This article describes how batch process simulators can be used to facilitate and expedite development and commercialization of pharmaceutical products.

The Role of Process Simulation in Pharmaceutical Process Development and Product Commercialization

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Introduction

The development and commercialization of a new pharmaceutical product is a painstaking process that takes 7 to 12 years to complete requiring sizeable investments ranging from $100 million to $500 million. In addition, 80 to 85% of products in development fail somewhere in the development pipeline, often after undergoing expensive clinical trials[1]. The pharmaceutical industry spends considerably more on the development and evaluation of products that eventually fail than on successful products. Consequently, any methodologies and tools that can be used to evaluate alternatives and speed up the development ef-fort can have a tremendous impact on the bottom line.

Computer Aided Process Design (CAPD) and simulation tools have been successfully used in the chemical and oil industries since the early 60s to expedite development and optimize the design and operation of integrated processes. Similar benefits can be expected from the application of CAPD and simulation in the pharmaceutical industries. The primary emphasis of this article is on the role of CAPD and simulation in expediting process development. The responsibilities of process development include:[2]

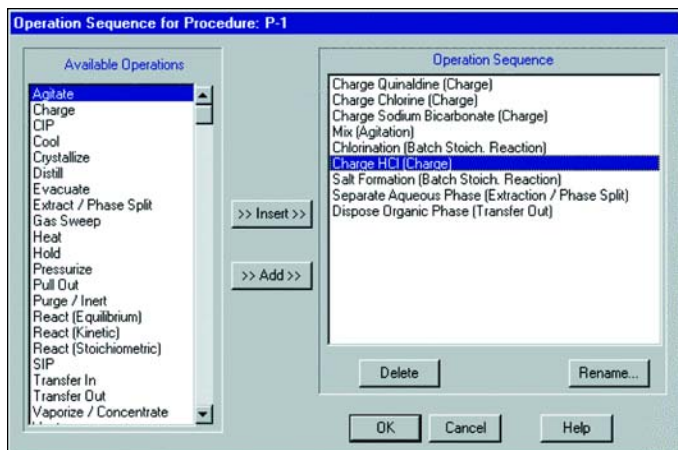*Figure 1. Addition of unit procedures and stream lines to the flowsheet.*
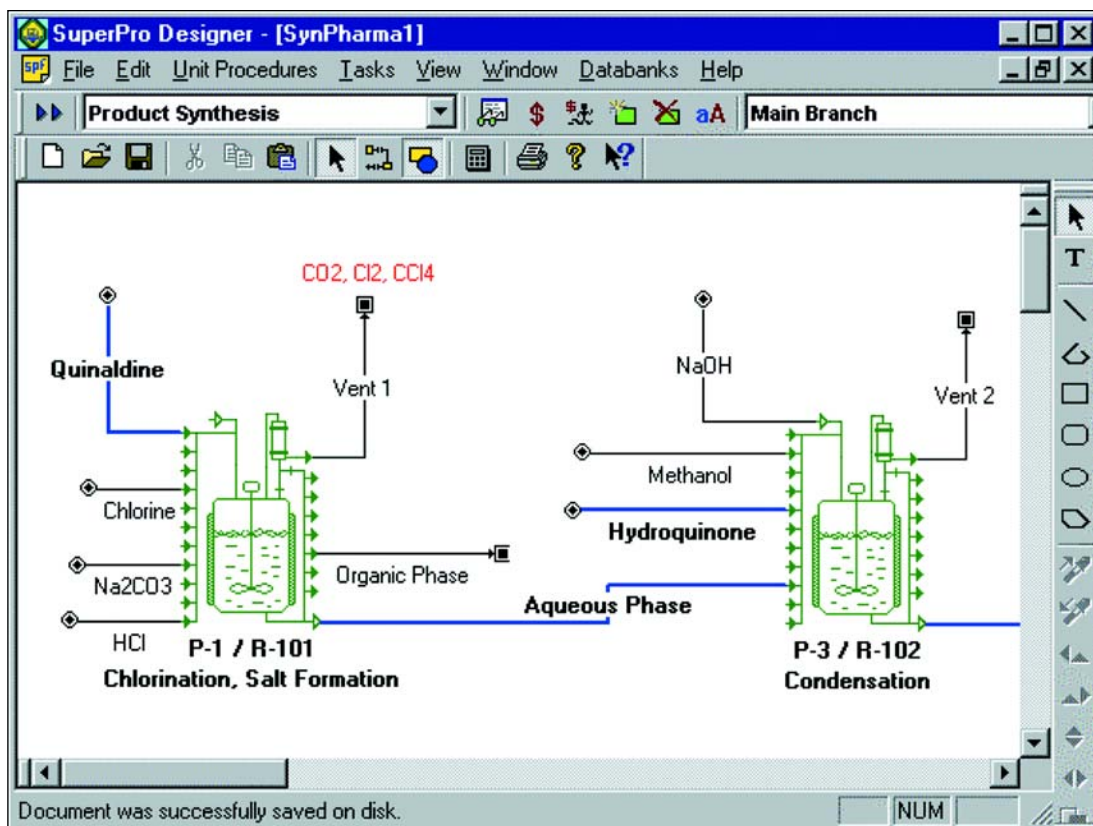
Figure 2. The operations associated with the first unit procedure of Figure 1.

- supply of initial quantities of the Active Pharmaceutical Ingredient (API) for toxicological screening and formulation studies

- supply of Drug Product (DP) to support clinical trials

- development of a practical, environmentally sound, and economically feasible route for producing the API and DP on an industrial scale

- selection, scale-up, and validation of these processes, ensuring the smooth transfer of technology from the pilot plant to the ultimate production site(s)

Process simulation tools can be used throughout the life cycle of process development and product commercialization. The benefits at the various stages of the commercialization process are explained below.

Idea Generation
When product and process ideas are first conceived, process simulation is used for project screening/selection and strategic planning based on preliminary economic analyses.

Process Development
While the pre-clinical and clinical testing of the candidate drug compound is going on, the company's process development group is looking into the many options available for manufacturing, purifying, characterizing the drug substance, and formulating it as a drug product. At this stage, the process undergoes constant changes. New synthetic routes are being investigated. New recovery and purification options are evaluated. Alternative formulations also are explored. Typically, a large number of scientists and engineers are involved in the improvement and optimization of individual processing steps. Simulation tools at this point can introduce a common language of communication and facilitate team interaction. A computer model of the entire process can provide a common reference and evaluation framework to facilitate process development. The impact of process changes can be readily evaluated and documented in a systematic way. Once a reliable model is available, it can be used to pinpoint the most cost-sensitive areas — the economic "hot-spots" — of a complex process. These are usually steps of high capital and operating cost or low yield and production throughput. The findings from such analyses can be used to judiciously focus further lab and

pilot plant studies in order to optimize those portions of the process. Being able to experiment on the computer with alternative process setups and operating conditions reduces the costly and time-consuming laboratory and pilot plant effort. The environmental impact of a process is another issue that can be readily evaluated with computer models. Material balances calculated for the projected large scale manufacturing reveal the environmental hot-spots. These are usually solvents and regulated materials that are costly to dispose of. Environmental issues not addressed during process development may lead to serious headaches during manufacturing. This is the case because after a process has been approved by the regulatory agencies, it is extremely costly and time-consuming to make process changes. This is particularly true for biopharmaceuticals where it is commonly said that "the process makes the product."

Facility Design and/or Selection
With process development nearing completion at the pilot plant level, CAPD and simulation tools are used to systematically design and optimize the process for commercial production. Availability of a good computer model can facilitate the transfer of process technology and facility design. If a new facility needs to be built, process simulators can be used to size process equipment and supporting utilities, and estimate the required capital investment. In transferring production to existing manufacturing sites, process simulators can be used to evaluate the various sites from a capacity and cost point of view and select the most appropriate one. The same can apply to outsourcing of manufacturing to contract manufacturers.

Manufacturing
In large scale manufacturing, simulation tools are primarily used for process scheduling, debottlenecking, and on-going process optimization. Simulation tools that are capable of tracking equipment utilization for overlapping batches can identify bottleneck candidates and guide the user through the debottlenecking effort.

Commercially Available Tools
Process simulators for continuous chemical processes have been in use in the petrochemical industries since the early 1960s. Established simulators for the petrochemical industries include: Aspen Plus (from Aspen Technology, Inc.), ChemCAD (from Chemstations, Inc.), HYSYS (from Hyprotech, Ltd./AEA Engineering Software), and PRO/II (from Simulation Sciences, Inc.).

The time-dependency of batch processes makes development of batch process simulators more challenging. "Batches" from Batch Process Technologies (West Lafayette, IN - www.bptech.com) was the first simulator specific to batch processes. It was commercialized in the mid 1980s. All of its operation models are dynamic and simulation always involves integration of differential equations over a period of time. This simulator has found applications in pharmaceuticals, biochemicals, and food processing.[3]

In the mid 1990s, Aspen Technology, Inc. (Cambridge, MA - www.aspentech.com) introduced Batch Plus, a recipe-driven simulator that targeted batch pharmaceutical processes. At around the same time, Intelligen, Inc. (Scotch Plains, NJ - www.intelligen.com) introduced SuperPro Designer. SuperPro has its roots in BioPro Designer, the development of which was initiated at MIT in the late 1980s to address the needs of the

> ❝ *Please be aware that the Garbage-In, Garbage-Out (GIGO) principle applies to all computer models. If some of the assumptions and input data are incorrect, so will be the outcome of the simulation.* ❞

biopharmaceutical industries. SuperPro Designer was created to address other related industries (e.g., synthetic pharmaceuticals, agrochemicals, food processes, etc.) as well as water purification and end-of-pipe treatment processes. More recently (late 1990s), Hyprotech, Ltd. (a subsidiary of AEA Engineering Software - www.hyprotech.com) introduced Batch Design Kit (BDK), a tool originally developed at MIT which is quite similar in philosophy and functionality to Batch Plus.

Batch Plus, BDK, and SuperPro Designer differ from "Batches" in their basic approach to modeling. More specifically, most of their unit operation models are not dynamic, but rather simple algebraic models, whose solution does not require integration of differential equations. This shortens the computation time and enables the user to evaluate a larger number of scenarios in a shorter period. Batch Plus is recipe driven. In other words, the user develops a model by creating a text recipe (similar to a batch sheet), and the modeling engine creates a Process Flow Diagram (PFD) as an output. BDK and SuperPro Designer build their process models using a graphical user interface with a PFD view. A batch sheet is generated as an output report. SuperPro Designer can handle batch and continuous processes equally well; whereas the other three tools are practically limited to batch processes.

SuperPro Designer will be used to illustrate the role of process simulators in the design and development of bulk synthetic pharmaceutical processes. Information on the role of process simulators in the design and development of biopharmaceuticals can be found in the literature.[4]

Generation of a Batch Process Simulation Model

To model an integrated process on the computer, the user starts by developing a flowsheet that represents the overall process. Figure 1, for instance, displays part of the flowsheet of a synthetic pharmaceutical process. The flowsheet is developed by putting together the required unit procedures (see next paragraph for explanation), and joining them with material flow streams. Next, the user initializes the flowsheet by registering the various materials that are used in the process and specifying operating conditions and performance parameters for the various operations. The simulator is equipped with two component databases, its own of 450 compounds and a version of DIPPR that includes 1,700 compounds. It also comes with a user database where modified and newly created compounds can be registered. All database files are in MS Access format.

Most bulk pharmaceutical processes operate in batch or semi-continuous mode. This is in contrast to petrochemical and other industries that handle large throughputs and use continuous processes. In continuous operations, a piece of equipment performs the same action all the time (which is consistent with the notion of unit operations). In batch processing, on the other hand, a piece of equipment goes through a cycle of operations. For instance, a typical Nutsche filtration cycle includes *charge of slurry*, *filtration under vacuum or pressure*, *cake washing*, *occasionally cake drying*, and *removal of cake*. In SuperPro, the set of operations that comprise a

processing step is called a "unit procedure" (as opposed to a unit operation). Each unit procedure contains individual tasks (e.g., charge, heat, react, etc.) called operations. A unit procedure is represented on the screen with a single equipment icon (for example, P-1/R-101 in Figure 1 represents the first procedure P-1 that takes place in stirred-tank reactor R-101). In essence, a unit procedure is the recipe of a processing step that describes the sequence of actions required to complete that step. Figure 2 displays the dialog through which the recipe of a vessel unit procedure is specified. On the left-hand side of that dialog, the program displays the operations that are available in a vessel procedure; on the right-hand side, it displays the registered operations. The significance of the unit procedure is that it enables the user to describe and model the various activities of batch processing steps in detail.

For every operation within a unit procedure, the simulator includes a mathematical model that performs material and energy balance calculations. Based on the material balances, it performs equipment-sizing calculations. Unlike typical models where batch time is specified, this simulator provides the ability to calculate batch cycle time by estimating the cycle-time of scale-dependent unit operations. If multiple operations within a unit procedure dictate different sizes for a certain piece of equipment, the software reconciles the different demands and selects an equipment size that is appropriate for all operations. In other words, the equipment is sized so that it is large enough that it will not be overfilled during any operation, but it is no larger than necessary (in order to minimize capital costs). In addition, the software checks to ensure that the vessel contents will not fall below a user-specified minimum volume (e.g., a minimum stir volume) for applicable operations.

Before any simulation calculations can be done, the user must initialize the various operations by specifying operating conditions and performance parameters through appropriate dialog windows. After initialization of the operations, the simulator performs material and energy balances for the entire process, and estimates the required sizes of equipment and the batch cycle time. Optionally, the simulator may be used to carry out cost analysis and economic evaluation calculations. The fundamentals of process economics are described in the literature.[4]

Other tasks that can be handled by process simulators include process scheduling, environmental impact assessment, debottlenecking, and throughput analysis. Issues of process scheduling and environmental impact assessment will be addressed in the next section. In throughput analysis and debottlenecking, the engineer analyzes the capacity and time utilization of equipment and resources (e.g., utilities, labor, raw materials), and tries to identify opportunities for increasing throughput with the minimum possible capital investment.

Having developed a good model using a process simulator, the user may begin experimenting on the computer with alternative process setups and operating conditions. This has the potential of reducing the costly and time-consuming laboratory and pilot plant effort. Please be aware that the Garbage-

In, Garbage-Out (GIGO) principle applies to all computer models. If some of the assumptions and input data are incorrect, so will be the outcome of the simulation. Consequently, a certain level of model validation is necessary. In its simplest form, a review of the results by an experienced engineer can play the role of validation.

Illustrative Example

The objective of this example is to illustrate how batch process simulators can be used to model, visualize, and analyze bulk pharmaceutical processes. This example deals with the production of around 171 kg per batch of an intermediate pharmaceutical compound. This task is accomplished using three 1,000 gal reactors, two 4 m² filters, and one 10 m² tray dryer.

Process Description

The entire flowsheet of the batch process is shown in Figure 3. It is divided into four sections: 1) Product Synthesis, 2) Isolation and Purification, 3) Final Purification, and 4) Crystallization and Drying. A flowsheet section in SuperPro is simply a set of unit procedures (processing steps). The unit procedures of each section are marked by distinct colors (green, blue, purple, and black for section one, two, three, and four, respectively). Due to space limitations, the description below is not compre-

hensive and is not intended to be an exact representation of the actual process. The following sections are merely intended to illustrate the usage of a simulation tool in designing and analyzing a sample process.

The formation of the desired product in this example involves 12 unit procedures. The first reaction step (procedure P-1) involves the chlorination of quinaldine. Quinaldine is dissolved in carbon tetrachloride (CCl_4) and reacts with gaseous Cl_2 to form chloroquinaldine. The conversion of the reaction is around 98% (based on amount of quanaldine fed). The generated HCl is neutralized using Na_2CO_3. The stoichiometry of these reactions follows:

Quinaldine + Cl_2 ===> Chloroquinaldine + HCl
Na_2CO_3 + HCl ===> $NaHCO_3$ + NaCl
$NaHCO_3$ + HCl ===> NaCl + H_2O + CO_2
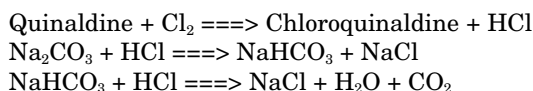
The small amounts of unreacted Cl_2, generated CO_2, and volatilized CCl_4 are vented. The above three reactions occur sequentially in the first reactor vessel (R-101). Next, HCl is added in order to produce chloroquinaldine-HCl. The HCl first neutralizes the remaining $NaHCO_3$ and then reacts with chloroquinaldine to form its salt, according to the following stoichiometries:
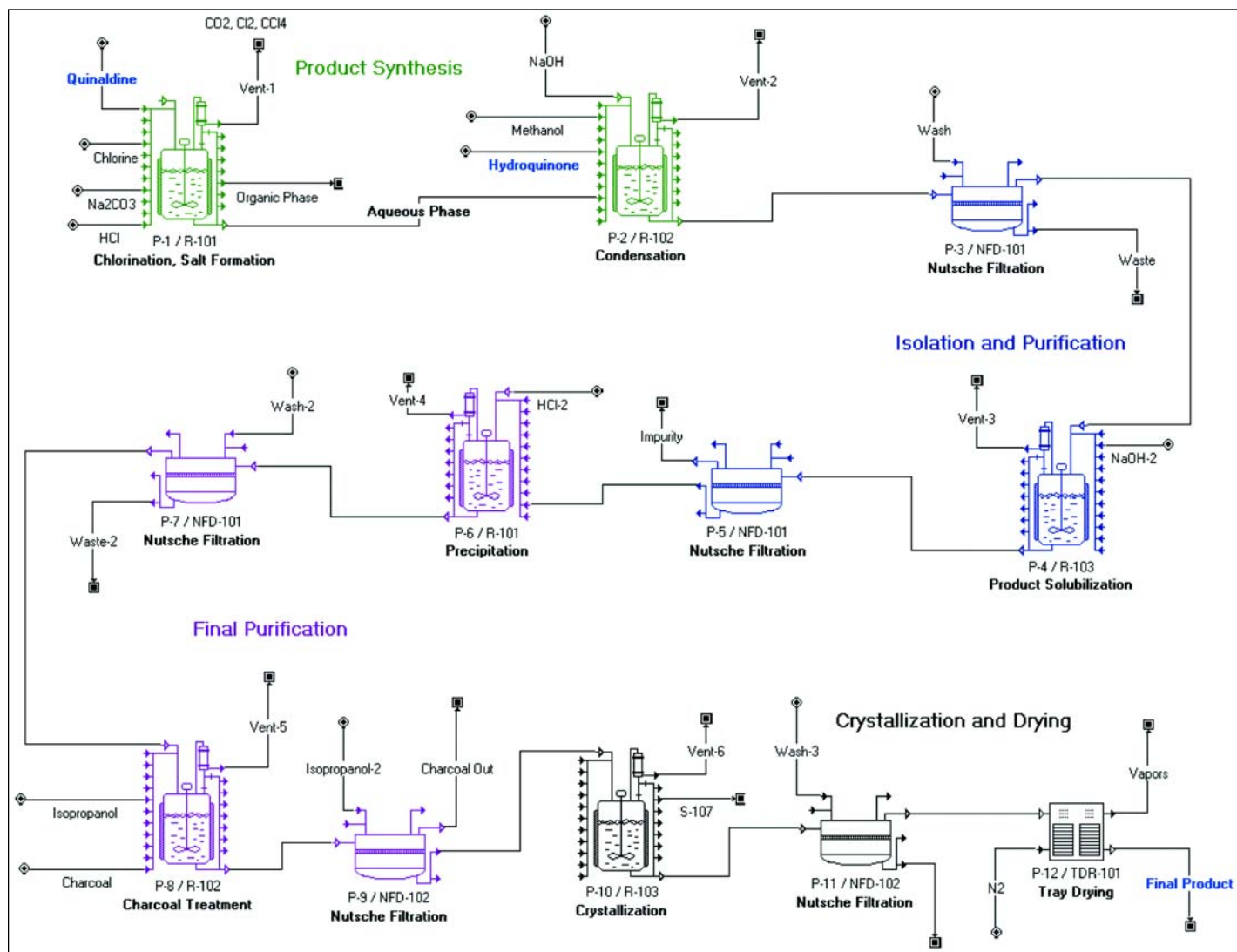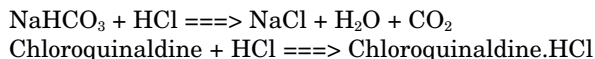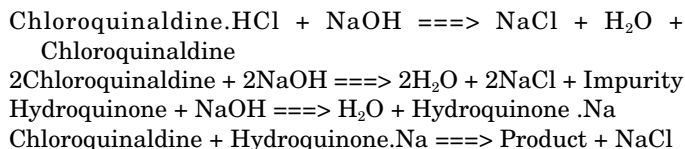

Figure 3. The flowsheet for the example pharmaceutical intermediate compound.

$NaHCO_3 + HCl ===> NaCl + H_2O + CO_2$
Chloroquinaldine + HCl ===> Chloroquinaldine.HCl

The small amounts of generated CO_2 and volatilized CCl_4 are vented. The presence of water (added with HCl as hydrochloric acid solution) and CCl_4 leads to the formation of two liquid phases. Then the small amounts of unreacted quinaldine and chloroquinaldine are removed with the organic phase. The chloroquinaldine-HCl remains in the aqueous phase. This sequence of operations (including all charges and transfers) requires about 15.8 hours.

After removal of the unreacted quinaldine, the condensation of chloroquinaldine and hydroquinone takes place in reactor R-102 (procedure P-2). First, the salt chloroquinaldine-HCl is converted back to chloroquinaldine using NaOH. Then, hydroquinone reacts with NaOH and yields hydroquinone-Na. Finally, chloroquinaldine and hydroquinone-Na react and yield the desired intermediate product. Along with product formation, roughly 2% of the chloroquinaldine dimerizes and forms an undesirable by-product impurity. This series of reactions and transfers takes roughly 16.3 hours. The stoichiometry of these reactions follows:

Chloroquinaldine.HCl + NaOH ===> NaCl + H_2O + Chloroquinaldine
2Chloroquinaldine + 2NaOH ===> $2H_2O$ + 2NaCl + Impurity
Hydroquinone + NaOH ===> H_2O + Hydroquinone .Na
Chloroquinaldine + Hydroquinone.Na ===> Product + NaCl

Both the Product and Impurity molecules formed during the condensation reaction precipitate out of solution and are recovered using a Nutsche filter (procedure P-3, filter NFD-101). The product recovery yield is 90%. The filtration, wash, and cake transfer time is 5.4 hours.

Next, the product/impurity cake recovered by filtration is added into a NaOH solution in reactor R-103 (procedure P-4). The product molecules react with NaOH to form product-Na, which is soluble in water. The impurity molecules remain in the solid phase, and are subsequently removed during procedure P-5 in filter NFD-101. The product remains dissolved in the liquors. Procedure P-4 takes about 10.9 hours, and procedure P-5 takes approximately 3.5 hours. Notice that filter NFD-101 is used by several different procedures. The reactors also are used for multiple procedures during each batch. Please note that the equipment icons in Figure 3 represent
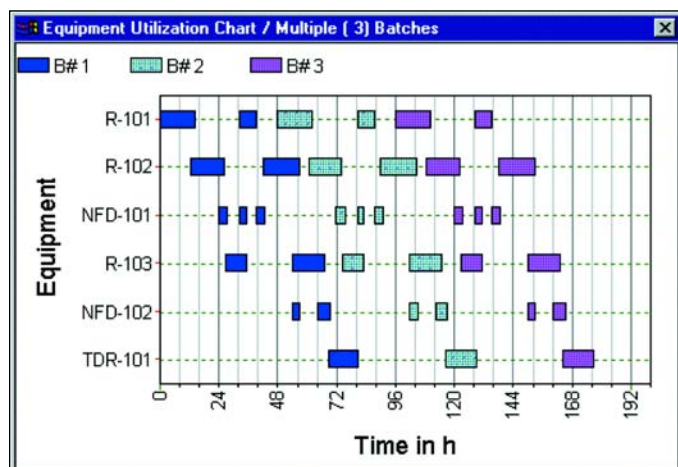
Raw Material	kg/Year	kg/Batch	kg/kg MP
Chlorine	14,534	89	0.52
Na2CO3	17,057	104	0.61
USP Water	481,484	2,936	17.12
HCl (20% w/w)	58,034	354	2.06
NaOH (50% w/w)	33,206	202	1.18
Methanol	89,827	548	3.19
Hydroquinone	27,836	170	0.99
Carb. TetraCh	80,743	492	2.87
Quinaldine	24,132	147	0.86
Sodium Hydroxide	12,041	73	0.43
Isopropanol	322,303	1,965	11.46
Charcoal	2,574	16	0.09
HCl (37% w/w)	35,325	215	1.26
Nitrogen	180,336	1,100	6.41
Total	**1,379,432**	**8,411**	**49.05**

Table A. Raw material requirements (1 batch = 171 kg MP).

unit procedures, as opposed to unique pieces of equipment. The procedure names (P-1, P-3, etc.) below the icons refer to the unit procedures, whereas the equipment tag names (R-101, R-102, etc.) refer to the actual physical pieces of equipment. In other words, the process flow diagram in this simulator is essentially a graphical representation of the batch "recipe" that shows the sequence of execution of the various steps.

After the filtration in procedure P-5, the excess NaOH is neutralized using HCl and the product-Na salt is converted back to product in reactor R-101 (procedure P-6). Since the product is insoluble in water, it precipitates out of solution. The product is then recovered using another filtration step in NFD-101 (procedure P-7). The product recovery yield is 90%. The precipitation procedure takes roughly 8.1 hours, and the filtration takes about 4.8 hours. The recovered product cake is then solubilized in isopropanol and treated with charcoal to remove coloration. This takes place in reactor R-102 under procedure P-8. After charcoal treatment, the solid carbon particles are removed using another filtration step in NFD-102 (procedure P-9). The times required for charcoal treatment and filtration are 17.6 hours and 4.4 hours, respectively.

In the next step (procedure P-10), the solvent is distilled off until the solution is half its original volume. The product is then crystallized in the same vessel with a yield of 97%. The crystalline product is recovered with a 90% yield using a final filtration step in NFD-102 (procedure P-11). The distillation and crystallization step takes approximately 13.1 hours, and the filtration requires roughly 3.6 hours per cycle. The recovered product crystals are then dried in a tray dryer (procedure P-12, TDR-101). This takes an additional 12.4 hours.
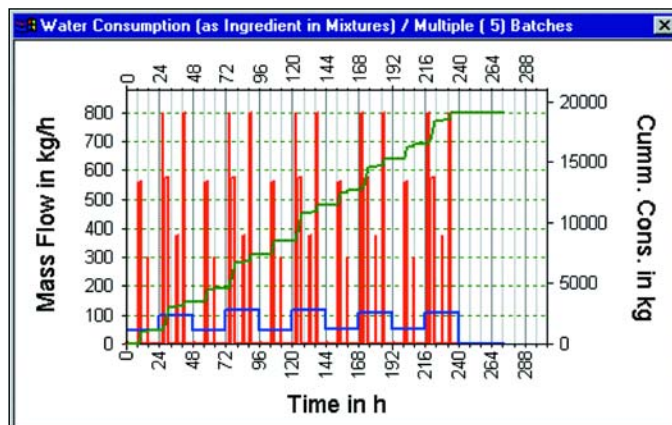

Figure 4. Equipment utilization in three consecutive batches.

Figure 5. Purified Water demand in five consecutive batches.

Direct Fixed Capital	$9.7 million
Total Capital Investment	$10.7 million
Plant Throughput	28,120 kg/year
Manufacturing Cost	$7.2 million/year
Unit Production Cost	$257/kg
Selling Price	$500/kg
Revenues	$14.1 million/year
Gross Profit	$6.8 million/year
Taxes (40%)	$2.7 million/year
Net Profit	$5.0 million/year
IRR (after taxes)	34.0%
NPV (for 7% discount interest)	$22.3 million

Table B. Key economic evaluation results.

Cost Item	Annual Cost ($)	%
Facility-Dependent	1,817,000	25.1
Raw Materials	1,752,000	24.2
Labor-Dependent	2,562,000	35.4
Lab/QC/QA	384,000	5.3
Waste Treatment/Disposal	724,000	10.0
TOTAL	**7,240,000**	**100.00**

Table C. Breakdown of manufacturing cost.

Material Balances

Table A displays the raw material requirements in kg per year, per batch, and per kg of main product (MP = purified product). The plant processes 164 batches per year. Note that around 49 kg of raw materials (solvents, reagents, etc) are used per kg of main product produced. Thus, the product to raw material ratio is only 2%, an indication that large amounts of waste are generated by this process.

Process Scheduling, Resource Tracking, and Capacity Utilization

Figure 4 displays the scheduling and equipment utilization chart for three consecutive batches. The plant batch time is approximately 81 hours. This is the total time between the start of the first step of a batch and the end of the last step of that batch. However, since most of the equipment items are utilized for much shorter periods within a batch, a new batch can be initiated every 48 hours. Multiple bars on the same line (e.g., for R-101, R-102, R-103, NFD-101, and NFD-102) represent reuse (sharing) of equipment by multiple procedures. If the cycle times of procedures that share the same equipment overlap, the program generates an error message. White space represents idle time. The equipment with the least idle time

Raw Material	Price ($/kg)	Annual Cost ($)	%
Chlorine	3.30	47,961	2.74
Na2CO3	6.50	110,870	6.33
USP Water	0.10	48,148	2.75
NaOH (50% w/w)	0.15	4,981	0.28
Methanol	0.24	21,558	1.23
Hydroquinone	4.00	111,345	6.35
Carb. TetraCh	0.80	64,594	3.69
Quinaldine	32.00	772,227	44.07
Sodium Hydroxide	2.00	24,082	1.37
Isopropanol	1.10	354,534	20.23
Charcoal	2.20	5,662	0.32
HCl (37% w/w)	0.17	6,005	0.34
Nitrogen	1.00	180,336	10.29
TOTAL		**1,752,000**	**100.00**

Table D. Cost of raw materials.

between consecutive batches is the *time (or scheduling) bottleneck* (R-102 in this case) that determines the maximum number of batches per year. Its occupancy time (approximately 44.2 hours) is the minimum possible time between consecutive batches (also known as Minimum Effective Plant Batch Time). This plant operates around the clock and processes 164 batches per year. The simulator also keeps track and displays the utilization of auxiliary equipment, such as Clean-In-Place (CIP) and Steam-In-Place (SIP) skids.

Scheduling in the context of a simulator is fully process driven and the impact of process changes can be analyzed in a matter of seconds. For instance, the impact of an increase in batch size (that affects the duration of charge, transfer, filtration, distillation, and other scale-dependent operations) on the plant batch time and the maximum number of batches can be seen instantly. Due to the many interacting factors involved with even a relatively simple process, simulation tools that allow users to describe their processes in detail, and to quickly perform what-if analyses, can be extremely useful.

Another characteristic of batch processing is the variable demand for resources (e.g., labor, utilities, and raw materials) as a function of time. For instance, Figure 5 displays the demand for Purified Water for five consecutive batches. The red lines represent the instantaneous demand; whereas the green line represents the cumulative demand and corresponds to the y-axis on the right-hand side. The blue line corresponds to daily demand (the averaging period can be adjusted by the user). High purity water is a common potential bottleneck in biopharmaceutical processes. It is commonly used for multiple processing steps simultaneously in activities such as fermentation media preparation, buffer making, and equipment cleaning. If not enough instantaneous (or cumulative) capacity is available, one or more process steps may be delayed, possibly with severe consequences. The graph of Figure 5 along with the raw material inventory graph (not shown here) play a crucial role in the sizing of utilities for a batch manufacturing facility. The program generates similar graphs for any raw material, heating and cooling utilities, and electric power consumption.

In addition to instantaneous demand of resources, the simulator provides the means to track the volumetric utilization of all vessels throughout the batch cycle. This allows the user to track maximum working volumes over time, and ensure that the minimum stir volume is always met at any relevant point in a process. The volume content of vessels is also used in sizing new vessels and calculating the capacity utilization of existing vessels.

Economic Evaluation

Cost analysis and project economic evaluation is important for a number of reasons. For a new product, if the company lacks a suitable manufacturing facility that has available capacity, it must decide whether to build a new plant or outsource the production. Building a new plant is a major capital expenditure and a lengthly process. To make a decision, management must have information on capital investment required and time to complete the facility. To outsource the production, one must still do a cost analysis and use it as basis for negotiation with contract manufacturers. A sufficiently detailed computer model can be used as the basis for the discussion and negotiation of the terms. Contract manufacturers usually base their estimates on requirements of equipment utilization and labor per batch, which is information that is provided by a good model. The simulator performs thorough cost analysis and

project economic evaluation calculations. It estimates capital as well as operating cost. The cost of equipment is estimated using built-in cost correlations that are based on data derived from a number of vendors and sometimes literature sources. The fixed capital investment is estimated based on total equipment cost and using various multipliers, some of which are equipment specific (e.g., installation cost) while others are plant specific (e.g., cost of piping, buildings, etc.). The approach is described in detail in the literature.[4] The rest of this section provides a summary of the cost analysis results for this example process.

Table B shows the key economic evaluation results for this project. Key assumptions for the economic evaluations include: 1) a new manufacturing facility will be built and dedicated to production of this product; 2) the entire direct fixed capital is depreciated linearly over a period of 10 years; 3) the project lifetime is 15 years, and 4) 28,120 kg of final product will be produced per year.

For a plant of this capacity, the total capital investment is around $10.7 million. The unit production cost is $257/kg of product. Assuming a selling price of $500/kg, the project yields an after-tax Internal Rate of Return (IRR) of 34% and a Net Present Value (NPV) of $22.3 million (assuming a discount interest of 7%). Based on these results, this project represents an attractive investment. However, if amortization of up-front R&D cost is considered in the economic evaluation, the numbers change dramatically. For instance, a modest amount of $10 million cost for up-front R&D amortized over a period of 10 years reduces the IRR to 15.3%. This reinforces the point that R&D expenditures should be considered in estimating and justifying the pricing of pharmaceuticals.

Table C breaks down the manufacturing cost. Labor is the most important cost item accounting for 35% of the overall cost. The program estimated that 16 operators are required to run the plant around the clock supported by four QC/QA scientists. This cost can be reduced by increasing automation or by locating the facility in a region of low labor cost. The facility-dependent cost, which primarily accounts for the depreciation and maintenance of the plant, is in the second position (25% of total). This is common for high-value products that are produced in single-product, small facilities. To reduce the impact of this cost, the pharmaceutical industry tends to use flexible, multi-product facilities, where a number of products are manufactured in campaigns throughout the year. Raw materials also make up a large portion of the manufacturing cost. Furthermore, if we look more closely at the raw material cost breakdown, it becomes evident that quinaldine and isopropanol make up by far the largest portions of this cost - *Table D*. Together they account for approximately 64% of raw materials cost. If a lower-priced quinaldine vendor could be found, the overall manufacturing cost would be reduced significantly. In terms of the isopropanol cost, perhaps the charcoal treatment procedure should be studied to determine whether the amount of this solvent could be reduced. Decreasing the amount of isopropanol would significantly improve the overall process economics because it would decrease the waste disposal costs as well as the raw material costs. Alternatively, perhaps some of the waste solvent which is currently being discarded could be purified and reused. This would decrease both disposal costs and raw material costs.

After a computer model for the entire process is developed, process simulators can be used to ask and readily answer "what if" questions and carry out sensitivity analyses with
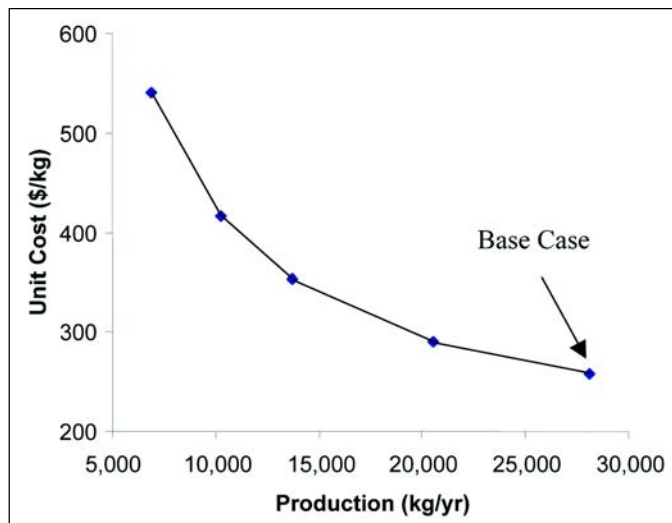

Figure 6. Unit cost as a function of production scale.

respect to key design variables. In this example, we looked at the impact of production scale on unit manufacturing cost. When a new drug is commercialized, it takes years to fully penetrate the market. During that period, production is gradually ramped up to meet demand. If the facility is designed to meet demand at full market penetration, then, in the interim it is underutilized. The unit production cost as a function of production scale in the interim period is shown in Figure 6. It was assumed that at lower production scale the plant simply processes fewer batches per year (e.g., two per week instead of one every two days) without handling any other products. At lower annual throughputs the unit cost increases substantially because the same fixed cost is charged to a lower amount of product.

Summary

Simulation tools can play an important role throughout the commercialization process. In process development, they are becoming increasingly useful as a means to analyze, communicate, and document process changes. During the transition from development to manufacturing, they facilitate technology transfer, and facility selection or construction. In manufacturing, they assist engineers in dealing with production scheduling and planning, throughput analysis and debottlenecking, and on-going process optimization.

Batch industries such as pharmaceuticals have just begun making significant use of process simulation to support process development and optimize manufacturing. Increasingly, universities are incorporating the use of batch process simulators in design courses. In the future, we can expect to see increased use of this technology and integration with other enabling technologies, such as advanced process control, computerized batch recipe generation, and on-line analysis and optimization. The result will be more robust processes developed faster and at a lower cost; making higher quality products.

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Acknowledgement

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Internet Data Centers (IDC) are required for the successful deployment of e-commerce applications. This article defines the requirements for facilities and infrastructure design, construction, operation, and maintenance criteria.

Facilities and Infrastructure Requirements for High Reliability E-Commerce Data Centers

by Clifford "Bud" Frith

Introduction

What does e-commerce have to do with the ISPE mission as the global resource for healthcare technology information? The key is "global resource" employing the latest advancements for communications and data transfer. Twenty-one years ago, the founders of the International Society for Pharmaceutical Engineering focused on the global healthcare professionals. Now, 24 hours a day, 7 days a week, we are in touch with technical specialists by e-mail and receive the latest information using the Internet, World Wide Web. The technology revolution, only 15 years old, has expanded at a rate that more technical information has been developed and efficiently stored for retrieval in the past 10 years than from the beginning of time.

Controlled environments, data centers, and now Internet Data Centers (IDC) are required to support the advancements of technologies and communications for the pharmaceutical, biotechnology, medical, aerospace, and semiconductor industries.

This article will discuss the facilities and infrastructure requirements for keeping pace with the e-commerce revolution. The recent events in New York City and Washington, DC have placed an even higher priority on the infrastructure and security requirements for high speed, reliable electronic communications, storage, and data transfer. The 100+ Megabits per second (Mbps) speeds and Terabits storage capacity are standard Internet terminology employing fiber optics carrier systems and secure networks. Reliability levels or "up time" requirements >five-nines (99.999%) are current standards for mission critical applications.[1]

E-commerce first appeared to be a sales and marketing responsibility. However, e-mail, web conferencing, electronic funds transfer, and on-line purchasing are now common requirements for almost every department. With the terrorists' activities of September 11, 2001 in the United States, we will experience a major paradigm shift in business practices for all domestic and international business.

The subjects of 21 CFR Part 11, Electronic Records and Electronic Signatures will not be addressed in this article, but will be covered in a future article. However, the reliability and security of the facilities and infrastructure for Internet applications are major issues that must be understood and addressed before the full potential of e-commerce will be realized in regulated industries.

Mainframe Data Centers to Internet Data Centers (IDC)

Data centers originated several decades ago as the critical requirements for mainframe and super computers were defined. Temperature, Relative Humidity (RH), and cleanliness

Figure 1. A programmable access card is used for high level IDC security.

levels were controlled with higher levels of security as the macro black boxes were scaled down to micro dimensions. Initially, the data center facility design, operations, and maintenance criteria used the cleanroom guidelines as their model without the airborne particle controls. Raised floors, Static Electricity Elimination (ESD), temperature, and RH control were standard construction requirements. Monitoring of these parameters included data acquisition systems. Special security protocols for data center access, the hardware, and software were initiated.

The recent invention of the Internet for global communications has continued to expand the demand for technologies and infrastructure that provide cost effective consumer, industrial, and government transactions. The semiconductor and telecommunications industries continue to achieve milestones according to Moore's law that states, "Advanced technologies will double every 18 months." With the micro-miniaturization scales projected and the increasing speeds and capacities forecasted, the environmental and security controls for the Internet are critical. Therefore, the Information Technology (IT) professionals must recognize the skills and knowledge of the environmental control specialists. No longer are the host servers, routers, and switching equipment safe in the office, the utility closet, or the air-conditioned "special" room. Connectivity to the Internet network backbones through several layers of service providers is unacceptable. And, the high speed, high capacity bandwidth must be scalable for the future requirements that may be as soon as next year. The Internet hardware requires its own controlled, secure environment and utilities with redundancy. The power requirements-Uninterruptible Power Supplies (UPS) and on-site back up generators are very important. A recent IT management survey reported; however, that 73% of companies had not inspected and verified their Internet Service Providers (ISPs) infrastructure and facilities.[1]

In-House or Outsourced IDC

Internet data centers for very large companies may be located in-house with the appropriate facilities and services. But these companies must have multiple locations with data centers to provide backup for their Disaster Recovery Plan (DRP). The IDC is not compatible with the mainframe computer data center required for managing the MIS or ERP operations. Network integration between the two data centers is possible, but the technical specialists employed for each center generally have different skills and training.

For most companies; however, co-location Internet data centers are the most cost-effective facility and managed services. With the explosion of the Dot coms in 1998-2000, very large co-location facilities were constructed in major metropolitan areas with 100,000-800,000 square feet of secure, environmentally controlled space with high bandwidth capacities, multiple carriers, and at least two redundant tier one ISPs. These facilities are called IDC "Hotels." Unfortunately, the IT specialists or network administration personnel need to travel long distances in metropolitan traffic to perform services for maintaining their Internet operations. This is expensive, time consuming, discourages the personnel, and is the reason to maintain all hardware in-house. Recently, the co-location IDCs began providing managed services with highly qualified personnel on a 24/7 basis. There still is some resistance for delegating such a sensitive responsibility to someone not an employee of the company and their IT department.

More recently, strategically located, smaller co-location IDCs are being constructed with the same secure, controlled facilities and services. These may serve as the primary data center or the mirror DRP back-up facility. Also, with the advancements in the telecommunications equipment industry for smaller foot print hardware, the large IDC hotels may become extinct.

Regardless of the decision for internal or external services, the financial requirement must be addressed. This means other budget items for the facilities and IT departments that usually have not been considered.

Facilities Requirements

The physical security, environmental controls, utilities, and connectivity including redundancy are the responsibility of the facilities group. A proper designed, constructed, operated, and maintained IDC is an insurance policy for mission critical e-commerce applications. Therefore, contracting to an Internet Service Provider (ISP) without providing adequate written requirements and a validation inspection is not acceptable.

Security

A programmable card access system (Figure 1) is typically used for independent one-customer rooms or suites. Customer shared open areas that house equipment racks or equipment cabinets are available on an "escort only" basis which requires Network Operations Center (NOC) personnel present at all times that customer(s) will be in the secured area. Only approved employees or agents for the customer are allowed in their specific data center area. NOC personnel are available 24/7.

A video monitoring system records all activities in and around the premises continuously. These records are available for review under specific conditions by IDC customers.

Security for the data stored and transmitted is an area that needs more technical development. Corporate management is usually skeptical since the internal sensitive information is not fully protected unless the proper security or "firewalls" are in place and tested frequently. The "hackers" or Internet terrorists have become very advanced with their tools and skills. Recent examples of high profile targets such as the FBI, CIA, and DOD are the reported cases. Many companies are exposed and are not aware of the intruders and to what files. New businesses providing internal and external auditing services to validate the security of the system are available.

Managed services at IDCs can provide very secure firewalls for software and hardware. Complete packages are available and require a limited amount of operator time for good security. In a co-location IDC, clients can manage their own firewalls or use the expertise of the IDC personnel and various network or server intrusion monitoring devices. The highest security level requires that all transmissions to and from the Internet must go through the firewall and be monitored. Charles Semeria, 3Com, published an excellent technical paper "Internet Firewalls and Security: A Technical Overview" that covers the subject at the novice level.[2]

Software "viruses" are a very big concern for both IT administrators and data center managers. The information "viruses" are just as dangerous as unwanted biological viruses. Excellent protection is available through commercial software packages, but constant surveillance is essential. There are on-line reports that advise of new virus activity. Specialist are available that have skills to detect and cleanse the network and

individual applications. E-commerce users must be on the alert constantly for virus disruption.

The external electric power wiring and communications cables are normally installed into the data center at two separate locations from two different utility sub stations and the Internet connectivity from at least two ISPs. Current construction practices require that only one digging project be active in proximity to the facility and all redundant conduits carrying power or communications cabling be 50 feet apart. Survey maps of the external conduits should be maintained for excavation projects. These requirements should be standard for new real estate developments that are specified as Technology Parks.

Environmental Controls and Monitoring

Temperature, relative humidity, equipment/power grounding, static electricity (ESD), smoke-fire detection, and suppression must be monitored and controlled with products designed for such operations.

HVAC

Redundant computer grade air conditioning units with humidity control are standard products for the industry - *Figure 2*. Design of the air handling distribution system is critical. Efficiency models prove that a raised floor with removable perforated panels to balance the heat load (Figure 3) and an under floor plenum with epoxy paint sealant and no utilities or plumbing is the best design.

Temperature controls within 70 °F +/- 2 and RH of 45+/- 5% are normal specifications with 45% RH minimum in dry geographical regions.

ESD

An area being ignored by most data center planners is the dissipation of the static electricity from personnel and activities in the IDC. Similar to microelectronic chip manufacturing, high speed and high volume electronic data transfer is very sensitive to the immediate environment. This is an issue that needs serious study as we advance to the gigabit/second transmission level. To protect the equipment and cables, a chemical grounding well adjacent to the building housing the IDC is required with special wiring and special grounded flooring tiles to eliminate even the lowest levels of static electricity. Water pipe grounding will not meet the conditions for protecting the equipment, power, and the transmission network. Equipment racks and cabinets, as well as electrical circuits, must have a proper grounding to the chemical well. This installation must be certified and documented. Levels <2 ohms resistance are recommended throughout the entire IDC.

Figure 2. Temperature and humidity are maintained with redundant computer grade HVAC units.

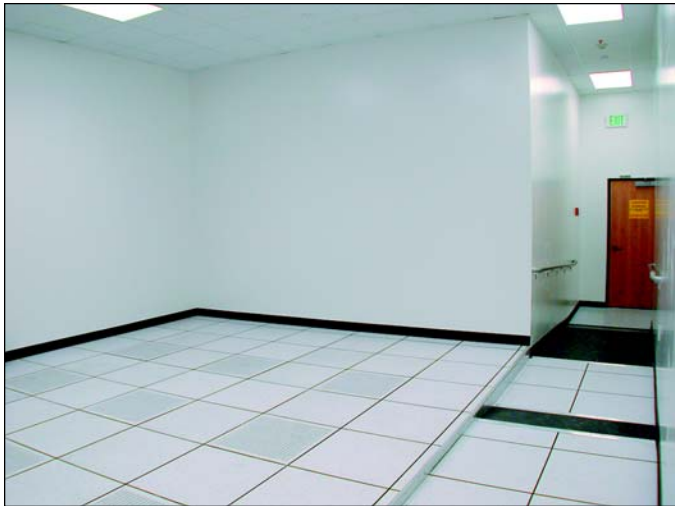Figure 3. Raised floor with perforated tiles provides an efficient HVAC distribution plenum.

Smoke and Fire Detection

The high tech cleanroom particle monitoring systems have been valuable for smoke and possible fire detection using submicron laser monitors - *Figure 4*. The trace out-gassing from an overheated fan or circuit card can sound the warning many days or hours before the source becomes an issue. Since particle counting is not required, normal IDC environment backgrounds are below the threshold of the out-gassing smoke particles. This macro-detection system can be set to release the fire suppression chemical in localized areas to minimize the impact on the entire IDC.

Smoke and Fire Suppression

Halon was used for many years as the best fire extinguisher in environments where water would not be effective or would destroy the expensive facility or equipment. Halon was very effective since it would extinguish any class of fire by quickly replacing the oxygen that was needed for combustion. Halon was removed from the list of chemicals acceptable for fire suppression, since it also was very dangerous to the personnel.

A new material FM200 is just as effective and is personnel safe and non-destructive to the facility and equipment. It is the same chemical used in inhalers for asthma patients, but is used as a very concentrated vapor. FM200 will break the bond between the material and the heat source in less than 15 seconds and then dissipate quickly into the environment. It is expensive to use, but the cost is relative when compared to the value provided in protecting the IDC and the equipment.

Electric Utilities

Global industries, especially in healthcare applications, are very aware of the supply and reliability issues for electric power. The recent issues in California and the instability of the world gas and oil suppliers make long range planning for reliable energy difficult. Both the power generation and distribution grid systems are a risk.

Onsite Generator

Backup electric power is provided by onsite generation with diesel or natural gas units. This is essential as outages are unpredictable and the quality of the utility supplied power is variable for the level required to support IDC operations. The

issues faced by IDC developers installing a generator are local regulations and possible resistance from the utility companies. The generator supplies the UPS, HVAC, lighting, security, and power outlets within the IDC.

Uninterruptable Power Supply (UPS)

The IDC must be operated with "clean" power that avoids spikes, fluctuations, and intermittent service. Redundant computer grade UPS units with battery backup are installed - *Figure 5*. The stable, sine wave, power supplied throughout the IDC is controlled by the UPS regardless of the source or quality of power. With the speed and volume of data being transferred, individual equipment UPS units are not acceptable. The grounding of the UPS is also very important.

Communications Transmission

E-commerce is becoming the cost-effective business process for successful companies to increase their profitable revenue. The speeds and volume of data being transmitted are accelerating at a dramatic rate. Fiber optic cabling is already installed worldwide in conduits that are projected to meet demand for 2005.[3] SONET Rings, a fail-safe transmission circuit, are installed around most metropolitan areas in the US. Technology advancements are predicted to improve the reliability and scalability factors four fold in the next three years which should enhance the profitability of this industry several times current performance. The 2003 revenue projections for the US Internet infrastructure industry exceed $16 billion.[3]

An example of the volume and speed of transmission is the recent report by Alcatel, a Paris based telecommunications-equipment producer. They claim the current world record for sub-ocean transmission by transmitting across the Atlantic Ocean, 6,850km, 3.65 Terabits/second (Tbps) on a single optical fiber. In layman terms, this is equivalent to the simultaneous throughput of 45 million voice calls, 552 CD-ROMs, 35 Encyclopedia Britannicas, or 16 high definition movies over a single optical fiber.[4]
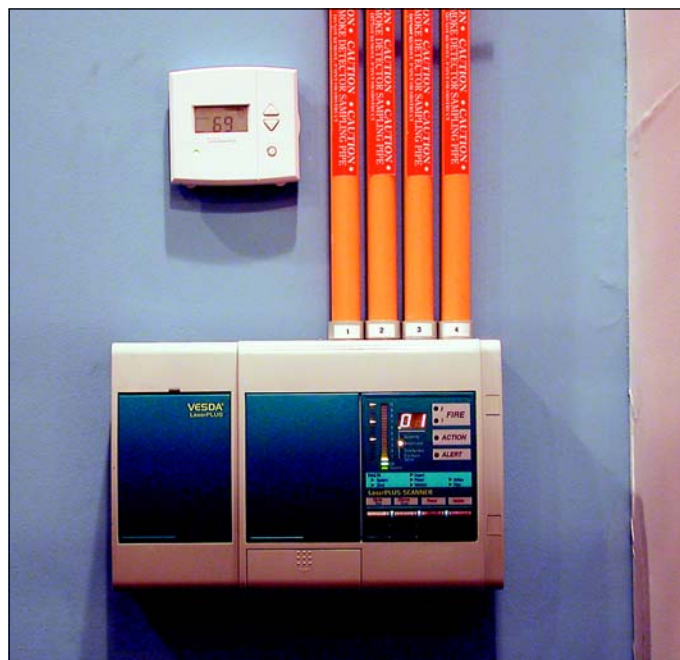

Figure 4. Laser trace smoke detector provides early warning of a problem.

Connectivity

The most confusing issues for Internet users relate to the level of service provided and how the Internet industry defines the terminology. In order for the Internet or World Wide Web (www) to be deployed successfully, a minimum level of conduit with "lighted" fiber was required. Major global telecommunications carriers initiated the process of installing parallel fiber networks in strategic locations. In its infancy, the Internet was operated through the standard copper telephone lines. However, the speed and volume of transmission was greatly restricted due to the capability of the telephone communications system which was already overloaded at peak times of the business day with voice and fax traffic.

In the US, the major ISPs are considered Tier One service providers. Most businesses are connected to the Tier One through regional Tier Two and Tier Three ISPs. Reliability can be influenced by the service each tier provides. The quality of service is a major issue since there are no standards established for the industry. Eventually, the Tier One performance will be available at most locations as the infrastructure is improved and standards are established.

Additionally, the redundancy of ISP services will prevent the interruptions or delays being experienced currently. This is a major advantage provided by most co-location IDCs as they are connected to multiple Tier One ISPs and manage the loading of their systems for optimum service.

Telecommunications Wiring Standards

The Electronic Industries Association (EIA) and the Telecommunications Industry Association (TIA) jointly prepared several building telecommunications standards and technical bulletins. These standards are being revised since building wiring codes before the 1990s were only for voice transmission (4kHz) and Local Area Network (LAN) with 10MHz.[5] Current levels of >100MHz and the new levels in the Gig Hz range need exacting standards to support e-commerce applications. Prewiring the buildings and data centers is inexpensive during new construction compared to wiring or cabling for renovation of an existing building. Certification of the cabling by the installing company is also recommended before the project receives final acceptance.

Bandwidth

The term for describing the capacity or capability for transmitting data, voice, and video communications from point to point is bandwidth. This is used for both analog and digital signals. It is a measure of the difference between the lowest and highest frequency of transmission. When expressed as n bits/second, it is describing the quantity of data a particular transmission line can carry each second.

The term T1 is common communications language and was developed in the 1960s using twisted pair copper wire transmission. It is now used for optical fiber, coaxial cable, and digital microwave. The first (T1) transmission rate, 1.544Mbps, is in wide use today. The T(n) designation corresponds to the digital service (DS) hierarchy. The following table illustrates the T system hierarchy:

T1 = 1.544Mbps   = 24 voice or data channels at 64Kbps
T2 = 6.312Mbps   = 96 voice or data channels at 64Kbps
T3 = 44.736Mbps   = 672 voice or data channels at 64Kbps
T4 = 274.176Mbps = 4032 voice or data channels at 64Kbps

Figure 5. Redundant UPS units provide "clean," reliable power to the IDC.

Therefore, a T2 rate is four times the capacity of a T1, a T3 is 28 times a T1, and a T4 is 168 times the T1.[6] Telecommunications companies lease lines to customers depending on capacity required.

Co-location IDCs rent bandwidth to clients either as 1) dedicated or 2) burstable services. This is a cost-effective method to achieve optimum levels of transmission for e-commerce operations. The dedicated service puts a cap on the amount of total bandwidth that can be used at a given time. The burstable service allows the sharing of bandwidth for peak demand and is billed on a use rate basis. An example of the burstable service is a client may lease a fractional T1 level, 512Kbps, and pay a flat rate. During a peak period, the actual use may exceed the base level and burst to 1.544Mbps. Monitoring by NOC operations allows the increase and the customer is billed for the additional percentage used over a 30 day period. Since leased bandwidth is very expensive if not used, this burstable plan for shared services reduces operating costs.

Transmission technology using optical fiber is the foundation of e-commerce. The designations for optical carrier levels (OC-1 to OC-192) are typical of the expanded capability, i.e. OC-1 = 51.84Mbps and OC-192 = 9,952Mbps.[6] Additionally, the advantage of the fiber circuit is the synchronous optical network (SONET), a standard protocol adopted by ANSI. The Internet will advance rapidly as connectivity using fiber to the local area networks is expanded.

Conclusion

The design, operation, and maintenance of the IDC facilities and Internet infrastructure for e-commerce have many areas that need standardization. The technology advancements are increasing at a high rate and the commitment to improved facilities and infrastructure must keep pace. Environment, security, utilities, connectivity, monitoring, and verification are critical areas that must be addressed to support successful Internet applications and our status as the global resource for healthcare technology information.

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Glossary of Terms and Definitions

ANSI - American National Standards Institute.

Bandwidth - A measure of the difference between the lowest and highest frequency of a data, voice, or video transmission.

ERP - Enterprise Resource Planning.

ESD - Electric Static Discharge.

Gigabits/second - 1,000 million bits per second.

HVAC - Heating, Ventilation, Air Conditioning.

IDC - Internet Data Center.

MIS - Management Information System.

SONET Ring - Synchronous Optical Network.

Tier One ISP - The highest level of network connectivity for the Internet, World Wide Web.

Acknowledgement

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This article discusses how to transform design basis criteria into readily accessible information within a database to help build cost-effective cGMP facilities.

E-Technology Approach Integrates Basis of Design through Turnover Package to Facility Management

by Daniel P. Collins, PE and Edward N. Pedersen, RA

We are in an era characterized by exploding technology, expanding regulation, and time to market focus for new therapeutic products. This has challenged current Good Manufacturing Practice (cGMP) facility planners, consultants, constructors, and facility managers to increase their efficiency and effectiveness. The design/build process generates a huge amount of raw data which needs to be captured and passed to the facilities manager. A way to do this is to transform design basis criteria into readily accessible information within a database system. According to Robert Lipman of the National Institute of Standards and Technology (NIST), "an effective project delivery process depends on the availability of current and correct information for all the participants, wherever they are and wherever they need it."[1] This information, once made available, can be used to create knowledge-rich and intelligent construction documents. At project completion, this informa-

tion can be packaged into a facility management system.

This approach can be called the e-technology approach, which when utilized produces the drawings and specifications required to complete construction, along with a way to organize the information the facility manager can refer to and rely on for years to come. This facility management system can be provided to the customer at approximately the same cost as the construction documents alone. This article describes a system recently developed in-house for a client.

Step 1: Harnessing the Data

A cGMP facility must be responsive and supportive of the business goals. The business strategy, organizational structure, and individual work environments must be defined through programming sessions with an open dialogue between all participants. Upper management, finance, production, human resources, material

Figure 1. User inputs.

Align Business and Functional Requirements

- Management Goals and Objectives
- QC/QA
- Manufacturing
- Regulatory Compliance
- The Facility Program
- Human Resources
- Materials Management
- Sales/Marketing
- Development/R&D
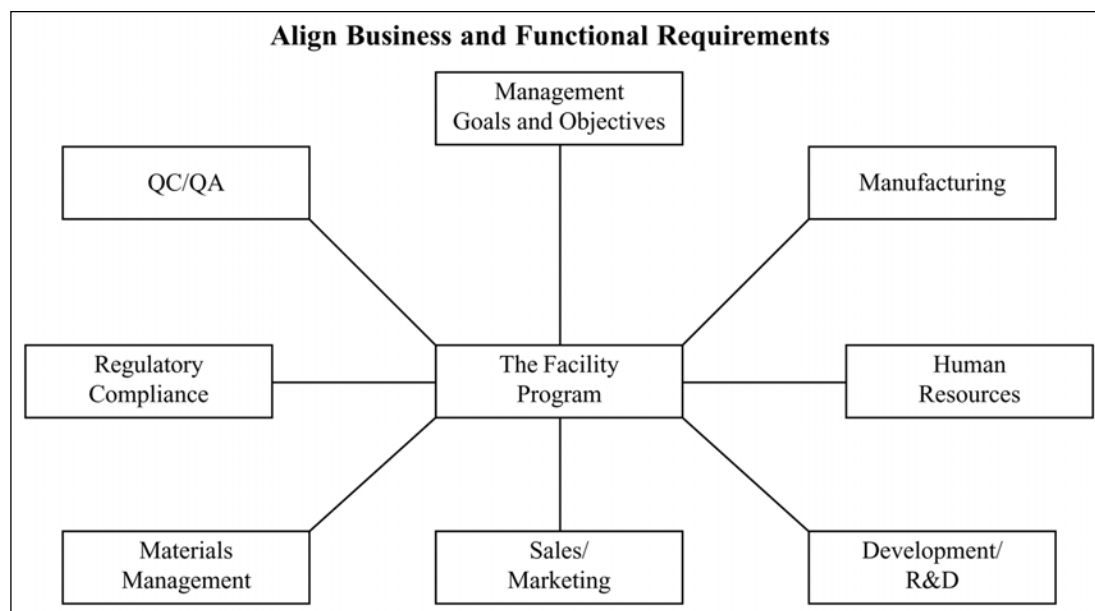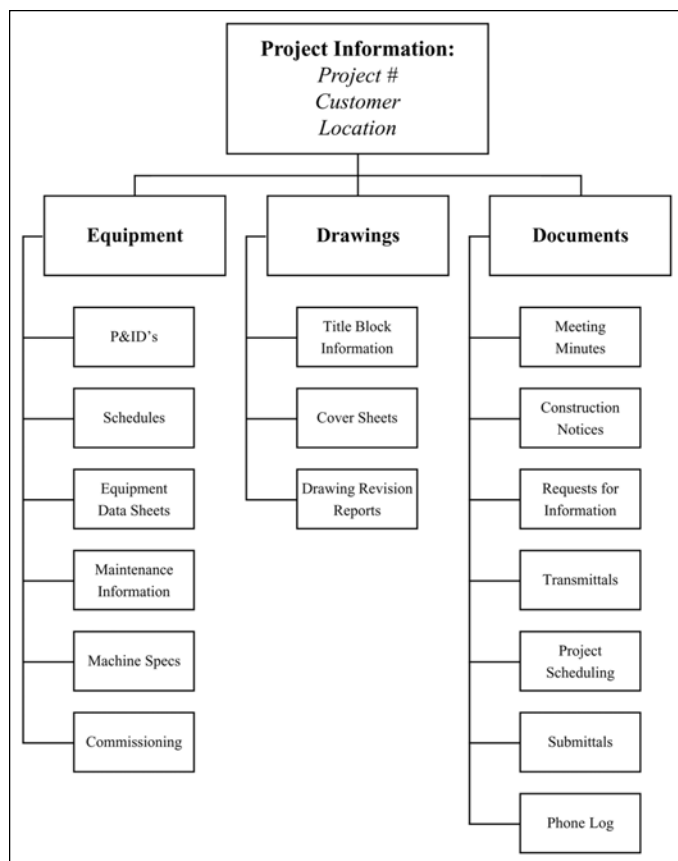
Figure 2. Database diagram.

handling, R&D, quality assurance, safety, information technology, regulatory, maintenance, and operations must provide data and information forming the Basis Of Design (BOD).[2] Figure 1 illustrates the user requirements to define the facility requirements and BOD. This BOD input becomes the database and is accessible to group pieces of data together, find single bits of information, format many kinds of output, and maintain the accuracy of that information. The database system allows many people to look at information simultaneously and from different locations.

The BOD database will include process/control criteria, an equipment list and unit equipment diagrams, and a listing of functional space that will house the required equipment, people, materials, and movement patterns. Space need allocations also must encompass infrastructure support and distribution spaces. Infrastructure support space includes laboratories, control rooms, weigh rooms, and maintenance areas. Distribution space includes piping corridors, locker rooms, storage and staging areas, quarantine areas, shipping, and receiving. In addition to allocating space for specific functions, allocations have to be made for unassigned spaces such as mechanical rooms and chases, structure, corridors, and vertical circulation. The final functional space listing with typical room sheets quantifies the design performance characteristics and technical requirements for each space including HVAC, plumbing, electrical, finishes and relationships to other spaces, equipment, and utility needs. The result is a quantified set of architectural and engineering parameters that define the scope of the facility and establishes the basis for a realistic budget estimate.

How is this data management accomplished? Data is broken into general categories: documents, drawings, and equip-

ment - *Figure 2*. Each of these categories has a dedicated database to manage that information. These dedicated databases are linked together by a common element (a project number or customer) enabling a free flow of information between these databases.

The Documents, or "Docs" database can include BOD information, Meeting Minutes, Construction Notices, Requests for Information, Submittals, Transmittals, and Project Schedules. Search functions are built in to allow quick and logical location of data. Like any database system, the use of consistent and constant updates is key.

Basis of Design

As PFDs, P&IDs, and construction drawings are created, an intelligent database file is written semi-automatically which records important data about each element of the design. Key data is recorded in the database, including vessel dimensions, pressure ratings, capacity, heat exchanger jacketing, material and thickness, and pipes to and from the reactor. As the PFD is developed into a more detailed P&ID, that same data may be accessed. Next, details such as pipe size, material, schedule, instrumentation, and control devices are added to the P&ID. Finally, a 3-D model of the process is constructed in Computer-Aided Design (CAD) software that shows the equipment using the correct dimensions and locations. In this way, the PFDs, P&IDs, and construction drawings are all linked to the design database.

The power and benefits of the 3-D model are realized during documentation for validation, construction, process safety management, operations, maintenance, and renovation. Despite the fact that all the data mentioned above is typically included in construction drawings or design reports under the conventional method of project design, the data is often searched for and keyed into multiple locations over and over again in order to create all the required documentation. However, using the 3-D modeling approach, all of this information only has to be reviewed and entered once. The data is subsequently manipulated and displayed in different formats to satisfy requirements such as equipment schedules, design reports, validation documents, and process safety management databases.

Meeting Minutes

The Meeting Minutes section enables the user to track individual action items or minutes across meetings and across projects for the same client. The user enters all associated meeting minutes, categorizing them as Action Items, Comment Only Items, or Long Term Items. These minutes are also categorized by discipline. Consequently, from that one data entry, the user can generate Meeting Minute Reports, Internal Action Item Summaries, Incomplete Item Reports, etc., all displaying consistent bits of information, but re-grouped and re-formatted to meet the needs of individuals. This system also enables cross project reports at the same site. For example, a discipline manager, at the click of a button, can find out what action items from his particular discipline across multiple projects have yet to be completed. Additionally, the Docs database enables the user to find in seconds, an individual meeting minute across projects, based on one or two remembered words. If these meeting minutes were generated in individual Word documents, that kind of searching and reporting could take days, not seconds.

Figure 3. RFI query/response.

Requests for Information

The Request for Information section of the database is a powerful way to track any questions that may be generated and submitted during the construction phase. Like the Meeting Minutes, the user can generate multiple reports from one data entry. Response reports, RFI logs, and RFI without Response logs are accurate and simple to generate. Additionally, a powerful search tool can be built into this database for locating individual questions or answers quickly. More importantly, the database can be used to track questions, for generating trends for quality management. A cross project report can show the numbers of certain types of questions asked. If the same types of questions are continually asked, then a quality management issue is uncovered that needs to be addressed. Again, this type of tracking is much more difficult when the data is scattered over multiple files.

Construction Notices

The Construction Notice database output shown in Figure 4 is used to track construction notices and sketch information. It contains searching capabilities and easy reporting available in other parts of the database.

As with RFIs, this part of the database enables tracking of trends and patterns. If, for example, a project manager can become aware that certain delays or changes consistently occur with certain contractors or at certain points within construction, that manager can anticipate these needs and address them more effectively. These features enable the system to become a quality assurance tool.

Project scheduling, transmittals, and submittals include all the features and benefits of the previously mentioned sections of the Docs database.

Project Schedule

The Project Schedule part of the database is used to track the project schedule and then generate reports for contractors of upcoming actions or milestones.

Transmittals

The Transmittal part of the database is used to enter and track transmittal information. One output shown in Figure 5 becomes the transmittal letter, and another the transmittal log.

Submittals

The Submittal database is used to enter submittal information, specify required submittals, and transfer submittal information to a project.

The Drawing Database (TBInfo)

The Title Block Information database (TBInfo) is used to track construction drawings - *Figure 6*. Drawings are logged by project with their associated revisions. From this information,

Figure 4. Construction notice.

the user can generate reports on drawing packages and latest revisions. TBInfo also enables the user to group drawings together by discipline or by date released. But perhaps the most powerful feature is the links built to CAD drawing platforms such as Microstation and Autocad. These links enable the user to generate coversheets, based on the groups of drawings in the database, create the title block on the individual drawing, and track the location of these drawings. This information can be entered either directly into the database, or entered from the drawing and the system tracks the date, scale, and drawn by information.

The Equipment Database
The equipment database tracks information about individual pieces of equipment to be relocated or newly purchased. This database has all the before mentioned benefits of a database, but is also the engine behind the next levels of this facility management system.

Step 2: Assigning/Relating Data for Turnover
During the design phase of a project, graphical and alphanu-

meric data is gathered. This data must be communicated to the team and client. The best way to do this is to create a realistic graphical model with alphanumeric data assigned to the graphics. This allows all parties to see and "query" every aspect of a project before it actually exists.

When a 3-D drawing is produced, database information can be attached to any given object - *Figure 7*. This allows the user to select any piece of equipment, piping, etc. retrieve all of its related information which is stored in the database. For example, the user records the size, manufacturer, pressure rating, and supplier for a specific valve on the first floor of a facility in the database. This information in the database is then linked to the 3-D drawing of that valve. The customer can now click on that valve and see the size, manufacturer, etc. without ever opening the database. If every piece of equipment in the drawing, i.e. every valve, every air handler, every fan, is handled in this way, the "Smart Drawing" is created. Additionally, this approach allows for maintenance information to be recorded. Now, at the click of a mouse, the client also can see the turnover or maintenance information on that piece of equipment. As the data is maintained in the database, the

Figure 5. Transmittal.

"Smart Drawing" becomes more and more valuable. Ultimately, up-to-date data coupled with easy access provides the information needed to make efficient and timely decisions. This approach to project information management is named the Standard Projects And Records Knowledge System, or SPARKS.

Now, let us take this one step further. If we group many individual smart drawings together into one "facility plan" and post them on the web, we have the e-technology facility navigator.

Step 3: Enabling Access to the Data

The Navigator is web-enabled access to multiple data sources. These data sources can be as diverse as facility and process drawings, operational and maintenance turnover records, space usage information, and employee data. Although the concept is quite simple, the power of the system comes from the design and upkeep of the databases.

Understanding the databases as the repositories for the information that is displayed by the Navigator is central to using this approach to data management. The Navigator provides the customer with a familiar window, the web, through which to view vast quantities of information. With this window, they do not need to buy third party software and train their employees on its use. The customer also is given the ability to update the information viewed by the navigator if they choose. When this updating of information is maintained, the Navigator becomes an invaluable tool for facility management, both during construction and long after construction is finished.

Life-Cycle Cost Improvement

This can be a powerful tool for the management and transfer of data both during the construction turnover and maintenance phases of a project. It also positively affects the bottom line. According to an August 2001 article in ENR, firms "go beyond interoperability to automation to slash 30 to 40% off

the cost and time of construction."[3] For example:

During the design/construction phase, savings can be found in the following areas:

- Constructibility reviews. The 3-D walk-throughs save money before and during construction by providing a virtual checking tool for all involved parties. For example, a customer can virtually "walk through" a building, and completely experience the layout long before hundreds of thousands of dollars are spent on construction. Additionally, an engineer can use this same 3-D walk through to find places where piping hits ductwork, and make alterations before this becomes a construction nightmare. By the time actual construction begins, problems have been solved and a viable and pleasing plan is in place both from a design and aesthetic standpoint.

- Interdisciplinary communication. With all project data located in one central location and accessible to all working on the project, interdisciplinary communication is greatly improved. Consider: the architectural lead holds meetings, and keeps his minutes in a file on the hard drive of his computer. Now, he decides in a meeting with a customer to re-design the atrium of the building, notes an action item to notify the other discipline leads in the minutes on his lap top, and then is out of town for a week. A week later, he notifies the other disciplines of the change, and they have to redo/undo a week's worth of work, wasting both time and money. Now consider this: this same architect has this same meeting with this same customer, and notes the same action item to tell the other leads, but this time it is noted in a centralized database. That action item now appears on the personal action item lists of the other two leads the very second it is written. The week's worth of lost work is now saved, and the project moves forward smoothly. This is one example of how the tracking and reporting project data in a centralized database greatly improves communication within all disciplines.

- E-Commerce opportunities. Consider the following: While designing an RTO system, two engineers carefully decide on the number, type, flow capacity etc. of their dust collectors. The first notes this information as text in a drawing, or

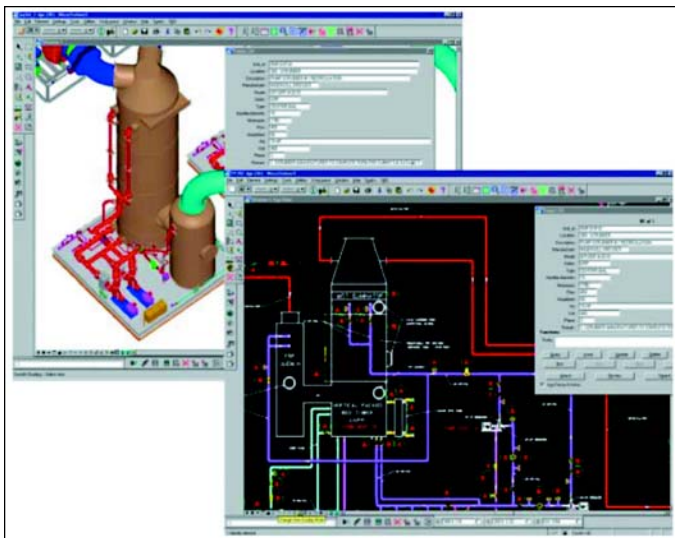
Figure 6. Title block information.

Figure 7. Smart drawings.

perhaps in an Excel spreadsheet, or even in a Word file. The second enters this information in the centralized project data management system and links it to his cad drawing. Now the contractor needs to know how many dust collectors of what type to order. The second engineer merely has to run a summary report and send it to the Contractor, who can pre-order the dust collectors. This pre-ordering minimizes equipment costs, giving the purchaser the opportunity to "shop around." Additionally, he has the opportunity to order it in a timely enough manner to have it arrive on time, rather than behind schedule. Start-up time for construction is minimized because there is an organized repository of all project information. The first engineer, on the other hand, has the specifications for the dust collectors scattered through cad drawings, excel spreadsheets, and word documents. He has to take extra time to locate, ensure accuracy, and compile the data. In this case, time and money is lost, and construction may be delayed.

Over the operation life phase of a project, savings can be found in the following areas:

• The data that proved so useful during design and construction now takes on another function. Where the technical data of the dust collectors was used before to pre-order them and save on construction time, it is now used for maintenance information. The data is linked to the maintenance work order system and can be accessed with one click on the equipment. Now, if the information is updated, a history of that equipment, including maintenance problems is displayed. A maintenance person is no longer looking through grimy logs with ripped pages, but viewing clear electronic files. Better preventative maintenance programs can be put into place to minimize potential downtime.

• In addition to maintenance information, the data that served as submittal information now turns into machine specs and vender information without any added work. When a piece of equipment breaks, the maintenance person can return to that same drawing he was using for maintenance, and click to find out the manufacturer of the person who sold the equipment and contact information for re-

pairs. This creates a central location for SOP, O&M manuals, and machine specs.

• Having one location and one system to learn, enables better training of maintenance personnel. They can get used to finding what they need in one way, rather than needing to learn one system for maintenance, another for repairs, and yet another for vender information.

The process of 3-D modeling can be modified to fit many different applications. For example, if PFDs and P&IDs already exist, it is still more cost-effective to create construction drawings using 3-D modeling. This is because the CAD operator only creates each design element once. It then selects and displays different views to produce plans, elevations, sections, and details. Commitment to this process has shown that it is actually less expensive to create 3-D models of facilities and processes for the production of construction documents than to utilize the conventional two-dimensional (2-D) approach.

Case Study

Finally, let us look at a case study of one customer using this system developed in house. Prior existing conditions:

• Schedules were created and input on a spreadsheet rather than a database. Schematics for new HVAC, piping, and electrical systems for that project were included on drawings. Once the project was complete, these schedules and schematics would be updated and included on as-built drawings.

• As-built drawings. Once the project had been completed, redlined drawings from the contractors would be forwarded to the engineer for input into the computer. Prints were made and issued to the customer for their use.

• Machine Specs have become a standard deliverable in late 1999. These are provided in paper form in binders for building managers and maintenance engineers to reference. Information, such as schedules, OEM manuals, SOPs, and spare parts are included in machine specs.

Problems
• As-built drawings created on a project by project basis start to accumulate either hanging on racks or in rolls in the customer's engineering and building manager's workspace.

• Troubleshooting and maintenance of equipment consists of finding the location of system and also pertinent information required from drawings, schedules, schematics, and machine specs. This includes sorting through rolls of as-built drawings to piece together systems, which could be shared with labs or offices from other projects. A quick response and troubleshoot was dependent on having correct data. Downtime of lab or process becomes costly.

• Programming of new projects – facility engineers have to locate as-built plans in rolls of drawings to scope out available space and capacity of existing systems to determine cost ramifications of new labs or process.

• Building managers incorporating the equipment numbering system take spreadsheet schedules and assign their

equipment numbers to them. Maintenance scheduling or histories of building systems require cross-referencing to the engineering drawings, schedules, schematics, and machine specs.

Solutions – Value Add

- The engineer is now creating as-built drawings, schematics, and machine specs by building rather than by project. Schedules are created using databases so that equipment numbers can be assigned early in the project and can be labeled on drawings, databases, schematics, and machine specs. This creates easy links between drawings and machine specs to equipment numbers to access pertinent data for maintenance and troubleshooting. It also creates means of asset management to track equipment for labs and processes.

- As-built drawings created by building allow the user to access floor plans, schedules, and schematics by building rather than by project. These building drawings have (or are) being created by the engineer and only have to be configured once. Each time a project is completed, the same drawing only needs to be printed with the new information. This creates less rolls of drawings for the customer to manage and it decreases time as-built information gets back to the customer after project is complete.

- The engineer created a Web-based knowledge system that will allow any user to look at building plans and locate information through the use of a common Web browser. This eliminates the need for CAD or database training to make use of the electronic data created for projects. It also organizes the information in a logical system that makes it easy to locate information that is required by the user.

There are costs for the engineer to create tools listed above as well as maintaining 3D model, facility drawings, and database structures once created. However, the use of these systems provides the customer with a useful tool and significant lost time savings. Below is a value-added analysis.

Benefits/Cost Savings

Time saved with implementation of Facility Navigator

• building managers	12 hrs/week
• maintenance engineers	4 hrs/week
• computer management engineers	8 hrs/week
• facility engineers	6 hrs/week
Total	**30 hrs/week**

• number of weeks/year	50
• estimated cost/hr	$ 60.00
• total cost savings	$90,000
• one time start-up cost	$65,000
• maintenance cost of system	$50,000
• first year cost to customer	$30,000
• annual savings to customer hereafter	$40,000

Summary

To ensure success in building cost effective cGMP facilities, the planning and design must begin on a strong foundation that carefully, but expediently organizes the client's requirements into a logical implementation plan that establishes the goals for the facility, determines the means of achieving those goals,

and identifies the resources required to complete the project. This plan must be derived from the active participants of all that will manage or operate the facility. The plan must carefully balance budget and functional issues, and consider providing the appropriate levels of technology, accommodation, and flexibility to meet the ever changing business goals of the company.

The use of the Navigator and its partner database in FDA regulated facilities is a streamlined approach that never sacrifices quality, innovation, or responsiveness. In fact, applying this e-technology at each stage of a project, from programming, design, construction turnover, record keeping, and commissioning, is important in creating and operating a highly cost-effective and flexible facility.

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Glossary of Terms

PFD - Process Flow Diagram

P&ID - Process and Instrumentation Diagram

RFI - Request for Information

CAD - Computer Aided Drafting

SOP - Standard Operating Procedure

O&M - Operator and Maintenance

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This article discusses what procedures, documentation, and practices are needed to establish an Integrated Power and Environment Monitoring System in a pharmaceutical facility.

Monitoring Mission-Critical 24/7 IT Data Centers in a Pharmaceutical Facility

by Nissan Cohen

T he IT environment is a non-production area of a pharmaceutical facility. The IT data center and all constituent components are included in FDA scrutiny. The IT environment includes the traditional IT equipment and non-traditional IT equipment. The latter describes power and environmental equipment installed to specifically support the IT environment. The power and environmental equipment are installed to maintain a 24/7/365 (24 hours a day/7 days a week/ 365 days a year) IT and communications network. The installation of a real-time Integrated Power and Environment Monitoring System (IPEMS) has been instituted at pharmaceutical companies to monitor, manage, alarm, and notify IT management on the health and sustenance of the local and remote IT environment.

What procedures, documentation, and practices are needed to establish this equipment in a pharmaceutical facility? How is the facility maintained? How can a monitoring system be installed in a 24/7 mission critical operation without unnecessary disruption? How can the prevention of downtime enhance performance goals? These questions are answered in the following article.

Information Technology and Non-Traditional Information Technology Definitions

The operation and sustenance of a data center relies on different tiers of structure and support: the Information Technology (IT) enterprise, the non-traditional IT infrastructure, operational and financial personnel, and engineering staff are needed to maintain coherent and efficient operations.

IT is a heterogeneous environment encompassing multi-vendored products. The single

Figure 1. Corporate pyramid based on Mission-Critical 24/7 Operations.

Availability Per Year
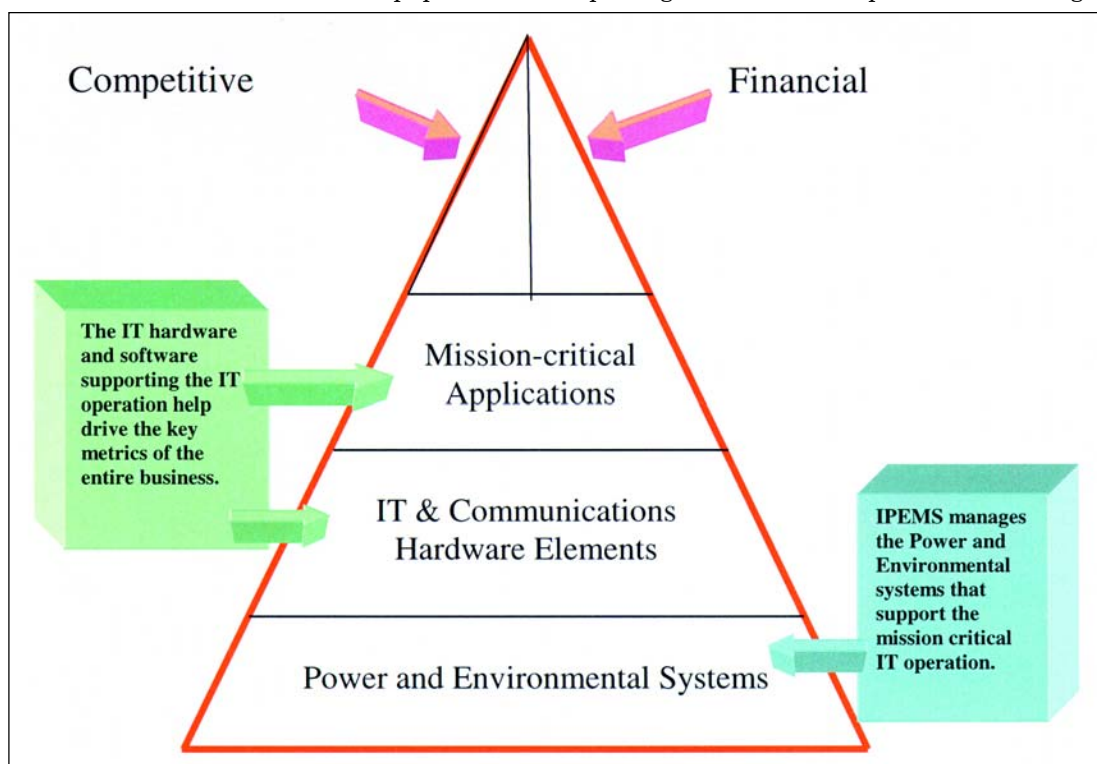
Percent Availability	Hours of Downtime/Year
99.0%	87.60
99.1%	78.54
99.2%	70.08
99.3%	61.32
99.4%	52.56
99.5%	43.80
99.6%	35.04
99.7%	26.28
99.8%	17.52
99.9%	8.76

Figure 2. Uptime availability per year and the calculation of annual downtime in hours.

crosslink to all components, regardless of vendor, is a Network Management System (NMS). IBM, HP, Compaq, Convergent, and Tandem products etc. are integrated into a concise enterprise using NMS software. The integration of divergent vendors has been accomplished due to open architecture software. Traditional computer hardware is only a small component of the IT environment. Telephone switching systems, PBXs, network routers, Internet connections, Intranet networks; WANs, and LANs are all 24/7 sub-groups of the IT environment.

Global, regional, remote, and local monitoring schemes are integrated into an enterprise monitoring system. This scheme permits the usage of a centralized Network Operations Center (NOC) to monitor the entire enterprise. The centralized NOC can serve as a clearinghouse for alarms and troubleshooting of unmanned and remote sites without the cost of physical on-site intervention. The mission-critical denotation is no longer applied only to the computers and mainframes of data center environment, but to all of the support and foundation equipment of the enterprise.[1]

Non-traditional IT equipment supports the mission-critical IT sector. Equipment, commonly denoted as foundation or support, is being emphasized as an integral element of the IT strategy. Power elements devoted to maintaining the uptime of IT equipment; Uninterruptible Power Supplies (UPS); Diesel and Gas generators; Automatic Transfer Switches (ATS), and Power Distribution Units (PDU) are being continually monitored as critical components in the IT strategy. Environmental elements of the Data Center are being scrutinized with the same veracity. Solitary air conditioning units, temperature, and humidity sensors are strategically placed in Data Centers to ensure maximum cooling and temperature stability. Electrostatic Discharge (ESD) monitoring is recommended to prevent static electricity build-up and discharge to the IT equipment. Hazard and safety components are regularly devised into the monitoring scheme to ensure IT safety from fire, flood, and external atmospheric influences. In total, all elements encompassing the IT environment (traditional or non-traditional), mission-critical applications, and a 24/7 enterprise are in jeopardy if any failure occurs.

A graphic pyramid of this interdependence on all aspects of the corporate structure can be illustrated in Figure 1. The base of the pyramid constitutes the non-traditional IT elements. The second tier denotes the traditional IT and communications equipment. The third tier controls all mission-critical aspects of the enterprise. Upper tier is divided into two sectors "Competitive Advantage" and "Financial Performance." Any element under the mission-critical banner affects the competitive advantage and the financial performance.

Downtime Calculation
Every facility has a downtime calculation. In the event of an IT outage, the pharmaceutical company can realize revenue loss, documentation loss, actual experimentation or batch loss, and loss productivity of employees. These losses can total a run rate of tens of thousands of dollars an hour to more than a million dollars an hour. A survey conducted in 1997 of the Fortune 1000 companies showed the average IT downtime lasted for four hours at an expense of $330,000 and an annual cost of almost $3 million dollars.[2] This included all companies of the Fortune 1000 in many different industries. Some industries are more susceptible to downtime than others.

Figure 2 shows the amount of downtime per year when the uptime is 99.0% - 99.9%. The downtime calculation of a 99.9% uptime operation is almost nine hours per year. If an hour of downtime can equal $1,200,000 when all totals are tallied, then the following scenario can be calculated:

- 99.9% uptime = 8.76 hours of downtime a year

- $1,200,000 x 8.76 hours = $10,512,000 per year of loss or unrecoverable revenue

At 99.0% uptime, the loss of revenue per year is staggering:

- $1,200,000 x 87.60 hours = $105,120,000 of lost and unrecoverable revenue

Obviously, hourly calculations of revenue loss are the easiest to calculate. Each pharmaceutical company has calculations for downtime and risk factors. Minimizing both factors is imperative. Uptime is costly, but downtime is more expensive!

Downtime Prevention
Prevention of downtime and guaranteeing uptime is paramount in all mission-critical 24/7 operations. The non-traditional IT infrastructure equipment is designed to enhance the uptime. Back-up systems for power, auxiliary power generation, and corresponding power distribution systems are designed to enhance and alleviate the "dirty" and intermittent power supply from the utility. Uninterruptible Power Supply (UPS) equipment conditions the power to supply constant and even voltage to the needed IT equipment within small tolerances of approximately 0.1%. Fluctuations from the power grid can easily deviate to 10% of the prescribed voltage.

Ensuring the traditional IT infrastructure with conditioned and back-up power is only one way to enhance downtime prevention. The ultimate assessment of uptime may rely on the power back-up scheme and its monitoring.

All equipment can malfunction. Small deviations from operational norms can cause catastrophic outages. One data center, susceptible to chronic network bank failure, had difficulty in pinpointing the cause. Use of a real-time monitoring and management system help diagnose the problem. The installed network cards were susceptible to Electrostatic Discharge (ESD). When the humidity in the data center room dropped to 28%, static build-up and subsequent discharge was sufficient to render the network cards inoperable. The implementation and use of an Integrated Power and Environmental Monitoring System (IPEMS) allowed the data center manager

to proactively assess and provide corrective actions inhibiting any further downtime due to ESD. The solution was simple: when the humidity fell to 30%, additional air conditioning and a stand-alone air conditioning unit provided humidity. The IPEMS can watchdog many different and dynamic situations on a second-to-second basis and help in the management of the infrastructure.

Although no system is infallible, use of IPEMS can improve uptime and reliability of the non-traditional infrastructure. A user of IPEMS in Denver had 100% uptime for more than six and a half years. This data center processes more than $50 million in transactions per day. One hour of downtime equates to more than $2 million in lost revenue. The cause of downtime after six and a half years of uptime was attributed to the engagement of an Emergency Power Off (EPO) switch, inadvertently. The ensuring of uptime more than a six and a half year period translated into an estimated $100 - 200 million in additional revenue to the company.

The IPEMS system should not be seen as a monitoring system only, but as a non-traditional infrastructure management tool.

Traditional Alarms Schemes versus IPEMS

Instantaneous data, on-line measurement, and immediate notification are inherent qualities of an IPEMS structure.

Proactive situational diagnostics of an excursion can impede or stifle an impending critical breakdown within the data center.

Traditional alarm schemes for status monitoring are of a Boolean nature. Status is monitored by a simple stop light scheme. Red denotes alarm conditions and green denotes normal operations. The traditional systems retain little or no data archive, no graphical interpretation, nor definitive proactive actions. When an alarm is annunciated, many alarms may simultaneously illuminate a panel or indicator board. Confusion may ensue due to the cacophony of buzzers and bells producing sensory overload. Since the indicators, panels, and boards do not archive historical data, "cause and effect" or "post-mortem" analysis will be severely hampered. A panel board with many illuminated red lights does not allow for diagnosis, rather it will indicate a change in status only, a basic change from "good" to "bad."

It is difficult to diagnose cause and effect where no historical data exists. Historical data is needed to compare normal operating conditions versus abnormal or alarm conditions.

Historical data, graphing, relationship graphing, "cause and effect" scenarios, and near-term tactical and far-term strategic planning can be elements of an IPEMS. IPEMS is comprised of various data inputs: analog, digital, serial, and derived signals. Live inputs of analog, serial, and digital signals allow for a comprehensive monitoring scheme, but lack
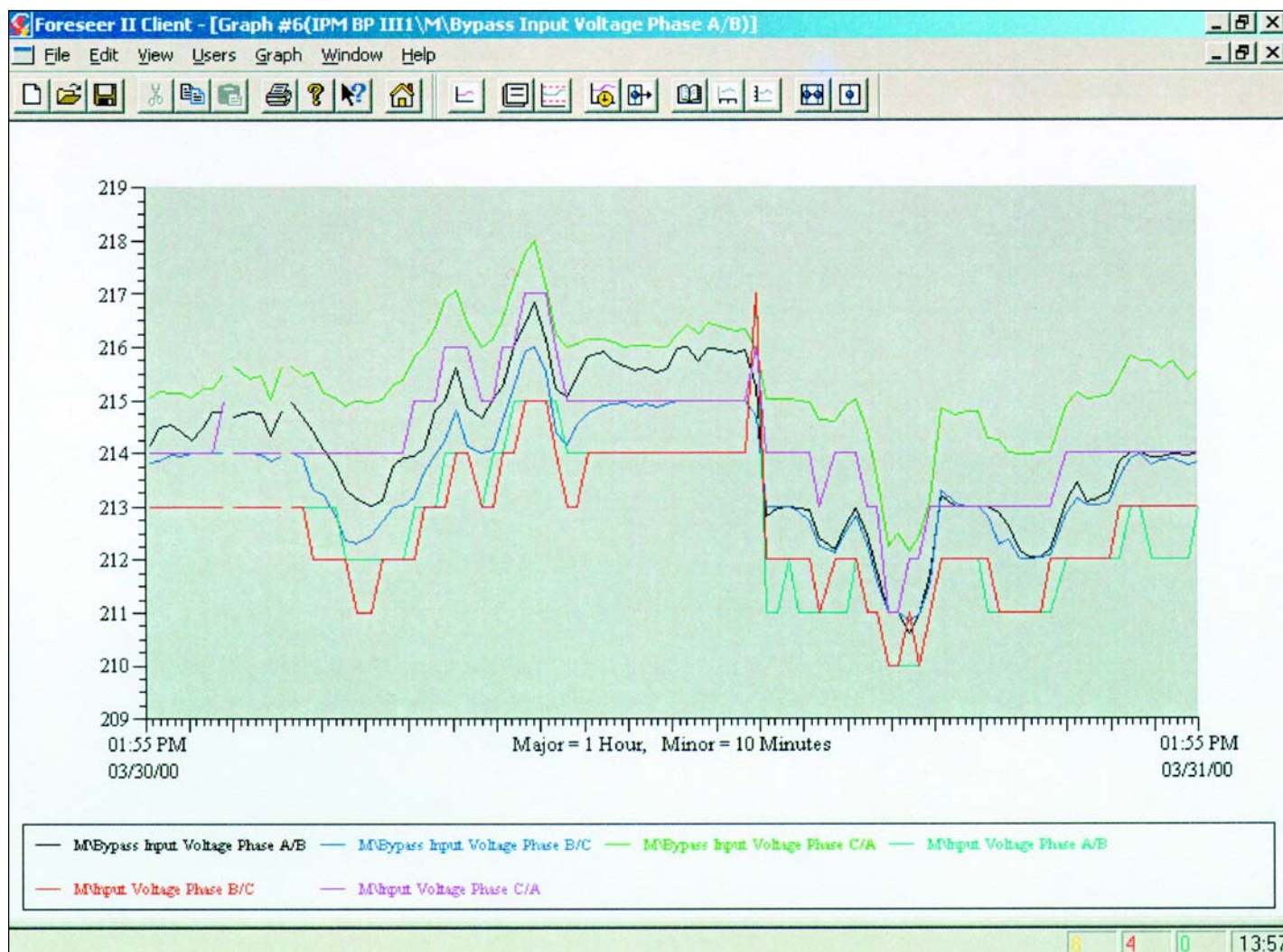

Figure 3. Multi-channel graphing describes input voltages and changes over a 24-hour time span.
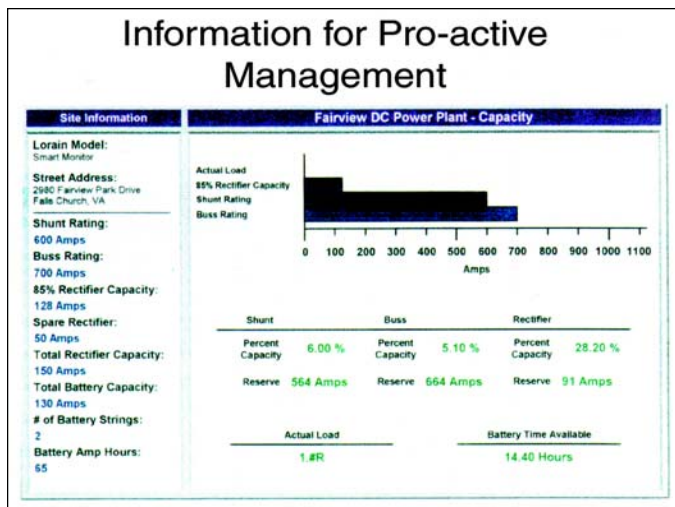
Information for Pro-active Management

Figure 4. Real-time information for pro-active management.

finesse to define the total picture – *Figure 3*. Figure 3 depicts the variations of voltages. A single voltage trace may indicate a condition or trend. The availability of multiple trace plotting and historical data display depicts the total conditions over a specific time period. Long-term, short-term, and projected trend analysis provides proactive management of the power train.

A simple example:

Temperature over a specified limit will cause an alarm.

Questions:

- How long was the temperature rising before reaching the limit?
- Was there a sudden deviation from the normal and mean temperatures? If yes, over what period of time?
- Are there other channels of related equipment currently being monitored which show a similar trend?
- If the trend continues, what are the liabilities or risks?
- Has a risk assessment been proffered of this condition previously?
- Are corrective measures, Standard Operating Procedures (SOPs) or procedure steps documented and applicable to this condition?
- Can a decision be implemented before criticality causes malfunction?

Although the questions above may seem trite, these questions are valid and need historical data for verification, validation, and corrective action development to ensure that a similar excursion in the future will be timely managed without disruption to the IT environment.

Commissioning and Documentation

Although no control is administered in the above scenario, verification and validation of the installation and operation of the system is imperative in a regulatory environment. Commissioning documentation is used during the installation and start-up of the system. Verification of point-to-point data channels is administered. Verification of values and alarm limits is performed. Verification of communications schemes is documented.

Adherence to compatible instrumentation Installation Qualification (IQ), Operations Qualification (OQ), and Performance

Qualification (PQ) documentation established in the pharmaceutical facility is paramount. The installation and use of sensors in the IT data center should correspond to the same documentation and maintenance rigors established for similar sensors in the production areas. The best example is the installation of temperature and humidity sensors in the IT data center. A pharmaceutical facility in the northeast installed similar temperature/humidity sensors as in the production area. These IT temperature/humidity sensors were validated using the same IQ, OQ, PQ, and maintenance documentation.

Pharmaceutical Facility Local and Remote Monitoring

Many large pharmaceutical companies have a campus environment. One pharmaceutical company in the Midwest uses a DataTrax Foreseer IPEMS for monitoring distributed data centers in a campus environment. All power and environmental factors are monitored in real-time. Equipment monitored includes Uninterruptible Power Supplies (UPSs), generators, power distribution units (PDUs), air conditioning units, automatic transfer switches (ATS), power meters, fuel management systems for the generators, and battery monitoring. Not all equipment is installed in each building.

The IT Operations Center in the main data center maintains the NT server. This NT server is the depository for all real-time and historical data, alarms, alarm acknowledgements, reports, and notification schemes for all equipment connected to the IPEMS server. Communication to the equipment installed in buildings outside the data center is via Transmission Communications Protocol/Internet Protocol (TCP/IP). TCP/IP is the common communications protocol used in Internet and Intranet communications. The NT server queries a communications device in the remote building. The remote communications device transmits the data from the remote equipment across the network to the NT server. Local personnel are responsible for the remote devices and buildings during business hours only. The IT Operations Center monitors all devices on the entire campus 24 hours a day. During non-business hours the IT Operations Center focuses on all operating parameters of the entire enterprise. If an excursion or alarm should occur, the IT Operations Center determines the severity or criticality, and notifies the proper personnel.

Each piece of equipment is polled once a second for all corresponding data. The DataTrax Foreseer IPEMS uses serial communication protocols to "talk" to a device. Serial communications allow for many different data values to be transmitted simultaneously. Serial communication schemes allow all of the data and channel values to be transmitted - not just a singular value as in a digital form "c" contact. Some equipment use digital contacts for summary alarms. Although the summary alarm provides adequate notification of an alarm on a given piece of equipment, it does not provide any data of why the equipment malfunctioned or what predicated the malfunction.

Local and Remote Monitoring

Monitoring schemes in the pharmaceutical industry include global, regional, citywide, campus, and individual system's environments. As described above, a campus environment is most often employed in the pharmaceutical industry. Many buildings in the campus are connected via a communications network using TCP/IP. Many sites on the campus can be

monitored in real-time using the network backbone provided by the IT department. Most multi-site pharmaceutical companies have Wide Area Networks (WANs). This communications backbone allows for Intranet and e-mail traffic at high-speeds. IPEMS are instituted to monitor the entire regional enterprise, which may encompass many sites in a regional area of the United States. The aforementioned northeast pharmaceutical company monitors their main IT data center, local campus, and a remote site in the Boston area on a single IPEMS system across the WAN. Still, other companies utilize IPEMS for monitoring of far-flung international operations in real-time across many time zones.

The crux of these operations is the imperative of providing data and IT services 24/7/365. Multi-national, national, and 24-hour pharmaceutical production facilities need access to data and IT operations at all times.

Capacity Planning Using IPEMS

IPEMS can manage the infrastructure, predict needed capacity, and forewarn impending barriers or bottlenecks. IPEMS can accurately manage the non-traditional IT equipment with no adverse affect.[3]

As a data center is being populated with racks of equipment, each additional piece of equipment installed strains the environment, power, and sub-systems. If an UPS and a PDU have certain capacities, the more equipment placed against those capacities will diminish the efficacy of the power supplied. What is the threshold of the "point of no return" when additional equipment will overtax the supply? How many racks and banks of computers will it take to reach that point? When racks of computers are added, how much additional heat is generated? How much additional cooling is needed to offset the heat generation? Are the smoke, fire, and leak detection systems operational for the newly populated area?

Figure 4 depicts the load capacities of a DC rectifier plant commonly used in telecommunication structures. The calculation for load capacities is in real-time and congruent with the peak and off-peak usage. Actual load calculations fluctuate on a second to second basis. As new equipment is populated the capacity, load, and reserve characteristics change commensurate with the equipment power draw, as depicted in Figures 5 and 6. These actual power calculations, for new equipment, can be pre-programmed as a derived channel and added to the existing software before actual installation, thus, creating a

Figure 5. Power capacity vs. real-time load measurements per Power Distribution Unit. Calculation of watts per square foot for power density.

"what-if" scenario with positive assessment before the installation.

IPEMS can help with the resources to systematically allocate the proper hardware for each population addition in the data center. As the new racks of computer hardware are installed, an equally important non-traditional IT component is installed and functional. This exercise can beneficially help financial planning, scheduling of installations, ordering of equipment, project management, commissioning, and human resources planning for the build, installation, initial, and continuous operation of a data center. All of these tasks are a lengthy description of capacity planning.

Summary

Mission critical 24/7 operations have unique and specialized functions and criteria. The investment by the data center operator in the computers, servers, networking equipment, routers, networks, communications, and connectivity devices is in the millions of dollars.

The non-traditional IT equipment installed to support the data center and communications gear is integral to the operation and IT availability strategy.

The monitoring of the power, environmental, and independent systems installed to support the IT and communications environment is imperative to countermand downtime.

Historical trending, data, reports, records, real-time data, alarms, notification schemes, capacity planning, and trending prognostication are elements shared by all financial, operations, and engineering personnel.

The implementation of commissioning documentation, IQ, OQ, PQ and maintenance documentation where appropriate to non-pharmaceutical production equipment, sensors, and areas can meet and/or exceed FDA guidelines.

Uptime equals revenue. Action by the appropriate personnel before an alarm or situation reaches criticality prevents downtime, maintenance issues, and inoperative equipment.
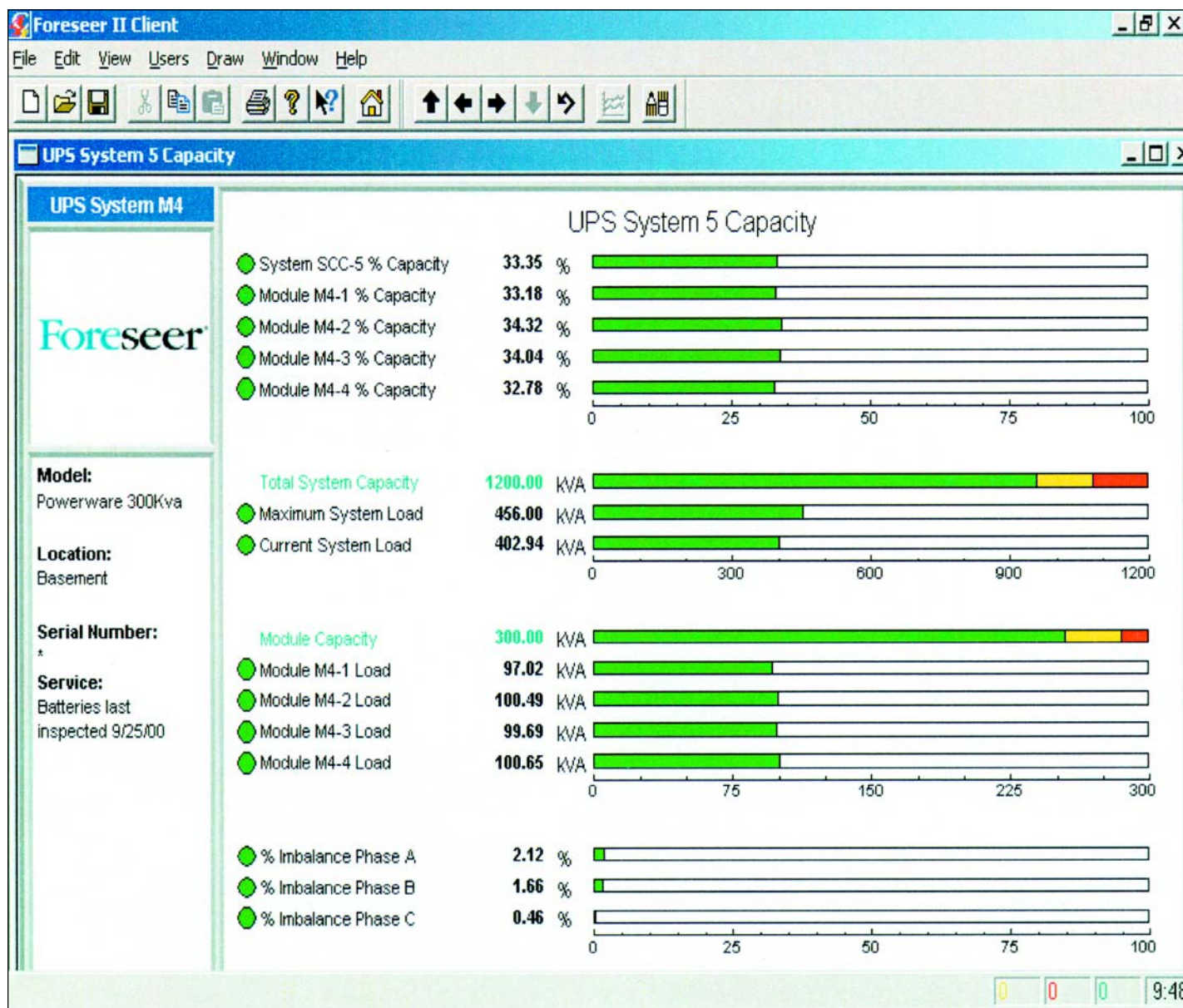

Figure 6. UPS power load vs. capacity, KVA usage, and phase imbalance in real-time measurements.

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AFCOM – The Leading Association for Data Center Professionals, Web site www.afcom.com.

About the Author

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This article was adapted from a presentation describing the effectiveness of Risk Assessment as a tool that allows validation resources to focus on critical areas of an automated system.

Risk Assessment for IT Systems

by Chris Clark

Introduction

In today's world of tighter regulation and seemingly ever increasing rates of change, it is becoming progressively more important that companies can manage **all** risks with the potential to adversely affect normal operations.

At present, companies will typically have formulated plans to resume business after some form of disruption or failure. Companies also need to understand the risks (and impacts) involved in installing new computer systems, both to **patient safety** and to the **business**. Such risks are commonplace, and may be as simple as the increased use of automation distancing production operators, who had the experience/ability to recognize and possibly prevent errors from the actual process.
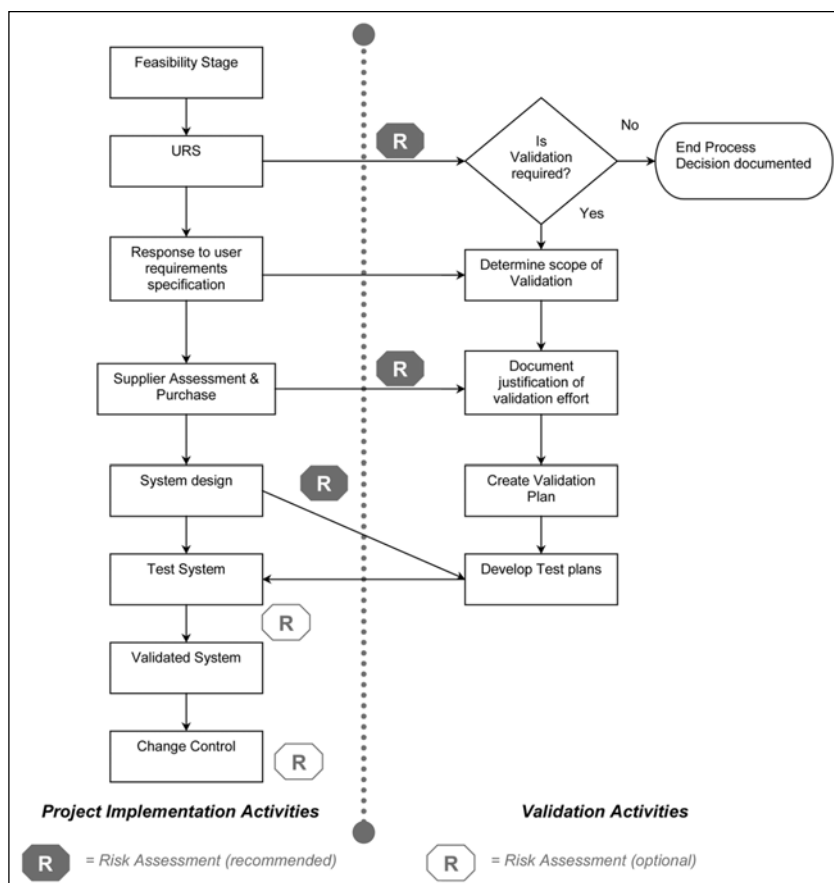
Forward thinking companies now plan for 'risk avoidance' or 'risk management' of both their day-to-day operations, and as part of new product, process, engineering, or information systems development. These plans aim to ensure the continued operation and readiness of critical business processes. The pharmaceutical industry also must consider the statutory obligations imposed by EU and US cGMP regulations in general, and specifically with regard to Traceability, Product Recall, Product (Qualified Person) Release, and Adverse Event Reporting. The widespread use of computerized systems throughout the industry means that these critical GMP functions are subject to regulatory requirements for qualification and validation.

The recognition that a computer system may require validation often initiates the Risk Assessment process. Regulatory authorities are very likely to inquire about such an assessment, particularly if the company has systems that have not been validated, but are apparently involved in GxP operations.

However, it is impractical and probably unnecessary to thoroughly test **every** aspect of a computer system. Establishing the extent of the validation required by a system is an issue that causes much debate among both regulators and validation practitioners. Risk Assessment is an effective tool in supporting the decision of which functions/subfunctions in a large enterprise system require formal validation testing. Resolving this issue, using a Risk Assessment process, allows the validation effort to be focused on critical areas, thereby allowing the most efficient allocation of resources.

The information provided in this ar-

Figure 1. Risk Assessment and the validation process.

ticle is based on a GAMP Good Practice Guide to be published as part of GAMP 4. The technique, based upon Hazard Analysis Critical Control Point (HACCP), Hazard and Operability study (HAZOP), and Failure Mode and Effects Analysis (FMEA) principles, involves the use of a structured process consisting of a series of steps. The aim of this process is to establish what types of risks exist (GxP/business), under what situations they may occur, and what level of impact they exert. This is proposed within a framework leading to formal documentation for subsequent review by the business and the regulatory authorities.

The relationship between Risk Assessment and the validation process is examined to determine the frequency by which assessments should be performed.

Risk Assessment and the Validation Process

Due to the dynamic nature of a typical project lifecycle, risk priorities can change over time. It is probable that risk assessments will need to be performed at different stages throughout the project. Although there is no specific rule regarding either the number or timing of the Risk Assessments, generally they

Figure 2. Overview of the risk assessment process.

are performed on a minimum of three occasions. Suggested points for performing Risk Assessments within the validation process are:

- following the generation of the User Requirements Specification (URS)
- following the Supplier Assessment and prior to the development of the Functional Specification
- following the completion of the Design Review prior to Validation Test Development

These are illustrated in Figure 1.

Performance of Risk Assessments at the above points enables:

- user requirements and project needs to be critically assessed, and alternatives defined
- aids the supplier selection process
- supports the definition of any mitigation steps
- additional validation requirements and/or testing for the project

The findings of these earlier Risk Assessments should be constantly reviewed at later key points in the project, such as prior to making any changes while in routine operation to ensure that assumptions and circumstances upon which they were founded are still valid.

In addition to those assessment points recommended in Figure 1, there is a requirement to consider the continued use of Risk Assessment throughout the lifetime of the system, particularly at two key points. First the risks should be reassessed at the time of signing off the validation and launching the live system. This need only be a simple exercise of reviewing the previous assessments performed earlier in the project to ensure all mitigation measures have been implemented or planned. The other key time to use the technique is during the process of **change control**. Many successfully validated systems fail to maintain this hard earned status as a result of poorly performed change control and the introduction of the Risk Assessment technique as part of the change control process will provide the means to avoid the unnecessary risk of failure. The technique will assist in identifying requirements for testing and qualification of the proposed changes, thus supporting the maintenance of the system validation.

The Risk Assessment Process
Identify Processes and GxP Risk
The first stage in assessing the risks affecting any system is the establishment of the context for the assessment – *Figure 2*. For new IT systems, this may be found within the User Requirement Specification and/or the Functional Specification. These documents can identify the system functions and their sub-functions (including any dependencies between them).

These functions/sub-functions must be formally documented and described via summary details, including a name, which should convey something of the purpose of the function/sub-function. Once identified, each function/sub-function should
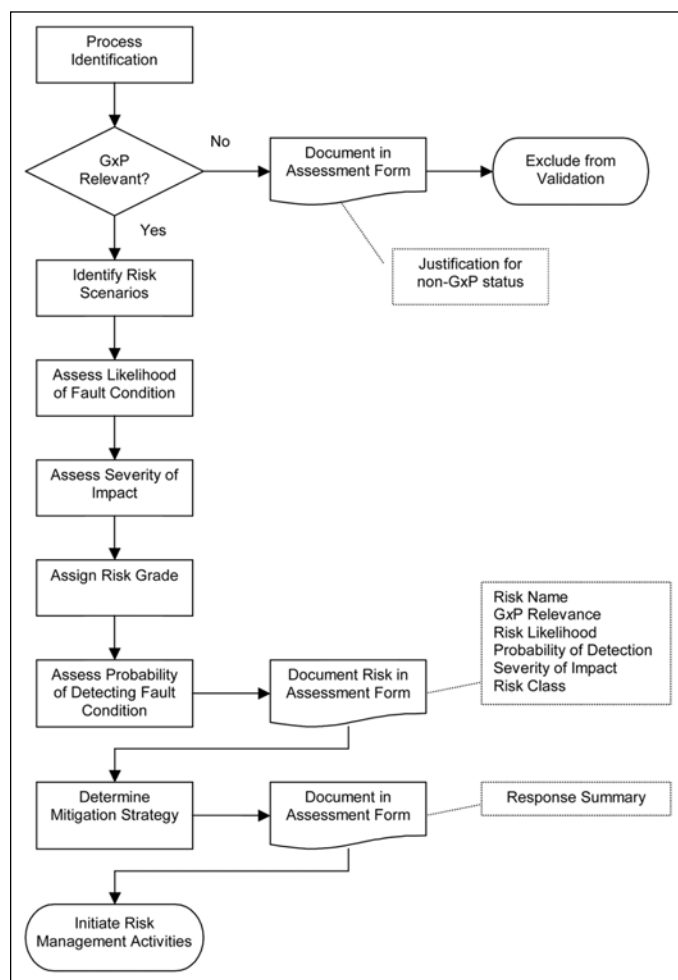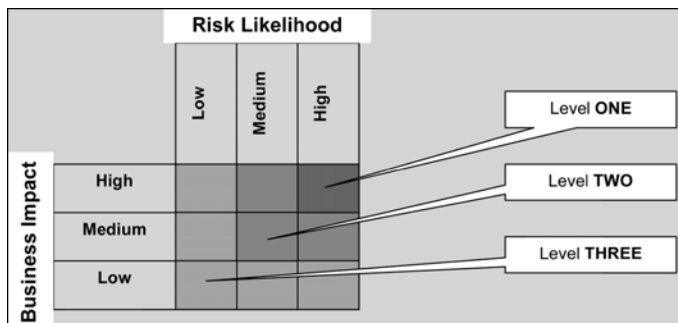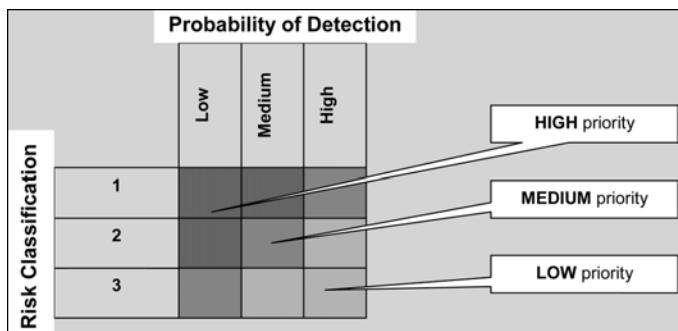
Figure 3. Risk classification.

Figure 4. Risk priority.

undergo a determination as to whether it represents a risk when assessed against a series of GxP criteria as laid down by the standard international regulatory guidelines. If, for example, the risks that may be applied to the pharmaceutical quality of the finished product are considered, they may include:

- incorrect composition
- raw materials errors
- packaging materials errors
- integrity of QC laboratory results
- incorrect batch status
- failure of storage conditions
- batch recalls
- lot traceability
- labeling errors

As each function/sub-function is considered, the project team should make an assessment of the GxP impact and document the outcome of their discussions on the assessment form. This formal documentation also should include the justification for items whereby no GxP risk has been assigned. This is useful for future reference to explain a particular validation approach to a third party, such as regulators.

This risk assessment approach also may be extended to include the identification of Business Risk. For example, risks to corporate reputation:

- adverse publicity
- shareholder responsibilities
- earnings impact
- competitive advantage

Identify Risk Scenarios and Classify Risk
Having determined that a particular function/sub-function may have a GxP or business risk associated with it, the assessment should proceed to identify the various **Risk Sce-**

narios (i.e., the events that could lead to the system being put at risk). It is useful to consider for each event what the likely outcome will be (note that each event may have more than one outcome).

As an example, consider the Procurement Function and the sub-function of raising a Purchase Order. Analysis may suggest that an adverse event might well be the input of the incorrect grade of material during order entry. This could result one of several effects, ranging from the receipt of the incorrect grade of material, the rejection of material on receipt/ analysis and an inventory shortage.

The next stage in the process is to determine the **Likelihood** (or **probability**) of an adverse event occurring. There are many ways to try to measure this concept, but a simple suggestion is:

Low: the probability of the event occurring is perceived to be less than one per year

Medium: the probability of the event occurring is perceived to be between one per month and one per year

Modification of process or system design elements
• **Avoidance:**
The risks are so high that the new way of working should not be implemented
• **Process design:**
One or more independent controls are incorporated into the computer-related process e.g., additional data verification checks within the system design in order to reduce data entry errors
• **External Procedures:**
Introduction of procedures to counter possible failures, such as double checking
• **Product (or System) design:**
Use is made of proven methods, tools and components; fault-tolerance may be built into the computer system (e.g., using replicated parts, system mirroring); the operating environment may be controlled
Modification of project strategies
• **Project structure:**
This refers to the people chosen for the project, their experience and qualifications; the type of project organization preferred; the amount of education and training provided
• **Amount of (auditable) built-in quality:**
Documentation is produced, approved and controlled – the usual method of demonstrating 'validation'
Modification of validation approach
• **Increased testing:**
Increase the scope and level of testing applied during various stages of the validation process, including the development of specialized testing aimed at the testing to failure of certain functions
• **Decreased testing:**
Decrease the scope and level of testing applied during various phases of the validation process due to the extremely low risk associated with occurrence and consequences of the fault conditions.

Table A. Mitigation strategies.

High: the probability of the event occurring is perceived to be between one per day and one per month

NOTE: If an estimate of the likelihood of an adverse event is difficult to agree, the default value of "**High**" should be assigned. As and when more information becomes available, this value can be re-assigned as necessary during the subsequent repeat Risk Assessments at later stages of the project.

Having determined the likelihood of the occurrence of an event, the process moves on to consider the **Impact** on the business of those effects, including impact on regulatory compliance, financial impact, company reputation with customers and suppliers, etc. For example, the immediate effect of a hard disk problem may be the corruption of some data stored on that disk, while the business impact of corrupt data relating to product distribution will eventually result in severe problems in conducting a product recall. This would result in a critical non-compliance with the regulatory requirements and could result in the company having its manufacturing license withdrawn by the regulatory authorities. Again, a simple rule can be applied as follows:

Low: expected to have a minor negative impact. The damage would not be expected to have a long-term detrimental effect.

Medium: expected to have a moderate impact. The impact could be expected to have short-term to medium-term detrimental effects.

High: expected to have an immediate and highly significant negative impact. The impact could be expected to have significant long-term effects and potentially catastrophic short-term effects.

The final step in determining the risk classification is to take the values obtained for both the **Likelihood** of the risk occurring and the level of **Impact** that such an event may have, and apply them to the simple matrix – *Figure 3*.

Plan Risk Management
First, the process requires evaluation as to whether the risk event can be recognized or **detected** by any other means in the system. For example, if a Level One Risk has a **high probability of detection**, it does not pose such a serious threat because it can be recognized quickly and suitable corrective action taken to mitigate its impact. Equally, if the same fault condition has a **low probability of detection**, then the team may need to seriously consider a review of the design or the implementation of alternative procedures to avoid the event.

A suggested method for estimating the probability of an event being detected is as follows:

Low: detection of the fault condition is perceived to be unlikely (i.e., less than one event in every three transactions or operations)

Medium: detection of the fault condition is perceived to be reasonably likely (i.e., one event in every two transactions or operations)

High: detection of the fault condition is perceived to be highly likely (i.e., one event in every one transaction or operation)

By combining the values obtained for **Risk Classification** with the **Probability of Detection** in the simple matrix in Figure 4, the team can set an order of priority for developing mitigation measures:

The resultant Risk Priority of the fault conditions now provides a focus for the validation effort, offering a structure for formulating a suitable mitigation strategy.

Mitigation Strategies
There are several mitigation strategies available to modify risk levels, and several of them may be appropriate for a given system. Some examples are listed in Table A.

It should be noted that while this risk assessment technique helps to **focus** the effort required for successful validation, it does not provide the definitive answer. In some cases, it may be necessary to increase the validation effort for certain failure modes, even if the risk is calculated as being a low priority, for instance, when regulatory requirements require a higher level of validation than the failure mode indicates.

Summary
The use of the simplified Risk Assessment process described in this article provides:

1. the **Support** required for the successful development and implementation of a computer system within the pharmaceutical business
2. the required **Focus** ensuring that only those functions critical and necessary for GxP and the business are validated to a high level of assurance
3. the ability to both **Scale-up** and **Scale-down** the validation effort as required
4. a formal means of documenting the **Justification** for those key decisions regarding the validation approach and the levels of effort expended

About the Author
Chris Clark is Head of Quality Assurance with NAPP Pharmaceuticals Ltd. and is responsible for the implementation and maintenance of the processes and procedures that form the basis of the company quality management system. The scope of this role covers all major functions of the company, including Production and R&D, ensuring compliance to current international regulatory requirements for GMP, GLP, and GCP. Included within this role is the responsibility for the management of the Validation Group who are involved in a variety of process-, product-, and equipment-related projects. He is currently involved as a member of the Core Project Team seeking to implement an international corporate-wide electronic document management and control solution. Clark is a member of the Industry Board and Steering Committee of the GAMP Forum and has spoken at ISPE conferences on subjects related to the qualification and validation of computerized systems. He has more than 22 years of experience of Quality Assurance within the pharmaceutical and healthcare industries, commencing with Sterling-Winthrop before moving to Baxter Healthcare Limited, joining NAPP in 1993.

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