the line. The consequence of scheduling is captured by Little's Law "Start Rate," which directly determines the cycle time. Scheduling in a "Push" environment can introduce increases in cycle time without an increase in throughput, when overloading the bottleneck. Other considerations such as equipment performance, WIP level through the line, staffing and due dates are important in the process of deciding what to run and when to run it. In most pharmaceutical-manufacturing environments, the release policy is the dominant factor influencing the cycle time.

Layout - can affect machine utilization, staffing, WIP distribution, walking distance, and material handling.

Capacity - having the required number of machines to support both the planned throughput and the cycle time goals. The illustrated curve emphasizes the relationship between cycle time and utilization. The lower the utilization of the manufacturing resources (lower relative to available capacity) in a process step - the shorter the cycle time of the step will be.

This relationship is depicted in Gross and Harris (1985), and a more detailed discussion of the queuing theory and the relationship between cycle time and utilization is provided there. Figue 3 depicts cycle time versus utilization.

$$W = \frac{1}{\mu - \lambda} = \frac{1/\lambda}{1/\rho - 1}$$

Increasing the effective capacity can reduce the utilization in a given start rate and will drive a smaller X-Factor. (X-Factor determines the ratio between the actual cycle time to the raw process time excluding queue, i.e., 5X means 80% of the time the batch/lot is in queue and only 20% it is actually in production).

Staffing - cycle time can be affected by both staffing levels and training effectiveness. Staffing levels affect cycle time by reducing wait times and increasing throughput. Adequate staffing levels also will reduce Mean Time To Repair (MTTR). Inadequate staffing and/or training will result in a longer duration for these activities. Inadequate staffing levels also will result in higher machine interference and higher speed loss.

Performance Indicators - support manufacturing in establishing feasible goals, tracking the performance, and prioritizing support to those areas that have the most contribution to the CT performance. Organizations that establish these measurements typically realize an immediate improvement in their performance.

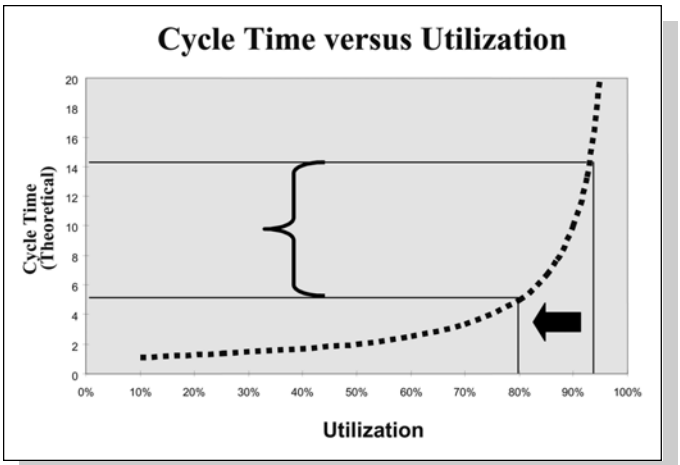


Figure 3. Cycle time versus utilization.

QA/QC - improving business processes, resource planning, scheduling, and allocation are keys to a QA/QC department meeting the overall cycle time goal. Reducing the time to release raw material, finished goods, and any in-process test that delays the manufacturing line are critical.

How to Approach Cycle Time Reduction and How to Sustain It

The complexity of cycle time reduction as presented above requires focus on the overall supply chain.

Moreover, cycle time reduction in almost every case has a twofold focus: manufacturing and the QA/QC as we will see in the following paragraph.

The program starts with a diagnostic study that is carried out in parallel in the manufacturing and QA/QC departments.

The diagnostic study involves data and business process analysis of the communication channels (both formal and informal) between manufacturing and QA/QC, the planning and scheduling practice, bottleneck (BN) identification, and the measurement system for cycle time control.

The execution of this stage will involve the evaluation of the tools for capacity and staffing modeling, Overall Equipment Effectiveness (OEE)[2] monitoring, and QA/QC resource and practices analysis. The outcome of this stage is a cycle time reduction roadmap with ranked action items and areas for the implementation phases. The roadmap will deal with issues such as communication channels, OEE and bottleneck analysis, QC release practices, capacity analysis, and scheduling. In addition, X-Factor contribution will be analyzed and used later in the program to set revised cycle time goals. (The X-Factor contribution analysis is necessary for prioritizing the areas of improvement based upon their contribution to the overall cycle time.) Figure 4 illustrates a high level cycle time reduction approach.

Getting Started

Manufacturing processes in the pharmaceutical industry differ so the intention of the diagnostic study is to identify the opportunities and rank the actions and areas for improvement. In this article, a few typical actions and methodologies are discussed to improve the cycle time performance with the caution that some may be more relevant for one facility than another. Getting started, as illustrated in Figure 5, involves capacity improvement and planning, QA/QC, planning and scheduling, raw material release and planning (from planner to warehouse).

Area-1 Capacity Improvement

One of the focuses is increasing capacity activities on the bottleneck equipment set(s) (i.e., change over reduction). Capacity improvement can relate to several areas of improvement:

- Better scheduling and starvation of the BN equipment can be avoided.
- Reducing the process time (theoretical CT) will reduce the total CT even if machine utilization remains unchanged.
- Improving the Overall Equipment Effectiveness (OEE).

This discussion will focus upon the OEE methodology and approach in the first focus area.

What is OEE?

The OEE is one of the tools used to assess both the tool performance and work methods in an area (i.e., packaging, compression etc.). The best and usually only way to accurately gather the data required for achieving significant productivity improvements is to concentrate on the production floor. OEE is defined as the percentage of time that equipment is used to produce sellable products at the maximum machine rate. Largely neglected in the past, OEE is becoming a crucial concept in the industry's continuous pursuit of productivity improvements that can be converted into cycle time gain.

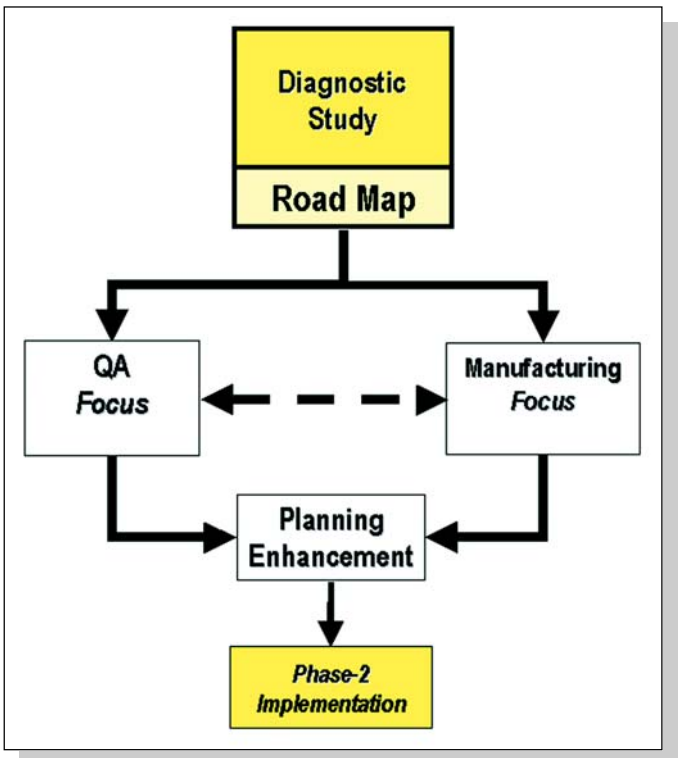


Figure 4. High-level cycle time reduction approach.

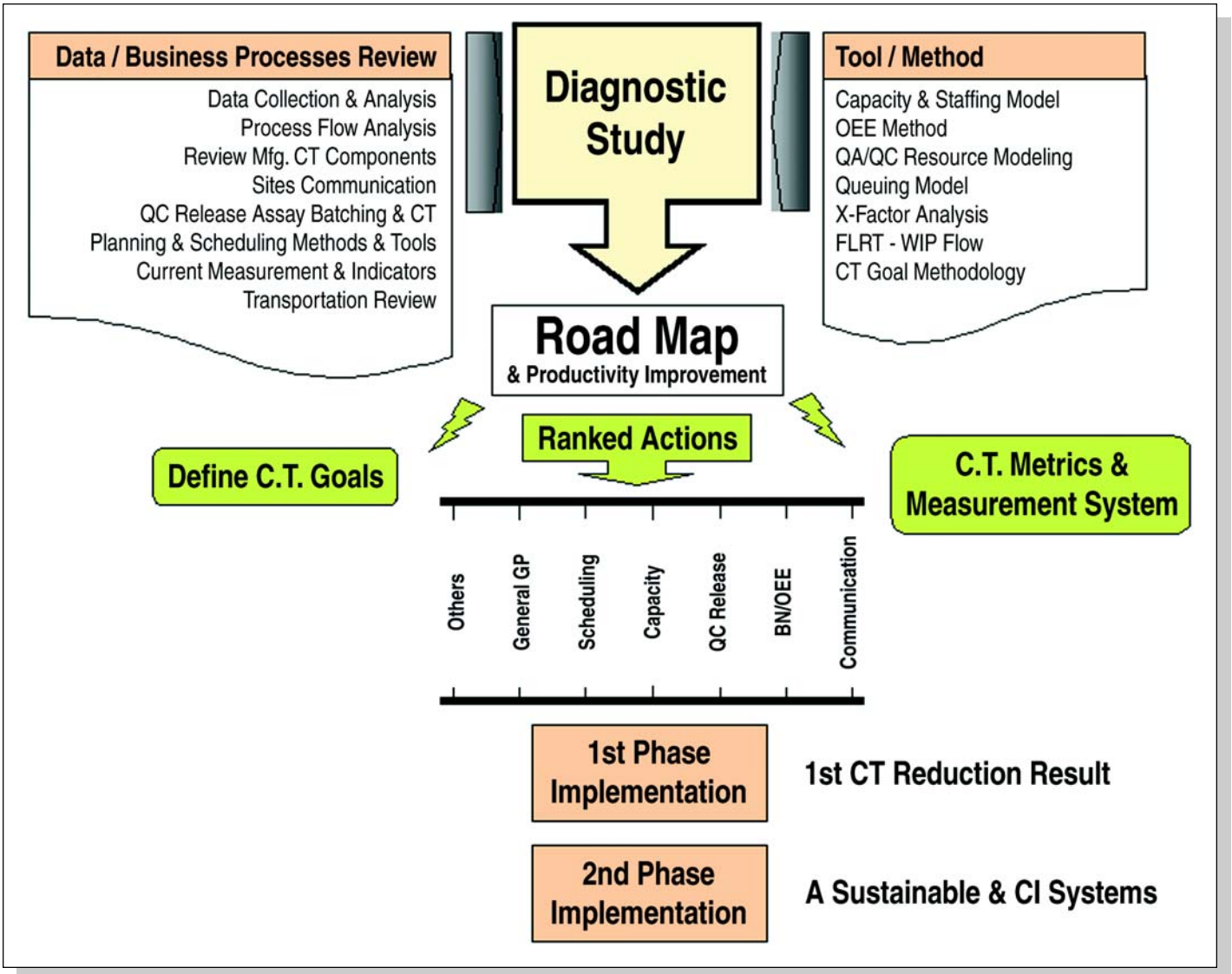


Figure 5. Cycle time diagnostic analysis and road map for improvement.

Definition of OEE

OEE is the ratio of actual equipment output to its theoretical maximum output. OEE can be viewed as the percent of time that equipment would need to run at its maximum speed to attain the actual output.

This measure of tool performance captures all equipment time consumed by the six big losses:

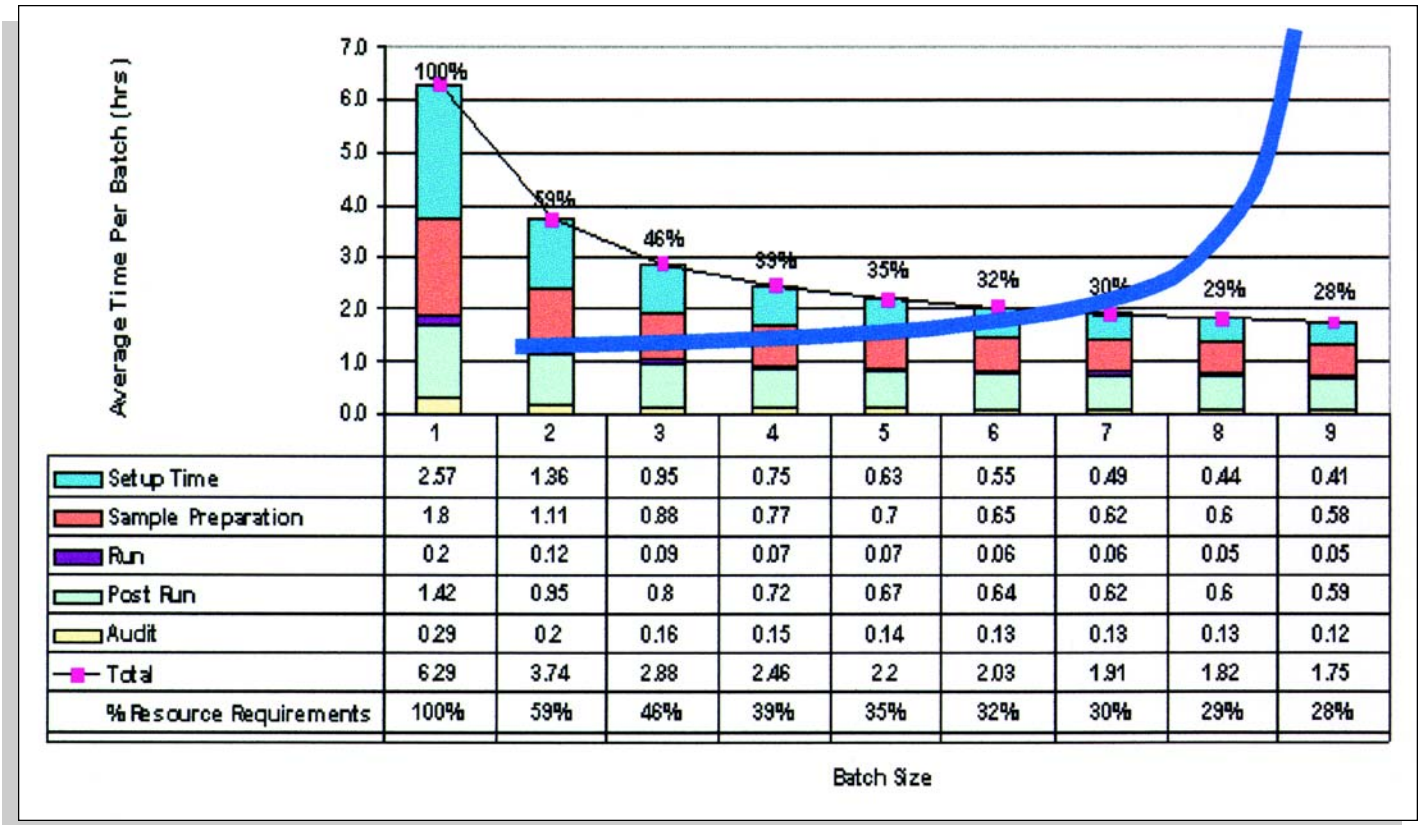
1. Equipment Failure (Unscheduled Downtime)
2. Setup and Adjustment (Including PMs & Engineering)
3. Idling and Assists (Wait for Operator, Minor Stoppages)
4. Speed Loss (Rework, Inefficient Batch Sizing)
5. Defects (Non-Fatal Defects)
6. Reduced Yield (Fatal Defects)

By systematically focusing upon the six big losses manufacturing can improve the effectiveness of its resources (BN) and increase the effective capacity to make cycle time improvement. For example, reducing changeover time will provide excess capacity which in turn can be used for quicker responses to changes. Also, reducing losses by operators decreases the wait for load/unload of WIP, thereby facilitating the movement of WIP to the next operation.

Area-2 Scheduling Improvement

Create (and execute) scheduling and dispatching logic to reduce cycle time. Improve the scheduling to the line by improving the scheduling parameters and algorithm. For example, going away from a push concept and initiating a pull system, improving the visibility of the line performance especially the BN, consideration of the WIP level in the line to maintain a controlled inventory level (as Little's Law describes the relation between inventory and cycle time).

Good On-Time delivery (OTD) does not always mean good cycle time or scheduling performance. Therefore, companies always have to review their scheduling method and cycle time



	1	2	3	4	5	6	7	8	9
Setup Time	2.57	1.36	0.95	0.75	0.63	0.55	0.49	0.44	0.41
Sample Preparation	1.8	1.11	0.88	0.77	0.7	0.65	0.62	0.6	0.58
Run	0.2	0.12	0.09	0.07	0.07	0.06	0.06	0.05	0.05
Post Run	1.42	0.95	0.8	0.72	0.67	0.64	0.62	0.6	0.59
Audit	0.29	0.2	0.16	0.15	0.14	0.13	0.13	0.13	0.12
Total	6.29	3.74	2.88	2.46	2.2	2.03	1.91	1.82	1.75
% Resource Requirements	100%	59%	46%	39%	35%	32%	30%	29%	28%

Figure 6. Batch campaigning affect on CT.

performance to ensure manufacturing excellence and new and improved goals.

Area-3 QA/QC Scheduling

In many companies QA/QC are the ones to blame for poor cycle time performance. This blame in many cases is justified since QA/QC controls WIP flow from delaying the raw materials to holding the finished goods. In order to allow QA/QC to improve their performance, an integrated schedule for manufacturing and QA/QC is required. A tool is needed that will download the manufacturing schedule and translate it into QA/QC workload. Within the QA/QC, a prioritization business process is needed to optimize the cycle time performance. In addition to scheduling a business process, re-engineering is typically needed in this department to accelerate the overall process, reduce the handling time for administration, and improve LIMs systems implementation. The above focus will result in a reduced cycle time and improve the overall QA/QC performance.

As soon as organizations view the QA/QC as part of manufacturing in the approach, the mindset, the scheduling needs, and the resource planning, the sooner the organization will achieve manufacturing excellence.

Figure 6 illustrates the traditional batches campaigning attempt to improve efficiency while affecting the overall cycle time exponentially.

There are many areas of focus and methodologies to reduce cycle time, yet they all need organizational focus and measurement systems. This article briefly discusses a few areas and methodologies. Areas such as purchasing, raw material planning, and administration prior to initiating the manufacturing cycle are not addressed in this article, but should be analyzed and improved as part of an overall comprehensive approach.

Sustaining the Effort

The establishment of an organizational focus upon cycle time (i.e., a continuous improvement process) is a key to the success of the initial effort. Rewarding the employees based upon cycle time performance measures, the results, and the improvement on a regular basis is crucial. There are many methods for sustaining the effort and applying continuous improvement techniques; however, this article will focus on the measurement and cycle time indicators (focus team and organization).

Measuring Cycle Time

In the process of establishing measurement and indicators for cycle time performance, the first step is to determine a cycle time goal for each process step. This goal should take into consideration the following:

- *Process time* - the theoretical time it should take to perform this step (zero queue).
- *Utilization/Availability ratio* - based upon the capacity model, how much excess capacity is available. Where in a high excess capacity situation we would tighten the goal and visa versa.
- *Window times* (where applicable) - this applies when there is a maximum layover between a completion of one process step and initiation of the next step.

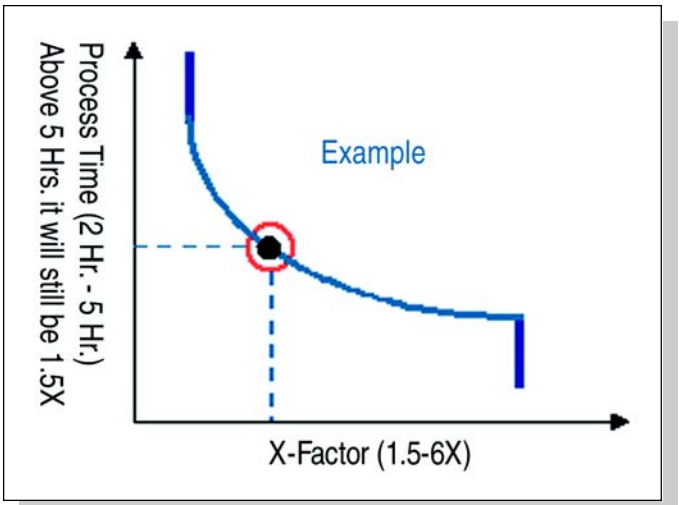


Figure 7. Cycle time's goal setting chart.

Figure 7 illustrates a conceptual relation between the process time and the cycle time goal. The longer the process time, the smaller the allowable queue as a multiple of the process (X-Factor is smaller as the process time is longer). When the process time is very short, a high queue multiplier actually contributes a minor value to the cycle time. This method allows a company to track the cycle time performance versus the established goal.

What To Expect at the End of this Program

Figure 8 illustrates typical CT reduction stages. The first step is typically aimed at 15%-25% reduction, depending upon the opportunities explored in the diagnostic step. The second step aims to add another 10%-15% improvement.

Expectations at the end of this effort in addition to the CT performance are:

- productivity improvements in key bottleneck processes
- improved QA/QC practices
- new and feasible cycle time goals for each process bucket
- planning enhancement
- road map for continuous cycle time reduction

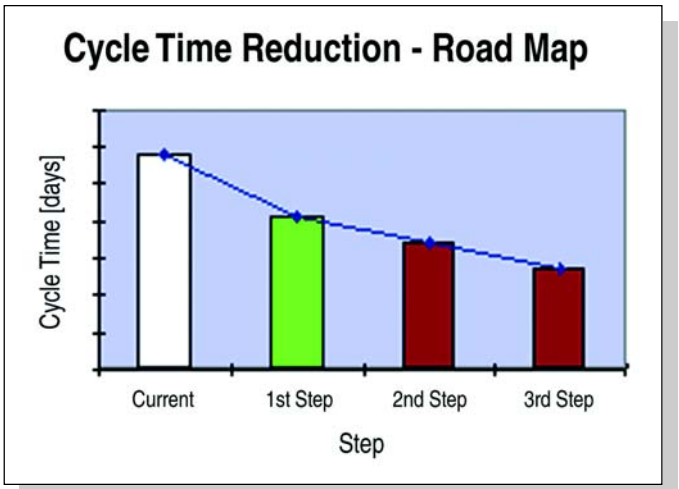


Figure 8. Cycle time reduction road map.

Summary

Since cycle time reduction is becoming a key in reaching manufacturing excellence, it is becoming a major industry focus. As discussed throughout this article, cycle time reduction encompasses a wide range of operations, QA/QC, and planning issues. Cycle time reduction is not possible without support from all the facility personnel, including top management. The benefits in reducing cycle time are, by far, greater than the costs associated with making the required improvements to resources and systems (and occasionally to equipment upgrades). The complicated relationship among cycle responsible for the East Coast region, focusing upon a wide variety of pharmaceutical and high-tech manufacturing. His years of experience include clients such as Ortho McNeil, Eli Lilly, RP Scherer, Bayer, and from the high-tech industry, clients such as Lucent, IBM, Intel, Motorola, and Siemens. He is currently responsible for more than 40 engineers, supporting clients in the areas of cycle time reduction, productivity improvement, cost reduction, layout design, production planning and scheduling amongst others. Rafi holds a BSc in industrial engineering and systems analysis.

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This article discusses the development and design of transfer panels as an integral part of an integrated manufacturing facility.

Reprinted from
PHARMACEUTICAL ENGINEERING
The Official Journal of ISPE
July/August 2000, Vol. 20 No. 4

Transfer Panel Design: Aseptic Solution Handling in Biopharmaceutical Facilities

by Ed Louie and Bruce Williams

Introduction

A major challenge in biopharmaceutical plant design is the handling of bulk aseptic transfers of process streams. Products are transferred downstream from fermentation and cell culture to purification steps. Solutions are transferred from centralized media and buffer preparation areas to their use points. Additionally, Clean-in-Place (CIP) and Steam-in-Place (SIP) operations need to be fully integrated with these transfer processes to facilitate cleaning and sterilization of the corresponding vessels and transfer lines. Transfer design is dependent upon multiple factors, including required process flows, manufacturing schedules and manufacturing layouts and is highly customized and often complex.

Different methods are used for handling process transfers. Flexible hoses are sometimes used for performing transfers within a given process area, but this is not a scalable process for transfers between rooms. Many firms install transfer lines between vessels, both within and between rooms, but continue to use flexible hoses to "jumper" between transfer lines. While this is an improvement on the former approach, these manual connections are subject to operator error. In either or both scenarios, sagging of hoses lead to fluid accumulation and preclude validatable SIP and CIP procedures.

Another approach is to manifold piping between the various vessels and use automated valves to isolate the desired flow paths. This allows for highly automated process operations. However, beyond the simplest switching operations, manifold complexity can increase rapidly and become relatively inflexible and costly. Also, this approach does not allow for absolute isolation of the various flow paths and presents a

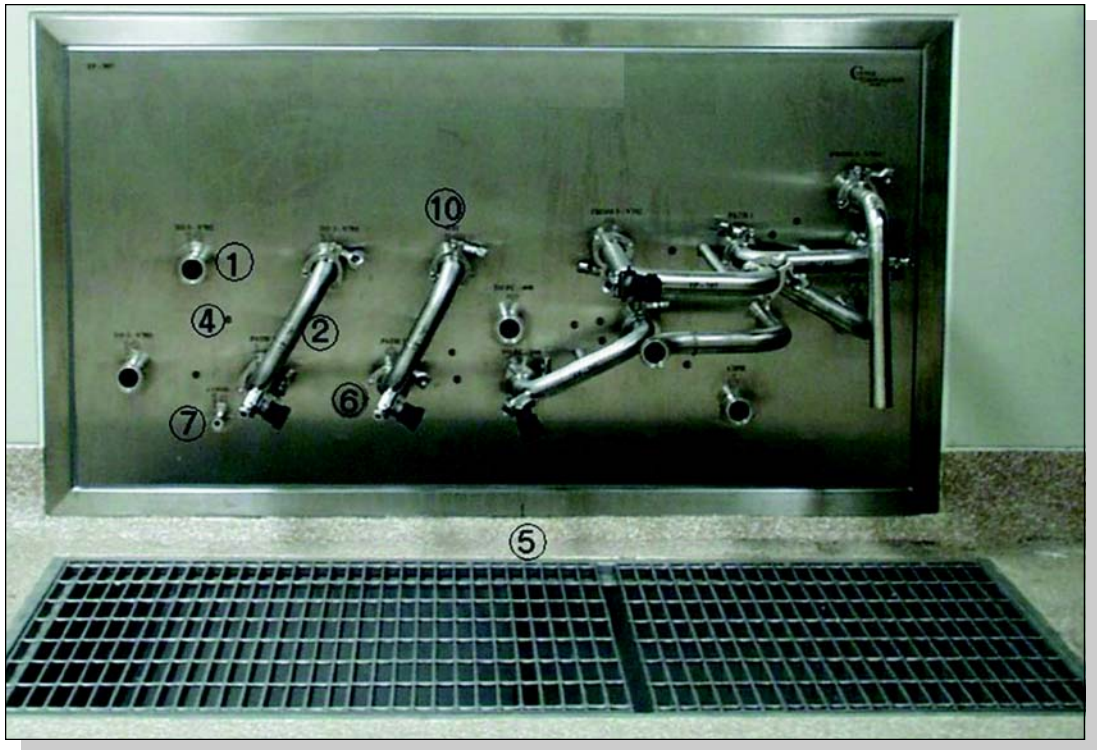

Figure 1. Media prep transfer panel.

potential source for cross-contamination, unless the system is sufficiently complex to include block and bleed capability at all junction points.

Transfer panels afford another solution to this challenge. Transfer panels are composed of a series of nozzles or ports attached to a plate, usually wall mounted. The nozzles are connected by hard piping to the inlets and outlets of process vessels or other process functions. The panel serves as a "switchboard" through which connections between various processes are made using sanitary "U-bends." Appropriate design allows operation with only a single size of U-bend. The operational panel shown in Figure 1 will be used to illustrate the design process in this article. Components identified by number on figures are discussed and keyed out in the section on Detailed Design.

The advantages of transfer panels are many. They provide physical isolation of transfer processes, visual confirmation of connection integrity and require minimal maintenance. They are both highly flexible and adaptable. The number of transfer permutations they support is high. If the physical layout is not too tightly designed, new processes can be added or changed by adding ports and/or piping changes without interfering with basic operations. Process utilities such as WFI, CIP Supply/Return and clean steam condensate return can be located on a transfer panel. By centralizing process operations, they make efficient use of process space and operator labor. Complete circuit or even multiple circuit cleaning can be accomplished with a single operation without the need for storage or handling of hoses. Maintenance is minimal and can be largely confined to non-classified areas behind the panel. With the addition of proximity switches, transfer panels enable electronic confirmation of proper line connections before a particular process circuit is initiated, thus preventing accidental mistransfers.

Transfer panels do have some limitations, but these are generally minor compared to the advantages. Setting up a process circuit is a manual operation and may require operator travel or coordination between different process areas. Since U-bend connections are dependent upon precise alignment between ports, fabrication of the panel is a precision process. Unlike hose transfers, permanent sanitary piping is needed between process vessels and transfer panels at additional cost and space. Finally, additional physical space is required behind the panel (usually in a mechanical space) for piping connections, valves, etc.

The relative advantages and disadvantages for the various transfer methods are summarized in Table A.

Transfer panel design requires a thorough knowledge of the different process operations: product transfers, CIP, SIP, manufacturing schedule as well as attention to detail to ensure that the final design performs all the desired functions. As with any design process, the design effort for transfer panels needs to include intensive programming early on to ensure that necessary conditions are well established prior to commencing detailed design. It should be done in a step-wise, iterative process that accounts for both feedback (boundary) and feedforward (physical design and function) conditions. The design process is shown in Figure 2 and will be discussed in detail in the following sections.

Schematic Design

A well-defined Basis of Design (BOD) is essential at the start of the design. A Process Flow Diagram (PFD) provides the basic information to tabulate the required process transfers. An equipment arrangement layout also will be needed to determine the location and number of transfer panels as well as what equipment they will serve. Preliminary coordination with other disciplines at this stage is essential, particularly with Architecture and Piping to ensure that panel physical requirements are accounted for in the facility layout.

COMPARISON OF TRANSFER METHODS

Attribute	TRANSFER TYPE		
	Flexible Hose	Valve Manifold	Transfer Panel
Initial Cost	+	-	+/-
Flexibility	+	-	+
Adaptability	+	-	+
Process Isolation	+	-	+
Scalability	-	+	+
Process centralization	-	+	+
Process validation	-	-	+
Process labor	-	+	+/-
Process Automation	-	+	+/-
Cleanability	-	+/-	+
Ease of Maintenance	+	-	+/-

+ = Relative advantage - = Relative disadvantage

Table A.

Other secondary boundary conditions are defined during schematic design. Preliminary determination of utilities to be supplied at the transfer panel is made. Manufacturing schedules are developed to establish the redundancies required at the panel and the number of transfer lines required between panels. For instance, it is not inconceivable that a media preparation transfer panel might need to handle simultaneously filter sterilization from a prep tank to a fermentation vessel, CIP of a second tank with associated transfer line, and WFI addition to a third tank. Basic CIP and SIP circuit requirements need to be defined. In some cases, it may be preferable to clean multiple transfer lines and/or line/tank combinations in one circuit to minimize CIP cycles.

Once the transfer, cleaning and sterilization requirements have been defined, it is useful to develop a Transfer Panel Flow Diagram. This conceptual level diagram graphically displays the transfer panels together with their required ports as well as the interconnections between transfer panels. The schematic layout can then be used to develop a detailed list of the transfer circuit permutations. This list will be subsequently used to test the proposed detailed design.

Figure 3 illustrates a media preparation transfer panel designed for a biopharmaceutical manufacturer. The manufacturing facility includes two cell culture production suites supported by a central media preparation area. There are three media preparation tanks that support four bioreactors in each of the cell culture suites.

We first worked with the client to define the various process transfers and the cleaning and sterilization requirements. We developed a manufacturing schedule, identified potential concurrent operations and further defined the optimal cleaning

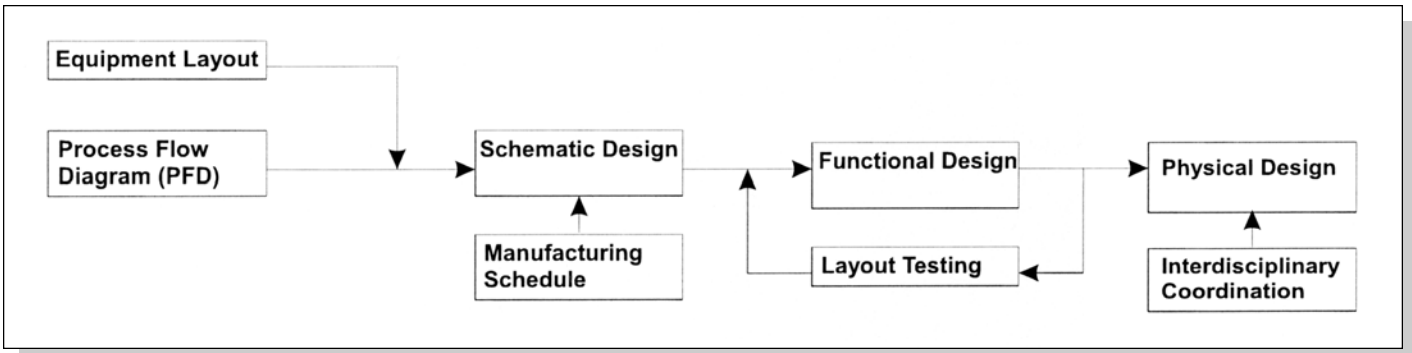

Figure 2. Transfer panel design process.

and sterilization circuits. From this information, we developed the transfer panel flow diagram shown.

The media preparation panel is provided with nozzles for the vessel inlets and outlets, a WFI supply which may be connected to either of the three tanks, the transfer lines to either of two cell culture suites and CIP return. CIP supply is not included in the media preparation transfer panel, since the CIP circuit for the media tanks and lines originates from the cell culture suites. This is a flow diagram, and does not incorporate the geometric relationships between the nozzles. The nozzle placement geometry is developed in the detailed design phase once the concept has been finalized. Note that this design requires only one WFI drop to service the preparation vessels rather than three drops (one drop for each of the three vessels). While all tanks require WFI service, the manufacturing schedule does not require concurrent media preparation among the vessels.

Generally, the transfer path is connected with the appropriate U-bends and J-bends prior to sterilization and use. After use, the path is cleaned prior to dismantling the U-bends and J-bends. Some examples will help to illustrate the operation and circuit development of the transfer panel - *Figure 3*.

1. *WFI Addition to Media Preparation Vessels.* The WFI supply is connected to the inlet of the desired vessel via a U-bend to complete the circuit, and valves are opened to allow WFI to flow into the tank.

2. *Transfer Contents from Vessel V702 to Bioreactor V102 in Cell Culture Suite 2.* During this transfer, the media is filtered in-line prior to entering the bioreactor. Connect Nozzle 05 to Nozzle 07 on the Media Preparation Transfer Panel. On the Cell Culture 2 Transfer Panel, connect Nozzle 11 to Nozzle 12, and Nozzle 13 to Nozzle 02.

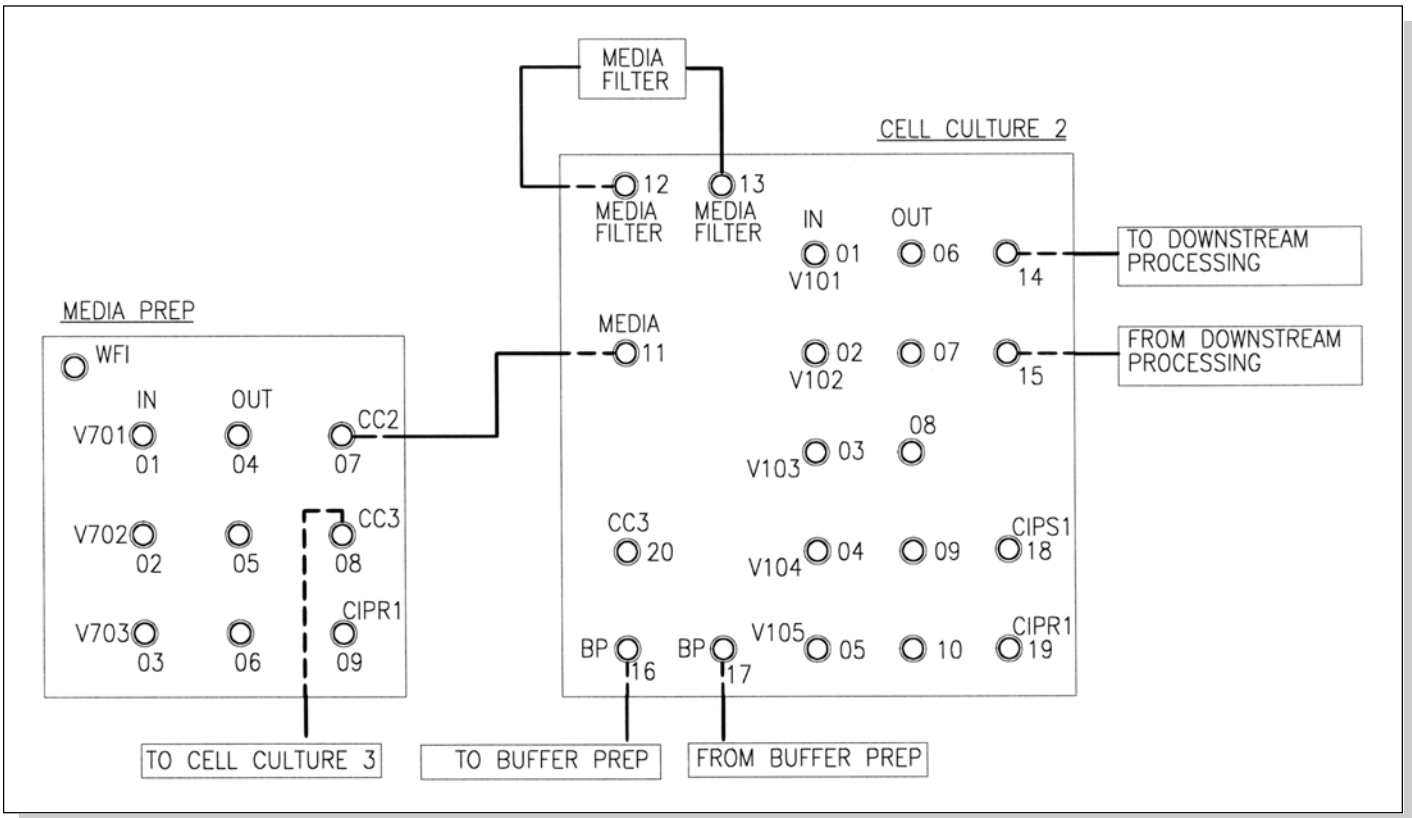

Figure 3. Transfer panel flow diagram.

> ***...the design effort... needs to include intensive programming early on to ensure that necessary conditions are well established prior to commencing detailed design.***

3. *CIP Bioreactors V102, the media transfer line, and the media preparation vessel V702.* On Cell Culture 2 Transfer Panel: Connect Nozzle 18 and 07. Connect the bypass line between Nozzle 07 and Nozzle 02 (The bypass line is a line that allows connection from Nozzle 07 to the top of the vessel). Connect Nozzle 02 to Nozzle 11. On Media Preparation Transfer Panel: Connect Nozzle 07 to Nozzle 02 and Nozzle 05 to Nozzle 09.

Detailed Design

Transfer Panel Components

An understanding of transfer panel components is a prerequisite for a functional design. Process contact surfaces and components need to match the system-wide specifications. Materials of construction and surface finishes must be chosen to be compatible with contacted solutions and cleaning requirements. Panels themselves are generally heavy gauge 316L SS plate and all welded construction. Valves, where used, are of the sanitary diaphragm type. The physical components of a transfer panel will vary, depending upon process requirements, but the following are major elements. The numbers for each component correspond to keyed items on Figure 1 and Figures 4 through 6.

1. Transfer Line Ports: these are the "plug-in" parts of the "switchboard," constructed of sanitary tubing with tri-clamp ends. For operation with U-bends, precise alignment of ports during construction is critical. Usually, these are welded into the transfer panel. A less costly approach by one fabricator treats the nozzles as bulkhead fittings through the panel with mechanical fastenings.

2. U-Bends: these are the "wiring" in the switchboard, jumpering transfer ports. Note that the ones shown come with a separate drain valve, particularly useful as condensate drains during SIP operations. Generally, one or at most two sizes of U-bends are preferred. J-bends may be useful where more than one supply/return line is needed to service multiple users. Ports labeled A and B on Figure 4 represent supply ports connected by J- and U-bends respectively to port C, the end user.

3. Behind-the-Panel Jumpers: These connect transfer ports behind the panel. They are an integral part of the transfer panel and are not reconfigured for different transfer operations.

4. Proximity switches are used to provide positive confirmation of proper process connections. They play a major role in the automation of the transfer panel design. There are several types of proximity switches that are available. The magnetic type is physically robust and does not require any direct electrical contact. A magnet is placed in a ¾" tube mounted on the jumpers. Switch contacts are mounted behind the panel so when proper connections are made, the contacts close. The contacts are wired to a controller such as a programmable logic controller (PLC) or a DCS (distributed control system) for integration into the sequence of operations.

5. Drains for capturing residual liquids from the transfer lines when panel connections are broken may be either a trough attached to the transfer panel or a separate floor pit at the base of the transfer panel.

6. Low point automatic drain valves are employed as an option to ensure full transfer line drainage, particularly between CIP steps, without disconnecting the U-bends. Valves located behind the panel are automated.

7. Steam traps may be incorporated into the transfer panel as part of integrated SIP processes. In our example, the actual trap is behind the panel; in operation, a sanitary ball valve would be attached to the port for isolation. In such applications, high point clean steam supplies also need to be included in the design, though not physically part of the panel.

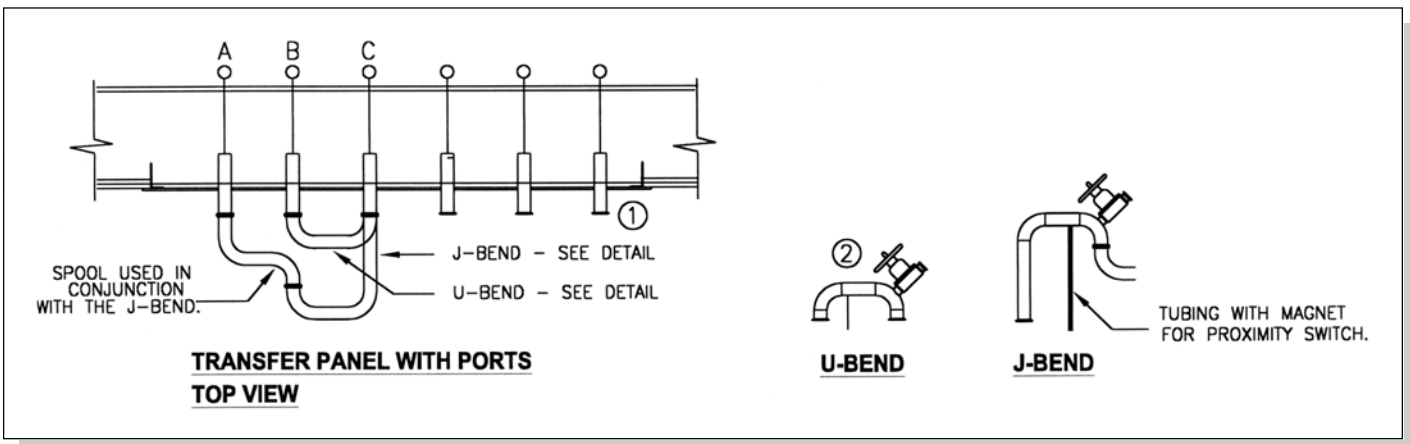

Figure 4. Ports, U- and J-bends.

Figure 5. Transfer panel integral filters.

8. CIP return pumps (not illustrated) are usually needed for centralized CIP operations to return vessel CIP drainage to its source. The pump needs to be capable of handling air/water mixtures and to be self-priming.

9. Filters of sanitary design for filtration of buffer and media are readily incorporated into the transfer panel. If filters are incorporated, the design must include appropriate low-point drains and steam traps for them as well.

10. Other process utilities, such as WFI may be incorporated into the panel with automatic valves behind the panel.

Functional Design

Schematic design identifies the operational requirements of the transfer panel. The goal of detailed design is to develop the simplest configuration that enables the various complex connections to satisfy the process requirements. Much of this is a problem that must be approached graphically and geometrically. The process involves determining the necessary connections needed between services and process elements, graphically displaying functional groupings of ports, testing the arrangements against the circuit requirements as defined in schematic design and laying out the panel to satisfy secondary boundary conditions. These secondary conditions will be taken up first since they should always be in mind throughout design.

> ***...the physical design should be clear and umambiguous, so as to minimize operator confusion or error.***

Transfer processes need to be free draining. Both for CIP and SIP operations, the transfer panel is generally the low point in the process. Hence, design must ensure that there are no pockets, to, from or within the transfer panel. The design should use the minimal number and sizes of U-bends needed to accomplish a transfer. This minimizes both the physical size of the panel itself and the operational complexity of setting up transfers. Finally, the physical design should be clear and unambiguous to minimize operator confusion or error.

We have found that a geometrical design results in the most efficient and effective layout, as opposed to ones that are simply laid out on a grid. This design starts with determining functional relationships. In general, a process vessel in a fully integrated transfer system will require CIP return, downstream connections and SIP condensate return connections from the vessel outlet and CIP and process supply connections to the vessel inlet (SIP supply is at the high point between vessel and panel).

The second step is to represent functional groups graphically, using a radial geometry for the port connections with services at the center and users along the arc. This enables a variety of connections with a single U-bend. Any other associated ports that require U-bend connections to elements of the same group can then be added. Note that the radii should remain fixed, but the angles are flexible.

The last step is to consider and incorporate needs for common and/or simultaneous services to multiple users, which may require J-bends or behind-the-panel jumpers. The J-bends are connected manually to the transfer ports as needed like U-bends. The behind-the-panel jumpers are fixed, and are an integral part of the transfer panel. At this point, each functional group should be tested for internal consistency. It should be confirmed that the necessary services are provided to all use points, and that the connections from a service to a group of common use points are made in a common fashion.

Once the functional geometrical groups have been established and displayed, the design must be tested against all non-equivalent circuit permutations and for non-draining pockets. The flow paths and U-bend connections can be represented graphically on the P&ID. It also is useful to analyze connections between transfer panels as hydraulic profile. This is a good test for low point drainage and additionally is a useful cross check of the circuit permutations developed in the schematic phase.

The end product of this design is a P&ID, as illustrated in Figure 6, with associated services. At first glance, this P&ID shows very little in common with the conceptual flow diagram shown in Figure 3. The ports have been arranged more strategically using the geometric arrangement discussed earlier. The port numbers have been changed to accommodate addi-

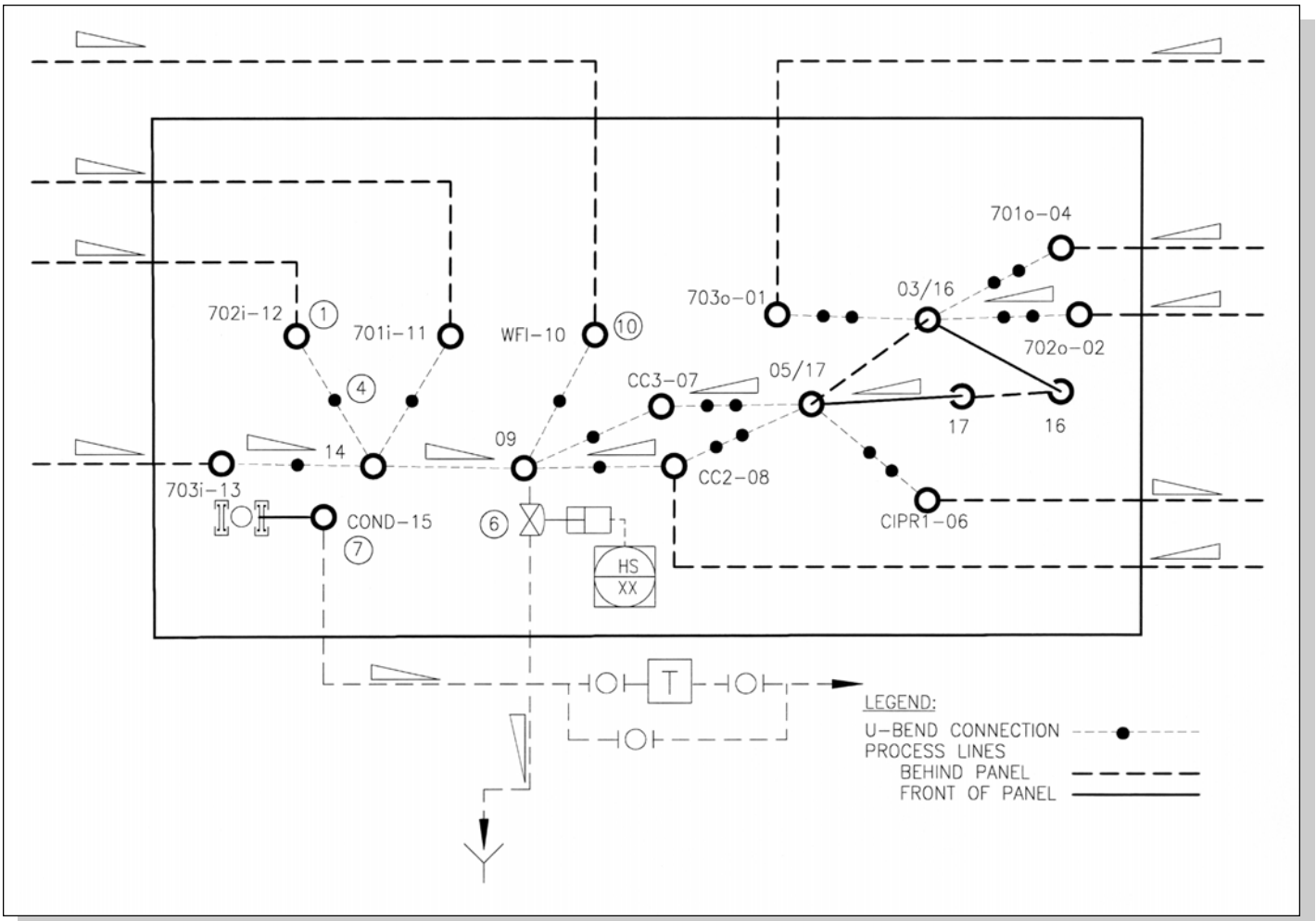

Figure 6. Transfer panel P&ID.

tional nozzle requirements not included in the flow diagram. The open circles represent the port nozzles, and the solid dots indicate location of proximity switches. The lighter broken lines represent U-bend connections and the heavier ones, behind-the-panel lines.

Note that a consistent port-labeling scheme has been incorporated into the drawing at this stage. This facilitates design tracking and testing and will later find its way into the sequence of operations, the control scheme (for panels equipped with proximity switches) and the actual physical labeling of the panel. We have found a two-part labeling scheme to be useful: an alphanumeric descriptive abbreviation of the port source (functional identifier) with a suffix to represent inlet and outlet and a unique (to this panel) two-digit identifier for sequence of operation development and proximity switch identification.

On the right side of the panel, the outlets of the three vessels are arranged in a common radius from the ports 03/16. Ports 03/05 and 16/17 represent pairs of U- and J-bend ports respectively, connected by behind the panel fixed jumpers. Figure 4 shows a plan view of the J/U-bend combination. This arrangement permits simultaneous CIP and/or media transfers from the tanks at this juncture. On the left side of the panel, the three vessel inlets are connected to a single transfer point. This is connected via a behind-the-panel jumper that allows connection to the WFI supply, and either of two cell culture suites. Note that the cell culture suites may be connected to either the tank outlets (media transfer to cell culture) or to the tank inlets (CIP through transfer lines from cell culture to media vessels). The WFI supply valve is automated so it does not require operator access to the rear of the panel.

Slopes are identified to ensure proper drainage of the system. As previously stated, the transfer panel is generally the low point of the system so all lines slope into the panel with the exception of the CIP return line which slopes towards the CIP return pump. Additionally, a low point drain has been located to facilitate drainage between steps in the CIP cycle. To minimize complexity to the panel, a single condensate return port has been located for SIP to be connected to tank outlets with flexible lines.

Interdisciplinary Coordination and Physical Design

As a key element of the overall process flow, transfer panel design does not occur in a vacuum; coordination with other disciplines is critical, particularly at the beginning and end of the design process.

As mentioned previously, physical space must be allocated for the panels in the equipment layout early in the design process. It is often advantageous to pair up transfer panels back to back in adjacent process areas, separated by a service chase providing space and access to common utilities, piping racks, and equipment that do not need to be in controlled areas and

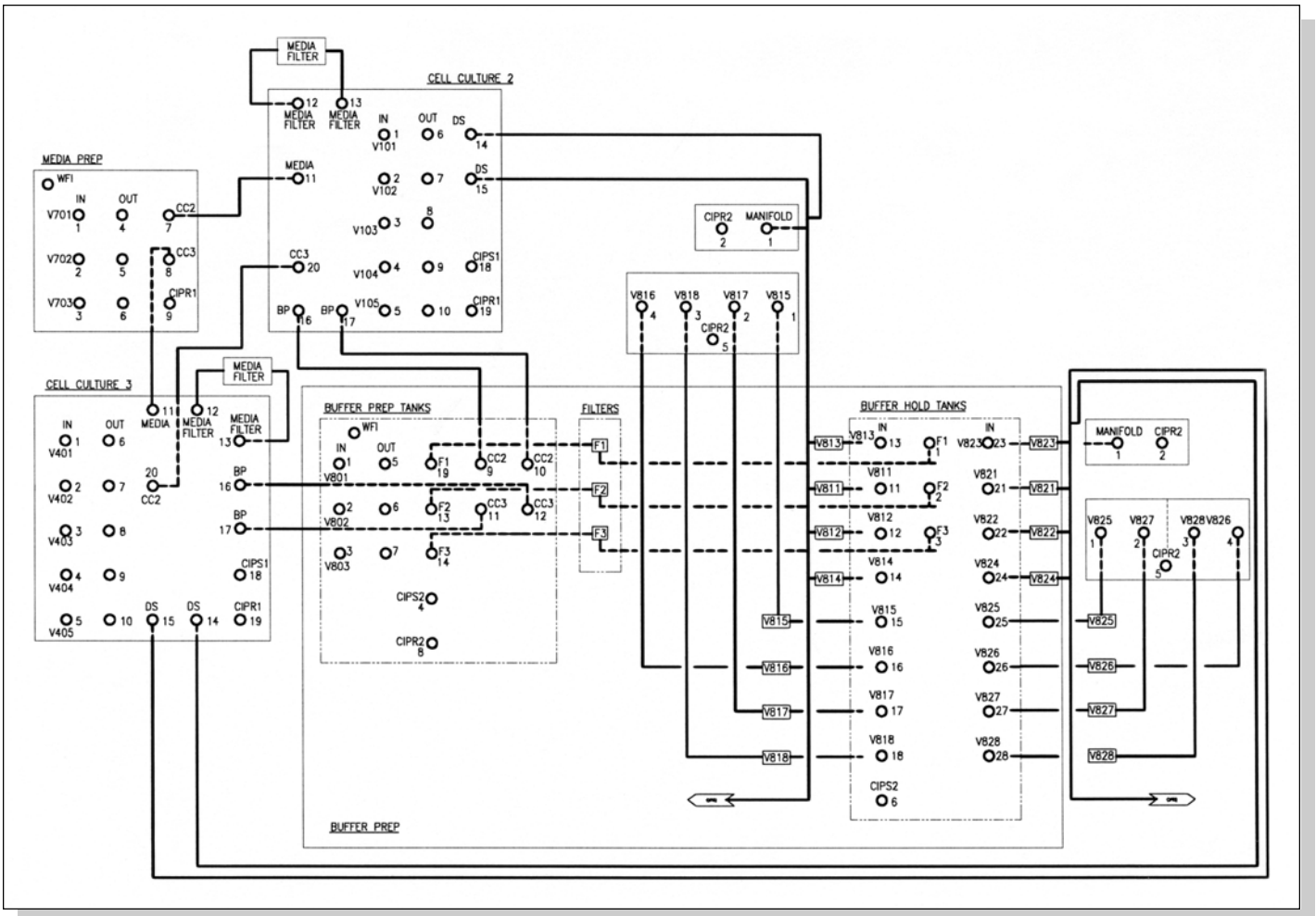

Figure 7. System transfer flow diagram.

where servicing might interfere with ongoing process operations. Clear wall space is needed for the panel and allowance for ample working space, particularly on the process side, should be made. Floor pits provided for drains, return pumps or other below grade work need to be coordinated with building foundation work.

Drainage is required at the base of the panel, but drains can present contamination and containment concerns, and this needs to be addressed on a case by case basis. A trough at the bottom edge of the transfer panel, piped to a covered drain that is only open during the draining process is one alternative. Another option is to pipe this to an open drain, but treat the drain with an appropriate sanitizing agent such as hypochlorite or caustic. This may be performed automatically either continuously or intermittently, or manually after each use. At a minimum, an air gap between the panel drain and the building drainage system is advisable.

Elevations are important as well; the transfer panel is usually a low point in process transfer and slopes must be maintained for free drainage, both to and from the panel, especially from tank outlets and to steam traps and CIP returns. These drainage requirements have an impact on tank bottom elevations and thus on overall tank heights and ultimately on room height.

Once the detailed design has been developed, the work needs to be translated to produce a functional, physical design. This includes detailed routing and layout for the necessary piping to and from the transfer panel, and any valves with or without actuators, steam traps, filters or other appurtenances, as well as the physical layout of the transfer panel itself. It is frequently advantageous in more complex panels to spread the ports horizontally to avoid interference in the vertical piping runs behind the panel. Because the panels are large, heavy and require a high degree of rigidity, reinforcement with heavy tubing is usually required on the back of the panel or in the wall itself. Proximity switches, if included, need to be incorporated, together with their wiring and junction boxes.

If the transfer panel incorporates proximity switches for confirmation of process connections or automatic valves, Instrumentation and Control functions become involved in the final design. A sequence of operations for each process transfer or operation is developed from the process transfer permutations generated earlier, incorporating all necessary valves and proximity switches operations needed to ensure that a particular loop is properly set up for operation. Interlocks are included in the programming of the transfer circuit, such that if a circuit is incomplete due to incorrect or missing U-bend connections, the circuit will not operate and malfunction alarms will occur. This alarm will be identified and displayed on the Operator Interface Terminal (OIT).

Only when all these considerations have been accounted for and reviewed is the design ready for release for bidding and construction.

Conclusion

To demonstrate the integration of the entire system, the full Transfer Flow Diagram is shown in Figure 7. In addition to the media preparation and cell culture areas, the transfer system accommodates buffer preparation, an intermediate buffer storage area and purification suites. The system includes transfer of cell culture harvest to the primary purification room. Buffer is prepared in one of three vessels in the preparation area, and is filtered in-line to be received by one of 16 vessels in the buffer storage rooms. From the buffer storage rooms, the buffers are directed to the appropriate purification rooms where the solutions are used. One of the buffers is fed into the cell culture suites.

We have chosen to illustrate only a portion of the transfer process in a manufacturing facility. Though the actual system is considerably more complex, the general design approach discussed herein can be applied to the entire system by "black-boxing" the panels to analyze the necessary connections between panels, then designing the individual panels.

Acknowledgments

The authors wish to acknowledge Baxter Healthcare Corp. for their input on the transfer panel design and analysis process and for use of the photographs and drawings.

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Reprinted from
PHARMACEUTICAL ENGINEERING
The Official Journal of ISPE
July/August 2000, Vol. 20 No. 4

Optimizing the Clinical Drug Product Supply Chain for Phase III Clinical Trials

Shortening the time frame for drug product development requires optimizing all developmental activities. This article will present some optimizing practices for supplying investigational drug products to the clinics which support clinical drug product development and medical research.

by Charles F. Carney

Introduction

The strategic advantages gained by pharmaceutical companies through rapid drug candidate screening and rapid determination of short term safety and efficacy in early clinical trials can be lost if the activities and processes are not optimized for Phase III Clinical Trials. An important aspect of this optimization must be the assurance of a continuing and adequate supply network for appropriately manufactured, packaged, labeled, and delivered drug product supplies.

Some successful strategies will be outlined and discussed for planning for the full needs of each program prior to implementation and for prioritizing work by task rather than by project. This prioritization and planning can be amplified by the development and implementation of a critical event and decision making strategy that evaluates all data both for controlling the forward process of the project and for ensuring an adequate learning pattern for the company. Such a strategy will have a well-defined set of quality criteria for each process utilized and product produced, and an effective quality control unit which can implement decision or change as needed.

Practical aspects also will be discussed which can ensure that the medical research plan and the product development plans are linked and coordinated. Practical exercises, such as developing protocols for shipping and storage of investigational drug product in environmentally challenging regions of the world having preestablished plans accounting for export and import requirements in the various regions and using multiple language labels with text from a standard database, are proposed, which could increase operational efficiency and effectiveness.

Support of all activities by validated electronic systems (records, databases, communications) will enhance the speed of processes and can increase the ability to track the information.

A model for ensuring market readiness for the final commercial market image at the time of registration dossier submission is outlined.

Planning

A planning process for all clinical trials which accounts for prioritization of tasks and appropriate allocations of personnel, equipment, and space must be developed. Such a planning process begins with the project team and ends with the various groups who must supply, run, and analyze the data from the clinical trials. Supply planning needs to account for the starting materials including excipients, actives, and packaging components, specifications, acceptance criteria, and analytical methodology, the appropriate manufacturing process at the correct scale, and the logistics for distribution to the various sites.

Today, Phase III Clinical Trials are run in multiple centers in multiple countries. Most companies plan to register their new products in every country in which the therapy is relevant and therefore try to have clinical experience in subjects in those countries. At Phase III, the excipients and drug substance particularly should be specified as the materials that will be used in the registered product. Time can be saved by having these specifications clearly established by the time of the manufacturing of the products for the Phase III trials. If they are not, the sponsor will probably need to repeat some important trials in the specific country for which the materials used to produce the products tested were not properly defined. Today, it is critical to ensure that all materials meet the requirements of the regulatory agencies in the major pharmaceutical regions, ie, US, EU, and Japan.

Likewise, analytical methodology should be at the state of validation that the data for the products used in the Phase III trials will be relevant for registration. The time frame for gathering the stability data for lots to be reported in registration documents is 6-12 months

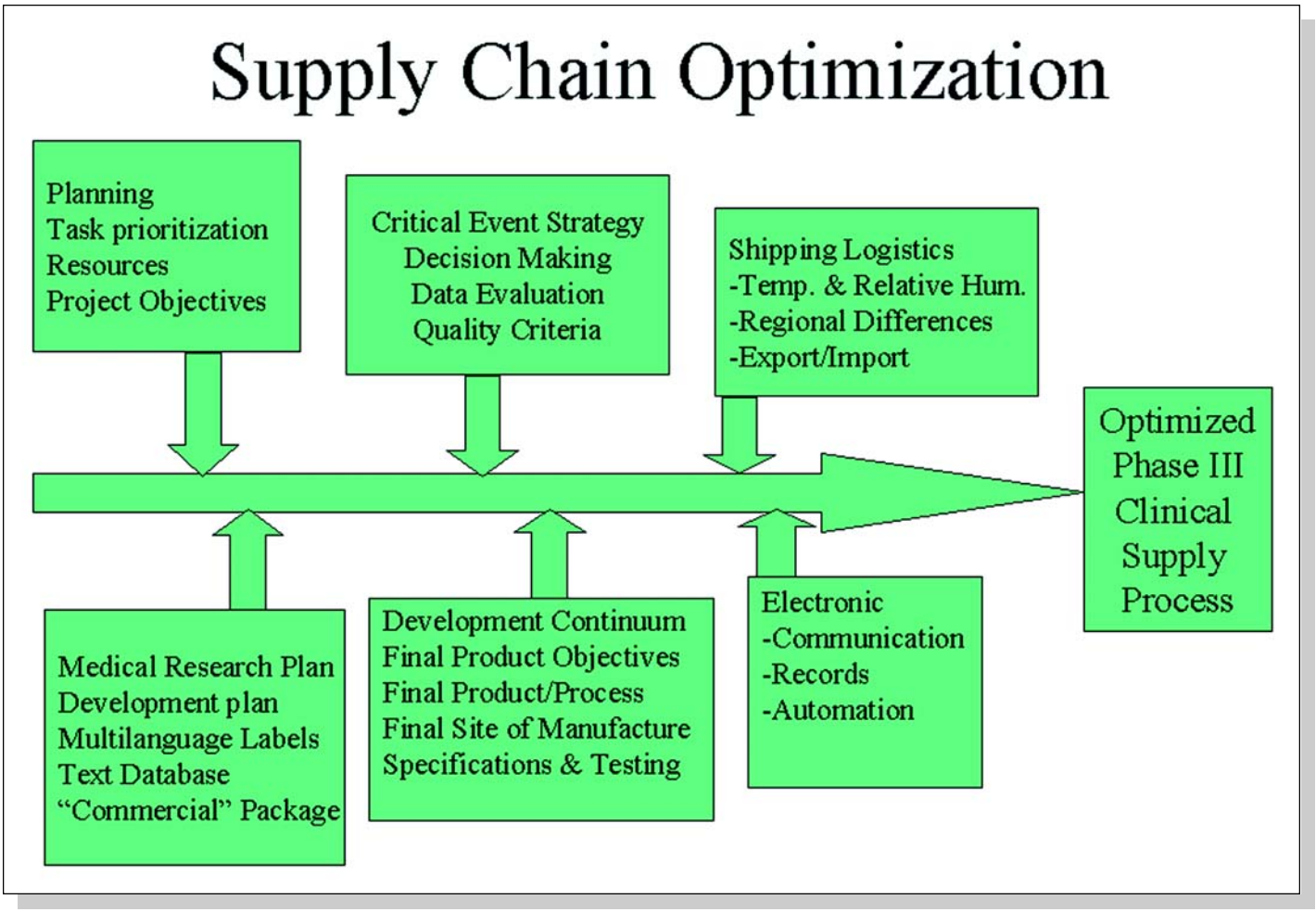

Figure 1. Factors for effective delivery of investigational drug products during phase III.

at the minimum. It's difficult to draw conclusions on the quality of the final formulation and process to be written into the registration documents in the case that the analytical methodologies are not in their final forms.

Early planning can eliminate such concerns for materials quality. Early planning also can assure that the appropriate scale of product manufacture will occur. This means that one should be planning for all of the trials which might occur during the Phase III studies not just the pivotal efficacy trials. It's often the case that operating personnel focus only upon those trials which are most visible. However, there are many other smaller trials designed to collect food effects, sex differences, age specific effects, concomitant medications, and concomitant disease interactions for use in getting the greatest applicability of the drug product in its labeling. In the event that these are not planned for, one can expect to allocate greater amounts of capacity for manufacturing the additional clinical supplies batches, testing these, and tracking and analyzing the data from them. This additional work will be unnecessary if one plans to make the larger scale batches to make sufficient supplies to supply all of the trials. Some additional considerations must be made for producing adequate amounts of blinded comparator drugs for positive control trials[1,2] and for supplying the properly packaged and labeled product for bioequivalence/bioavailability trials.[3] Appropriate strategies must be developed to ensure that sufficient products will be available for all clinical trial, reserve, and special regulatory sample needs.

All indications in which the product might be studied should be considered in this same context. This is even more important for the case that all indications can be studied using the same strengths of products. The efficiencies of scale for manufacturing and testing larger scale lots can be quantified in terms of the extra dollars for personnel time, machine changeovers, testing time and reagents, and warehousing for multiple lots of each strength vs. one lot of each strength.

An important prerequisite for the manufacture of the drug product is the adequate supply of the final form of the drug substance. The points stated above for the drug product must be put into place even earlier for the drug substance, perhaps in early to mid Phase II, in order for this strategy to work.

Early planning also can ensure that the appropriate scale of equipment and any new technologies have been purchased, installed and qualified. Similarly, allocations of existing personnel or planning for the addition and training of new or part time personnel can be ensured. If contracted capacities or technologies will be utilized, early planning will assure that these capacities are available when they are needed. Any co-development and co-marketing strategies should be developed clearly and early in order to ensure that the Phase III research program will capture all of the information of interest to and needed by both parties.

> ***A strong decision making process needs to be in place. This implies a need for a strong, well-educated, objective, and mature Quality Control Unit.***

Shipment Logistics

Phase III trials are performed in many different regions and many different countries. It is important to know that the clinical supplies package will be appropriate for the country to which it is being shipped both from the perspective of product stability and from the perspective of the acceptance of the use of that package in that country. Not all countries have the same degree of air conditioning or refrigeration possibilities as the USA. Therefore, for temperature or humidity sensitive products and for products requiring freezer conditions, some initial thinking should account for whether the required capabilities exist in all the countries into which the clinical supplies will be shipped. If the capabilities do not exist in the chosen clinic sites, then these can be added prior to the initiation of the trials in order to ensure the optimal supply chain capabilities for receipt and storage according to the needs of the products.

Particular attention also should be paid to the container closure system, especially for liquid or semisolid products. Preformulation packaging and shipping experiments designed to ensure correct package type (primary and secondary) for shipment to any region for Phases I-IV Clinical Trials should be considered. Some problems have been experienced by others. Unexpected freezing of liquid products or thawing of frozen products can occur when the transportation stream is interrupted and materials must sit in uncontrolled conditions in a terminal while the transportation plans are redefined. Some liquid protein products can degrade physically because of agitation or temperature changes. Pre-filled syringes can leak as a result of pressure changes during air transportation. Friction closed (push closures) plastic tubes can open as a result of some pressure changes during air transportation if the top and bottle are not properly designed or fitted with a tamper evident and safety closure device to hold the closure to the container. Such possibilities for your products and container/closure systems can be discovered and evaluated by simple shipping experiments with specific combinations of the possible various formulations and container closure systems.

While the exportation of clinical supplies from the USA was made easier by the Enhancement Act of 1996,[4] the importation requirements into other countries continue to evolve. Adequate understanding of these requirements and the timing for ensuring the ease of importation into each country for each shipment of clinical trials supplies will help in the planning for efficient execution of clinical trials. The CTA or CTN process is somewhat different in each country that uses this format. And, even in countries which do not use this approach, the application and receipt of import licenses may follow a different, but equally tortuous pathway. Personnel in your organization will need to be experts in the various aspects for the countries for which they are responsible or should hire some local experts in each country to facilitate the process. Unanticipated delays for importing the clinical supplies into any country can jeopardize the clinical trial from two aspects. First, the delay will add to the total time for the administration of the supplies to the subjects and for collecting the data. This country then may become the rate-limiting factor for locking the database and analyzing/reporting the data. Second, this delay may be sufficiently long that the drug supplies exceed their expiration period and must be replaced. This could take additional time making the results from this country even more critical in the timeline. Finally, it's important to plan for exporting to any non-'Tier-One' country from the USA. If the trial is not performed under the US IND, exporting to a non-"Tier-One" country will require the application for and receiving of an export authorization from FDA prior to shipping the supplies. As the eastern European and Latin American countries become more important in supplying subjects and clinical trial sites for international clinical trials supplied from the USA, this aspect of export authorization will be a very crucial aspect to be considered in Phase III trials' planning and execution.

In order to avoid some time-wasting discussions during the execution of Phase III trials, the required money for paying transportation costs and importation duties should be estimated and budgeted during the planning phase. These should be budgeted in that part of the organization that will need to make the payments. Any time delay resulting from discussions at time of shipment or at time of receipt about who will pay is unacceptable in an efficient project management philosophy.

Critical Event Strategy and Decision Making

"Unexpected Things Happen" might be a paraphrase statement for many of "Murphy's Laws." One needs to develop and formalize a process which can minimize deviations in manufacturing and testing activities for the Phase III drug products. An important aspect is to ensure appropriate development of specifications and acceptance criteria for materials, in-process controls, and finished drug products. On-going review of results with respect to expectations and goals of the product should be performed with the requirements for the final drug product in mind. This review should not be just whether the results conform with the provisional requirements established, but also should be challenging of the acceptance criteria with respect to the future robustness of the product. For example, early criteria for dissolution testing may be set somewhat liberally during the development process while the experiential data are being gathered. When a result is seen which is near the lower acceptance boundary, but still within the acceptable range, it is insufficient merely to accept the lot and go on, particularly if this value is different from what has been seen previously for this product. Constant comparisons of new data to those from previous lots should be made and a proactive attitude for strenuously investigating those lots for which the data are somewhat different. Similarly, experiences gained during manufacturing operations with respect to time required to complete manufacturing and accountabilities for material balance, especially for unexpected yields resulting from losses, should be evaluated very carefully. Every chance for learning about the product and its manufacturing process should be taken.

A strong decision making culture and process needs to be in place. For clinical supplies operations, this implies the need for a strong, well-educated, objective, and mature Quality Control

Unit. Under the current pharmaceutical industry paradigm of developing a greater number of innovative products in a shorter time frame, quality aspects must be maintained in the business atmosphere of taking greater risks. Of course no risk should be taken that jeopardizes the wellbeing of clinical trial subjects or the clinical research goals for that drug product. However, not every unexpected result should be a "show-stopper." A process needs to be in place that an efficient, effective evaluation can be made by the appropriate personnel in order to reach a decision and document it in order to continue with the project. This means that a corporate philosophy for level of perfection needs to be developed and understood by all. It also means that clear assignments for operations control and decision making must be made and accepted by all of the interacting personnel. Finally, an efficient and effective means for communicating the issue, the evaluation, and the decision needs to be in place. This will ensure that other parts of the organization do not get embroiled in the internal time wasting that results from "arm-chair analysis and re-analysis" of the issues of another department or division.

Effective Product Development

Product development needs to be considered as a continuum. Formulation design, process development, clinical supplies manufacturing, scale-up, and commercial production should be considered as sequential processes with constant feed-back of information and proactive planning to meet the final goal. Thinking of these various activities as a continuum and performing all tasks as part of this whole will ensure and optimize the technology transfer process and production of the pivotal lots. This should include all aspects of packaging and labeling for the clinical trials. Choice of container closure system and labeling text for clinical trials should support final choice of container closure system and labeling statements. Treating the development process as a continuum also will ensure that everyone learns from the project. This is equally true for the Regulatory Affairs and Marketing personnel as it is for the R&D and Production personnel. Such learning will be good for the immediate project, and many of the lessons can become baseline knowledge for better planning and execution in the next project.

A useful model that might be considered for ensuring the rapid and efficient development of a product is the following. Final drug substance process, scale, and site of manufacture should be available as early in Phase II as possible. Final drug product process, scale, and site of manufacture should be available one to two years before the expected submission of the registration documentation. The final specifications, acceptance criteria, and associated validated analytical methods also should be established in this same time frame. Validation and registration lots can then be prepared, and the associated stability studies in the final container/closure systems for commerce with the registration analytical methodology can be initiated in order to gain the 12 months of data required for inclusion in the registration package. This work can occur in parallel with the completion of the Phase III Clinical Trials which can utilize the registration lot materials. This model will ensure that when the medical research is complete and successful, the capability for production and control of the commercial product will be ensured.

Effective Clinical Supplies Handling and Utilization

Utilization of personnel capacities must be optimized. Clinical trials are becoming larger and more complex with multiple countries and multiple sites within each country. Multiple indications for the drug product (and ideally for the same formulation and strengths of the product) are being studied in parallel. A significant factor in ensuring the optimization of personnel will be the early understanding for numbers of subjects (expectations for total initiated subjects as well as total evaluated subjects) in each trial for each indication, numbers of countries, and numbers of sites in each country. One can optimize the packaging and labeling aspects for this complexity by producing products which comply with the packaging requirements in all of the countries and for which multi-country labeling has been applied. The decision for universal container/closure system, minimal package count, and multi-country labeling should be reached early and agreed by all. Such multi-country labeling can be achieved for the case of one to three countries in the space available on the usual label stock. The information is printed in the three alternative languages in the appropriate fields on the label. For a greater number of countries, there is usually insufficient space on the usual label on the container for all of the countries. In this case, it is possible to have a printing company print small booklets. The front page of the booklet is attached to the container. Each page within the booklet has the identical information for the trial in a specific language for each of the countries in which centers for the trial will be located.

An aid to such printing will be the development within the corporation of a universal label text database. Such a database will contain the proper translation of specific text for clinical labels in each language. Once the text has been developed for the labeling in the trial in one language then the exact equivalents for the other languages can be called immediately. This will save significant time for label approvals because translations will not have to be performed each time. In fact, such label approvals can then be done in one location. The labeling will not have to be circulated to many sites around the world for country specific review and approval. Developing and validating such a system, providing the training of all personnel, and developing the faith in the system that the authority for approval now resides in one group will cost some time and effort and may require some paradigm shifts within the company. However, the pay back in shortening the development timeline will be well worth the initial efforts.

Even though there will be some projects or even some protocols within the project for which such universal packaging and labeling will not apply, nevertheless this should be an objective for all projects. The flexibility that this provides in being able to make post-start changes in choice for numbers of subjects in each of the countries or the ability to add additional sites in a particular region will result in time savings. In addition, savings in costs and capacities will be realized by the groups producing and testing the trial supplies. Such savings can allow for the greater numbers of projects and shorter development time-lines desired by the company. Having said this, one must be careful about trying to use this flexibility for country to country transfers (site to site). The additional costs

and complexity, particularly for issues concerning export/import, and for assuring package integrity, product stability, and regulatory acceptability with such transfers must be assessed prior to performing the task in order to make a cost-effective decision.

Electronic Automation/ Information Management

The electronic age has arrived. Any information retrieval, recording, formatting, analyzing, and reporting that can be automated with the aid of computer systems should be encouraged. The caveat of course is that all such systems, including the personnel operating systems, need to be validated. And of course, for any information that will be reviewed by the FDA, the determination of whether these produce electronic records should be made[5] and the appropriate assurances of system conformance applied.

Summary

Every company must choose its own best practices to ensure the efficient development and registration of new drug products. However, each of these strategies needs to account for adequate planning, adequate training, and performance of operating personnel, and adequate philosophy of product development in order to deliver the proper clinical trials supplies in support of the most effective Phase III program. This article has discussed some of the concepts which seem universally applicable in all organizations.

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About the Author

Charles F. Carney is currently responsible for all manufacturing, packaging, labeling, and inventory control activities for clinical trial supplies at Boehringer Ingelheim Pharmaceuticals, Inc. His responsibilities have included preformulation and formulation development for new chemical entities, release and stability testing of all clinical trial dosage forms, and all operations associated with the preparation and distribution of clinical supplies. Carney serves on an international working group within the BI Corporation which has the responsibility for harmonizing and establishing one GMP concept for clinical supplies worldwide for the corporation. He served on the Clinical Materials Committee of PMA from 1991 to 1994 and was a member and past Chair of the ISPE Clinical Materials Committee. He has published and presented papers in the areas of preformulation, formulation, and control of manufacturing operations for clinical drug products.

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Reprinted from
PHARMACEUTICAL ENGINEERING

The Official Journal of ISPE
July/August 2000, Vol. 20 No. 4

This case study presents how one pharmaceutical manufacturer used computer simulation to decide whether to renovate its existing packaging facility or build new.

Support Planning with the Aid of Computer Simulation

by Konstantin Bluemel

Introduction

Computer simulation is a valuable aid in the consulting and planning of pharmaceutical production facilities and increasingly supports the path to optimal solutions. At the same time, it successfully conveys complex facts to all levels of the planning team.

The Use of Computer Simulation in Consulting and Planning

Computer simulation systems have been used in the planning of pharmaceutical production facilities for more than six years. Computer simulations are dynamic models of real facilities and provide the planner with an expert system to very quickly and efficiently review his planning options.

In the first years, the main focus of the use was largely to optimize apparatus capacities, the flow of materials, and stock sizes. This area of use has been expanded into the optimization of corporate organizational structures and can be applied today to the optimization of direct production costs.

The example presented here shows how efficiently simulation systems can be linked with questions of economy.

Available Experience

The company described is a chemical and pharmaceutical producer with worldwide production facilities. Simulation tools, which differ according to need, have already been used for some time as part of the planning. In the field of chemistry, programs calculate the reaction times from thermodynamic formulas, while in the pharmaceutical field, they take the shape of discrete simulators, also described as logistical simulators.

The planning of an almost completed new building for bulk tablet production also was underpinned by simulation studies during the concept phase. Thanks to the use of simulation studies, it was possible to optimize packaging processes at a very early stage. In this way, the future production costs were already known during the discussions over planning scenarios. For the decision-makers, future operators, and

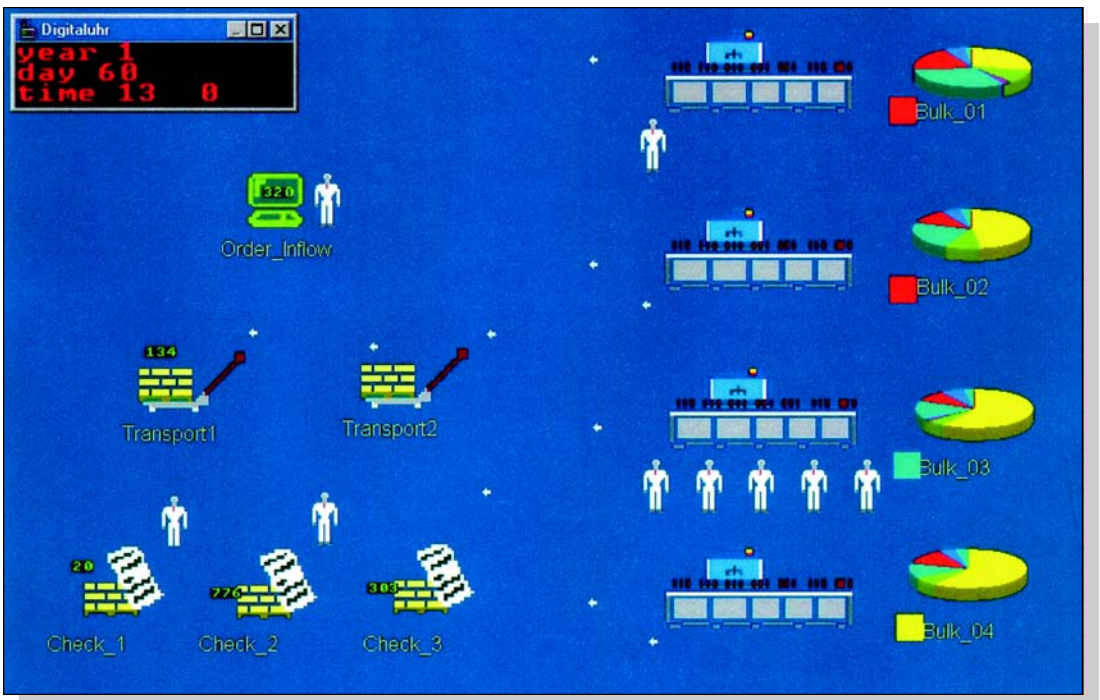


Figure 1. Part A of the PC simulation screen.

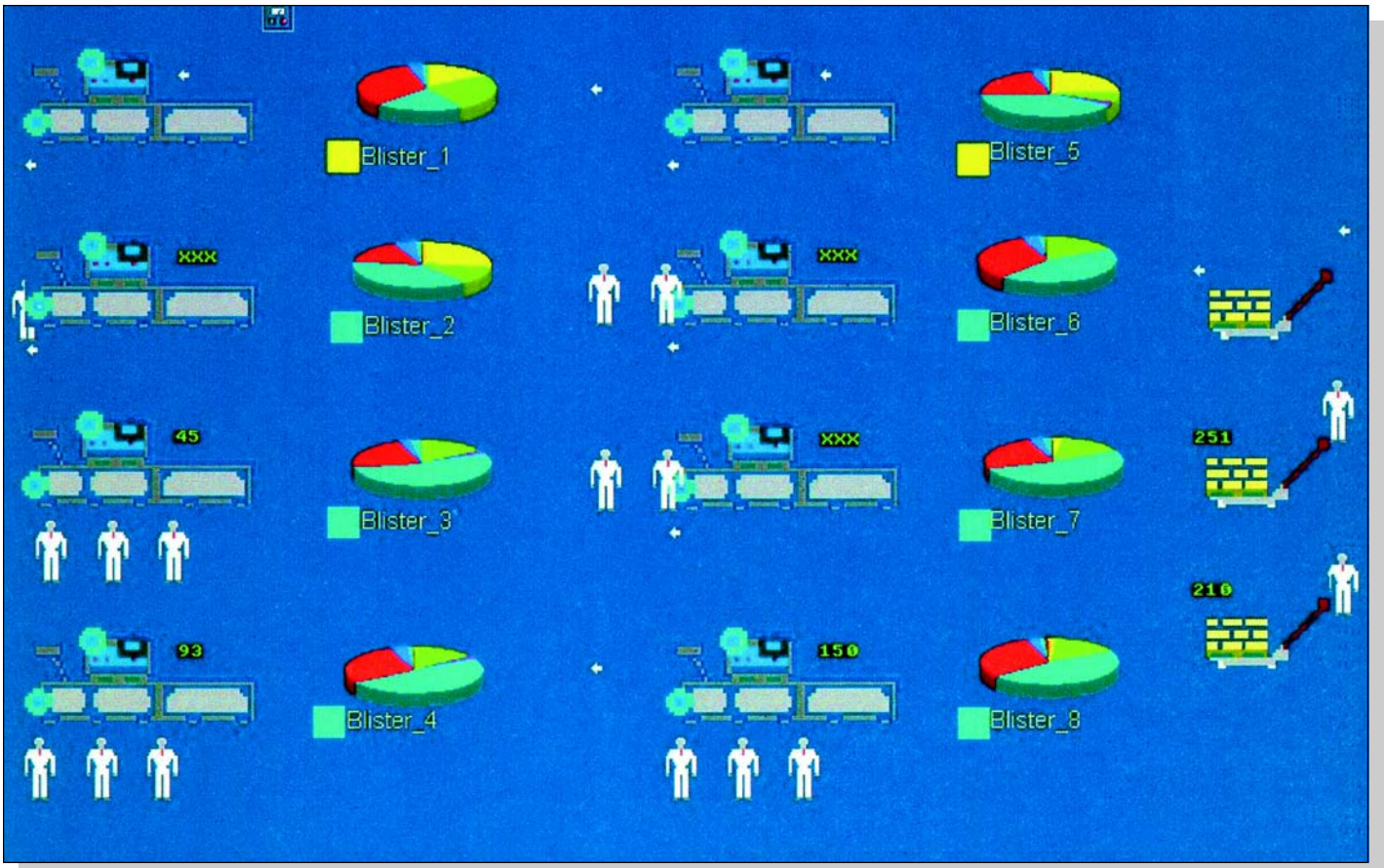


Figure 2. Part B of the PC simulation screen.

the planners, this meant a considerably heightened knowledge of the project basis data in comparison with conventional concept and planning phases. This was the reason why computer simulation was used in the new planning presented here.

Case Study

Now that the construction of the new bulk tablet production facility at the described location is largely completed, consideration was given to a packaging plant that is directly connected to the production facility from a logistics perspective. The plausible assumption was that an organizationally and economically more efficient unit could emerge from the direct connection of bulk production and packaging.

The existing packaging plant is likewise situated on the plant premises; however, it is physically separated from both the existing and the future bulk production facilities. Logistically, it is connected via intermediate and temporary storage facilities.

As with most established factory structures, the situation with regard to material and personnel flow, hygiene zoning, and general business processes is less than perfect. Because of the high pharmaceutical requirements, there is pressure for constant optimization of the internal organization, which in turn entails costs. In the existing old building the possibilities for improvement are naturally limited and, moreover, relatively expensive once there is need for extensive structural alterations of the building.

The alternative of a new-build; however, also should be critically examined. The investors and future operators would like to know whether and how the options regarding material flow, logistics, and a working model will affect both the sum needed for investment and the running costs.

Finally, the project team was asked to provide an independent assessment of the economic efficiency of all options in both the old and new buildings with regard to level of investment, production costs, running costs, and length of the amortization period. The project team was staffed in accordance with these tasks. The customer provided the capacity for cost estimates and controlling; the author's company supported the study by developing and implementing the simulation.

Project Organization

The project was structured into workshops and project meetings. To begin with, the requirements of the simulation were clearly defined. The subsequent meetings were designed to ensure that all team members shared the same knowledge and to guarantee the management of the project. Although the study was the result of a team effort, individual work packages were dealt with by varying staff constellations. In each case, progress reports were provided in the meetings.

Developing the Simulation

Since the desired goals determine the development of the simulation, particular attention had to be given to this point. The degree of abstraction with which a simulation model is

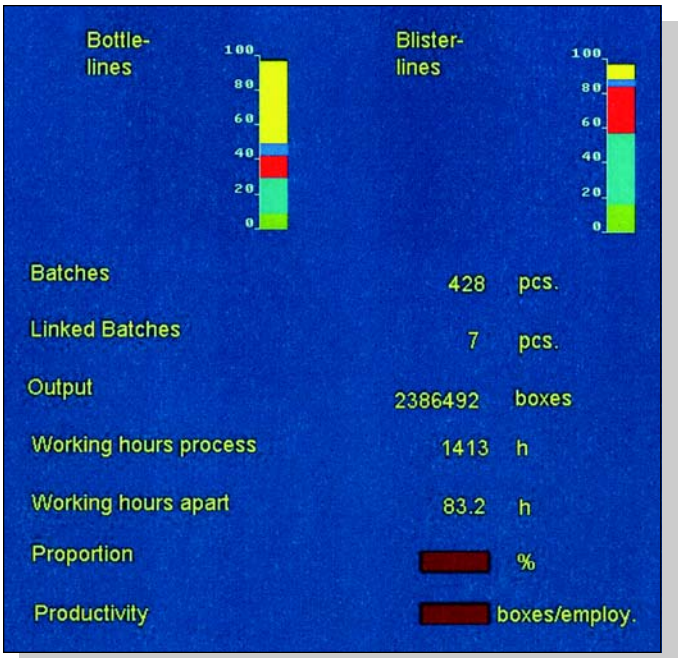


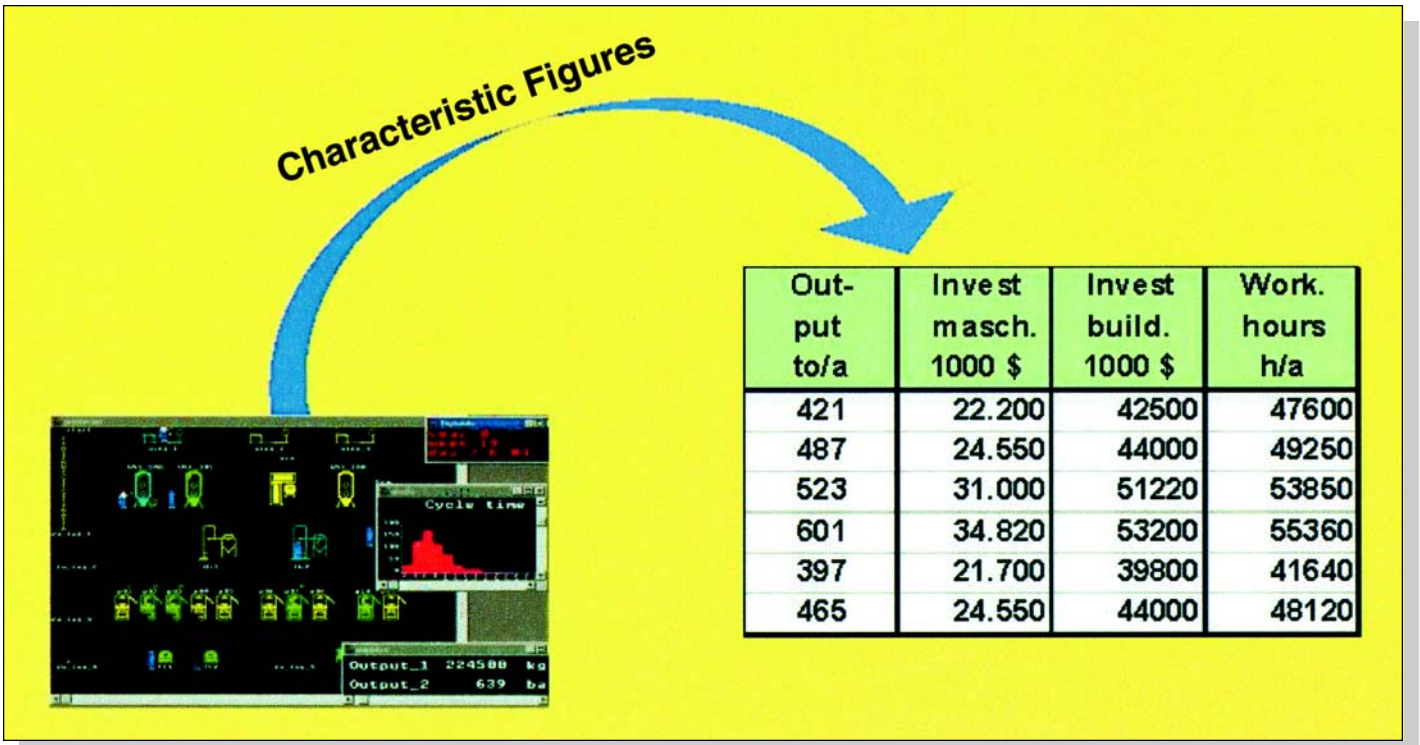
Figure 3. Some steadily written or calculated figures on the simulation screen.

drawn up and to which it reflects reality, is largely determined by the questions the model is supposed to answer. A later reformulation of the aims of the simulation in the middle of an up and running project always carries the difficulty that the simulation model used up until that point is perhaps no longer suited to answering the new questions. Often in such cases, a completely new model must be drawn up. The goals formulated in the example presented here were as follows:

- The consequences of planning decisions on investment costs and production costs must be made transparent.
- Planned measures relating to factory organization such as, e.g. working time, must become measurable in terms of costs.
- The consequences of differing machine technology and automation concepts must become discernible in terms of costs.
- The consequences of differing production planning systems on production costs must become transparent.
- Differing degrees of automation in production logistics must be measurable in terms of costs.
- The influence of various growth scenarios on production costs must be depictable so that the project decision is future-proof.

In our example, the costs for machines, buildings, and labor had to be provided, and the share of machine and personnel capacity that is required for packaging had to be accurately represented.

As can be seen in abstract form (as icons) in the screenshots (Figures 1 and 2), the simulation covered not only the processes directly at the machines, but also preparation work, transportation work, and integrity controls. It should be pointed out that the part played by these secondary works has a substantial impact upon the overall productivity of the plant. Additionally, there is a set of parameters also which determine the virtual events. Figure 7 shows how scenarios are put up as a combination of them. Theoretically, 144 different combina-



Out-put to/a	Invest masch. 1000 $	Invest build. 1000 $	Work. hours h/a
421	22.200	42500	47600
487	24.550	44000	49250
523	31.000	51220	53850
601	34.820	53200	55360
397	21.700	39800	41640
465	24.550	44000	48120

Figure 4. Characteristic figures are transferred from the simulation software into spreadsheet programs.

Figure 5. Cumulated packaging form percentages for one year. Nearly 900 different forms are packed.

tions are possible; approximately 60 were tested.

How Does Computer Simulation Work?

By definition, simulation means representing real processes with the help of a computer model. All available software enables a dynamic observation of the events on the screen and - more importantly - a statistical evaluation for all designed elements like machines, products, and operators over a certain period of virtual time. Here the simulation is based upon a one virtual year period achieved within approximately two minutes of simulation time. The required details have to be established as a database. Depending upon the utilized software, the data entry is more or less easy to handle.

A batch of packaging products is defined by the following:

- a running batch number
- the batch size in kg or dosi
- the packaging order size and number
- the product name or number
- packaging information (e.g. 12 dosi/blister, 4 blister/box, Swiss leaflet, 20 boxes/carton)
- information regarding product characteristics (high potent, hormone)
- specific information to guide this batch through the virtual production

Packaging machines are defined by:

- a machine name
- a capacity in e.g. blister/h
- a failure quote in form of statistical events
- requirements regarding operator availability
- requirements regarding service personnel
- affiliation to a defined shift model

Additional information has to be provided including pooling of batches, length of transport ways, size of storage areas, type and duration of manual or automatic controls, details of the shift models, number and qualification of personnel. These details determine the production environment, and only a few changes may produce very different results after one virtual production year.

The software used in this example is Witness, but the functionality is provided by other manufacturers, too. The available programs vary, usually disproportionally when it comes to ease of use and technical capability. The more straight forward the utilization, the more modest the result.

The following discussion provides explanations of important individual points regarding the development of the simulation.

Working Time

The simulation works like a proper production facility. This includes daily, monthly, and yearly working time models for the virtual employees. In contrast to reality, the impact in the simulation of various working time models on production costs, productivity, or just on the plant's total annual output can easily be examined. The first question regarding the optimum working time model usually concerns the number of shifts per day and the number of working days per week. Furthermore, still more complex shift models also can be reviewed. In the virtual model, various working groups can be allocated to different working times. In this way, the most productive variants of employee deployment can be established.

Organization

In the same way as the working time model, corporate labor structures play a big part in productivity and thereby the cost situation of a plant. The classic questions about the role of technical staff in a packaging plant (integrated into the line personnel or a separate organization?), or the maintenance of a call workforce are asked at every large packaging factory. Here too, simulation systems allow a rapid and reliable review of the consequences of possible changes with regard to the status quo.

Building Layout

The layout of a virtual plant influences its productivity in the same way as in reality. Long distances, complex operations involving manual transportation over possibly several floors, or the bringing together of the required materials, labels, and bulk products from various rooms to the machines requires working time. Thanks to a layout that has been optimized on-screen, considerable productivity gains can be realized in some cases. These are shown at the end of the virtual production year and are incorporated into the profitability projection as a matter of course.

Production Planning

Production planning has a significant influence on the running costs of a packaging plant. In the example presented here, approximately 200 different bulk products are packaged in approximately 900 different designs with approximately 2,500

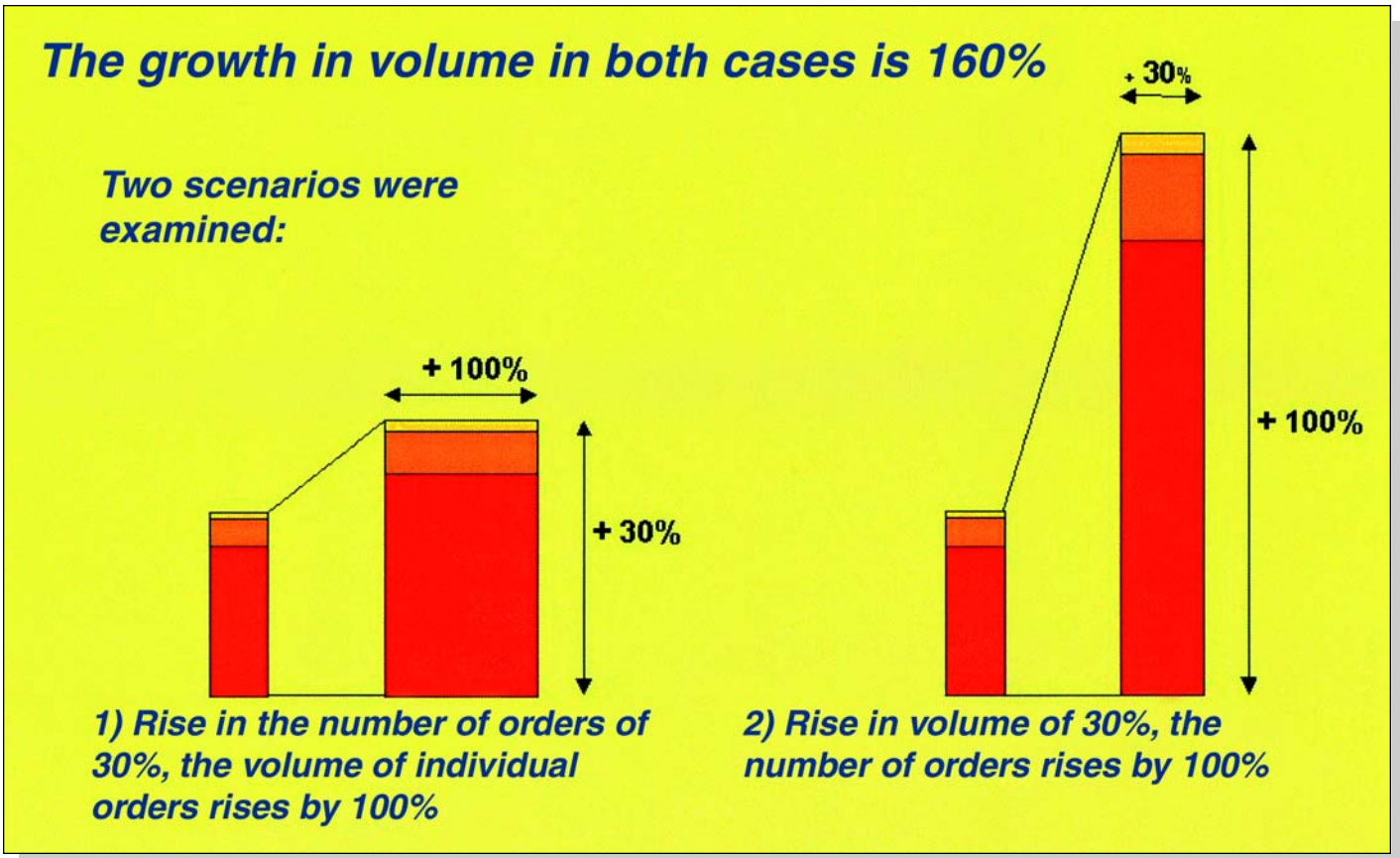


Figure 6. Two scenarios of possible growth. With different parameters (Volume and Number), completely different results will be achieved.

orders per year. As with other producers, a small proportion of these packages is produced relatively often, whereas the majority is manufactured less often or only once a year. This relationship is clearly illustrated in Figure 5. Only about 10% of the orders account for almost 75% of the number of orders. The ranges for these A products, which are manufactured too often, at times only span across one week of the plant's operational routine. However, products which are manufactured every week could be manufactured substantially better and more efficiently if they are manufactured once a month. A precondition for this is effective production planning with appropriate IT systems in order to be able to realize the required planning horizon.

The questions raised here are:

- Is it worth the expense of setting up a new system, or expanding the available systems?
- How does a more effective pooling of several orders over the course of the year affect the cost structure?

The simulation gives clear answers here too. The financial and organizational expense of the implementation can be calculated in the shortest time.

Growth Scenarios

In the case study presented here, the projected growth in production is largely unknown. Although short-term forecasts exist, the figures from the marketing department are to be viewed with caution even in the medium term. This applies not just to the level of production, but especially to the product mix, depending upon the number and volume of individual production orders. The same growth in volume from currently 100% to e.g. 260% in five years time can come about in completely different ways - *Figure 6*. The consequences for planning are enormous since smaller packaging orders often require longer secondary time for the packaging than the machine running time. Simulation systems impress in this regard because of their speed. In a short time dozens of scenarios can be played through, which demonstrate to the planners, and above all, to the investor, whether the current planning variant is in fact as future-proof as expected.

Machine Technology

Machine technology has ostensibly the most direct influence on smooth running within the packaging factory. Next to cycle figures, which are dependent upon the product or the order, down times are the most important aspect regarding the effectiveness of the use of machines. Happily, data for the simulation was available for the existing machines from a company data processing system so that the data put into the model were very realistic. The length and frequency of individual disturbances resulted in considerable down times in some cases. Of course, the planning also included the assessment of variants that were equipped with new machines. An analysis of the down times revealed; however, that only a small proportion of the down time was attributable to the age, design, or the type of the machine; instead it was the differ-

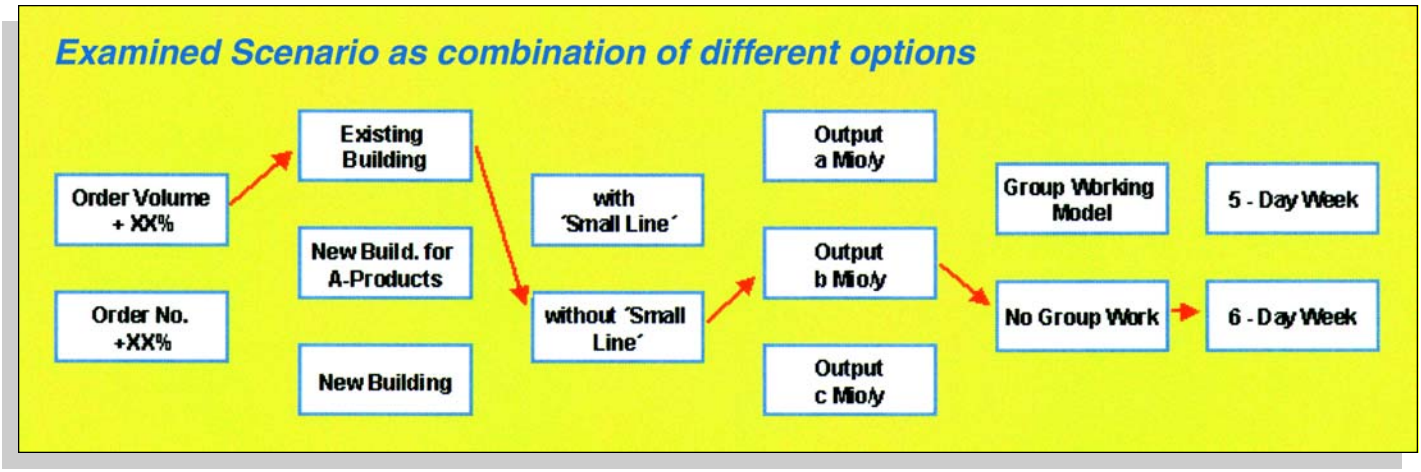


Figure 7. Scenario as combination of planning options.

ences in the products and packaging material, which were familiar to every manufacturer, that led to stoppage or at least delay. The simulation was thus able to prove that the impact of the choice of machine on the plant's overall productivity is relatively small.

In contrast, there was a significant effect in terms of the allocation of certain sizes of order to individual lines. The assumption that a small-capacity line with relatively short start-up times could be economical was fully confirmed. Capital spending on such a line would put the plant in a position to generate double-digit growth in overall productivity.

Profitability Analysis

The findings and results of each simulation run must be documented and laid out in a comparable manner. To this end, it is advisable to use a minimum number of key data that are as unambiguous as possible. In the project presented here, employee productivity alone was chosen as the decisive indicator. This key figure is expressed as the performance of the plant in 1,000 packagings per employee and per year. Figure 3 shows the screen with results and key data. The figures arrived at in the simulation extended up to approximately 190%, if the existing plant is assumed at 100%.

This potential rise of 90% in employee productivity must not be confused with a similarly high fall in the overall packaging costs. In order to realize this 90% increase, capital spending is required, which puts a considerable burden on the current operating profit via depreciation and maintenance. Moreover, a remaining question in this regard is whether such investment spending is at all feasible, in view of the length of the amortization period. For this reason, a further assessment of the suggested scenarios was made using the group-wide profitability analysis. In this way, the results could be presented immediately within the company.

Figure 4 shows another possibility for making operational costs transparent. Here the production costs are calculated directly by the PC. The procedure can be described as follows: first, using the customer's calculation of production costs that is already used in daily practice is recorded in the form of a spreadsheet. Next, the key data necessary for the calculation at any one time during the running of the simulation are generated and incorporated into this calculation scheme. In this way, the production costs for the planning variants being investigated are available immediately after each running of the simulation. In doing so, virtually no limits are set to the complexity of the production costs calculation. Of course the model must be constructed in sufficient detail for the required values to be generated reliably.

Result

The clear result of the study is that it is more economic to reconstruct the existing packaging building than to build a new one. The reasons are:

- It was proven that more high capacity lines do not lead to lower packaging costs. The required space for high capacity lines and the therefore necessary logistic was one important reason for a potential new building.

- It could be shown that a small line for small products saves potential production time significantly because it disencumbers the high capacity lines. Not more, but less machinery would help to lower packaging costs. For a small line, there is no need for a new building.

- The Influence of organizational soft-facts count at least as much as the installation of improved machines. All IT related improvements for realization of a better pooling of orders does not presuppose a new building structure. This also is valid for new working time models.

Conclusion

Within the context of the simulation study, a series of changes to the operating and packaging process were examined and their effects on productivity presented. A systematic differentiation took place between those measures for which a new building would be necessary, and those which also could be realized in the existing old building. Each of the variants examined led to a reduction in the existing machinery and to a decline in production costs. In the ensuing profitability analysis, these measures were examined in terms of the length of the amortization period. This examination showed that there were after all no economically feasible reasons for the new-building variants. The analysis found that the amortization periods for rationalization investments – this is how these measures were classified – were not of sufficiently short

> ***A systematic differentiation took place between those measures for which a new building would be necessary, and those which also could be realized in the existing old building.***

length. Here, of course, it is incumbent on the investor to use the economic measure that is appropriate for him. If, however, the spending is treated as spending on replacement or expansion projects, the set of criteria would change and with it the ensuing conclusions.

For the conversion planning of the manufacturing plant, this means that the productivity-enhancing ideas examined can flow directly into the basic design. Indeed the concepts were already dealt with in the study. The investor knows the cost-effective factors of his business process and has high projection reliability with regard to the decision taken.

It is enormously important for the implementation of the planned measures to secure a general acceptance among all the parties involved. Because simulation systems offer a good visualization of the effect of even highly complex organizational measures within a business, they are easy to understand for all concerned, which ensures objectivity in the discussion. This can be extremely helpful when, for example, working-time issues have to be communicated in the staff council.

However, most important is that the decision reached is guaranteed to be future-proof. By examining the variants with differing growth scenarios, it can be ensured that a decision that is right today does not turn out to be wrong in one year's time.

About the Author

Konstantin Bluemel is a freelance consultant and executive of S·O·P in Frankfurt. He holds a Dipl.-Ing. degree in process engineering and worked for the last 10 years with Pharmaplan GmbH as a Project Manager. He has experience with planning, commissioning, and start up of different dosage form plants worldwide. The last years he concentrated on consulting and computer simulation.

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