This article describes advancements in process modeling in biopharmaceutical manufacturing focusing on fermentation and chromatographic separation.

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Process Modeling Proposition in Biopharmaceutical Manufacturing

by Sei Murakami, PhD, Peter Watler, PhD, Takashi Ishihara, PhD, and Shuichi Yamamoto, PhD

Introduction

Process modeling and simulation are expected to enable the identification and evaluation of product and process variables that may be critical to product quality and performance. They also may identify potential failure modes and mechanisms and quantify their effects on product quality before and during the actual processing.

However, in spite of those benefits, process modeling for biopharmaceutical manufacturing has not been developed extensively due to its reaction and molecular structure complexity. In order to contribute to the process understanding in the biopharmaceutical industry, advancements in process modeling in biopharmaceutical manufacturing focusing on fermentation as an upstream and chromatographic separation as a downstream representative unit operation will be described.

Upstream - Fermentation

Limitations in Similar Figures Scale-Up

Large-scale mammalian cell culture for biopharmaceutical production is always intricate due to mammalian cell's extreme fragility and complex nutrient requirement. Avoiding cell damage, while optimizing oxygen supply and carbon dioxide extraction, is the key to the mammalian cell culture scale-up. In order to characterize such fermentation conditions for predicting scale-up results, various empirical equations have been introduced. Since most of such equations are dependent on the figures, there needs to be similarity between experimented equipment and scaled-up fermenter. Accordingly, fermentation scale-up has been accomplished with similar figures in order to keep reliability of such empirical equations usage. However, all fermentation characteristics cannot be kept constant simultaneously during the similar figures scale-up.[1] For example, when we scale-up a fermenter from 200 to 10,000 liters with constant impeller tip speed, volumetric power input decreases to almost one quarter - *Table A*.

Accordingly, the actual manufacturing record for the cell culture fermenter shows a rapid decline in volumetric power input during scale-up, resulting from a restriction of constant impeller tip speed - *Figure 1*.

Model Development

To facilitate a more flexible scale-up with quantitative culture environment predictions, a fermenter model independent of figures similarity needs to be provided. Modeling of a fer-

Table A. Empirical equations for similar figures scale-up.

Characteristics	Empirical Equations			200 L	10,000 L			
Power Input	Volumetric Agitation Power	Pg/V	$\propto \frac{n^3\, Di^5}{V}$	1.00	1.00	0.20	0.27	13.6
Mass Transfer	Volumetric Oxygen Transfer Coefficient	k_La	$\propto \left(\frac{Pg}{V}\right)^{0.4} Us^{0.5}$	1.00	1.92	1.00	1.14	5.45
Hydrodynamic Intensity	Shearing Rate by Impeller Tip Speed	$(dU/dz)_{max}$	$\propto nDi$	1.00	1.54	0.90	1.00	3.68
Homogeneity	Circulation Rate	Qi/V	$\propto \frac{n\, Di^3}{V}$	1.00	0.42	0.24	0.27	1.00

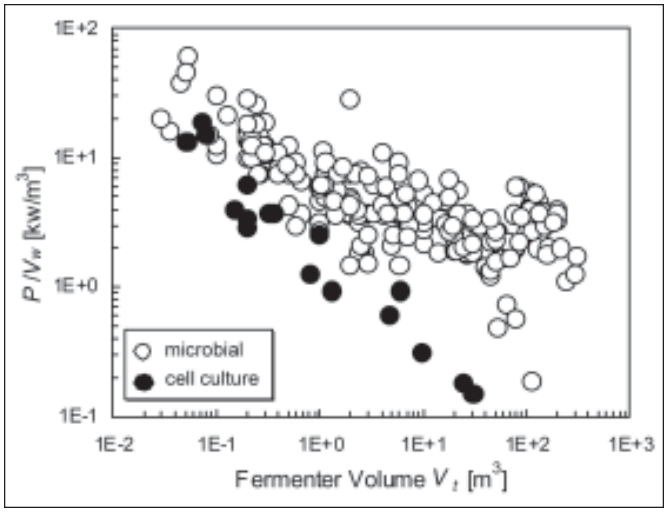

Figure 1. Volumetric power input of various scale fermenters.[2]

menter requires addressing the following problems: turbulent flow, gas-liquid multi-phase flow, and moving boundary conditions of impellers and baffles.

In addition to using a direct solving method of the three-dimensional Navier-Stokes equation, turbulent flow has been addressed utilizing the eddy-viscosity model, the Reynolds stress equation model, the large eddy simulation, and the vortex method. Among them, a subset of the eddy-viscosity model, k-ε model,[3] has been widely used due to its wide applicability and a moderate computational resource requirement. In spite of limitations of the k-ε model, such as dependence of six empirical constants and an isotropic turbulence assumption, its applicability to mixing vessel simulation has been confirmed and excellent representation of experimentally measured values, especially flow velocity, have been reported.[4]

Modeling of multi-phase flow includes the Eulerian and Lagrangian models. The Eulerian model assumes each phase to have a separate velocity field and a common pressure field, whereas the Lagrangian model tracks representative bubbles through the domain. A large number of bubbles often observed in fermenter operation renders it unrealistic to apply the Lagrangian model's bubble tracking. A simpler subset of the Eulerian multi-fluid model is drift-flux model,[5] which assumes the dispersed phase, bubbles, move relative to the continuous phase, liquid, at their terminal velocity. In the drift-flux model, bubble acceleration and physical property change, usually not significant in fermentation, are neglected. With gas hold up, bubble diameter, and hydrodynamic parameters, a volumetric oxygen transfer coefficient k_La can be described. Consequently, dissolved oxygen and carbon dioxide distribution can be calculated by solving oxygen and carbon dioxide transport equations.

If a fermenter vessel does not have baffles, boundary conditions can be simpler and do not need to be changed with time by defining it rotating with impellers. However, most fermenters are furnished with baffles or other internal fixed structures making the simulation model's boundary condition multifarious. In order to avoid the complexity of time dependent boundary conditions, a method with an equivalent cylindrical block having experimentally determined boundary conditions of flow velocity and turbulence representing the rotating impellers has been introduced. Although it is simple to calculate, an impeller representative cylinder always requires actual scale experimental measurement and cannot be used for unrealized scale-up study. To avoid the empirical dependence, the dynamical multi-block method[6] and the sliding mesh method[7] have been introduced where impellers and baffles are modeled in a separate block rotating relatively to each other.

One of the descriptions of hydrodynamic damage to the cultured cells is Kolmogoroff Eddy Length Scale, which is assumed to be the minimum eddy size before dissipated by viscous force. If the Kolmogoroff Eddy Length Scale is smaller than that of solid particle such as suspended cells, the particle may not move to release the hydrodynamic force and may receive some damage on its surface. On the other hand, if the Eddy is larger, the particle can float on the eddy, and thus, hydrodynamic damage can be avoided.[8]

Based on the above modeling, empirical equations for fermentation characteristics shown in Table A can be substituted by the following elemental and overall parameters independent of figures similarity among different scales.

Because these parameters are independent of reactor figures, they can be used for various fermenter shapes.

Simulation

Using models described above, one now can perform fermen-

Characteristics	Elemental Parameters		Overall Evaluation	
Power Input	Turbulent Energy Dissipation Rate	$\rho\varepsilon$	Total Turbulent Energy Dissipation Rate	$\frac{1}{V}\iiint (\rho\varepsilon)\, dxdydz$
Mass Transfer	Local k_La	$(\alpha/Db)\, f\,(Sc, v, k, \varepsilon)$	Total k_La	$\frac{1}{V}\iiint (k_La)\, dxdydz$
Hydrodynamic Intensity	Kolmogoroff Eddy Length Scale	$(v^3/\varepsilon)^{1/4}$	Minimum Eddy Length Scale	$\left[\left(\frac{v^3}{\varepsilon}\right)^{1/4}\right]_{min}$
Homogeneity	Local Concentration	C	Standard Deviation of Concentration	$\sqrt{\frac{1}{V}\iiint (C-\overline{C})^2\, dxdydz}$

Table B. Elemental parameters and overall evaluation for fermentation model.

tation environments simulations, which provide liquid flow vector, gas hold up, hydrodynamic damage, volumetric oxygen transfer coefficient, k_La, dissolved oxygen, dissolved carbon dioxide, etc. Due to culture liquid physical characteristics that cannot be predicted precisely prior to the simulation, primary simulation results might differ from experimental results. Consequently, appropriate adjustment for a particular fermentation is essential. This adjustment can be done by performing a couple of simulations for established bench or small-scale fermentations, then comparing the simulation and experimental results.

Process Optimization

Hydrodynamic damage, dissolved oxygen, and dissolved carbon dioxide are the key critical fermentation conditions for mammalian cell culture. The following discussion describes some of the applications of the proposed model and simulation for evaluating and optimizing a fermentation environment.

As a hydrodynamic intensity evaluation example, Kolmogoroff Eddy Length Scale distributions are shown in *Figure 2*. Depending on the size of the particle, such as a suspended cell and a micro carrier, appropriate impeller type and agitation speed, which has larger Eddy Length Scale, can be found by changing the impeller profile in the simulation.

The dissolved carbon dioxide that is often increased by scale-up will likely reduce cell growth and productivity. Because liquid surface mass transfer has a significant effect on carbon dioxide extraction, a fermenter aspect ratio needs to be optimized. Figure 3 shows an effect of bioreactor aspect ratio on dissolved carbon dioxide reduction.

As described above, flexible fermenter configuration and operating conditions evaluations provide minimum hydrodynamic damage and dissolved carbon dioxide which lead to productivity maximization. This simulation for process optimization can be executed not only in a scale-up, but also in a scale-down experiment for an existing fermenter.

Downstream - Chromatographic Separation

Chromatography Processes for Biopharmaceutical Products

Separation and purification processes of recombinant protein-based pharmaceuticals and other biological products involve a series of chromatography steps. Highly advanced simulation software is available for separation unit operations in chemical and petrochemical processes such as distillation. This type of software is now routinely used for operation and optimization of processes as well as process design. However, chromatography processes are still designed and operated on the basis of the knowledge empirically obtained or on the trial-error approaches. Therefore modeling and simulation of chromatography are important for rational design, optimization, and stable operation of processes.

Several modes of chromatography are available to exploit the charge, hydrophobicity, and size differences of the contaminants and the product. In addition, chromatography columns can be operated in various modes such as flow-through or adsorption mode with isocratic or gradient elution. Current chromatography column technology has enabled the size of preparative columns from a few centimeters to up to two meters capable of holding hundreds of liters of packing materials.

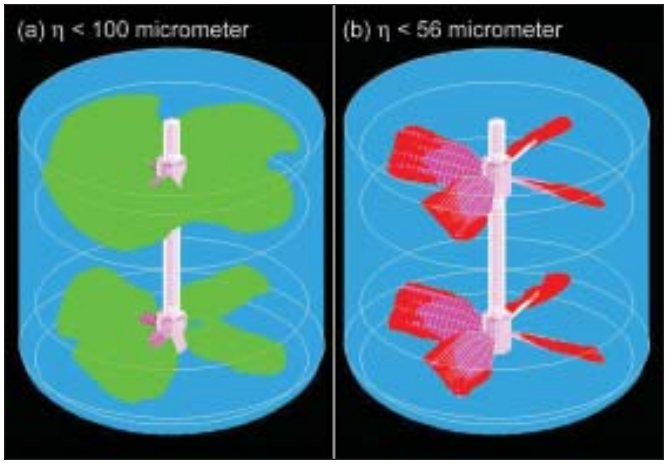

Figure 2. Kolmogoroff Eddy Length Scale distribution.

To take advantage of these many advancements, it is critical to have a well-planned development strategy and solid understanding of the separation mechanism to successfully design, scale-up, and implement a cost effective chromatographic process. Indeed, this ability is a key factor in the success of a company's process development effort and subsequent product commercialization.

When a certain chromatography process can be predicted by a model simulation, it is easy to optimize the process by tuning the operating variable and designing a better performance process. Plant constraints such as buffer and tank volumes and process time also can be incorporated into the model. The model allows rapid assessment of buffer usage, retention times, peak volumes, and estimates purity, recovery, and productivity. Also it is easy to change the conditions to observe how the separation changes. The model provides a solid understanding of the process, which parameters are important, and how and why they affect the separation.[9-12]

The following discussion will describe how to apply models to chromatography processes and what can be done with models.[9]

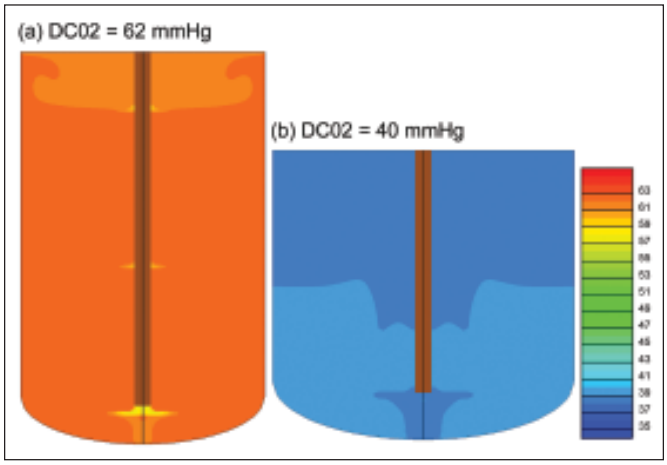

Figure 3. Dissolved carbon dioxide distribution.

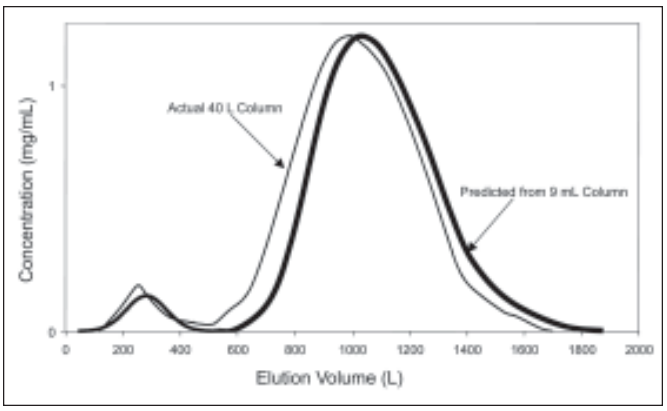

Figure 4. Comparison of isocratic elution curve predicted from the model using a small (9 mL) column linear gradient elution data and actual elution curve of a 40 L column: CM Sepharose FF.[9]

Use of Model for Scale-Up to Industrial Size Column

Chromatography peaks are characterized with the retention volume and the peak width. The retention volume is related to the distribution coefficient K, and the peak width is expressed by $HETP = Z/N$ (Z: column bed height, N: plate number).[9-12] The model parameters K as a function of salt concentration I, and $HETP$ as a function of velocity are determined from a series of small-scale Linear Gradient Elution (LGE) experiments.[9,13] These data also can be applied to isocratic elution. As shown in Figure 4, the model can be used to predict isocratic elution behavior of a large-scale industrial column. The predicted chromatogram closely approximated the actual chromatogram from a 40 L column with predicted retention volumes within ~15% of the actual retention volume.

Use of Model for Linear Gradient Elution Optimization

One of the most useful applications of a chromatography model is for screening operating conditions to characterize and optimize the separation. To assess the separation and challenge the model, extremes of column length, gradient length, and initial ionic concentration were evaluated.

A tall bed height with a shallow gradient slope typically maximizes peak separation, but also increases the separation time and the elution volume. Such conditions were screened with the aid of the model by adjusting the operating conditions to a 20 cm bed height and 30 (Column Volume) CV gradient. Under these conditions, the model predicts relatively broad and late eluting peaks with baseline. To verify the model, the actual chromatogram obtained under the same operating conditions is shown in Figure 5. The predicted and actual chromatograms show similar peak shapes and peak widths, and baseline separation with the main peak eluting at ~70% of the gradient. The model provided an accurate prediction of the separation under conditions for high resolution.

After identifying and verifying a high resolution separation, the operating conditions were modified to search for conditions that gave good resolution, but were more scaleable and offered higher productivity. A shorter bed height will have lower pressure drop upon scale-up, and a more moderate gradient length will lower buffer consumptions. To compensate for the shorter gradient length, gradient slope was reduced by increasing the initial ionic concentration, I_0. The predicted chromatogram from the more moderate operating conditions of 12 cm bed height, 20 CV gradient, and I_0 = 28 mM showed near baseline separation of the peaks with the product peak eluting earlier at ~55% of the gradient and with a narrower peak width[9] - separation was verified experimentally, showing that the LGE model provided an accurate prediction under moderate operating conditions.[9]

Finally, the separation behavior under extremely low resolution conditions was studied. A very low bed height (5 cm) and a very short gradient (7 CV) required minimal packing materials, buffer and tanks. However, the model predicted that the pre-peaks merged with the product peak, appearing as a small shoulder on the product peak resulting in very poor resolution.[9] In addition, the model predicted that the product peak eluted toward the end of the gradient (~90%). The actual chromatogram obtained at these operating conditions was very similar to the predicted chromatogram, showing a very sharp, late eluting peak with little resolution.

As discussed above, chromatography models can be used to screen a wide range of conditions in order to optimize and characterize the separation. It is important to empirically verify the proposed conditions prior to specifying them for scale-up. Table C shows that the model predicted how the elution volume and peak width changed at various column and gradient conditions. Predicted retention volume was within 3% of the actual volume for the product peak. The model showed that peak width decreased with sharper gradients and lower bed heights, but under-predicted values by 21-41%.

Use of Model to Improve Productivity

Productivity is defined as the amount of protein of a given purity, produced per unit time per liter of chromatography packed bed volume. Models can be employed to rapidly scout conditions which give the highest productivity for a given purity requirement. For the separation shown in Figure 4, the optimized isocratic operating condition gave a productivity of 0.16 g/L.h - *Table D*. This is largely because of the long cycle time due to the high distribution coefficient of the product peak under isocratic elution at 40 mM NaCl. One method of addressing a high K value is to use gradient elution. The model showed that a very large gradient volume (60 CV) gave comparable resolution with a somewhat higher productivity of 0.21 g/L.h. From this starting point, operating conditions were varied to search for increased productivity. A moderate bed height of 10 cm and a moderate gradient of 10 CV gave sufficient resolution to achieve 99% purity and very high (99%) recovery. One of the features of the model is that the starting ionic strength can be varied to adjust the gradient slope. Increasing the starting salt concentration to 40 mM, resulted in almost immediate

desorption of the pre-peaks as was indicated by the *K-I* curve. At this gradient slope, the product peak elutes earlier resulting in a short cycle time and higher productivity. Another feature of this separation is that the steeper gradient results in sharper peaks and a lower product pool volume. Productivity under these conditions was 0.61 g/L.h, nearly 400% higher than the initial optimized isocratic conditions.

Use of Model for Characterization and Troubleshooting of Separation

To maintain process consistency, validated large-scale processes typically have a constraint to maintain elution volume within ±5%. This is often needed as tank volumes are fixed and elution must be completed within planned production times. While column size, flow-rate, and protein loading are fixed by the manufacturing procedure, resin ionic capacity, buffer pH, and ionic strength will vary due to lot-to-lot variations. To assess the consistency of the separation, the model can be used to characterize and troubleshoot the effect of these fluctuations. In this application, the model can be used to elucidate the binding characteristics and to quantify changes in elution volume with variations of media ion-exchange capacity and buffer ionic strength and the pH.[14] For illustration, a model separation system of β-lactoglobulin near its isoelectric point on a weak cation exchanger, CM Sepharose at pH 5.2, was selected.[14] Although the isoelectric point of this protein is 5.1-5.2, it is retained on both anion and cation exchange chromatography columns at pH ~5.2.[15] According to the manufacturer, the ion-exchange capacity Λ of CM Sepharose FF ranges from 90 to 130 mmol/mL-gel. Such variations can greatly affect the retention time since the distribution coefficient is related to Λ. For the recombinant protein separation shown in Figure 4, a 22% increase in the total ionic capacity from 90 to 110 mM mmol/mL resulted in a 47% increase in the distribution coefficient and the relative retention volume.[9]

In a production environment, it is impractical to consistently obtain resin of a specific ionic capacity. In order to control the retention volume, it is necessary to adjust the salt concentration I_E, of the elution buffer. In the above-mentioned model separation system with β-lactoglobulin, the relationship between the relative elution volume and I_E was examined. It was found that the NaCl concentration must be adjusted by ±0.015 mol/L to elute the protein within ±5% of the reference elution volume.

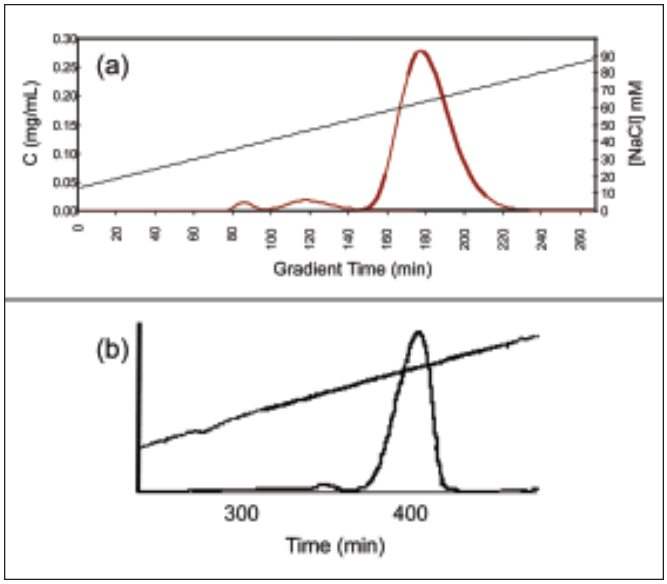

Figure 5. Comparison of predicted chromatogram (a) and actual chromatogram (b) for CM Sepharose FF, Gradient = 30 *CV*, diameter = 1.6 cm, height = 20 cm, Io = 16mM NaCl, superficial velocity = 120 cm/h.[9]

This is typically done by trial and error. However, as discussed above, the distribution coefficient as a function of ionic strength can be obtained from gradient elution experimental data. Once this *K-I* information is obtained for a given Λ, the elution volume can be predicted and the elution buffer ionic strength can be adjusted. Hence, the chromatography model can serve as a convenient tool for tuning and troubleshooting very sensitive isocratic chromatography processes. In addition, there is usually a variation in the salt concentration of elution buffers prepared at production scale. In this example, the salt concentration of the buffer must be within ±0.002 mol/L in order to meet the ±5% elution volume criteria.

Due to inherent variability during preparation, buffer pH also will vary at production scale. Buffer pH affects the charged state of the of the ion exchanger which affects elution volume. The ion exchange capacity of CM-Sepharose decreases with pH below pH 6.[10] The relative change in elution volume, resulting from changes in the ion-exchange capacity, Λ as a function of operating pH was investigated for the model separation system. Although variations in the relative elution volume are smaller compared with the salt concentration

Operating Conditions			Retention Volume (mL)		Product Peak Width (mL)	
Bed Height (cm)	Gradient (CV)	Initial Salt Concentration (mM)	Predicted	Actual	Predicted	Actual
20	30	16	164	162	71	44
12	20	28	110	110	56	42
12	50	16	230	228	---	---
5	7	16	66	68	42	33

Table C. Comparison between predicted and actual experimental retention volume and peak width for the product peak under various gradient elution conditions and column geometries, CM-Sepharose FF superficial velocity = 120 cm/h.[9]

Operating Conditions			Recovery (%)	Productivity (g/L.h)
Bed Height (cm)	Gradient (CV)	I_o (mM)		
12	Isocratic	40	100	0.16
12	60	0	100	0.21
20	30	16	100	0.24
5	7	16	28	0.53
10	10	40	99	0.61

Table D. Optimization of operating conditions using chromatography model simulations. Comparison of recovery and productivity for various operating conditions, CM-FF, If = 100 mM NaCl.[9]

and the ionic-capacity, it is still important that the buffer pH be within ±0.1 pH unit. It is additionally important to control buffer pH since as discussed above, the interaction between the protein and the ion-exchanger changes with pH especially near the isoelectric point. However, controlling the effect of pH is more complex than controlling salt concentration or the ion-exchange capacity.

Conclusion

Advancements in process modeling for fermentation and chromatographic separation were described.

For a fermentation process, hydrodynamic and the mass transfer model have been incorporated into CFD, which enables us to overcome contradictions in similar figures scale-up. While all parameters expressing fermentation conditions cannot be kept constant simultaneously during the scale-up, the proposed model facilitates the scale-up environment prediction along with flexible fermenter configuration and operating conditions for productivity maximization. This simulation method also can be used for analyzing and understanding an existing fermentation process for further quality and productivity enhancement. Appropriate adjustment for a particular fermentation by performing a couple of simulations for established bench or small scale fermentations is necessary for more accurate performance prediction.

For a downstream process, the model simulation is a useful tool for process design, diagnosis and operations. It also is helpful to understand the mechanism of very difficult and unstable separations. We have applied the model analysis to the separation of protein variants near the isoelectric points,[15] the separation of monoclonal antibodies,[16] and the separation with monolithic columns.[17] Further study is needed to establish a fast and simple method for determining data needed for the model simulations, and a method for obtaining important information with the aid of rapidly developing "bioinformatics."[12]

Both models for upstream and downstream biopharmaceutical manufacturing described here will provide insight and understanding of the critical process attributes, which enable superior performance prediction, proper process monitoring interpretation, in-process adjustment, and versatile troubleshooting.

FDA's regulatory framework (Process Analytical Technology or PAT) is intended to facilitate progress to the desired state of pharmaceutical manufacturing.[18] In one of the PAT Tools "Multivariable tools for design, data acquisition, and analysis," mathematical relationships and models are expected to provide scientific understanding of the relevant multi-factorial relationships. In conjunction with recent biopharmaceutical manufacturing technology development concerning other PAT Tools, i.e. "Process Analyzers," "Process Control Tools," and "Continuous Improvement and Knowledge Management," these models possibly will contribute to the progress of the PAT framework.

Nomenclature

C	concentration for fermenter homogeneity evaluation [-]
CV	column volume [L]
Db	bubble diameter [m]
D	diffusivity [m^2/s]
Di	impeller diameter [m]
$HETP$	height equivalent to a theoretical plate [cm]
I	ionic strength of buffer [M]
I_0	initial ionic strength of buffer [M]
I_E	ionic strength of elution buffer [M]
K	distribution coefficient [-]
k	turbulent energy [m/s]
k_La	volumetric mass transfer coefficient [s-1]
n	rotation speed [s^{-1}]
Pg	sparged mixing power [w]
Qi	impeller pumping flow rate [m^3/s]
Sc	Schmidt number [-]
Sct	turbulent Schmidt number [-]
u	velocity vector [m/s]
Ui	impeller tip speed [m/s]
Us	reactor superficial gas velocity [m/s]
V	reactor volume [m^3]
Z	column bed height [cm]
α	gas hold up [-]
ε	turbulent energy dissipation rate [m^2/s^3]
η	Kolmogoroff Eddy Length Scale [m]
Λ	ion-exchange capacity [µmol/mL-gel]
ν	kinetic viscosity [m^2/s]
νe	turbulent kinetic viscosity [m^2/s]
ρ	density [kg/m^3]

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About the Authors

Sei Murakami, PhD, is a General Manager of Industrial Systems Div., Hitachi, Ltd., Tokyo, Japan. He earned a BS from Osaka University, Japan, and holds a PhD in engineering from the Yamaguchi University, Japan. His responsibilities include pharmaceutical manufacturing plant development, engineering, design, and construction. He participated in a mammalian cell culture research project at MIT in 1989. He is a member of ISPE, PDA, ASME, Japanese Association for Animal Cell Technology, Institution of Professional Engineers, Japan. He can be contacted by email: sei.murakami.dg@hitachi.com

Hitachi, Ltd., 2-9-7 Ikenohata, Taito-ku, Tokyo, 110-0008 Japan.

Peter Watler, PhD, is a Senior Director of Manufacturing, VaxGen Inc., South San Francisco. He earned a BS from the University of Toronto, an MS from the University of Toronto, and a PhD in engineering from the Yamaguchi University, Japan. He can be contacted by email: PWatler@ vaxgen.com

VaxGen, Inc., 347 Oyster Point Blvd., Suite 102, South San Francisco, California 94080 USA.

Takashi Ishihara, PhD, is a Research Scientist of Pharmaceutical Division, Kirin Brewery, Takasaki, Gunma, Japan. He earned a BS from Kyusyu University, Japan, an MS from Kyusyu University, and a PhD in engineering from the Yamaguchi University, Japan. His responsibilities include biopharmaceutical purification process development, and he has accomplished various process development and manufacturing of biologics. He is a member of the Society of Chemical Engineers, Japan. He can be contacted by email: t-ishihara@kirin.co.jp

Kirin Brewery, Co., Ltd., 100-1 Hagiwara,Takasaki, Gunma, 370-0013 Japan.

Shuichi Yamamoto, PhD, is a Professor of Biochemical Engineering, Department of Chemical Engineering, Yamaguchi University, Ube, Yamaguchi, Japan. He earned a BS from Kyoto University, Japan, and an MS and PhD from Kyoto University, Japan. His research interests include engineering analysis of chromatography and drying of biological products. He is a Director of the Society of Chemical Engineers, Japan, an official of the Japan Society for Food Engineering, and a member of AIChE. He can be contacted by email: shuichi@yamaguchi-u.ac.jp.

Yamaguchi University, Tokiwadai, Ube, Yamaguchi, 755-8611 Japan.

This article describes the use of a technology assessment diagram in the biologics and pharmaceutical industry, and presents the steps to develop, and evaluate the scope options for a facility or process.

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Project Scope Determination and Cost Control Using Technology Assessment Diagrams – A Biopharmaceutical Example

by Mary Ellen Craft

Introduction

How does your company make decisions? Can you locate the decision history of your company? Are those decisions shared with the team?

> *"One would think that employees had a common process to sort, organize, and analyze information. Think again. More than four-fifths of both managers and workers, when asked if such a practice existed in their organization, either said "no" or reported that they did not know. Of those who stated such a practice did exist in their organization, 31% of workers and 29% of managers said their management takes no action to ensure that the process is used, or, if it does, they don't know about it."*[1]

Every team can improve its performance by utilizing simple communication and control tools. A technology assessment diagram is one of these tools. It provides a one-page overview that allows the team to see, analyze, and make decisions on almost any topic.

Ron Evans, a partner at Kepner-Tregoe®, which is a management consulting and strategy company, in an interview in *Executive Forum*, stated:

> *"The use of critical thinking to address business issues seems to be lacking. We find that businesses are very good at trying to understand the content around an issue, such as the facts and technical data, but they are sometimes deficient in the use of a common process to organize and analyze that information."*[2]

Each person thinks differently from another. Each person uses his or her own methods to make a decision. Team decisions do not just happen. In order to allow a team to jointly make decisions and remain unified in those decisions, it is a valuable, almost imperative asset, to possess a common method for using a visual tool. This tool should aid in the decision-making process, record the options considered, and identify the solution(s) determined. A visual tool also may be needed when communicating decisions/choices, and the justifications for those decisions to management.

Management is more often demanding, *"I not only want to see what the decision is and what information you've got, but I want to see how you processed that information in your recommendation."*[2]

This article presents a modified decision matrix with the use of a weighted ranking system to determine and analyze the target scope/functionality or user requirements of many desired components or parts necessary for the construction of biopharmaceutical facilities.

Many decision-support software programs are available on the market. Most of these programs are based on a decision matrix or a decision tree. However, *"Computer programs cannot set goals, think up alternatives, assign weights, or evaluate criteria. You have to do that."*[3] Computer programs can be valuable in crunching numbers and asking questions that might be overlooked without the program. How-

Item A Header _____

AREA or ITEM:	Item D	Item D	Item D	Item D	Item E
Item C FUNCTION:	ATTRIBUTE #1	ATTRIBUTE #2	ATTRIBUTE #3	ATTRIBUTE #4	CAPITAL COST
OPTION 1 Item F		Item G			
OPTION 2 Item F			Item G		
OPTION 3 TARGET FUNCTION				Item G	
OPTION 4 Item F					Item G

Item B Footer _____

Figure 1. Technology Assessment Diagram (TAD) basic template.

ever, decision support software only allows one to see and work with one column or one row of the decision matrix at a time. While discussing the benefits and drawbacks of computer decision-support programs, Jared and William Taylor, as authors and management consultants, further state that:

> *"In the final analysis, all a decision matrix does is sum up weighted attributes of the alternatives. Why can't you do this with a spreadsheet? You can…spreadsheets can be made to function as a decision matrix."*[3]

This article presents technology assessment diagrams and a decision-making process that can easily be used by your team. This simple tool utilizes a spreadsheet as a decision matrix.

What can a Technology Assessment Diagram Do for Me?

A Technology Assessment Diagram (TAD) can help you make decisions, capture your project requirements or components, and document solutions. It also can help you to keep your project within budget. A TAD gives your team members, whether internal or external, a visual way to consider alternatives or options and view, at a glance, the cost and technology impact of those alternatives.

TADs aid in each of the following:

- communication within team and to management
- defining and documenting physical and functional options
- determining target functionality or baseline scope
- analyzing scope content, its quality and associated costs
- controlling project costs
- providing support documentation for the following:
  - project estimates
  - change management systems
  - value engineering exercises

After a project is defined, any team can use TADs for further defining, analyzing, controlling, and tracking components of that project.

What is a Technology Assessment Diagram?

A TAD uses a spreadsheet as a decision matrix. It uses a structured methodology to assist in decision making while providing a documented trail of scope options and their impact on project cost. See Figure 1 for layout of a basic TAD template.

How do I Construct and Use a Technology Assessment Diagram?

The steps in developing TADs are:

1. Begin with your project specific template
2. Divide your project into parts to be analyzed and begin a TAD for each of these parts
3. Identify attributes for each part, area, system, or function
   - Assign weights to the attributes
4. Further define the scope by developing scope function options
   - Select target functionality (baseline scope)
5. Evaluate and analyze your options
   - Cost Each Option
   - Apply Ranking

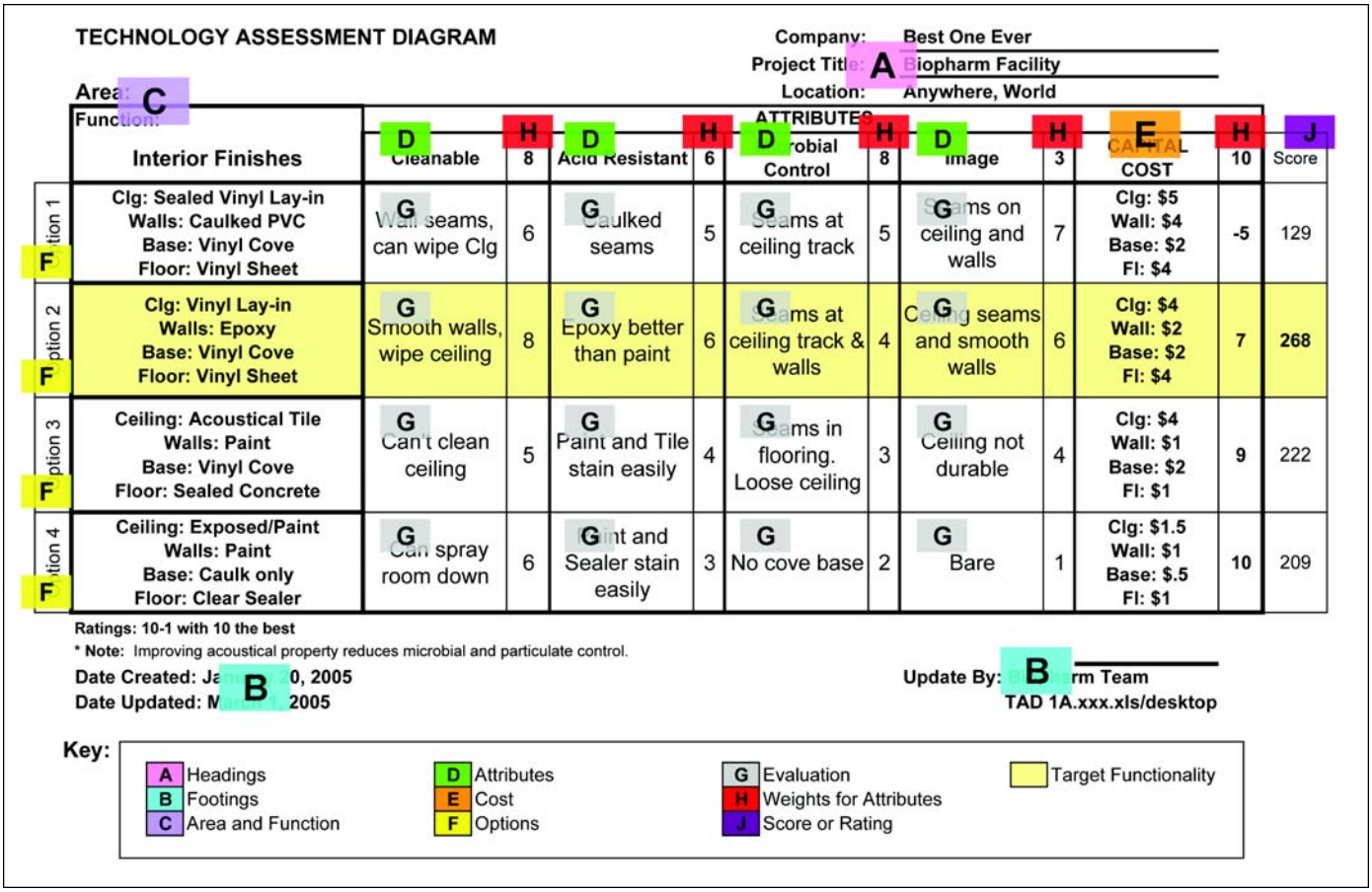

Figure 2. Project specific TAD template.

- Analyze Options by Attributes

6. Justify or alter the scope target functionality

This article uses the design of a new biopharmaceutical facility as the basis for examples given. This article illustrates how to use TADs. Your team can use them to establish the quality level of construction materials, systems, and equipment as well as to determine and document the functional and aesthetic aspects of project components.

1. Begin with your Project Specific Template

Insert your project specific information in the header and footer with information such as your company name and logo, project name and logo, project number, location and/or building name and number, page number, key to grading scale, author's name, date generated, revision date or log, and file name and path. Refer to Figures 1 and 2, Item A: Header and Item B: Footer.

2. Divide your Project into Parts

After your template is set up, begin dividing the project into areas, divisions, categories, or items to be analyzed. Next, identify the area or item being evaluated. For a facility design, a TAD can be used to evaluate the physical parts and systems for your proposed facility. The planned facility could be divided into physical parts such as structural systems exterior building walls, roofing, doors and windows, casework, landscaping, signage, and interior materials, and room finishes by area, robotics, processing equipment, or cooling towers. It also can be divided into building systems, such as automation, unit operation integration, power, emergency systems, water and other utility systems, chemical storage, chemical distribution, waste treatment, and security systems. Another division could be functions such as sampling, warehousing, maintenance, or training. In other words, your imagination and your needs are the only limits to its application. Examples of possible areas and functions are shown in Table A.

Enter both the area and the function to be analyzed. Refer to Item C in Figures 1 and 2. After the main parts, areas, and processes are identified, construct a TAD for each.

3. Identify Attributes for each Part, Area, System, or Function

Make a list of attributes that apply to each of your project divisions, categories, or sections to be analyzed. Examples of attributes are:

- Appearance
- Chemical Resistance
- Cleanable
- Code Requirement
- Company Standard
- Constructability
- Image
- Life Expectancy
- Maintainability
- Match Existing
- Reliability
- Security

Site Areas	Building Areas	Systems	Equipment
Roads and Parking	Manufacturing	Purified Water	Fermenter
Central Utility Building	Laboratory	HVAC	Boiler
Administration Building	Administration	Lighting	Cooling Tower
Production Building	Packaging	Fermentation	CIP Skid
Shop and Warehouse	Receiving	Communications	AHU's
Building G	Mechanical Support	Security	MCC's

Table A. Examples of areas and functions (Item C).

- cGMP Requirement
- Delivery Time
- Durability
- Ergonomics
- Expandibility
- Flexibility
- Service Support
- Size
- State of the Art
- Spare Parts
- Training Need
- Upgradable

Note: Attributes can and will differ from physical part to physical part, system to system, or function to function.

For each specific project part, area, system, or function being diagrammed, enter the most important attributes as column headings. Refer to Item D in Figures 1 and 2. Each column becomes an attribute to be evaluated. Cost is always the final attribute and usually the most important. Refer to Item E in Figures 1 and 2. Operating, replacement and capital costs can each be a separate cost attribute. Note: Attributes can be whatever is important to the team for each specific project component or category.

After attributes have been assigned, they should be weighted with more points assigned to the more important attributes, in preparation for analyzing the options later. Note: If your team decides to use Kepner-Tregoe® Matrix or K-T Analysis,[4] then there is an additional step at this point to determine which attributes are essential (must haves) and which attributes are desired, but not essential (wants). Kepner-Tregoe® (K-T) Analysis is a methodology for identifying and ranking factors critical to a decision. See Table B for the basis steps in K-T Analysis.

4. Further Define your Scope by Developing Scope Function Options

A TAD is a spreadsheet which charts functional or physical options. These options are identified and recorded on the assessment diagram. This data is gathered through interviewing users, holding group brainstorming meetings, referencing documents such as your company standards or planning documents such as P&ID's, or from viewing the area, the system, or activity in actual operation.

Brainstorm options, then list the different options in the far left column. Refer to Item F in Figures 1 and 2. Options may then be sorted, usually with the most extravagant solution at the top and the most utilitarian option at the bottom. Then number the options for ease of discussion.

Select target functionality. This will be the option that is either covered in the budget, the company standard, or the least (lowest) option that appears to meet the project and user requirements. Note: The team may need to evaluate all options before determining the final target functionality.

5. Evaluate and Analyze your Options

Cost options - before analyzing the options as a whole line item, price each one. Determine the total cost of an option if possible. If the options are not yet designed, then price a unit of that option. If total capacity, quantity, size, or area is unknown, then use unit prices that can be easily compared. For example, for physical items, one could price units such as per Square Foot (SF) or per Linear Foot (LF), per ton or per one lot of a determined number of items, such as 100 pieces.

Select and implement a ranking system. Either subjective or objective scales may be used. Whether your team uses a subjective or an objective scale, care should be taken to use an even number of rankings so that the team must determine if something is above or below average. An odd number of rankings allows the team to choose the middle ranking and thereby "sit on the fence." A subjective scale uses rankings such as low, medium, high and highest or poor, fair, good, and excellent. Note: The grading scale for different attributes may vary in a subjective ranking system. Also, subjective rankings may be reversed on different attributes. A low ranking may be good for one attribute and bad for another. It is easier to score a subjective scale, if numbers are applied to the ranking. In other words, **low** could equal 1 (or 10), **medium** could equal 4 (or 7), **high** could equal 7 (or 4), and **highest** could equal 10 (or 1). So, if you have a reverse scale, be careful that numbers have been properly assigned before adding the total score.

It is difficult to remain objective, especially when a decision impacts you, your team, your facility, and your company. One way to take some of the subjectivity out of the equation is to use an objective ranking system. An objective scale uses numbers for ranking. Just remember to use an even number of numbers. An even number of choices requires the ranking to be more one way, either better or worse, than the other. In other words, you cannot select the middle number, because it

	K-T Analysis	Technology Assessment Diagram
1.	State the Purpose	Separate Project Scope into Parts
2.	Establish Objectives	Establish Requirements or Attributes
3.	Classify Objectives by MUSTs and WANTs	Explore Options
4.	Weigh the WANTs	Assign ranking Weights to the Attributes
5.	Compare Alternatives	Analyze Options with Weighted Scores
6.	Choose the Best Course of Action	Determine Target Functionality

Table B. Comparison of steps in K-T Analysis vs. a TAD.

isn't there. One to 10 is the most common scale used. This author recommends the use of an objective ranking system, such as K-T Analysis.[4,5] A comparison of the step descriptions for K-T Analysis and the steps in utilizing a TAD are shown in Table B.

In order to perform an evaluation with K-T Analysis, one must first identify the items that are must haves. Refer to Step 4 in Table B. The must haves are absolute items that are required no matter what. Therefore, the option will either meet the criteria or not. If the option meets the must have attribute, it is a yes and remains in consideration. If the option does not meet the must have requirement, then it is rejected and no longer considered. If an attribute is not a must have, then that attribute becomes a want, or a desired but not necessary item. (Refer to Step 5 in Table B.) The want attributes are then ranked on a scale of 1 to 10, with 1 low and 10 high. The rankings are multiplied with the weighted score of each attribute and the scores are tallied. The highest score wins.

Information blocks on the TAD can be analyzed with the K-T Analysis or another objective ranking system. The evaluation can be more objective using attributes where actual numbers can be applied, such as GPM, cost data, ROI, years of life expectancy, light reflectance, or assigned points for a given range, etc.

Assign a ranking (1-10) to each block where an option intersects an attribute. Note in our completed TAD example shown in Figure 2, not only is the ranking shown, but an explanation is written in each block. The explanation can help the team remember why and how the rankings were applied and identify the justification for those choices.

Analyze the evaluated options by multiplying the option ratings with the attribute weights. Enter the score for each scope function option. Using a TAD, the team can immediately see the benefits, restraints and cost impact of options for each component that was analyzed.

6. Justify or Alter the Scope Target Functionality

Your target functionality option on each individual TAD should coincide with the option gaining the highest score. If they are not the same, then check all items on both the original target function option and the final preferred option with the highest score. Verify that you have selected the least scope that will meet your specific project requirements. If the highest score is the least scope that meets project requirements, then change your target functionality to that option. However, take time to justify this change. Take extra care in this step to ensure that your subjective self does not overrule your objective analysis.

Benefits realized from the use of TADs are:

- Communication – as a tool, it is one of the best ways to convey design requirements to the owner/user and to convey his/her needs and choices to the design team - especially when used in conjunction with graphics, sketches, manufacturer's specifications and catalog cuts, photographs, samples, or color and material boards.
- The full team can easily view the same data in a logical format
- Documented basis of the team decisions – the TAD serves as a reminder to the design team of the project requirements, including quality and cost of the components.
- Documentation of target scope/functionality and deviation from that scope – the TAD traces the decision-making process and makes the team justify deviations from the original target functionality.
- Basis of review and control of changes during construction and in future alterations can be used as a check of the construction estimate material content. The TAD document not only can help track scope changes, but also can show the impact of those changes on the project cost. One of the ugliest enemies of any project is scope creep that escalates the cost of the project. Scope creep can be caused by increasing size or quantity, by raising the level of quality, customizing the solution, or by chasing that illusive special image.
- Aid to cost control of project elements.
- TADs can be used later in value engineering exercises. They can remind the team of options that have already been evaluated and hopefully save time by keeping the team from repeating decisions that have already been determined.

The major benefits derived from this method are scope clarification, efficient programming, promotion of teamwork, and gaining the buy-in of all stakeholders. An added benefit is that the graphics are great for presentations, which are often necessary to secure financial appropriations.

Summary

In summary, the information contained in your TAD should give a clear understanding of what is included for components of the project scope. This decision-making method removes much of the subjectivity and replaces it with objective reasoning. An important team goal to remember is to design to meet requirements and remain within the budget. TADs help do this and more. They serve as a graphical tool to track the decision-making process and to control material, equipment and system design, automation, or other quality upgrades.

This tool, especially when used in conjunction with graphics, sketches, catalog cuts, photographs or color and material boards, is one of the best ways to convey design requirements to the owner/user, and to enable them to convey their needs to the design team. Size or quantity is usually controlled with review of plan view drawings, elevations, and building sections. Layouts give square footage of areas and relative equipment size and their quantity, which are generally used as a basis for cost analysis of the project. However, floor plans do not indicate the quality of materials and equipment. A

change in equipment model number, software, custom design, material, or finish can greatly affect the overall cost of the project. TADs are useful for defining scope and target functionality, communicating the impact of change, facilitating and documenting group decisions, and for controlling project scope and costs.

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About the Author

Mary Ellen Craft received both a Bachelor of Architecture and a Bachelor of Applied Arts, which is a shared topic major in interior design, art, and architecture, from the University of Kentucky. She is currently a Project Director in Fluor's Life Sciences Group. She is experienced in design management for biotech and pharmaceutical facilities in the U.S., Ireland, and Spain. Craft has developed and delivered multiple seminars on project management and technical training for the pharmaceutical industry. She has been a course leader and speaker for ISPE at the Chapter and international level. Craft has also spoken at management meetings for several pharmaceutical manufacturers. She formerly served as president of the ISPE Great Lakes Chapter, and currently chairs ISPE's Editorial Committee and Pharmaceutical Engineering Subcommittee. She is also a member of the Pilot Journal Task Team and lead author of the regulatory chapter in the Laboratory Baseline® Guide now under FDA review. Craft is a Registered Architect, and a certified Project Management Professional (PMP). She may be contacted by telephone at 1-864/281-4605.

Fluor Enterprises, Inc., 100 Fluor Daniel Dr., MS-C202D, Greenville, South Carolina 29607 USA.

This article presents ways to improve documentation structure incorporating requirements traceability and risk analysis.

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Practically Validated – Maintaining the Tested Baseline

by David Paspa

This article offers some simple and specific ways to improve documentation structure and incorporate requirements traceability and risk analysis. It provides tools that can be used to improve the level of compliance to perform the job correctly from the beginning.

The techniques defined can be used for any type of validation project including computer validation, equipment qualification, and process validation.

For many, validation is still a grey area and there are good reasons for this. Pharmaceutical and biotechnology are diverse industries comprising:

- many different and sometimes complex processes
- most engineering and scientific disciplines
- sophisticated regulations that govern the manufacture of products which are scattered throughout a variety of sources and often require a fair amount of interpretation

It is probably impossible to find a single person who truly understands all of the chemistry, engineering, and governing regulations related to drug manufacturing. To complicate this further, manufacturing companies often sell to multiple international markets where regulatory expectations and enforcement varies.

Validation

The term ***validation*** itself is poorly understood at best. One classical definition is:

> *"…to provide documented evidence which provides a high degree of assurance that systems, operated within their specified design parameters, are capable of repeatedly and reliably producing a finished product of the required quality."*

That's all well and good, but what should people actually ***do***? Unfortunately, the term and its definition do not give specific direction on the physical tasks to be performed. Perhaps for this reason, it is often left until later in the project planning process. Sometimes it is just an afterthought, applied for the wrong reason – because of fear of the regulators rather than as a means of self-assurance.

Qualification

Many of the same comments that have been made about validation also can be made about ***qualification***. While the term is a little vague, the physical activity that people actually ***do*** is ***testing***.

What's the difference between qualification and testing? Qualification involves testing systems to demonstrate they do what they are supposed to. In other words, Qualification ***is***

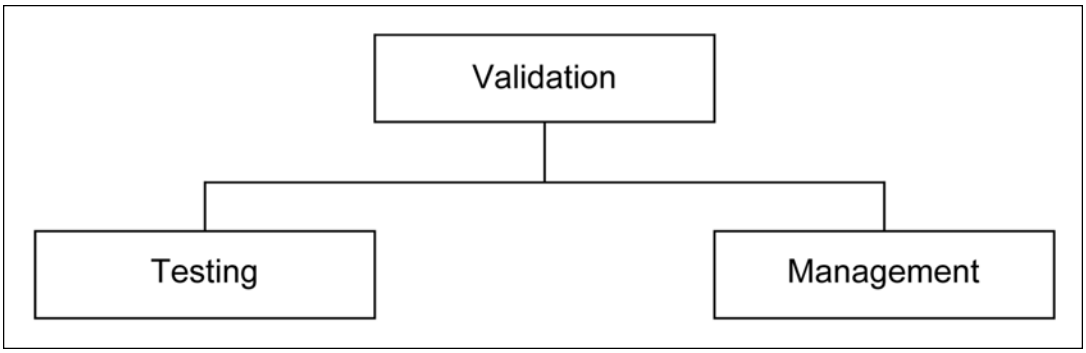

Figure 1. Validation = Testing + Management.

testing.

Testing has meaning only when systems are tested against what is required of them. It must first be stipulated "*this is what it is supposed to be"* and then tested to show "*this is what it is."* There is no point testing to say "*it is what it is, which must be what it is supposed to be*" and yet this approach is still used frequently.

An example would be to say "Test that chair." It would be difficult to make a sensible test because there is uncertainty as to what to look for. However, if it was first specified that "This chair is designed to support the weight of an 80 kilogram/176 pound person," then it would now be possible to devise a rational and quantifiable test that can measure whether the design intent has been accomplished.

So, a qualified system is simply a tested system.

Qualification = Testing

In order to test anything, in any industry or context, the requirements must be defined first. This is a fundamental and important point. It is not meaningful to test something unless it has a specified requirement.

Why Test?

When a system is tested a ***tested baseline*** is achieved. For a given set of inputs, the system has a predictable response and provides a known output. Any test result for that system is valid over time provided the system does not change.

Once a system has changed, the test may or may not be valid. A judgement based on the nature of the change would need to be made to determine whether the test results were still considered valid or whether the system would need to be re-tested to find out if that same result is received the second time around. The change may be such that a new test needs to be devised to demonstrate some new system requirements or attributes.

It requires the investment of significant time and money to achieve a tested baseline through a rigorous program of specification and testing. Therefore, it makes sense to protect that asset by ***managing*** the system so there is confidence that the tested baseline is current over time.

In order to achieve this, all aspects of the system need to be controlled, including:

- the physical components of the system
- the people who use and maintain the system
- associated information and documents
- ongoing changes made to the system, both planned and unplanned

To summarize, an activity-based definition of validation consists of *testing* and *management* to ***maintain the tested baseline***.

Testing and management are equally important - *Figure 1*. A tested baseline that is not managed quickly becomes outdated. Procedures that are implemented to manage a system that hasn't been properly tested, do not improve the assurance of the system response for a given set of inputs, regardless of management efforts.

The tested baseline should be thought of as a physical thing, such as a ball. Don't drop it! The majority of the discussion that follows proposes ideas and techniques that can be employed to develop and maintain the tested baseline. The format of the tested baseline and the way in which it is created are critical factors in its ongoing maintainability. The ideas presented are intended to promote and facilitate this maintainability.

Most "validation" projects are in fact "qualification" projects. There is often very little management of the *tested baseline* that is handed over at the end of the project. As a result, the tested baseline is nearly always compromised with the passing of time resulting in systems "falling out" of validation. This usually results in the whole qualification exercise having to be repeated.

To avoid this situation, it might be useful to focus on the activities being performed. Rather than describing a system as "validated," as if it were a property of the system, it would be better practice to say the system is "under validation." This better indicates there is a method in place to continuously manage and control the system in an ongoing way to keep the tested baseline current.

It is interesting to note that testing and management are commonly understood activities which have been performed by humans for thousands of years to achieve some quite remarkable things. When good science and engineering and good project management are used, validation is nothing new and nothing extra.

Now, in order to formulate meaningful tests, there ***must*** be pre-determined requirements. There must be a specification that says "*this is what it is supposed to be"* and then a corresponding test that shows "*this is what it is."*

- If there are no specified requirements, there can't be meaningful testing.
- If there are no meaningful tests, it is not possible to achieve a tested baseline.
- If there is no tested baseline, there is nothing to manage.
- If there is nothing to manage, the system can't be "under validation," i.e., under control.

Therefore, it can be deduced that requirements are fundamental to validation. And yet, it is still common to find "validated" systems with no definition of what the system is supposed to do.

Requirements

When writing requirement specifications, it is crucial to remember the document is not the job. The purpose of the exercise is in fact not to write a document, but to convey information to the reader of that document so they understand what is required. *The document exists to be read, not written*.

To facilitate understanding, it is good practice to:

- use simple short statements

- keep each premise separate
- stick to the facts; less text gives rise to more understanding

One approach to writing specifications is to number individual requirements to aid discussion and traceability. This is the same approach used in numbering equipment, like valves and pumps, with a unique tag number - *Table A*.

Unique, clearly identified, and testable specifications provide greater understanding to all. There is no point in having a specification or requirement if it cannot be tested in some way. How can it be confirmed as even having been delivered by the supplier? In fact this does not just apply to validation in the pharmaceutical industry. Regardless of the industry, at some point suppliers expect to be paid for goods delivered or services rendered. It is common sense to assure oneself that the product is what was wanted and is what it purports to be before it is paid for. This is just prudent contract and financial management.

One way to ensure requirement numbers are unique in this way is to use a dynamic outline numbering field code to generate the serial number. These are available in most word processing programs. When the document is complete, these dynamic field codes can be unlinked which converts them to static text. From that point on, each reference number is just plain text and is inexorably linked to the corresponding requirement text. The reference number can then be safely used to refer to a requirement from outside the document with confidence that the reference cannot be broken.

New requirements can still be added if there is a change to the document and they take on the next highest unused serial number. Also, old requirements and their reference numbers can be deleted. Thus, the requirement reference numbers must be unique, but they do not have to be consecutive. Also, numbers may be missing if superseded requirements have been deleted. Therefore, to be able to find a specific number and therefore a specific requirement, a ***Requirement Reference Number Table of Contents*** is used to list all of the numbers in order and bookmark its page - *Table B*.

V-Model

The V-Model defined in the Good Automated Manufacturing Practice (GAMP® 4) Guide provides a structured framework for specifying requirements and then testing them to demonstrate they have been correctly delivered. In its simplest form, it defines the phases shown in Figure 2.

However, design is a continuous process. At best, the V-Model is a quantum approximation of what is actually going on during the design continuum. While requirements are "lumped" into User Requirements Specification (URS), Functional Specification (FS), and Design Specification (DS) documents and drawings, the real-life process is actually two steps forward and one step back (often with a side step thrown in for good measure). Even agreeing and documenting the user's requirements in the URS can be a difficult task when there are a number of stakeholders involved.

Keeping that in mind, how does the V-Model assist in the design process? The advantages are:

Ref	Requirement
U12	Purified Water shall have a microbial load of £ 0.1 cfu/mL.

Table A. Requirement reference numbers.

Table B. Requirement reference number table of contents.

- It clearly separates requirements which have a different purpose.
- It clearly separates requirements which have a different importance.

User Requirements

Not all of the design information for a project is of the same importance. The user requirements are the most important because they define what the process requirements are. The "process" may be a production process to manufacture a pharmaceutical product or may be a business process such as change control. Regardless of what gets implemented, it is this "process" that must be delivered by the designer. These requirements are fundamental to the user's business and are not-negotiable as far as the designer is concerned.

Any parameters which are critical to achieving the user's desired level of GMP should be clearly identified in the URS.

Functional Requirements

The second level of importance is the functional requirements. These define ***what*** has to be done to implement the process, but at this point don't stipulate how to do it. This is also referred to as ***conceptual design.***

These operational requirements are often important to the client, but less so than the user requirements. For instance, if another concept which saves time and money was proposed, the client may accept the alternative to what they may have stipulated they initially wanted because it is good

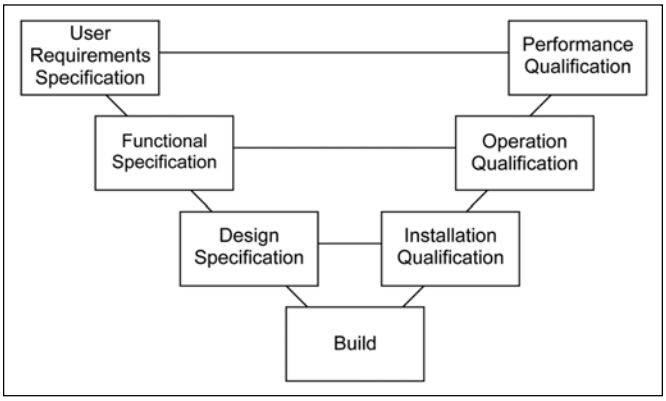

Figure 2. GAMP V-Model.

Parent	Ref	Requirement
U12	*F201*	The system shall maintain a line velocity of 1 m/s in all pipework.

Table C. Functional requirement reference numbers and traceability.

Parent	Ref	Requirement
F201	*D177*	The supply pump shall be rated to deliver 120l/min at 5 bar.

Table D. Design requirement reference numbers and traceability.

practice to save time and money.

Note the functional requirements define what has to be done, but not how to do it. There may be multiple design solutions to implement the operations required, but these are not determined at this level. Try to focus only on what has to be achieved.

The FS should comprise unique, clearly identified, and numbered requirements similar to the URS. In addition, the functional requirements should be traceable to the higher level user requirements. This parent/child relationship or hierarchy is inherent in the V-Model from URS to FS to DS - *Table C*.

Notice in the example above that the cross-reference to the parent specification requirement has been placed right into the child specification document. This is a useful tool that can be used to ensure all parent requirements are addressed in lower level design documents.

Design Requirements

The design requirements are the third and lowest importance requirements. For the first time, a definition is provided specifying ***how*** the operations identified in the Functional Requirements are going to be implemented. The design requirements are the most negotiable and offer great opportunities for time and cost saving.

The same format and cross-referencing methodology can be used to define these requirements which are referred to as ***detailed design*** - *Table D*.

Design requirements talk about how the functional requirements will be implemented using physical objects. They define what objects will be used and specify their configuration and orientation.

Software Design Specification

For a software project, the DS should talk about software structure, software modularity, data definition, and data flow. In this case, the design specification is especially crucial because it is the only physical embodiment of the structure of the code. A mechanical design has piping, pumps, and valves, and it can be physically seen how the design has been manifested in the real world. In a software project, there is nothing to "see," and hence, the design specification is all the more crucial.

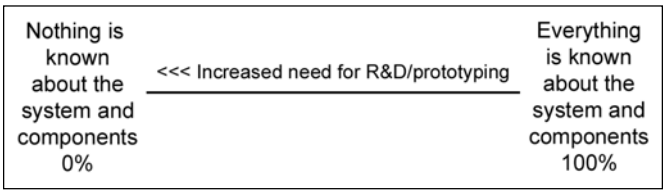

Figure 3. Design development.

Prototyping and R&D

Sometimes it is essential to prototype or pilot the design before starting to write the DS. Prototyping is an excellent design tool, but problems can arise when considering the wasted time and effort writing down things that may never be used. Does the prototype design have to be documented? It is highly likely the design will change dramatically as a result of the prototyping exercise.

To address this issue, consider what is involved in specifying anything. Key elements are education, research, consultation, experience, assumptions, etc. The reality is that all of these things are the sum total of people's trial and error experiments over time. A vast amount of what is known today was found out by just trying. Thus, R&D and prototyping are in fact usual and valid activities to help define a specification (i.e., a bit more trial and error). Design does not just include writing a document in a word processor. All kinds of activities and types of information can be described as "design," including drawings, calculations, models, lists, data, etc.

The amount of up front documentation without R&D effort depends upon the certainty and amount of knowledge the designer has of the final design. If nothing is known, it is probably a good idea to spend some effort playing around with components to learn how they behave before starting a formal documentation process. If a lot is known about the system, usually because the designer has done something similar before, then the documentation process can be started at the very beginning with a high level of confidence that the work will be useful.

For process applications, R&D from pilot plant or laboratory batches may be the only way to identify and characterize the critical process parameters. The process design should take into account these critical parameters and mitigate their risk to the product or process through a well thought out risk mitigation strategy. The knowledge gained from this R&D exercise allows resources to be directed at managing and testing these critical points in accordance with a sensible, risk-based approach.

While it is good practice in any R&D effort to record what was done to retain and reuse the knowledge gained from the experiments, it is not practical to try to formally specify up front all aspects of the prototype design because they are just not known.

Separating Information

Many organizations cannot or do not distinguish between the differing levels of requirements and priorities. It has already been established that when trying to convey what is important to the reader it is important to keep things short and separate. Therefore, it is of the greatest advantage to keep the design requirements (the most negotiable requirements)

Ref	Parameter	Risk Classification	Justification	Failure Mode	Effect	Probability of Detection	Risk Priority
F371 F372 F373 F219	Purified Water conductivity directly after the RO/EDI plant.	High	Direct indication of current water quality	Input C028 under-range or over-range	Standard PLC function detects bad input and raises alarm. PW no longer available to users.	High	Low

Table E. Risk assessment.

separate from the process requirements (which are not negotiable). Simply by calling these varying requirements different things conveys important information.

The amount of information put into the URS depends on the project execution model and the purpose the URS is intended for.

- Issue the URS to a supplier – in this case, it is important that the supplier is told enough to ensure clients get what they want. This would comprise the process requirements and also identify any functional and design constraints that the supplier must work within; i.e., the client is not giving the supplier a blank sheet to start from. Sometimes a client can have a supplier do the work of writing the URS on their behalf, but the client must still approve the document and take responsibility for its content.

- Use the URS as part of client's in-house project – in this case, just include the process requirements. Any functional constraints and design constraints can be directly included in the FS and DS documents that the client controls.

Whatever the approach, it is important to note that information can be conveyed to the reader simply by the structure of the documentation.

Document Modularity

It is advantageous to keep documents modular and use multiple "buckets" when following the V-Model. Using multiple buckets also minimizes the scope of a change. For example, if there was a detailed design change, the design specification would need to be updated, but the user requirement specification and potentially the functional specification documents would not need to be changed. In this example the IQ on the affected component would presumably need to be updated, but the OQ and PQ may be unaffected.

Time Dependency

An interesting question to pose is "Where is the time axis on the V-Model?" It isn't explicitly drawn on the diagram, but the model does infer precedence from left to right. There is precedence of document approval down the left hand side of the V and precedence of order of testing IQ, OQ, to PQ going up the right hand side. This precedence must be adhered to because it is a regulatory requirement.

A fast track project demands an early start on all activities, design and construction included. However, an ideal quality-based project, would demand a late start to ensure a succeeding phase wasn't started unless the preceding phase was reviewed and approved. The reality is that most projects demand a compromise between these two scenarios to manage what is considered an acceptable level of business risk. Similarly, nowhere does it say that succeeding documents in the V-Model can't be started before preceding documents are complete, but the level of business risk needs to be managed. However, the precedence of document approval and testing must be adhered to.

Legacy Systems

These are really the ultimate in project fast tracking. No sooner are the documents started than the system is already built; i.e., time is effectively compressed to zero. So how does the V-Model apply to a legacy system? The exact same strategy and documentation approach can be implemented for a legacy system as for a prospective new system. In this context, a legacy system is considered to be any system which already exists.

In these cases, it may be possible to justify a reduced amount of testing as part of the risk analysis if pertinent historical data is available for normal operation of the system allowing a focus on the system's abnormal condition handling to demonstrate robustness and reliability. Legacy system qualification offers an ideal opportunity where a sensible, risk-based approach can dramatically reduce the workload.

Risk Assessment

The unique reference numbers for each requirement can continue to be used as part of the risk assessment process. This risk analysis is usually performed during the conceptual design of the project to "design out" high-risk situations in the first place. The designer's goal is for the true quality assurance and validation of the system to be intrinsic in the system's design, rather than being in some associated documentation on a bookshelf.

The results of the risk assessment also can be used to identify those requirements which will not be formally tested due to a determination of risk to the process or system. There are many methods available to perform risk analysis, such as according to a calculated *risk priority* as defined in GAMP *4*.

Typically, requirements can be grouped according to system parameters and their failure modes. This can be used as part of an argument to reduce the scope of abnormal condition testing by justifying why certain test cases do not need to be executed. For instance, it may be stipulated that only High *Risk Priority* failure modes need to be tested and these might relate to parameters with a High *Risk Classification* and a Low *Probability of Detection*. GAMP suggests the use of a

Parent	Ref	Requirement
	F200	The system shall do something.
U12	*F201*	The system shall maintain a line velocity of 1 m/s in all pipework to limit bacterial growth.
U13	*F202*	The system shall do this.
U27		
U10	*F203*	The system shall do that.
U27		
U41		

Table F. Requirement cross-referencing.

medium level risk priority as well.

There are many risk assessment approaches available, also commonly looking at impact of a failure, likelihood of failure, frequency of occurrence, residual risk after corrective measures are put in place, HAZOP, HACCP, etc. The Internet is an excellent source of information. At the end of the day, a simple approach is often the most sound.

Requirements Traceability

Requirements traceability refers to the process of tracking higher level requirements down through the lower level requirement documents and even across to the associated test documents.

For instance, why is a certain pump put in a certain position? Or why has a certain piece of software been purchased or developed? Lower level design elements are included because of a higher level functional requirement. Similarly, functional requirements come about because of higher level user requirements (i.e., process requirements). It is prudent to check that all of the higher level requirements have been addressed by lower level conceptual and detailed design elements and make sure that nothing has been overlooked.

Requirements traceability is usually addressed by cross-referencing the section heading numbers in two or more documents in a table or matrix. Unfortunately, this is a retrospective method. Also, using section headings is perilous because when someone updates the document, they can forget that inserting a new section will automatically renumber the existing sections in the document and place the Requirements Traceability Matrix (RTM) out of date.

A prospective method of requirements traceability can be used as a useful tool to ensure that all requirements have been addressed as the documents are being written, not after they are complete. The unique reference number applied to each requirement in the specification, as shown previously, can be used to provide the vertical requirement traceability down the left-hand side of the V-Model.

A functional specification might look something like that shown in Table F. The document has two columns on the left hand side in front of each written requirement; a parent requirement reference number, and a unique child requirement reference number. Requirement reference numbers might be F1, F2, F3, F4, etc. up to, say, F203. Similarly, the user requirement specification numbers might be U1, U2, U3, U4, etc. up to, say, U50. When writing the functional specification, the text U12 would actually be written against the corresponding functional requirement F201 to demonstrate the link between the higher level URS. Similarly, U13 and U27 might correspond to F202. U10, U27, and U41 might correspond to F203, etc. All requirements F1, F2, F3, etc. and U1, U2, U3, etc. can be cross-referenced in this way. For some reason, F200 may not directly relate to a parent requirement.

The child requirement reference numbers in the document must be unique, but may cross-reference with multiple parent reference numbers. Thus the requirement traceability information from a higher level specification is put right into the lower level requirement specification as it is being written. This provides traceability down the left-hand side of the V.

Requirements Traceability Matrix

Tabulating the above information gives rise to an RTM. This provides an overview of the traceability put into the requirements specifications. This table can be quickly generated from the requirements specifications many times while writing the specifications to help close out the cross-referencing to make sure all high level requirements have been addressed in some way.

Sometimes lower level functional or design requirements are there for associated design reasons or for consequences from the parent specification which have not been explicitly stated. In these cases, the lower level requirements do not map onto a higher level parent requirement and a justification can be provided in the RTM as to why that is so. An

	UNRF	JUST	F200	F201	F202	F203
UNRF			X			
JUST			A			
U10						X
U11	X	B				
U12				X		
U13					X	
LEGEND: A: Functional requirement added due to existing operational constraint of target system. B: User requirement refers to project schedule and not an operational technical requirement.						

Table G. Requirements traceability matrix.

Parent	Ref	Test Method	Expected Result	Actual Result	Pass / Fail (Initials / Date)
F201	*T1*	Confirm that the system maintains a line velocity of 1 m/s in the tank outlet leg pipework by performing the following method: 1. Attach a calibrated flowmeter at the point... 2. Ensure all user valves are open. 3. Measure the flow rate over a period of... 4. Attach a trace of the trended flow rate over the measurement period.	The independently measured line velocity is at least 1 m/s at the tank outlet leg.		
F349	*T2*	Perform the following tests at the tank inlet line: 1. Attach a calibrated flowmeter at the point... 2. Ensure all user valves are closed. 3. Etc.	The line velocity is at least 1 m/s at the tank inlet line.		

Table H. Test protocol format.

excerpt of an RTM is shown in Table G.

The RTM is useful evidence to contribute to the ***design review*** process by demonstrating that all requirements have been addressed. Note that it only contributes to the review process because it doesn't assure that the design sensibly or completely meets the requirements from a technical point of view. Technical design reviews which ***test the design*** to ensure it correctly implements the intended parent requirements and complies with applicable statutory and GMP regulations still need to be performed.

Test Protocol

Once the requirement specifications have been written and approved in accordance with the appropriate design and document reviews, the issue of testing documents to demonstrate these requirements can be addressed.

Test protocols should contain the following information for each test:

1. A ***test method*** needs to be devised that will demonstrate that each requirement has been met. This method should be sufficiently detailed so that someone could repeat the test at a later date as it was first carried out. However, too much detail tends to become unnecessary and even erroneous, causing test failures due to incorrect test documentation. Over-specifying the test method also can lead to a blinkered approach by the tester during testing. Sometimes a compromise with some "monkey" testing is useful to have the tester use their initiative to try to "break" the system in question by performing a series of actions which could not have been foreseen and formulated when the test protocol was written.

2. An ***expected result*** should be stipulated which defines the ***acceptance criteria*** for the test. This should be detailed enough so that the tester can clearly identify a pass or fail condition when the test is executed.

3. An area where the tester can record the ***actual result*** should be provided. These are the observations of what actually happened during test execution.

4. There should then be a clear indication of the ***test result.*** This should be an unambiguous statement of *pass* or *fail* rather than a simple tick or other mark which could have ambiguous meaning.

5. There should be space for the tester to provide an ***initial*** and ***date*** for each test.

Table H shows the tabulated format.

There should be a ***witness*** of the tests and the test environment. The witness needs to supervise the testing process and needs to have final signoff on the results, especially for critical tests. This verification by an independent witness is performed in accordance with GMP regarding critical steps in a manufacturing process.

The witness does not need to sign off on each and every single test, but can sign the protocol a page at a time or even just once on the front page for the overall document.

Test Traceability

Test protocols can be structured in a similar way to requirements specification documents with a unique test reference number that is linked to the parent document requirement number. Sometimes one requirement must be demonstrated over a number of tests or a single test may address multiple requirements. An RTM can be generated in the usual way to summarize these relationships.

The V-Model is usually drawn with dashed lines from the qualification steps back to the corresponding specification steps. Usage of the requirement reference number as a test reference number provides these links on the horizontal axis of the V-Model.

A design change can quickly be traced from the design specification across to the corresponding tests using the requirement and matching test reference numbers. Redrafting and repeating the affected tests facilitates the tested baseline being re-established in a very transparent way.

Test Data

Associated data collected during execution of the tests is used as evidence to support the test result. This data should be cross-referenced to the test numbers that were executed to produce it.

Summary

Documents and their contents should be kept modular in accordance with the V-model. Use of requirement reference numbers aids requirement traceability up and down the vertical axis of the V-model as well as test traceability along the horizontal axis of the V-model.

By carefully structuring specification and test documents and by using reference numbers, systems can be put in place to promote the establishment and maintenance of the tested baseline.

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About the Author

David Paspa, BE (Hons), is Operations Director at Synertec, a life sciences consulting company with offices in Melbourne, Sydney, and Singapore. He is a Director and Treasurer of the ISPE Australia Affiliate. He has worked in the pharmaceutical and biotechnology industries since 1990 on large and small projects for the manufacture of sterile and solid dose products, veterinary products, and APIs. His involvement has been in the areas of software specification, design, development, and commissioning with an emphasis on documentation and validation. Paspa also has been involved in process engineering activities, including plant modelling, throughput optimization and debottlenecking. He has worked as both a client and a supplier. He can be reached at david.paspa@synertec.com.au.

Synertec Pty. Ltd., 84 Johnston Street, Fitzroy 3065, Victoria, Australia.

This article describes procedures to test gloves, shortcomings of plastic glove behavior, and glove fixation. In addition, it presents a new impulse technique for the improvement of reproducibility and repeatability of a pressure decay test.

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Safe Access using Glove Ports – Facts and Fiction

by Johannes Rauschnabel, Albrecht Kühnle, and Kuno Lemke

Introduction

Barrier systems, such as aseptic isolators, Restricted Access Barrier Systems (RABS) and glove boxes are being used more and more in pharmaceutical production, research, and laboratories. The purpose of these barrier systems is to separate a process area from a surrounding environment – either to shield the process from contaminants coming from outside, or to shield the environment from hazardous products inside. If manual operator access is needed either during processing, for maintenance reasons, or for environmental monitoring inside the barrier, glove ports are needed.

The integrity of these glove ports is crucial for maintaining sterility of the barrier system. Therefore, frequent inspection of the glove ports is required. The FDA guidance for industry on aseptic processing[1] asks for "*With every use, gloves should be visually evaluated for any macroscopic physical defect. Physical integrity tests should also be performed routinely,*" while EC GMP [2] requires "*Monitoring should be carried out routinely and should include frequent leak testing of the isolator and glove/sleeve system.*" Thus, some kind of leak testing has to take place in addition to visual inspection.

Challenge

Glove leaks have many reasons: mechanical damage through contact with sharp equipment, tools or broken glass, which cause cuts in the glove material. Clamping gloves in mechanical installations very often results in holes that are less discrete and hard to detect. The most frequent types of leaks come from heavy use of gloves and aging. The commonly used glove material "Hypalon" has a layered structure, which tends to flake off over time, therefore causing precarious perforations of the glove membrane. The glove membrane do not only show elastic behavior, it also has viscous properties, especially if it is stressed by tension or mechanical load. These stressed areas have a reduced membrane thickness and are more sensitive to mechanical impacts. Membrane rupture is very often the consequence of over stressing gloves locally. Chemicals can have a similar effect: some are capable of reducing the tensile strength of the glove.

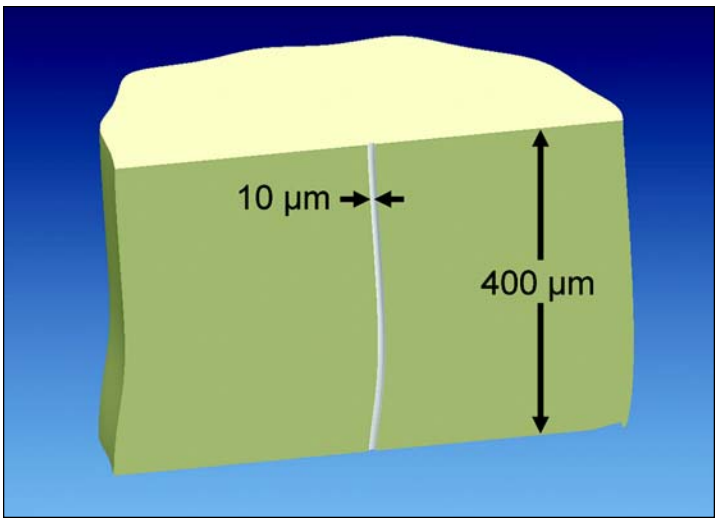

Figure 1. Proportions of a 10 μm leak in a 400 μm membrane.

Any type of leak should be detected with a physical glove testing procedure - at any position on the sleeve, cuff ring, or glove assembly.

The standard for operating isolator systems is to work with a second disposable glove (80% of all users)[3] – so that direct contamination is not very likely even in the case of a small leak. Additionally, in most isolator systems, an over pressure is applied inside barrier isolators, which prevents ingress of airborne contamination from out

side to inside. But germs are able to grow through holes – against any pressure level. Bacterial spores have a diameter down to 1 µm, while vegetative bacilli and yeasts grow to diameters of 10 µm and more. By above mentioned diameters, the acceptance criteria for a glove tester seems to be given. Figure 1 demonstrates the proportions of a 10 µm hole in a 400 µm thick glove membrane (~15 mil).

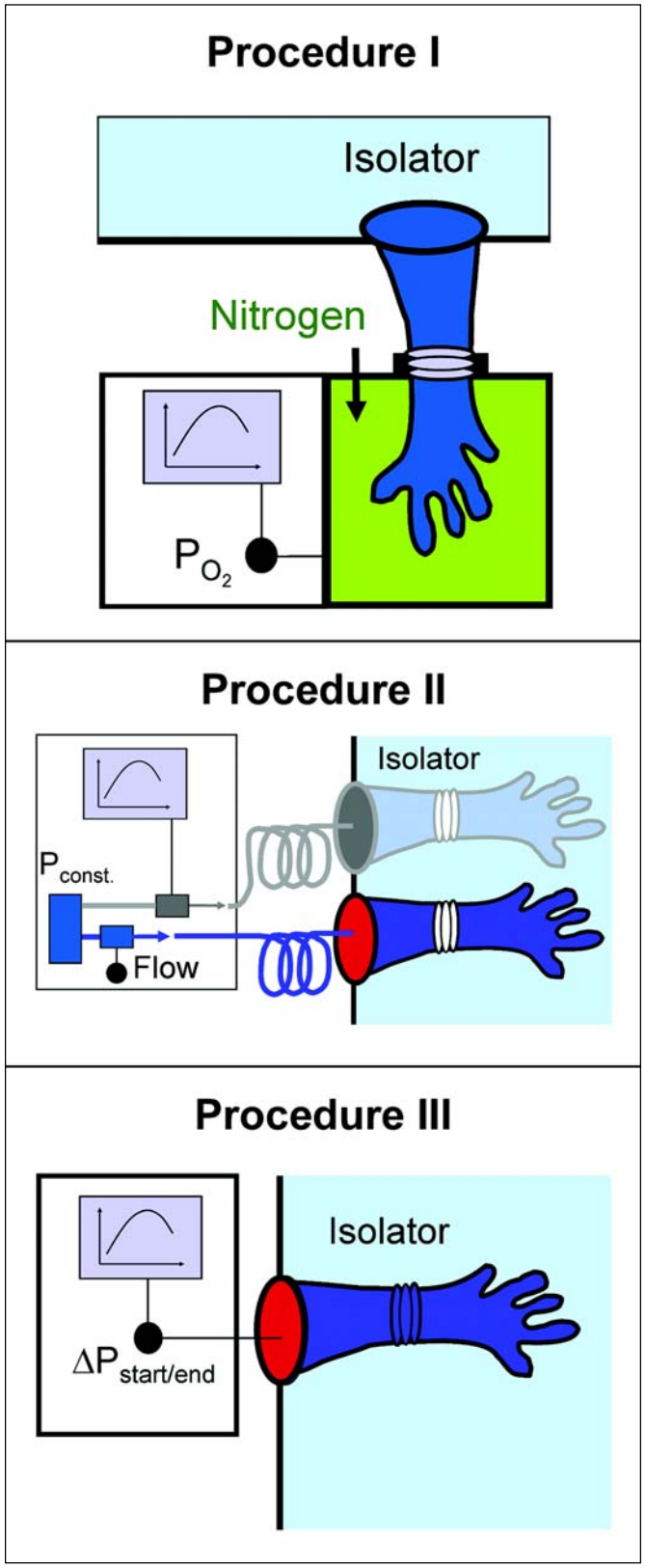

Figure 2. Procedures for glove testing applying pressure difference.

However, no existing physical test method is capable of detecting leaks in glove assemblies down to 1 µm diameter. What is worse: cuts of 100 micron scale may not be detected in every position of the glove assembly.

Existing glove test devices for the pharmaceutical industry apply different procedures utilizing pressure difference between inside and outside of the glove, including (I) oxygen measurement in a nitrogen chamber, (II) air flow measurement, and (III) pressure decay measurement - *Figure 2*.

Other techniques such as the bubble test, ammonia test, or Helium leak test are useful to detect the leak location, but do not give quantitative results, which help to decide 'passed' or not 'passed.' And conductivity measurement of a glove filled with electrolyte in a tub with distilled water can't be applied for in situ testing.

For test procedure (I), the glove is placed with a special cuff ring into a vacuum chamber, which is evacuated and filled with nitrogen. If there is a leak, air (containing 20% oxygen) from inside the glove leaks into the chamber, where a gas sensor measures the oxygen level. This level can be correlated to a leak rate. The procedure is sensitive due to high test pressure of 4000 Pa and is very accurate (acceptance criteria is an oxygen concentration of 500 ppm, which refers to an artificial 40 µm hole). Gloves can be tested during production, but the test is not able to challenge the complete glove assembly.

Test procedure (II) pressurizes the glove over a certain time at about 600 Pa. The air volume per time needed to compensate pressure loss by leakage is measured with a flow meter and correlated to a leak rate. Theoretical calculations come to a minimum acceptance criteria of 2 ml/min, which would correlate to a hole diameter of approximately 66 µm. In practical testing, this method can only achieve results down to minimum 100 µm diameter, but reproducibility is poor. The 'history' of the glove/sleeve assembly plays an important role (see below).

Test procedure (III) 'pressure decay' is the most common physical testing method with pharmaceutical isolators. According to the ISPE 2004 isolator survey, [3] more than 70% of responses apply some kind of pressure decay testing. In this procedure, a positive pressure expands the glove (assembly). Either directly or passing a certain pressure level, the measurement starts. After a certain time, the end pressure is taken. From the pressure drop, a leak rate can be calculated. The principle of this test is very simple and can be performed with a pressure gauge and a stopwatch only. But the downside of this procedure could be lack of reproducibility.

All these procedures take as a basis the perfect 'virtually new' glove, which always behaves the same way during measurement. But this is fiction and not reality.

During pressure difference testing, the following two parameters can not be kept constant: air volume and glove elasticity. Air is compressible, which has to be accepted and will not vary with other parameters kept constant. A glove is not a fully elastic system, but shows some plastic behavior. The glove expands non-proportionally to the pressure level

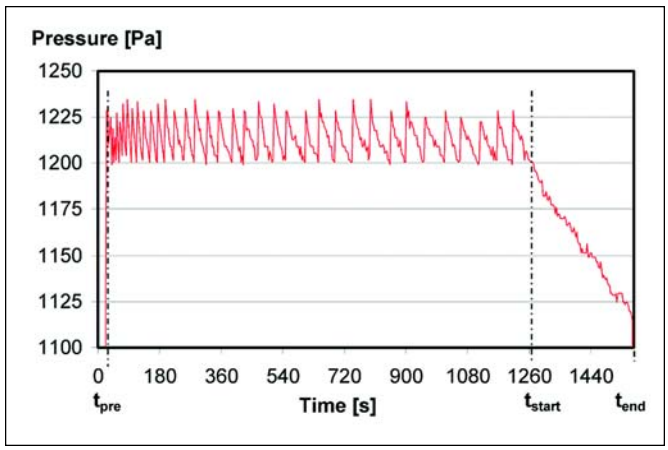

Figure 3. Measurement preparation utilizing impulse technique.

and does not keep its volume while keeping the pressure constant. This behavior is dependant on glove material, glove thickness, age, and history of the glove. Results differ with new gloves, heavily used gloves, freshly tested gloves, and aged gloves from stock, in addition to temperature fluctuations during measurement, which impact air compressibility and glove elasticity. From all these shortcomings, physical glove testing could be questioned principally.

Innovation and Results

There is one aspect, which gives a glimmer of hope for reproducible testing: the influence of this non-linear behavior decreases with stress level. This means that with higher pressure or by longer period of pressurization, the glove converges to a kind of 'equilibrium state,' from which glove behavior could be taken as constant.

Higher pressure levels should help, but have their limits. A 3000 Pa pressurization of a standard glove/sleeve assembly (400 µm membrane thickness) results in inflating the sleeve to balloon size while the glove keeps the shape. Therefore, the high pressure difference for test procedure I (4000 Pa) – which is principally useful – can only be applied for the glove alone.

The alternative – prolonging the period of pressurization – is feasible for complete glove/sleeve assemblies, but could take hours, which is not very practical.

A new approach stresses the glove/sleeve assembly by repeated pressure impulses, which are applied as soon as the pressure inside the glove drops below the starting pressure level (1200 Pa). The equilibrium state is achieved within 10 to 20 minutes depending on glove/sleeve thickness and material. As shown in Figure 3, the impulse frequency reduces over time, which is an indicator for approaching the equilibrium state. All following results are achieved by that technique.

To demonstrate the influence of stressing time, glove/sleeve assemblies in two states (brand new, old/used) were performed - *Figure 4*. The results are the average value of three measurements. The longer the stressing time, the smaller the deviation. The same can be observed for the pressure level: the higher the pressure, the better the reproducibility; 1200 Pa showed to be the optimum pressure level for standard glove/sleeve assemblies.

To demonstrate the repeatable equilibrium state at the beginning of the measurement, a series of tests were performed with varied pause time between each run: from no pause to two hours - *Figure 5*. The results spread in a window of 20 Pa, which is sufficiently accurate for reliable detection of an artificial 100 µm hole with standard glove/sleeve combinations.

A prototype of reinforced Hypalon sleeve combined with a standard Hypalon glove was tested. The results were very positive: test pressure could be doubled (2400 Pa) without overstretching the sleeve. Stressing time could be cut in half and resolution doubled allowing reliable detection of 50 µm holes.

Practical Aspects

Holes of a 100 µm diameter or less can hardly be detected during visible inspections. Even cuts of a millimeter in size could remain undetected could remain undetected by visual check. Under unfavorable circumstances, the detection of these cuts also could be a challenge for physical glove testing procedures. Depending on the location and orientation of such cuts, the force induced by pressurization is either sufficient to open the leak or not. And it is not only the pressure level that affects opening probability, but also the direction of the cut in relation to the tension from pressurization - *Figure 6*. Cut locations in the sleeve can easily be detected, but cuts on the finger tip are much more difficult to be opened – this is because of geometrical aspects (see above), and also due to the higher glove thickness at the finger tip.

Another important aspect is the tightness of the complete assembly: port, sleeve, cuff ring, glove. The performance of the whole system is determined by the weakest link. Glove and sleeve fixations are critical points. The very common fixation by expanded o-rings clamping the glove (sleeve) on a ring is not the way o-rings should be used. They have there best sealing properties with being pressed between two faces of a connection. In case of oval shaped glove ports, the o-ring used as an expander shows a high contact pressure at the small radius sections compared with insufficient contact pressure at the big radius sections. What is more: Hypalon material tends to crawl under mechanical load – such as contact pressure by an o-ring – which has an effect on the tightness. Therefore re-adjustable fixations have advantages

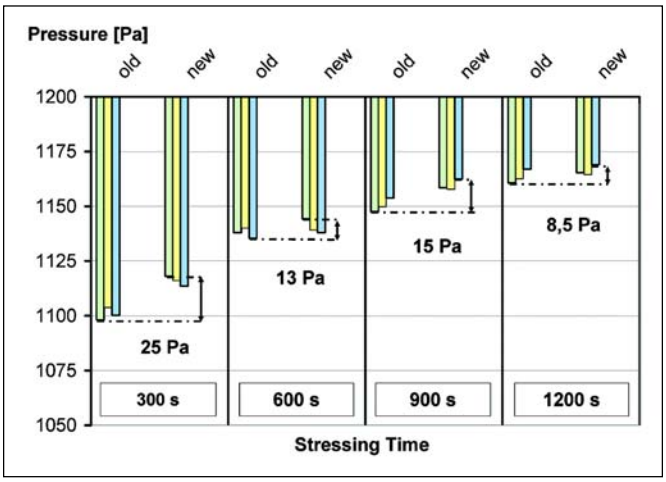

Figure 4. Variation of stressing time with set of old vs. new gloves.

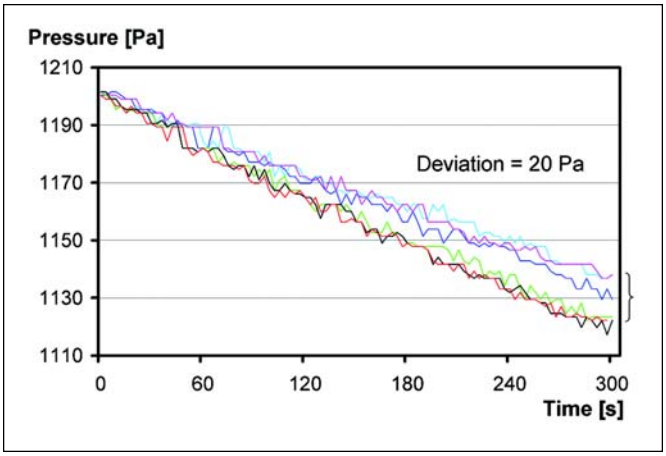

Figure 5. Repeated measurement with variated pause time between the runs.

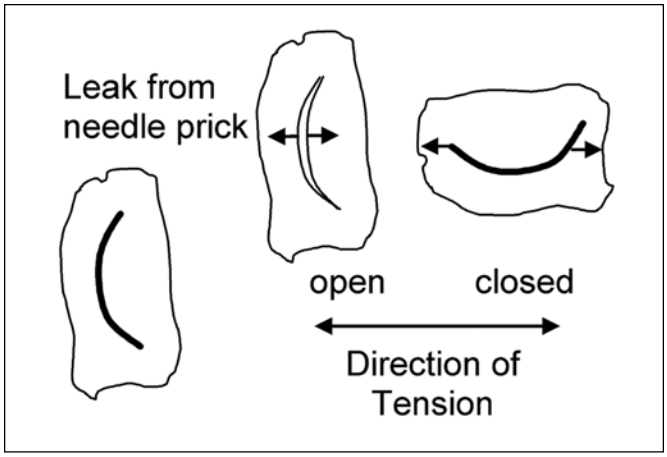

Figure 6. Behavior of leaks from needle prick in relation to leak orientation.

over expanding techniques involving o-rings.

Experience on filler isolators show that many perforations or leaks in glove/sleeve assemblies are caused by interventions with stopping machinery. Routine work – such as environmental monitoring in the isolator, transfers, and routine adjustments do not have impact on glove integrity as often. Leaks in the sleeve are very common, typically coming from overstretching (bad ergonomics), wear through leaning on the glove port ring, and untrained or inappropriate handling by the user.

Hypalon is the favorite glove material for use in isolators because of its stability against oxidizing agents, such as hydrogen peroxide vapor. In case of Restricted Access Barrier Systems (RABS), which are installed inside cleanrooms of high air quality (at least ISO 7), the gloves have to be sterilized prior to transfer into the operations room. The cost of glove/sleeve assemblies is very high – so for economic reasons, being able to sterilize glove/sleeve assemblies multiple times can be an important requirement although autoclavability of Hypalon gloves is poor. The mechanical properties change after 6 – 8 autoclave cycles and result in leakage after 12 – 15 cycles. Alternative glove materials could be an option to overcome that disadvantage.

With containment systems, the risk of operator contamination require a different glove approach. The need for mechanical stability and leak tightness comes from GMP and HSE requirements. For aseptic containments with positive pressure, leaks could blow contaminants into the operator area. Therefore, thicker gloves or two layered types can be the better choice. In addition to gloves with improved mechanical properties, single piece types can be recommended to reduce interfaces.

For containment operation in general, glove testing is an important part of health and safety precautions. The measurement procedures described above are applicable, but thicker glove membranes require higher pressure levels to detect small leaks.

Summary

Physical glove integrity testing is required by regulatory guidance. Investigations demonstrate that gloves to be tested applying pressure difference should be prepared in order to achieve reproducible results. Increasing the pressure level or prolonging the stressing time shows improvement in reproducibility of the test results. A new impulse technology helps to save time. Recommendation from practical experience emphasizes the need for a reliable glove fixation/sealing technique. Utilization of gloves in RABS, isolator, and containment systems requires a slightly different approach, but it should be performed in conjunction with integrity testing.

Physical glove testing with a reliable procedure helps to reduce dependence from adherence to visual inspection SOPs.

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About the Authors

Dr. Johannes Rauschnabel is Product Manager at Bosch Packaging Technology. He is responsible for Bosch barrier systems and the Bosch PharmaLab. He has more than 14 years of experience in research and development. Dr. Rauschnabel graduated as a chemist from Eberhard-Karls University of Tübingen and holds a PhD in organic chemistry. He can be contacted by email: johannes.rauschnabel@de.bosch.com.

Albrecht Kühnle is a Mechanical Design Engineer at Bosch Packaging Technology. He has 10 years of experience in development of washing, sterilizing and filling processes, and machines for liquid pharmaceutical products. Presently, he is focused on the development of Bosch barrier systems, mainly on isolators and cRABS, as well as appropriate components, such as transfer systems, glove ports, glove testers, etc. He graduated with a mechanical engineering degree at FH Aalen. He can be contacted by e-mail: albrecht.kuehnle@ boschpackaging.com.

Robert Bosch GmbH, Blaufelder Strasse 45, D-74564 Crailsheim, Germany.

Kuno Lemke is Design Engineer for Bosch Packaging Technology. He has 33 years of experience in hygienic design of packaging machinery with focus on aseptic applications for food and pharmaceutical. He is involved in development and advanced engineering of equipment for sterilization and testing. Lemke graduated from the school of technology at Ludwigsburg/Germany. He can be contacted by e-mail: kuno.lemke@boschpackaging.com.

Robert Bosch GmbH, Stuttgarter Strasse 130, D-71332 Waiblingen, Germany.

This article considers the benefits of validating plant access control systems to support consistent product quality and to lift productivity improvement.

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The Case for cGMP Compliant Plant Access Control Solutions for Pharmaceutical Laboratories and Manufacturing Areas

by Walfried Laibacher

Introduction

Historically, validation of automation systems has focused on information technology and process control solutions. Building Management Systems (BMS) were thought to be 'no-impact systems' to product quality. How things have changed.

This is supported by new methods and tools available for Good Manufacturing Practice (GMP) assessment. They, in turn, leverage US Food and Drug Administration (FDA) guidelines for pharmaceutical companies adopting a risk-based approach to product quality. But, even before the "Pharmaceutical cGMPs for the 21st Century" were announced,[1] BMSs were categorized as a one process control system[2] type – one with direct impact upon drug quality, and therefore, patient safety.

Figure 1. Access Card Terminal with integrated display (shown here in conjunction with the Time and Attendance application, a security management function within an integrated building management solution.)

A multitude of regulated manufacturers around the world are embracing Heating, Ventilation, and Air Conditioning (HVAC) environmental control solutions – one of several BMS applications – in their inventory of GMP critical computerized systems as a must for reducing risk of non-compliance and business disruption. GMP-relevant records typically confirm temperature, humidity, and differential pressure as well as particulate matter in critical cleanroom, laboratory, and production environments.

Forward-thinking regulated manufacturers are increasingly turning their attention to plant access control systems as an integral part of the BMS – encouraged also by FDA's 21st Century initiative for risk-based management to use new automated systems for enhancing the quality of the product being manufactured.

Early adopters are looking to manage physical access to their laboratories and manufacturing facilities in much the same way. But how can a plant access control solution impact drug quality and what drives these organizations? After all, it is not just a case of regulatory compliance with GMP. The author, Walfried Laibacher, a regular participant in ISPE's European seminar program, argues that, independent of plant design, access control solutions may be increasingly considered as critical to product quality, and hence, need compliance to regulatory requirements. But more than

that, GMP compliant access control solutions constitute a key differentiator in a complex, mission-critical environment.

Access Control Solutions as a Direct Impact System

When assessing the GMP impact of automated systems in pharmaceutical plants, some typical questions come to mind:

- Does the system preserve the product status?
- Does it produce data to support product acceptance or rejection?
- Does the system control a process (e.g., a Distributed Control System or DCS) that can impact product quality?
- Is there independent verification that the control system is performing as intended?

These same questions apply to automated access control solutions.

It is likely that regulators are looking at the physical access to your plant areas. There are at least two pharmaceutical companies in Southern Europe that were inspected by their local regulatory body and asked about their method of identifying and segregating people accessing critical areas. Both decided to introduce computerized access control systems and rated them as "direct impact system." Indeed, the FDA has already issued a 483 on the subject in the United States. Here is the example:

"... Controlled by an automated building security system that functions with the use of electronic key cards assigned to personnel... ...management relies upon physical security to access the system. There are some concerns regarding the software controls for this security management system:

- ...functional design requirements are not established.....
- ...design control documentation has not been established... (e.g., user groups are not defined, specified configurations for individual user groups are not defined)
- ...records of periodic review of the personnel assigned to each user group are missing
- ...there is no Standard Operating Procedure (SOP) to assign any one user to a specific user's group on the system.

Not only is the FDA criticising the lack of system specification, it is taking an operational perspective and raising awareness of the potential risk of non-qualified people being able to access the system. This, inevitably, courts risk. Upon entry operators could add users, grant them access to non-controlled critical areas, and deactivate vital security configurations - anti pass-back mechanisms for example.

A risk analysis of current business practices would have shown this pharmaceutical manufacturer's access control system to be vulnerable. This, in turn, may have prompted a change to its classification - from non-GMP relevant to GMP-relevant. Without a specification detailing how the system should operate, this manufacturer could not provide sufficient qualification evidence. Failure to do so put regulatory compliance and product quality at risk.

Why is Access Control so Vital?

The following discussion will review the GMP-impact assessment process of computerized systems in pharmaceutical plants.

Any regulated manufacturer has a variety of automated solutions, all of them formally listed in an inventory together with their respective validation approaches. This provides the framework for the validation planning process and determines the classification of such systems into GxP-critical or GxP-non-critical.

Applying the GMP-Impact Assessment questionnaire to access control systems invariably prompts an affirmative response to one or more issues. This confirms its categorization as a direct impact system – one that accords qualification for confirmation of regulatory compliance.

Here are some ways in which access controls impact security and why they are so critical to preserving product integrity:

- Poor management of access control risks unauthorized personnel gaining entry to storage rooms and tampering with the product or vital ingredients. An access control system would govern access permissions to critical zones within the pharmaceutical plant. Only those with current permission to enter would be able to do so.
- Physical permissions to critical areas require current SOP training certification. 'Hygienic requirements in cleanroom zones' call for appropriate protective suiting for example. The two inspected European pharmaceutical companies mentioned before also were asked how they can assure that people accessing critical areas are trained about procedures in place for those. Integration of access controls with an electronic training management system will deny employee access to this area in the event of lapsed or unavailable training records. Instead of granting entry to a qualified drug production area, the key card reader display would stop access, flag up the reason why, and recommend the necessary remedial action. In our example it might say: "Entry prohibited. No training on SOP Hygienic Instruction, Rev 1.2. Please contact site training administrator." See Figure 1 for Access Card Terminal showing individual messages.
- Robust audit trails, supported by documented evidence, provide further proof of entry and egress. They give additional assurance that the

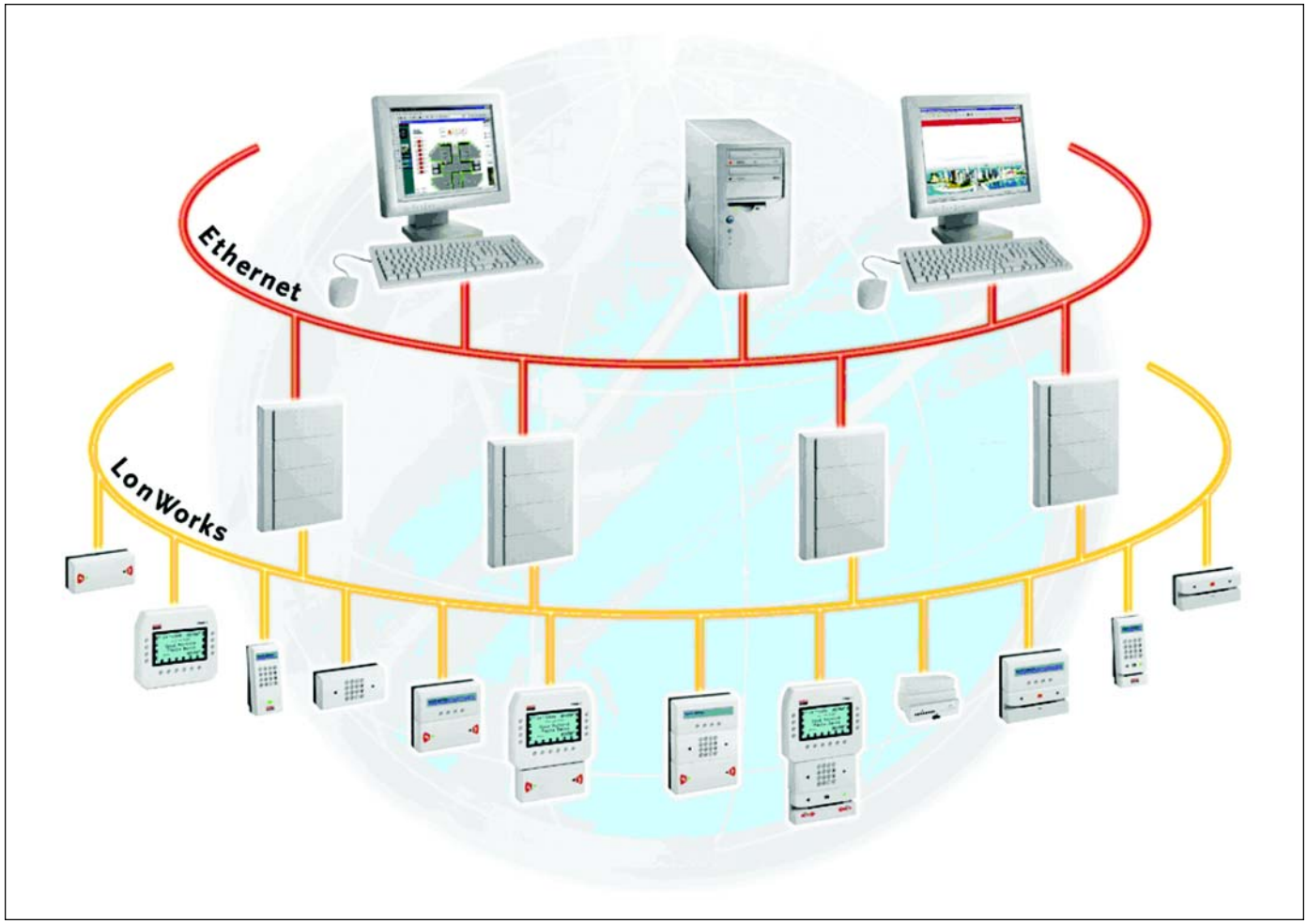

Figure 2. Typical system architecture for a plant access control system (software configuration at all three levels).

process consistently operates in accordance with its predefined specification – in other words, validation ensures the automated system works as originally intended.

These are just three examples, but there are many other opportunities for GMP compliant access control systems. Some pharmaceutical manufacturers video record door entry points to critical production areas. Resulting footage can support a security system, providing for a visual check of SOP deployment – real time and/or historically. Such electronic video records are used by a pharmaceutical manufacturer in the UK to demonstrate compliance with SOP deployment on hygienic instructions – ready for GMP inspections. Security management solutions can even deliver alert notifications of anything improper such as the wrong color clothing or attempted entry at an unscheduled time.

Intelligent access control systems also can be used to accept or reject a product.

Not only will they alarm in the event of unauthorized entry to a critical plant area, the transit log report will provide documented evidence supporting product acceptance/rejection. As an example, it turned out that an already dismissed employee has a criminal background. Transit log reports helped identify to which areas this person had access. This is particularly important given the increasing incidence of pharmaceutical counterfeiting.

Furthermore, smart access controls can govern entry to areas housing direct impact systems such as DCS or Enterprise Resource Planning (ERP) - another good reason for rating them as a direct impact system.

But the argument doesn't stop there.

Qualification supports the use of integrated building and process management solutions by making use of the same electronic key cards for accessing rooms and DCS login.

Alerts are generated automatically in the event of the DCS being accessed by a key cardholder fraudulently using a second key card to make system changes under a different name. Even though this second card would, in principle, give access to the process control system, the DCS login is denied because the corresponding key owner has not physically entered the control room. Verification between integrated systems only serves to enhance security in a regulated manufacturing environment.

Returning to the principles of GMP impact assessment, a single 'yes' in the GMP assessment questionnaire does not necessarily require you to qualify the whole access control system. System boundaries focus qualification and

validation effort on the mission-critical components of the direct impact system. This would not, for example, include a car recognition subsystem granting access to the parking lot.

ISPE's Baseline® Guide on Commissioning and Qualification[3] provides a useful guide and process for determining system boundaries at the planning phase.

How Best to Achieve a cGMP Compliant Access Control System?

ISPE's Good Automated Manufacturing Practice Guide (GAMP®) for the validation of automated systems – is the 'de-facto' industry standard for validation of automated systems. It is recommended by the FDA as an effective tool for these purposes.

A proven GAMP-based validation approach for validating HVAC environmental control systems (as one part of the BMS) can be directly applied to access control solutions. This is because access control architecture follows the same three-layer model as for environmental management - *Figure 2*.

- **Supervisory Level:** the level of presentation (status and alarms), human-system interface (application parameters, system configuration, and system control), and historical data management (events, values, and transits).

- **Peripheral Level:** the level of decision-making and feedback, it comprises controller devices specializing in the management of specific applications.

- **Field Level:** the level at which the system interacts with the external world (employees, visitors, gates, and detectors for example). It is made up of readers, displays, keyboards, actuators, and digital sensors.

On the environmental side, there are temperature, humidity, and pressure sensors controlling, for example, an air handling unit. With access controls, there are key card readers or any biometric devices and door contacts.

For both systems, the application logic resides at the peripheral level. The management application on the supervisory level may even be the same in state-of-the-art, integrated building management solutions.

As discussed in the ISPE Baseline® Guide on Commissioning and Qualification, components of all three levels are obviously identified as critical components requiring qualification: the card or biometric readers (palm reader, retinal scans, or others), followed by the application configuration in the independent working controller of the peripheral level. Finally, the setup to configuration, analysis, and reporting means provided by the supervisory level also require qualification, having documented evidences about the system setup that only authorized operators can perform changes to the access control system and that such changes are recorded to support audit trail requirements. The system should have proven mechanisms in place to reject electronic record tampering and may have been configured so that critical control actions can just be performed by electronic signature means as defined in 21 CFR Part 11. This just gives an example which emphasizes that qualification has to address the whole system far beyond the visual system components like key card readers or biometric devices.

GAMP groups software into five different categories, from category one, describing the validation approach of software type 'Operating Systems,' to category five, 'custom or bespoke code.'

HVAC environmental control systems, DCS or SCADA systems fall into category four software, 'configurable software package' (though specific business operations may vary from this assessment). A computerized plant access control system also can be assigned to this group.

From this, it follows that a lot of common practices for HVAC hardware and software qualification can be duplicated and applied directly to access controls. As example, transit management, key card management for users and zones, Present-in-Zone, and anti-passback configuration are functions that come to mind in respect of Operational Qualification (OQ).

Keeping the Validated State in the Operational Phase

Qualifying access control solutions for compliancy is relatively straight-forward.

In the context of an environmental control system, for example, set point changes on room temperature will avoid costly 'out-of-specification' wastage in a production environment; they will force adoption of control parameters in line with SOP on change control. Correct change control deployment is vital to staying GMP compliant.

However, access control systems rarely require change control deployment. For the most part, this only comes into play in the event of system expansion. Rather, day-to-day actions in the operational phase - visitor management for example – are recorded in the event buffer for audit trail.

There are obviously less changes to such a plant access control system needed which makes it much easier to maintain the validated operational state.

Access Control Solutions Compliant to 21 CFR Part 11?

The ability to qualify an access control solution enables pharmaceutical manufacturers to leverage further productivity improvement in their day-to-day business operations. In line with FDA 21 CFR part 11 guidelines it allows for Electronic Records and Electronic Signatures (ER&S), and with this, electronic data reports for regulatory inspection.

It also satisfies other crucial FDA 21 CFR part 11 criteria including the following:

- generation of exact, timely, and tamper-proof records

- Chronological audit trails, another key aspect of compliance. Synchronization with a master clock on an organization's IT network is one solution guaranteeing that all events and transits are in the same

time reference as all other company systems.

- Training. Although usually covered under operational procedures, the access control solution can help to ensure that only trained personnel monitor and configure the system. This necessitates operators being assigned a profile that contains information on their security level and area assignments. Classification in this way can be used to manage operators; to restrict them to seeing and controlling only those parts of the system for which they are currently trained. Their scope can be changed, on-line, as new training occurs. Operator permission can be configured down to the smallest detail. Within a given area for example, an operator might be able to monitor and configure certain procedures. Timely refresher courses also can be managed in this way, thus, preserving product integrity and ensuring optimal plant uptime.

These are just few items to be considered in the scope of ER&S usage in addition to the application examples using ER mentioned in previous sections.

The recently released GAMP® Good Practice Guide[4] on ER&S is now available to help pharmaceutical firms around the world to identify their critical e-records. In seeking to provide a focused approach on this subject, it follows the more efficient top-down principle on critical evaluation of e-records by applying a risk based approach rather than cost intensive, bottom-up evaluation of computerized systems. With that, it follows the FDA's 21st Century initiative for risk-based management and considers and complies with international regulations. Being aligned to the principles presented in the 2004 FDA Part 11 Guidance, its recommendations are well thought-out.

Today non-GMP; Tomorrow GMP

Fact: things change. New legislation and the interpretation of it according to industry guidelines and current thinking is constantly evolving. New guidelines point to regulatory direction and provide support for improving current operational practices. Even though a pharmaceutical manufacturer may currently assess its access control system as a non-GMP system, best practice may change as the 'c' in cGMP comes into play.

What does this mean in the context of a plant access control solution?

If it is assessed as a "no-impact system," then the supporting specifications, installation and commissioning specifications need not stand up to the stringent criteria for qualification documentation. Should, in time, it become GMP classified as a result of integration with another direct impact computer system for example, a retrospective validation might be appropriate. This would provide the necessary data and information needed to support system documentation and the requisite validation as very clearly outlined in the PIC/S Guidance[5] for inspectors of computerized systems in regulated "GxP" environments.

But retrospective qualification is no small task. More often than not, it is more expensive than implementing a prospective validation framework. Experience shows that many companies faced with such a dilemma chose to upgrade - even replace - their existing computerized system rather than backtrack.

Stay Ahead of the Curve

It is common knowledge that the regulatory bodies regard plant access controls as a direct impact system in certain manufacturing environments. This requires validated evidence of compliance.

Mandatory or not, early adopters of best practice are staying ahead of the game and driving performance gain by validating their automated access control systems. Indeed, putting a GAMP-conforming validation process in place not only ensures that your access controls are working as intended, it delivers big business rewards. Not only does it prove regulatory compliance, in the long run, it cuts costs dramatically and protects product integrity.

In short, it makes good business sense. A sound prospective validation approach to project delivery and operation is infinitely preferable to cumbersome and often complex remediation by retrospective validation. A proactive stance also gives regulated manufacturers the opportunity to implement electronic records and signature and lift productivity improvement still further.

There are plant access control solutions available today that can do this; that are ready to meet the requirements for 21/CFR part 11 compliance. Not only do they give pharmaceutical manufacturers a perfect understanding – and record – of their access control processes, they bring about reduced risk of business disruption. They enable pharmaceutical companies to:

- stay ahead of the curve by attending to their peripheral systems today
- be proactive – to be an early adopter and leader of best practice
- guarantee product quality and regulatory compliance – and, from this, strengthen competitive advantage

It's in your hands.

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About the Author

Walfried Laibacher holds a diploma in applied sciences for electrical engineering. He is currently the Validation Service Lead for Honeywell Building Solutions in Europe, Middle East and Africa. Based in Germany, he oversees Honeywell's specialist validation sales and engineering teams, ensuring that they apply common validation practices for environmental conditions to the company's growing pharmaceutical customer base. This includes on-site project support, recently as the validation consultant in a multi-million Euro process control project for a major European biotech company. Since joining Honeywell in 1988, Laibacher has held several positions in software development from software engineer to project leader for HVAC and building management solutions in an SEI CMM level 3 certified organization. As a member of the German speaking GAMP D-A-CH Forum, he contributes to a GAMP SIG on "Cooperation Models between Users and Suppliers." He is a regular on the European lecture circuit, his speciality being new-generation validation solutions and integrated building automation systems and how they satisfy pharmaceutical customer needs for compliant environmental control. He can be contacted by e-mail: walfried.laibacher@honeywell.com.

Honeywell GmbH, Honeywell Building Solutions, Seligenstädter Grund 11, D-63150 Heusenstamm, Germany.

This article investigates the staging option to analyze an existing case study that involves the potential licensing of a drug compound that is in development. It demonstrates how options analysis is a useful tool in adding insight to the decision making process when conventional valuation methods are not decisive.

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The Staging Option and Drug Development

by Neal Lewis, PhD, David Enke, PhD, and David Spurlock, PhD

Introduction

Research and Development (R&D) projects are routinely evaluated to determine if the projects are feasible and worthy of continued funding. Most R&D organizations have more ideas than they have resources to fund them so projects must compete for available resources, including money and talent. A widely used technique for evaluating projects is Discounted Cash Flow (DCF). In this method, the Net Present Value (NPV) is determined by discounting forecasted future cash flows by a required rate of return, as shown in equation 1.

$$NPV = -I_0 + \sum^{T} \frac{FV_T}{(1+r)^T} \qquad \text{(Eq1)}$$

where

I_0 is the original investment
FV_T are the future cash flows
r is the interest rate
T is the time increment

The discounted cash flow method is widely used to determine the value of projects, and has been widely embraced by industry. Despite its wide use, discounted cash flow biases evaluators toward conservative conclusions. Good ideas are sometimes not pursued because the method provides an NPV that is often too low.[1] Management usually has flexibility during the course of R&D projects, and this flexibility is not accounted for in the DCF technique.[2]

Projects with NPVs that are very high are considered good investments from the DCF perspective. Projects with NPVs that are negative are generally abandoned because they will not deliver the required return. Projects with NPVs close to zero require significant additional effort to determine if such projects should be funded or abandoned. Real options analysis can be used to add insight to the funding decision, especially when DCF analysis finds an NPV that is close to zero. Real options analysis offers an alternative that determines a value for managerial flexibility and provides an Expanded Net Present Value (ENPV).

Table A. Option variables.

Variable	Financial Options (such as stock options)	Real Options (such as projects)
T	Time to expiration	Time to expiration
r	Risk-free interest rate	Risk-free interest rate
X	Exercise price	Implementation cost
S	Stock price	PV of future cash flows
σ	Volatility of stock price movement	Volatility of future returns

Options

A financial option is an asset that gives the owner the right, without an obligation, to buy or sell another asset (such as a quantity of corporate stock) for a specified price at or before some specified time in the future. A real option is a potential investment, such as a project, that is funded only if the firm decides it is in its best interest to do so. The option to invest in a project (or not to invest) has value. In real options analysis, the option to invest in the project creates an ENPV, which is defined as:[3,4]

$$ENPV = NPV + \text{Option Value} \qquad \text{(Eq2)}$$

When NPV is quite large, the option value will not have a significant impact on the decision: the NPV signals that the project is worthy of investment. When NPV is very negative, even the best option values will not be large enough to create a positive ENPV, and the project should not be pursued. If the future cash flows are known with certainty, then the DCF technique should be used. Real options have their best use under conditions of uncertainty, and where management has the ability and the

Phase	Average Chance of Success, %		
	Average[14]	Small Molecule[10]	Large Molecule[15]
Preclinical	35	---	---
Clinical Phase I	75	73	75
Clinical Phase II	50	45	50
Clinical Phase III	70	---	73
Approval	90	---	81

Table B. Probability of success for drug approval.

willingness to exercise its flexibility. The option value places a price on the value of this flexibility, and the ENPV identifies how much the firm should be willing to pay to keep the project (or option) open.

Real options analysis is based on the mathematics of financial options, and has received widespread attention and acclaim since the early 1990s. Few companies have extensive experience with real options. However one notable author feels that real options will replace NPV as the central method for investment decisions in the future.[1]

There are five primary variables involved in the option value calculation for financial assets. The Black-Scholes pricing model estimates the value of a simple call option (C) based on the current stock price (S_0), strike price (X), volatility (σ), risk-free interest rate (r), and the time to expiration (T). The equation is:

$$C = S_0N(d_1) - Xe^{-rT}N(d_2) \qquad \text{(Eq3)}$$

where

$$d_1 = \frac{(1n\frac{S_0}{X}) + (r + \frac{\sigma^2}{2})T}{\sigma\sqrt{T}}$$

$$d_2 = d_1 - \sigma\sqrt{T}$$

$N(d_x)$ is the cumulative standard normal distribution of the variable d_x.

The five variables of financial options have direct equivalents in real assets - *Table A.*[3,5] Note: of the five variables used in real options analysis, four are used to calculate NPV and are usually available to the analyst. The new variable that needs to be considered is the volatility of the project's future rate of return.

The value of simple options can be quickly calculated using the Black-Scholes model, but the math becomes very complex if the option becomes more complicated. Binomial lattices also can be used to determine the value of financial and real options, and is a preferred method for complex options. This technique is explained later.

Compound options are those options that are dependent on the value of other options.[6] Compound options can be sequential, and are sometimes called staging options. Many projects are funded in phases; good project management encourages this approach. If there is a phased investment, and succeeding investments are dependent on previous investments, then a sequential compound (staging) option may exist.[7] Virtually all drug development projects are phased investments, and most are sequential compound options.[8]

The Costs of Clinical Trials

In 2003, the average cost for testing and successfully launching a new drug was estimated at $900 million.[9] While there are significant costs involved in launching a new product, much of the total cost is associated with clinical trials. The costs of a clinical trial include trial design, patient recruitment, clinician cost, product cost, monitoring, data analysis, close out and reporting results, coordination with regulatory authorities, and administrative costs.[10] Antibacterial trials are particularly expensive to run, and can cost $50,000 per patient; one Phase III trial can cost half a billion dollars.[11] Clinical trial costs vary depending on the type of drug, the number of people involved in the trial, and the product claims that are trying to be proven. Increasingly, marketing claims are driving additional clinical trials in order to 'position' a product in the marketplace.[12]

Case Study

The following hypothetical case study was published as an example of evaluating a drug development opportunity.[13] The case has been used in several business schools as an example of how to use decision trees to perform valuation studies.

A small pharmaceutical firm has developed a new chemical compound that they believe has a good chance of becoming a prescription drug. The chemical is called Davanrik, and has the potential to treat both depression and obesity. The small firm lacks the resources to complete the approval process, and so has approached a large pharmaceutical company with a proposal to license the chemical and complete the drug development process. At the time of the licensing offer, Davanrik was finishing pre-clinical development and was

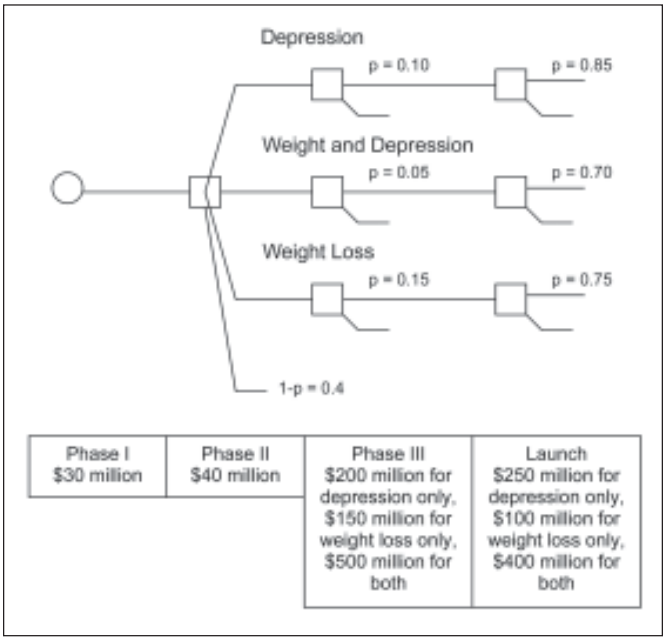

Figure 1. Davanrik decision tree.

getting ready to enter clinical testing.

The testing and approval process was expected to take seven years. If all went according to plan, Davanrik would have 10 years of exclusive marketing rights, beginning with the New Drug Application (NDA) approval. The typical probabilities of success for each clinical phase are known in the drug industry; these are shown in - *Table B*. One of the largest risks in the drug industry is the clinical development process. The value of a drug development project is determined in part by evaluating the probabilities of success at each stage of the clinical process.

During clinical testing, Davanrik would be given to 20 – 80 healthy people to determine human safety.[16] The testing was expected to cost $30 million and take two years to complete with an estimated 60% chance of success.

During clinical testing, the chemical would be given to 100 – 300 people to determine the efficacy for treating depression and/or weight loss. The probability of success for the depression indication was estimated at 10%, the probability of success for the weight loss indication was estimated at 15%, and the probability of both indications being successful was estimated at a 5% probability. Phase II testing was expected to require two years to complete, and would cost $40 million.

In Phase III clinical testing, Davanrik would be given to 1000 – 5000 people to determine safety and efficacy in a broad spectrum of the population. This testing was expected to take three years to complete and depended on successful results from Phase II. If the earlier testing demonstrated that the chemical was effective only for depression, then the Phase III trials would cost $200 million and have an 85% chance of success. If Davanrik were found to be effective for weight loss only, then the trials would cost $150 million and have a 75% chance for success. If Davanrik were found to be effective for both, then the cost of Phase III would be $500 million with a 70% chance of success.

Davanrik has the potential of generating large profits. If the drug were approved only for depression, it would cost $250 million to launch, with a present value of future cash flows of $1.2 billion. If Davanrik were approved only for weight loss, it would cost $100 million to launch with a present value of future cash flows of $345 million. If the chemical were approved for both depression and weight loss, it would cost $400 million to launch with a present value of future cash flows of $2.25 billion. All costs have already been discounted to the present time. While the development costs are high and the chances of success are low, the potential payout is very high if success can be achieved. The question therefore becomes: Should Davanrik be licensed?

The Decision Tree and Traditional Valuation

Figure 1 shows a decision tree for the Davanrik problem. The tree starts in year zero with the beginning of Phase I; this phase lasts two years and costs $30 million. The probability of success is 60%. If Phase I is successful, then Phase II may begin. Phase II lasts two years and will cost $40 million. The chance of success for Davanrik as a depression medication is 10%; the chance of success for weight loss is 15%; and the chance of success for both is 5%. This relatively low probability of success is in line with industry norms.[10] If any of these are successful, then Davanrik may enter Phase III testing. Each of the indications has its own cost and probability of success. If Phase III is successful, then the product may be launched, pending FDA approval.

Indication	Discounted Income	Discounted Cost	Net Present Value
Depression	58.14	42.75	$15.39 million
Weight Loss	22.13	38.25	- $16.12 million
Both	44.89	41.40	$3.49 million

Table C. NPV results.

We can analyze this information using traditional methods. The most commonly used valuation method is NPV. Using the potential income, potential costs, and the probability of each, a Net Present Value can be determined for each indication. First look at costs, beginning at time T = 7 years. Normally, costs would need to be discounted back to time zero, but the costs have already been discounted. It is assumed that payments are made at the conclusion of each phase. Assuming Phase III is successful, we have two costs at T=7: the Phase III cost and the product launch cost. The Phase III clinical study will need to be paid for, but the product will be launched only if it is successful. For the depression indication, this includes $250 million for the launch and $200 million for the Phase III study. At year seven, the probability-adjusted costs are (*Figure 1*):

Depression cost = 200 + (.85)(250) = $412.5 in Year zero dollars
Weight loss cost = 150 + (.75)(100) = $225
Both cost = 500 + (.70)(400) = $780

Assume that the $40 million cost of the Phase II clinical study is divided equally between the three possible indications. At year four, the probability-adjusted costs are:
Depression cost = 40/3 + (412.5)(0.1) = $54.58
Weight loss cost = 40/3 + (225)(0.15) = $47.08
Both cost = 40/3 + (780)(0.05) = $52.33

At year two, the end of Phase I, the probability-adjusted costs are:

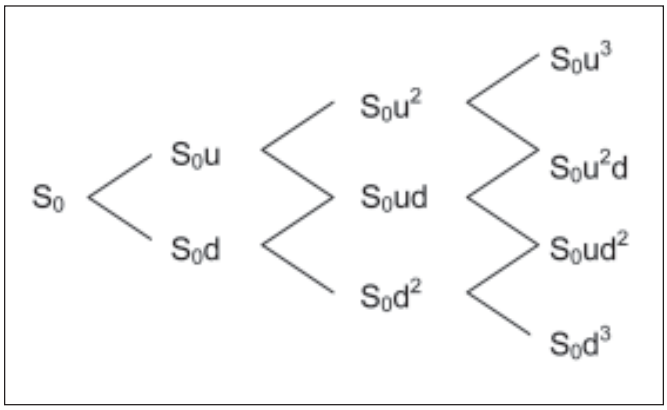

Figure 2. The Binomial lattice.

Indication	NPV	ENPV
Depression only	15.4	740.18
Weight loss only	-16.1	120.3
Both depression and weight loss	3.5	1367.8

Table E. NPV and options analysis results.

Depression cost = 30/3 + (54.58)(0.6) = $42.75 million
Weight loss cost = 30/3 + (47.08)(0.6) = $38.25 million
Both cost = 30/3 + (52.33)(0.6) = $41.40 million

Because all of these costs were already discounted to year zero, these are also the probability-weighted costs for the three options at year zero.

The income also can be determined using decision trees. The income streams have already been discounted so we do not need to adjust for time, only probability. The income stream will occur only if all tests are successful so the probability is based on success of all clinical trials. A royalty of 5% is assumed, decreasing all future income to a factor of 0.95.

Depression income = (1200)(0.6)(0.10)(0.85)(0.95)
= $58.14 million
Weight loss income = (345)(0.6)(0.15)(0.75)(0.95)
= $22.13 million
Both = (2250)(0.6)(0.05)(0.70)(0.95)
= $44.89 million

We can determine the NPV by subtracting the costs from the income - *Table C*.

Strictly speaking, the NPV technique indicates that the project should be undertaken for depression and for the dual indication, but not weight loss. If the weight loss indication were not pursued, the costs that were assumed by the weight loss indication would need to be shifted to the other options, increasing their costs. At year four, the probability adjusted costs then become:

	Depression	Weight Loss	Both
PV of the future cash flows	1200	345	2250
Royalty paid (5%)	60	17.25	112.5
Effective PV of future cash flows, S	1140	327.75	2137.5
Launch cost, X4	250	100	400
Phase 3 cost, X3	200	150	500
Phase 2 cost, X2	13.33	13.33	13.33
Phase 1 cost, X1	10.0	10.0	10.0
Time for the launch (years)	7	7	7
Time for Phase 3 (years)	7	7	7
Time for Phase 2 (years)	4	4	4
Time for Phase 1	2	2	2
r (risk-free interest rate)	5%	5%	5%
Estimated volatility	40%	40%	40%

Table D. Davanrik variables.

Depression cost = 40/2 + (412.5)(0.1) = $61.25
Both cost = 40/2 + (780)(0.05) = $59.00

At year two, the end of Phase I, the probability-adjusted costs are:

Depression cost = 30/2 + (61.25)(0.6) = $51.75
Both cost = 30/2 + (59.00)(0.6) = $50.40

The Net Present Value then becomes:

Depression NPV = 58.14 – 51.75 = $6.39
Both cost = 44.89 – 50.40 = -$5.51

The NPV for "Both" is not viable, making it so that the depression indication must assume all Phase I and Phase II costs. When the NPV for the depression indication alone is calculated in a similar way, the result is -$20.61. The recommendation would be that the Davanrik licensing agreement should not be pursued.

Even the most generous of organizations would have concerns over funding this project. The payback method, still used by many organizations, shows that the project will not pay its costs until late in the project's life. The Internal Rate of Return (IRR) analysis shows that the project might return the weighted average cost of capital under the best of conditions, but not much more. Under any traditional test method, if the weight loss indication is not pursued, the other projects cannot afford to cover the fixed costs of the early clinical testing. This is a scenario where NPV is close to zero, and management spends significant time gathering information in order to make the best possible decision. An advocate of this project will need to produce a different rationale to justify moving forward. Options analysis could help such an advocate.

The Davanrik Project as a Sequential Compound Option

The value of the real option can be calculated with the binomial options approach, using a lattice to demonstrate alternative possibilities over time.[17] The starting point is the present value of the future cash flows (S_0). Over time T, two conditions can result at each decision point: one positive up outcome and one negative down outcome (hence the term binomial). Over several time steps, we can create a lattice as shown in - *Figure 2*.

The option valuations require a risk-free rate of return. For the binomial lattices to work correctly, costs will be compounded at the risk-free rate so that standard time value of money equations can be used for discounting. In effect, the costs and incomes will be compounded at 5% so that they can later be discounted at the same 5%.

In order to calculate the option value using binomial lattices, the variables need to be identified. For the Depression indication:

Present value of future cash flows, PV = 1200
Royalty paid (5%) = (1200)(0.05) = 60
Effective PV of the future cash flows, S = 1200 – 60 = 1140
Cost of product launch, X4 = 250
Cost of Phase III, X3 = 200

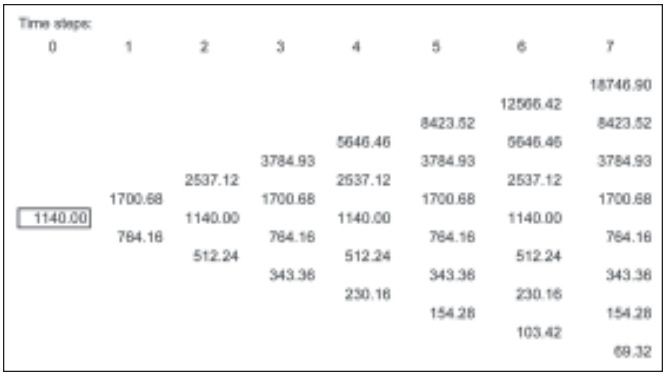

Figure 3. Depression underlying lattice.

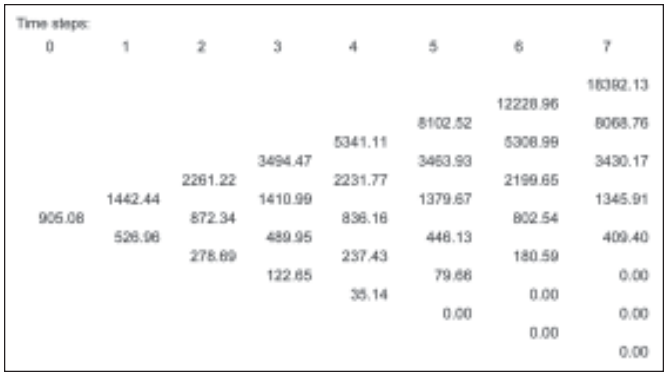

Figure 4. Depression equity lattice at Launch.

Cost of Phase II, X2 = 40/3 = 13.33
Cost of Phase I, X1 = 30/3 = 10.0
Time for the launch and for Phase III = 7 years
Time for Phase II = 4 years
Time for Phase I = 2 years
Risk-free interest rate r is assumed to be 5%
Volatility must be estimated

There are several ways to estimate the volatility of projects, but these methods will not be investigated in this article.[18] Merck generally begins an analysis based on a volatility of 40%; [19] and we will use the same.

We need to determine a few variables that are used to solve the binomial lattice. The up step (u) is defined as:

$$u = e^{\sigma\sqrt{\delta T}} \qquad \text{(Eq4)}$$

where δT is the change (δ) in time (T) for the step.

The binomial lattice is constructed so that each time-step is equal to one year, so δT = 1.

$$u = e^{0.4\sqrt{1}} = 1.492 \qquad \text{(Eq5)}$$

The down step (d) is defined as 1/u,

$$d = 1/u = 0.670 \qquad \text{(Eq6)}$$

Instead of discounting our cash flows at a risk-adjusted rate, as is often done in discounted cash flow analysis, we can determine a risk-neutral probability and then discount our cash flows at a risk-free rate. This is the standard technique used for building binomial lattices as they are used in valuing options.[20] The risk-neutral probability p is

$$p = \frac{e^{r\delta T} - d}{u - d} = \frac{e^{0.05*1} - 0.670}{1.492 - 0.670} = 0.4637 \qquad \text{(Eq7)}$$

The variables for the other indications can be calculated if they are not given. A summary of the input variables is shown in - *Table D*.

The option value for the depression indication may be calculated using the technique for sequential compound options.[20] In this case, we have four sequential options. Phase I clinical testing occurs first, and future work may not continue without success in Phase I. Therefore, Phase II is dependent on the successful completion of Phase I. Similarly, Phase III is dependent on Phase II, and product launch is dependent on Phase III (as well as FDA approval). Due to the complex nature of this sequence, the binomial lattice method is the simplest method for the calculation of the option value. The calculation consists of five lattices, each related to the previous one.[20] Microsoft Excel is used to speed the calculations. The first lattice is the underlying lattice, starting with the value of S on the left ($1140 million). This is shown in Figure 3 with time steps of one year. Each step is calculated with an up-step being

$$u = e^{\sigma\sqrt{\delta T}} = e^{.4\sqrt{1}} = 1.492$$

The up-step is 1.492 times the previous value, and a down-step is 1/u, or 0.670 times the previous value.

The next lattice is the equity lattice for the execution of the project - *Figure 4*. For this lattice, the cost incurred for the launch of the project is subtracted from the value at year seven (shown in the right hand column - *Figure 3*). This forms the basis for the new right-hand column - *Figure 4*. The successive columns to the left are then discounted by the equation

$$V_{t-1} = [(p)(V^{+}) + (1-p)(V^{-})]e^{-r\delta T} \qquad \text{(Eq7)}$$

where
V_{t-1} is the value in the next column to the left
p is the risk-neutral probability
V^{+} is the upper value (the up-step)
V^{-} is the lower value (the down-step)
r is the risk-free interest rate
δT is the length of the time step

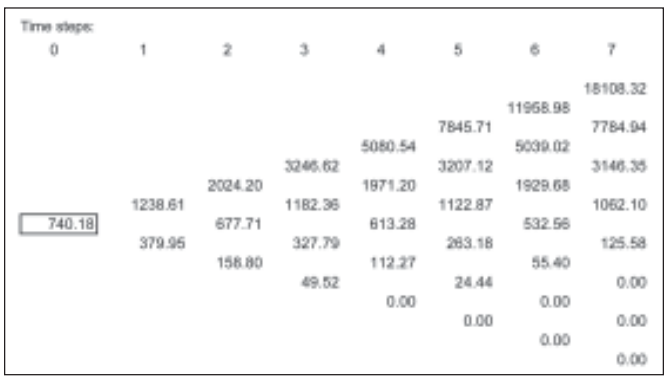

Figure 5. Depression equity lattice at Phase 1.

The entire lattice is completed from right to left. Given the values in year seven, the top number in the lattice for year six is V_{t-1} = [(0.4637)(18392.13) + (1-0.4637)(8068.76)]$e^{-(0.05)(1)}$ = 12228.96.

The next lattice is the equity lattice for Phase III of the project. This lattice is not shown by itself, but can be seen in the top right corner of the five-lattice diagram of - *Figure 6*. For this lattice, the cost incurred for the third clinical phase is subtracted from the value at year seven in the previous lattice, creating the new right-hand column. The successive columns to the left are discounted using the same risk-neutral probability.

The next lattice is the equity lattice for Phase II of the project. Again, this lattice is not shown by itself but can be seen in Figure 6. The cost incurred for the second clinical phase, which occurs in year four, is subtracted from the value at year four in the previous lattice. This lattice will have the same values as the previous lattice for years five, six, and

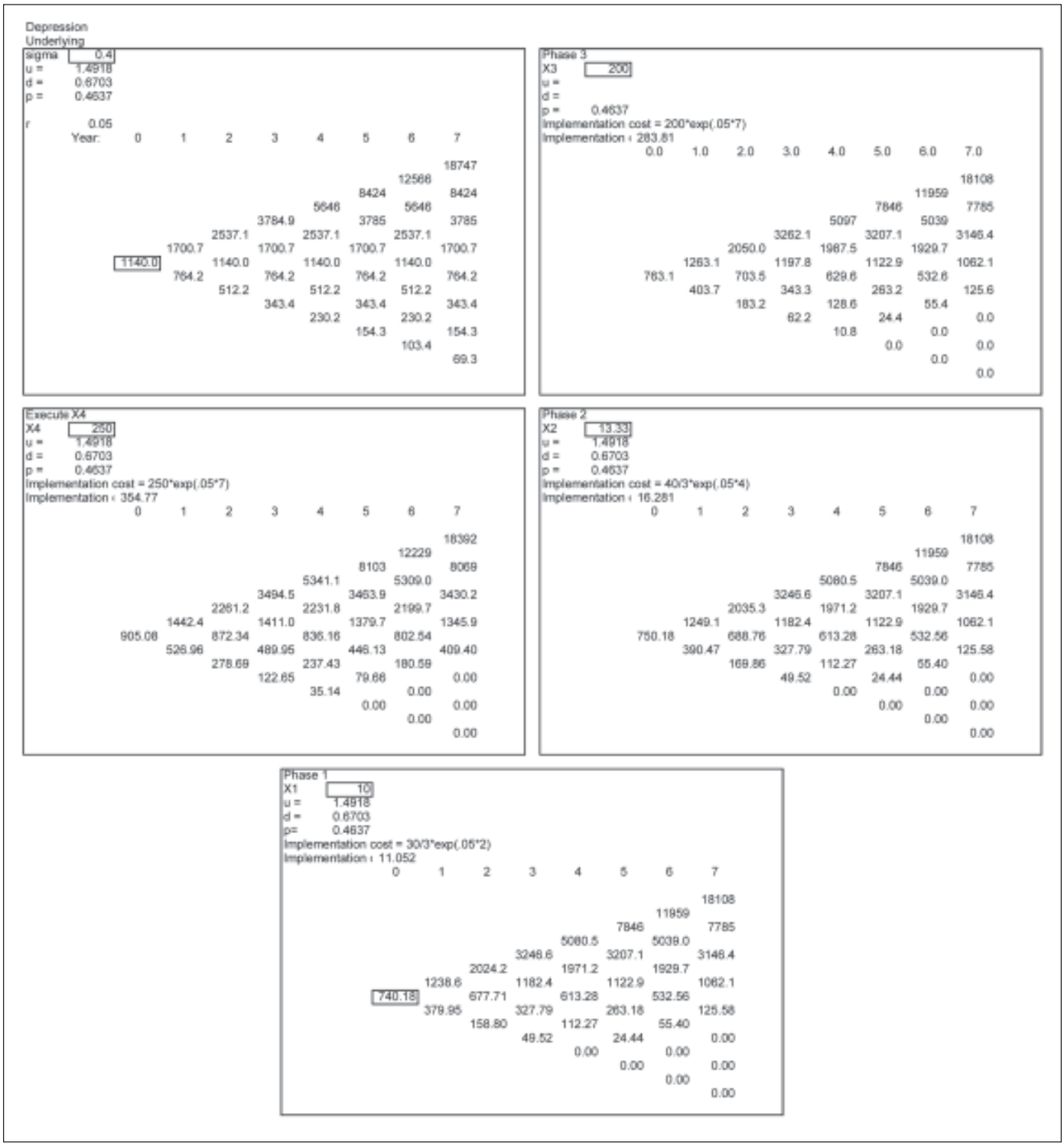

Figure 6. Five-lattice binomial calculation, depression indication.

seven. A new year-four column is created and the columns to the left are again discounted as before.

The final lattice is the equity lattice for Phase I of the project - *Figure 5*. For this lattice, the cost incurred for one-third of the first clinical phase, which occurs in year two, is subtracted from the value at year two in the previous lattice. This lattice will have the same values as the previous lattice for years three through seven. A new year-two column is created, and the columns to the left are calculated as before. The far left hand column of this last lattice represents the value of the option in year zero, and provides the value of the option. This is also the ENPV of the project. The ENPV for the Depression indication is $740.18 million.

The value for this option is clearly higher than the NPV calculation of $15.39 million. This is due to several factors. First, the option never achieves a value below zero. If conditions indicate that the value would be negative, then the option (or project) would not be executed and the value is simply zero. This represents the value of management's flexibility to not fund a money-losing project. Second, this is a high-risk project with a very large potential payout. Whereas NPV decreases the value of the project when risk is present, options analysis increases the value when risk is present. The chances of having a positive decision are enhanced with options analysis.

The primary question at this point is whether it is worthwhile to fund the beginning of this project. For the Depression indication, the project needs to justify the expenditure of $10 million for its fair share of Phase I clinical testing. Managers are not being asked to fund the entire project, only the first phase. Based on the option analysis, this method says that project expenditures of up to $740.18 million are justified.

Similarly, the option values for the other indications can be calculated. A summary of the results is shown in - *Table E*. For all indications, the ENPV is substantially higher than the previously calculated NPV.

The ENPV gives a clear signal that the project should be undertaken. Real Options Analysis was able to improve the decision where NPV analysis was not clear. The project should be continued if the Phase I clinical trials are successful. If they are not successful, then the project should be abandoned. The project should again be evaluated before Phase II money is committed. The complete five-lattice binomial calculation is shown in - *Figure 6*.

Implications for the Pharmaceutical Engineer

The valuation of a project is an aspect of project management that can be crucial to the success of a project. Valuation is discussed extensively in the academic literature and in the popular business press. The issue is relevant to anyone who is attempting to justify a project. Valuation is also relevant to business accounting and finance, and is an important part of tax law. Discounted cash flow analysis is widely used in the pharmaceutical industry, and engineers need to be aware of the problems that these methods present. Discounted cash flow undervalues many projects, whereas the use of real options helps to determine a more accurate project value.

A key advantage in the use of the staging option is that it assumes that future costs will be spent only if it is in the best interest of the firm to do so. A future phase will be undertaken only if the previous phase is successful. This is a much different assumption than NPV, where future costs are adjusted only by their estimated probability of occurrence.

Options analysis has been criticized for being a "black box." Many managers do not understand the methods and do not understand how a given option value is calculated. The binomial lattice approach is a flexible technique that is based on simple mathematics. The method is easy to learn and can be understood by a wide range of interested parties. Advanced mathematics such as calculus is not needed when using the binomial lattice approach. This method helps alleviate the "black box" mentality that has hindered the application of options analysis in the past.

Real option values are determined based on a set of forecasts, including future cash flows and future costs. It is therefore necessary to realize that option values are estimates, and are only as accurate as the input variables. When necessary, sensitivity analysis can be applied to option analysis.

The staging option is one of several related real options tools available to the pharmaceutical engineer. Projects are sometimes delayed until additional information can be obtained. In this case, a deferral option may be a useful analysis tool. Projects are abandoned for a variety of reasons, in which case an abandonment option could prove useful. Projects can be expanded or contracted depending on market success, and the expansion option or the contraction option can be used to better define the worth of such projects. While these options are beyond the scope of this article, they are analysis tools that can aid in project valuation.

Conclusions

Staging options can be used to provide a more accurate project valuation when NPV is not decisive. By approaching projects with a staged investment strategy, we limit the investment and the risk at the early stages. This also provides time for better understanding of the future cash flows and costs, allowing managers to make better decisions as uncertainty is resolved and project outcomes are more clearly defined. This approach can be used in a variety of industries, and is very applicable to medium and large projects. It is especially useful in the pharmaceutical industry where drug development is required to be a staged investment.

Drug development can often be viewed as a sequential compound option. As an option, funding of a development project first hinges on the decision to fund the first round of testing. The entire project does not need to be funded at one time. Management has the option of either funding or abandoning the project at a later date, and this option has value. Early stages require a relatively small initial investment compared to the potentially large future funding requirements so options analysis may alter the decision of whether to fund the project. Most of the information needed to perform the options analysis is the same as would be used to determine a project's NPV with the exception of volatility. The

volatility of the project's future returns must often be estimated, and this volatility can be difficult to determine. Furthermore, calculation of the expanded NPV is more complex than determining the traditional NPV, but the binomial lattice approach provides a value without the use of complex mathematics. The calculation method using the binomial lattice has been demonstrated, and shown to be a relatively straight-forward method for calculating option value.

The staging option is an important approach for all kinds of projects since much of the project work is performed using staged funding. The demonstrated case study clearly shows how the final decision can change when viewed from an options perspective.

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About the Authors

Neal Lewis is an Associate Professor in the College of Information Technology and Engineering at Marshall University. He is the coordinator of the MS program in technology management in the division of Applied Science and Technology. He earned his BS in chemical engineering and PhD in engineering management from the University of Missouri - Rolla, and an MBA from the University of New Haven. He has more than 25 years of industrial experience with Procter & Gamble and with Bayer Corporation. He can be contacted by email: lewisn@marshall.edu or by telephone: 304-746-2078.

Marshall University, College of Information Technology and Engineering, 100 Angus E. Peyton Dr., South Charleston, West Virginia 25303.

David Enke is an Assistant Professor in the Engineering Management Department at the University of Missouri-Rolla (UMR). He is the Director of the Laboratory for Investment and Financial Engineering and is a member of UMR's Smart Engineering Systems Lab, Intelligent Systems Center, and Energy Research and Development Center. He received his BS in electrical engineering and MS and PhD degrees in engineering management, all from UMR. His research interests are in the areas of financial engineering, financial risk, financial forecasting, investment, engineering economics, and intelligent systems.

David Spurlock is an Assistant Professor in the Engineering Management Department at the University of Missouri-Rolla. He earned a PhD in organizational psychology from the University of Illinois at Urbana-Champaign and has more than 10 years of engineering and management experience in the industry. His research interests include individual and group judgment and decision making processes; managing people in organizations; organizational change, organizational development and program evaluation; and the influence of technological change on workplace behavior.

University of Missouri-Rolla, Dept. of Engineering Management, 1870 Miner Cr., Rolla, Missouri 65409.

Country Profile

A look at the Pharmaceutical Industry in

INDIA

Produced in collaboration with ISPE India

ISPE
Engineering Pharmaceutical Innovation

Reprinted from
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Dear ISPE Members,

On behalf of the ISPE India Affiliate, I am pleased to present the profile of the Indian pharmaceutical industry as it has evolved over the past few decades.

A profile of the healthcare system in India would be incomplete without a mention of the two renowned ancient Indian ayurvedacharyas, Sushruta and Charaka. Indians have always been health and medicine conscious giving the Indian pharmaceutical industry a strong base. Roots are very strong.

The profile also discusses how the Indian industry has developed in the last 50 years. The proactive functioning of various associations and bodies, which have enhanced the growth of the Indian pharmaceutical industry, also deserve mention.

The profile also looks at the regulatory systems in India at present with a focus on the Drugs Controller General of India (DCGI) and his role in price control of various preparations. The aim in the Indian setting is to provide effective drugs and affordable prices. Hence today the pharmaceutical industry in India is faced by numerous challenges. But there are many opportunities as well. The Indian pharmaceutical sector is fast being recognized by international markets and is expected to emerge as the global driver in the coming years. Research and development, a key factor for progress of any drug industry, also has been discussed in sufficient detail.

With strong roots, and a proactive present, India has tremendous future potential. India has taken a significant step forward in achieving the goal of becoming a globally competitive market in the 21st century. India is also taking fledgling steps into the global arena by forging contacts with research and marketing based companies. Alliances with both companies and institutions like ISPE are giving Indian companies an opening into the world's global research networks and the chance to gain access to new technologies like Process Analytical Technology (PAT).

We hope this profile succeeds in its intention to give a contemporary overview of the pharmaceutical industry in India.

Yours truly,

Ajit Singh

President
ISPE India Affiliate

This feature in *Pharmaceutical Engineering* is designed so that you can tear it out, three hole drill (if desired), and keep it with other Country Profiles as they are published.

Look for the Country Profile on Thailand in the January/ February issue of *Pharmaceutical Engineering*.

A Look at the Pharmaceutical Industry in India

by Shabbir Badami, Pharmacist, ACG Worldwide and Rajshri Srinivasan, Free-lance Journalist and Copywriter

The History

The healthcare industry in India is one of the oldest known to mankind and is steeped in tradition. *Ayurveda* (Sanskrit: ayu: life; veda: knowledge of) or ayurvedic medicine is a comprehensive system of medicine based on a holistic approach that is more than 6,000 years old. This art of healing had been held in high esteem in ancient India. It was elevated to a divine status and Dhanvantari the practitioner of this art was defined as the God of Medicine. Even ordinary practitioners of this art the Ashwinikumars - were given a special status in mythology and folklore.

Two early texts (from centuries BC) of Ayurveda are the Charaka Samhita and the Sushruta Samhita. They outline remedies for practically every conceivable condition starting from cancer, diabetes, cholesterolemia to fever, pain, and depressive disorders. The main objective of Ayurveda is *removing the cause of illness with little or no side effects and not just curing the symptoms.* With such strong roots, Indians have always been health and medicine conscious, thus, putting the pharmaceutical industry on a firm footing from ancient times.

A Country of Contrasts

India is a country of contrasting cultural and economic backgrounds. Because of the vast cultural and economic diversities, disease profiles and subsequently treatment measures are very distinct and disparate. Diversities in India are not restricted only to culture, language, and tradition, but are also reflected in lifestyle patterns. Hence these affect the way the pharmaceutical market behaves. The pharmaceutical industry in India manufactures drugs and medicines to cater to the needs of a variety of disease conditions for patients from various economic strata of society. Medicines are accessible at registered retail outlets, in urban as well as rural areas, covering every corner of the country.

This huge contrast poses challenges as well as opportunities to the pharmaceutical sector. They are like two faces of one coin, two poles of one magnet. The challenges and opportunities that the Indian pharmaceutical industry is encountering currently have never been so gigantic. Nevertheless, because of its large and youthful human resource, low-cost, diversity, and democracy, it is becoming evident that this century is *'India's Century.'* It is not only that most of the jobs are coming to India; even for most of the developed countries it is essential to keep attracting Indian human resources for their betterment.

The Pharmaceutical Industry

Today, the pharmaceutical industry in India is in the front rank of India's science-based industries with wide ranging capabilities in the complex field of drug manufacture and technology. It holds a leadership position in the third world in terms of technology,

Continued on page 4.

A Look at the Pharmaceutical Industry in India

Continued from page 3.

Type	Quantity
Medicine	302
Chemistry	1,799
Biological Science	221
Analytical Technique	90

Table A. India's patent count.

quality, and range of medicines manufactured. From simple headache pills to sophisticated antibiotics and complex biotechnology derived products, almost every type of medicine is available in India. The industry has about 10,000 active units, out of which 300 are in large and medium sectors. More than 400 Active Pharmaceutical Ingredients (APIs) and more than 60,000 formulations in 60 therapeutic categories are manufactured here.

The organized sector of the pharmaceutical industry has played a key role in promoting and sustaining development in this vital field. International and Indian companies associated with this sector have stimulated, assisted, and spearheaded this dynamic development in the past 57 years and helped to put India on the pharmaceutical map of the world. Several Multi-National Companies (MNCs) produce a large volume of the world's production in India. The value of the pharmaceutical market in India was US $5 billion in 2003. It grew by 5.1% over 2002. Globally, the ranking of the Indian pharmaceutical industry is 4th in volume terms and 14th in value terms. Its share of the global pharmaceutical market is 1.8% in value and 8% in volume terms. The differential is largely due to the much lower market selling prices in India.

The pharmaceutical units in India are hi-tech hi-GMP and the industry has the largest number of US-FDA approved units outside the US, while the number of Drug Master Files filed with the US FDA was 126, higher than Spain, Italy, China, and Israel put together in 2003. In addition, the Indian pharmaceutical sector is mature and is supported by a strong manufacturing base.

Turnover in US$ Billion	Number of Companies		
	2002	2003	2004
>1.11	6	6	5
0.55 - 1.11	16	15	21
0.208-0.55	19	21	20
0.113-0.208	33	32	33
0.577-0.113	31	36	32

Table B.

For the year 2004, the Indian pharmaceutical industry registered an annual turnover of US $5.97 billion with a growth rate of 6.4%. Exports accounted for US $4.06 billion with a growth of 10.2%. 300 bulk drugs were manufactured and the bulk drug production was valued at US $2.08 billion. More than 60,000 formulations were manufactured in 60 therapeutic categories. The OTC market was valued at US $0.93 billion and the alternative medicine market touched US $0.97 billion. The export of bulk drugs and formulations in 2003 were to the extent of US $3.1 billion. The US $0.051 billion vaccine market is growing at the rate of 20% annually.

2004 saw six additional companies added to the US $0.55-1.11 billion bracket - *Table B*.

The Indian pharmaceutical market has some unique advantages. The country has a solid legal framework and strong financial markets. More than 9000 companies are publicly listed. It has a good network of world-class educational institutions and established strengths in IT. The country is now committed to an open economy and globalization. Above all, it has about 200 million middle class individuals with growing entrepreneurial spirit. India has the third largest English speaking scientific and technical manpower in the world. For the first time in many years, the international pharmaceutical industry is finding great opportunities in India. The process of consolidation, which has become a general phenomenon in the world pharmaceutical industry, has started taking place in India. With its rich scientific talents and research capabilities, India is well set to mark its place as the sunrise industry.

The Indian pharmaceutical industry is a success story providing employment for millions. It has a pool of personnel with high managerial and technical competence, as well as a skilled workforce. The employment is provided directly by the organized and small scare units or indirectly through the trade and ancillary industry. The organized sector, which comprises of MNCs and indigenous companies, employs 0.29 million individuals, while the small scale units hire 0.17 million persons. The area of distribution and trade offers job opportunities to nearly 1.65 million persons while the ancillary industry hires 0.75 million persons. Hence the pharmaceutical industry offers job openings for nearly 2.8 million persons in the country.

The Pharmaceutical and Allied Industries

The ancillary industry is also very well developed. All

A Look at the Pharmaceutical Industry in India

manufacturing equipment and machineries are locally available. While some excipients continue to be imported, India is self sufficient and well developed in the ancillary industry requirements.

A full range of pharmaceutical manufacturing equipment is locally produced as are glass bottles and vials, empty two-piece capsules, as well as soft capsules, blister and packaging films, aluminum and laminated tubes, and almost all other requirements for a fast growing vibrant formulation and bulk drug industry. India is important among the world leaders in the volume of production of most such items. India is an important exporter to both advanced as well as developing countries.

Research and Development

Investing in R&D, Contract Manufacturing, and Biotech Research

India's track record and development, particularly in the area of improved cost-beneficial chemical synthesis for various drug molecules, is excellent. The industry offers tremendous opportunity in the area of research and development without compromising quality. The R&D in itself is emerging as a rapidly growing industry with an estimated annual revenue of US $1.25 billion. There are almost a dozen major companies engaged in innovative research to produce New Chemical Entities (NCEs). The R&D expenditure is US $0.26 billion, 4% of sales (some companies are spending 6% of their sales on R&D).

Similar is the case of contract manufacturing. Because of economics, a genetically diverse population, a significant number of qualified providers with expertise in conducting and supervising clinical trials in accordance with global standards, India is emerging as an important hub for Contract Research and Manufacturing with patenting and certification activities assuming a prominent position in the country. In the changing scenario, acquisitions and mergers are no longer rare.

The biotechnology industry in India is in the nascent stages. About 85% of the fast growing biotechnology market is contributed by six products, all of which are manufactured in India for captive consumption. Among these are Erythropoeitin, Hepatitis B vaccine, Growth Hormones, Interferons, and Insulin. The total biotech market in India is estimated to be US $1.4 billion. About 60% of this market is accounted for by biopharmaceuticals; however, today, this market is gaining increasing importance.

Regulation of Medicines

About five decades back, when the Indian pharmaceutical industry was in its early stages, it depended heavily on imports. Today, the industry has evolved tremendously. It is at a level where it is almost completely self-sufficient and has also developed a sizable exports market globally. The regulatory apparatus has evolved along with the industry. While industry occasionally reports red-tape and over-regulation, in a huge diverse and democratic country like India, both regulation and distribution present their own challenges.

The industry has a well-evolved regulatory system and a well-defined legislation, which operates on the principles of licensing all activities related to drug manufacturing distribution and sales. It has defined systems to monitor the import of drugs, new product introductions, and good clinical and laboratory practices. The legislation also provides separate rules for psychotropic and narcotic drugs. The Indian Pharmacopoeia (IP) is an independent body, the work of which is looked after by the pharmacopoeial commission. Ayurvedic, siddha, unani, and homoe-pathic medicines have separately defined legislation and GMP requirements. The legislative requirements are continuously reviewed and upgraded due to fast and

Company	Market Share (%)			Growth (%)		
	2002	2003	2004	2002	2003	2004
Cipla	5.25	5.51	5.51	15	11	7
GlaxoSmithKline	5.92	5.64	5.44	-2	1	3
Ranbaxy	4.63	4.70	4.48	7	7	2
Nicholas Piramal	3.39	3.41	4.25	9	6	3
Sunpharma	2.92	3.08	3.29	18	11	14
Dr. Reddy's	2.80	2.64	2.43	20	-1	-2
Zydus Cadilla	2.41	2.45	2.42	17	7	5
Aristo	2.10	2.19	2.32	12	10	13
Abbott	2.32	2.29	2.31	7	5	7
Alkem	2.26	2.17	2.18	12	1	8

Table. Top ten companies in the Indian market.

Continued on page 6.

A Look at the Pharmaceutical Industry in India

Continued from page 5.

complex growth and with an eye on evolving international requirements.

The law defines products under price control and drug related advertisements are monitored through the Drugs and Magic Remedies Act.

The pharmaceutical industry has quality producers and many units are approved by regulatory authorities in the US, UK, and other advanced countries. India has the largest number of US FDA approved manufacturing facilities outside of the US. About 70 units have been cleared by US FDA and nearly 253 units have an approval from well-recognized international agencies. A large number of our new modernized units meet global standards. Newer and innovative dosage forms have been developed.

The prime mover in influencing the operating environment of the pharmaceutical industry is the government's drug policy. Currently, the Drug Policy of 1986 as modified and rationalized in 1994 is in force. The Drug Price Control Order (DPCO) outlines the classification of controlled and decontrolled products and methods of price fixation and revision. The DPCO has a three-tier control: on bulk drugs, formulations, and overall profitability. At present, there are 74 drugs under price control (40% of the retail market).

The National Pharmaceutical Pricing Authority (NPPA) monitors the fixing and revising of the prices of a number of drugs. Policy makers have realized the need for giving incentives for R&D to the Indian pharmaceutical industry. They also believe that the import liberalization process will assist the industry to further improve its quality and competitiveness.

Future Potential

The Indian pharmaceutical industry is mounting up the value chain. From being a pure reverse engineering industry focused on the domestic market, the industry is moving toward basic research driven, export oriented global presence, providing a wide range of value added quality products and services. Government policies will play an important role in defining the future of the pharmaceutical industry. The effect of product patent regime coming into effect from January 2005 is being watched with interest.

The Indian pharmaceutical companies have been doing extremely well in developed markets such as the US and Europe, notable among these being Ranbaxy, Dr. Reddy's Labs, Wockhardt, Cipla, Nicholas Piramal, and Lupin. Such companies have their strategies in place to leverage opportunities existing in formulations, bulk drugs, generics, novel drug delivery systems, new chemical entities, and biotechnology. By the year 2010, the R&D revenue is expected to touch US $4.89 (The Boston Consulting Group) while projection for the pharmaceutical market is US $25 billion (The McKinsey report).

With a prodigious knowledge pool and skilled manpower expertise in process chemistry and proven leadership in the field of IT, India has the necessary ingredients to become a dominant player in pharmaceuticals.

A Look at the Pharmaceutical Industry in India

Moreover, the Indian pharmaceutical industry is passing through a wave of consolidation with the objective of strengthening brand equity and distribution in what is essentially a branded-generics market. In the period 1995-98, the Indian pharmaceutical industry witnessed as many as 20 mergers, acquisitions, and takeovers.

In the coming years, India is poised to become a major player in the global healthcare industry. Quality coupled with the availability of technical and non-technical manpower availability makes India the ideal global center for pharmaceutical outsourcing.

Sources

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- IPMMA Newsletter
- Ernst and Young report
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- Interview with Mr. Ashwini Kumar, Drugs Controller General India
- Interview with Dr. Venkateswarlu, Deputy Drug Controller General India
- Interview with Mrs. Bhavna Shah
- ICRA Industry watch series - The Indian Pharma Industry
- ISPE India Affiliate Web site - www.ispeindia.org
- IDMA, OPPI, and BDMA Web sites

About the Authors

Shabbir Badami is a pharmacist and works with the corporate marketing team of ACG Worldwide. He has been associated with the Indian pharmaceutical industry for more than two decades and has worked with several multinational and Indian companies like Schering Plough (Fulford), Zydus Cadila, and Intas Pharmaceuticals. He has been responsible for brand promotion and marketing activities within India, as well as on a global level, giving him broad experience in the pharmaceutical industry.

Rajshri Srinivasan is a free lance journalist and copywriter. In her career span, she has interviewed eminent medical and pharmaceutical personalities and edited and written articles for financial, medical, and pharmaceutical journals and newspapers. During her time in the pharmaceutical industry, she also has trained field staff on various aspects of disease and drug profiles. Her work has taken her to nearly all parts of India.

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CONTACT US!

ISPE India Affiliate
c/o ACG Worldwide
10th Floor, Dalamal House
Nariman Point
Mumbai 400 021 India
Tel: 91-22-2287-2557
E-mail: espy@ispeindia.net

ISPE Asia Pacific Office
73 Bukit Timah Road
#03-01 Rex House
Singapore 229832
Tel: 65-6330-6755
Fax: 65-6336-2263
E-mail: asiapacific@ispe.org

Pharmaceutical Associations and Organizations in India

The Indian pharmaceutical industry is represented by various associations prime among them are: the Organization of Pharmaceutical Producers of India (OPPI), the Indian Drug Manufacturers' Association (IDMA), and Bulk Drug Manufacturers' Association (BDMA). These bodies effectively represent the pharmaceutical industry and issues facing it today. Another association that represents the industry are the trade associations Retail Drug Manufacturers' Association (RDCA) which represents and tackles issues facing the trade, retail, and distribution outlets. The Indian Pharmacy Association (IPA) represents all the aspects of pharmacy and pharmacy education including hospital pharmacy, community pharmacy, institutional pharmacy, and retail pharmacy.

• • •

Organization of Pharmaceutical Producers of India (OPPI)

Peninsula Chambers
Ground Floor
Ganpatrao Kadam Marg
Lower Parel
Mumbai 400 013 India
Tel: 91-22-24918123,
91-22-24912486, or
91-22-56627007
Fax: 91-22-24915168
E-mail: indiaoppi@vsnl.com

http://www.indiaoppi.com

The OPPI was first established on 27 December 1965 with Dr. Homi R. Nanji as the first President. This association was set up with the aim of promoting development of the pharmaceutical industry in India. The first annual report was published on 31 December 1966.

Today, OPPI is a premier vibrant and knowledgeable organization. Its scope of activities include OTC, animal health products, biotechnology among others. OPPI members (70 in number) manufacture 300 bulk drugs. OPPI members adhere to the code of pharmaceutical practices

Indian Drug Manufacturers Association (IDMA)

Head Office (Mumbai):
102-B, Poonam Chambers
Dr.A.B.Road, Worli
Mumbai 400 018 India
Tel: 91-22-24944624 or 91-22-24974308
Fax: 91-22-24950723
Email: idma@vsnl.com
or idma@idma-assn.org

Delhi Office:
2nd Flr, B-4/115
Safdarjung Enclave
New Delhi 110 029 India
Tel: 91-11-6171367
Fax: 91-11-6171369
E-mail: Idma_del@vsnl.net

http://www.idma-assn.org

IDMA was founded in 1961. Today, it is a premier association of the Indian pharmaceutical industry and has come to be regarded in government, media and industry circles as the Voice of the National Sector. IDMA members comprise large, medium, and small companies from all over India, manufacturing bulk drugs and formulations. IDMA plays a vital role in the growth and development of the industry, by taking up with the government major issues such as price control, patents, and trade mark laws, quality and GMP, R&D, Exports, etc. and promoting better understanding with the consumer organizations, the press and other media on problems faced by the industry.

Bulk Drug Manufacturers Association (BDMA)

C-25, Industrial Estate
Near SBH
Sanathnagar, Hyderabad
500 038 A.P. India
Tel: 91-40-23703910 or 91-40-23706718
Fax: 91-40-23704804
E-mail: info@bdm-assn.org

http://www.bdm-assn.org

The BDMA India was formed in 1991 with Hyderabad as its headquarters. This is an all India-body representing all the bulk drug manufacturers of India. The Association works for the consolidation of gains of the industry and serves as a catalyst between the government and the industry on the various issues for the growth of the industry.

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Key Principles and Considerations for the Testing of GxP Systems

by the ISPE GAMP® Testing SIG

This article presents key principles of GxP critical testing including test objectives and business benefits.

The final published GAMP® Good Practice Guide may differ from this article as a result of the ISPE external review.

Introduction

The GAMP® Testing Special Interest Group (SIG) has developed guidelines on the testing of computer and software based systems that impact product quality, patient safety, or patient confidentiality in the regulated healthcare industry. The *GAMP® Good Practice Guide: Testing of GxP Systems* aims to provide users and suppliers with guidance on the following commonly asked questions by those responsible for the testing of GxP systems:

- What should I test?
- How much testing is enough?
- How should I conduct tests?
- How should I document my testing?

Specifically, this GAMP® Good Practice Guide (GPG) is intended to take the principle of risk-based validation (as established in GAMP® 4) and provide practical advice on the application of this principle in the planning and execution of risk-based testing.

The intended audience for the *GAMP® GPG: Testing of GxP Systems* includes:

- users (responsible for the testing of GxP applications)
- suppliers (responsible for the testing of standard software and systems used in the regulated healthcare industries and for the testing of customized software developed for specific users)
- systems integrators (responsible for the configuration of the product into a specific application which may contain custom code)

The GAMP® GPG has been written by users and suppliers primarily associated with the pharmaceutical industry. This is reflected in some of the terminology defined and used throughout. However, the principles and guidance given may be of equal relevance in other sectors of the regulated healthcare industry, such as medical devices, biotechnology, biomedical, and healthcare.

Finally, in the preparation of the GAMP® GPG, the members of the SIG have deliberately chosen not to redefine general principles of testing best practice used in the wider software development and testing community. Focus is given to the practical application of these prin-

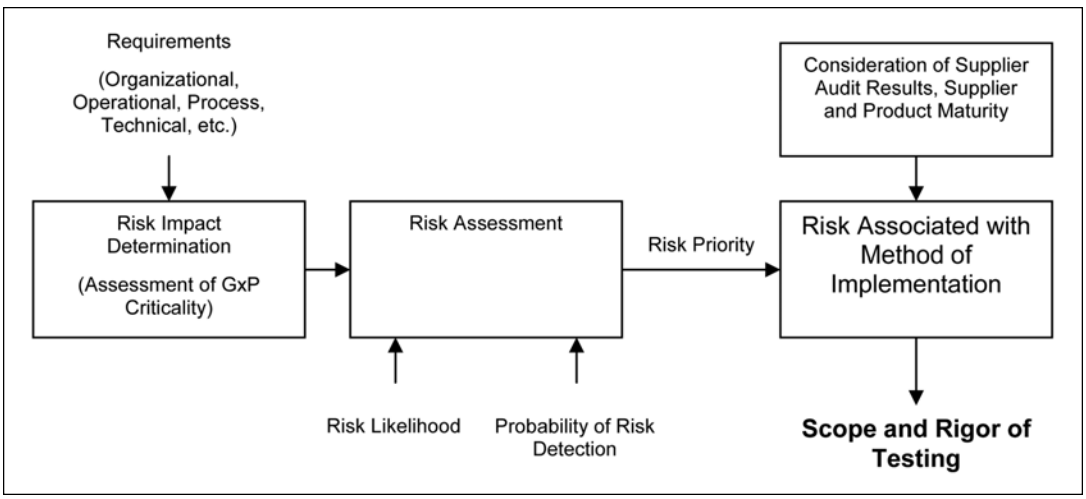

Figure 1. The use of risk assessment in determing the scope and rigor of testing.

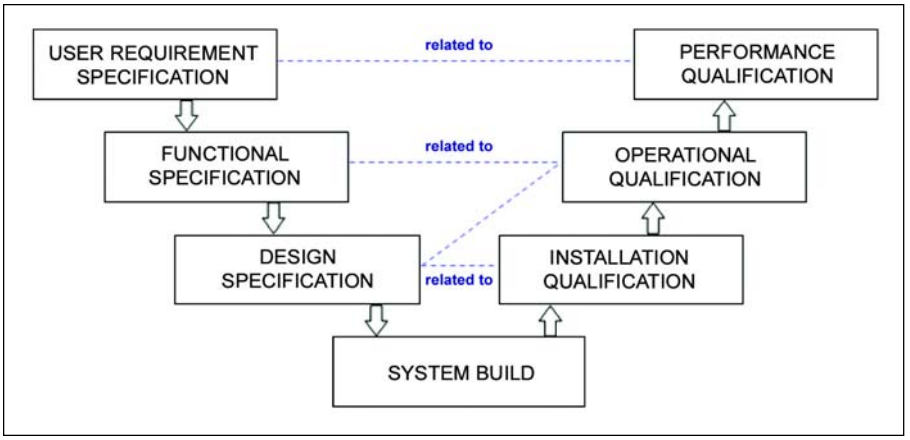

Figure 2. GAMP® 'V' model.

ciples to the testing of GxP systems and references for further reading are provided, where appropriate.

This article presents an extract from the GAMP® GPG, including test objectives and business benefits, and the key principles of GxP testing:

- use of risk assessment
- testing in the life cycle
- testing strategies
- testing and hardware/software categories
- testing responsibilities – supplier and user

This article includes an overview of user and supplier responsibilities and concludes with an overview of the content of the GAMP® GPG. The *GAMP® GPG: Testing of GxP Systems* is expected to be placed on the members' area of the ISPE Web site at the end of 2005 in electronic format.

The Objectives of Testing

For users, the basic underlying reason for testing a computer-based system or application is to provide a high level of assurance that the system is fit for its intended use, prior to the system being used in the live environment.

For suppliers, the basic underlying reason for testing is to prevent the presence of avoidable defects in the supplied system.

There are a number of different reasons why this is desirable, which may be summarized as:

- assuring the safety of users, consumers (patients), and members of the general public
- increasing user confidence in the system
- reducing the cost of on-going support

Business Benefit

The principle business benefit from testing systems is that it is more cost effective to move into the live environment with systems that are fit for purpose.

Anyone who has been involved in a project with insufficient or inappropriate testing learns that those problems exposed only after testing are usually the most time consuming and troublesome to resolve.

Where there is pressure to implement systems in timescales that are unrealistic, there are several potential knock-on effects:

- reduces the effectiveness and efficiency of the system at 'go live'
- increases the maintenance and support costs
- requires a costly program of corrective actions to be implemented, to correct faults, and meet the original requirements
- at worst, roll out a system that does not meet the basic user requirements

The net effect is to increase the overall cost of implementing and owning the system and to delay or prevent the effective and efficient use of the system.

Regulatory

Testing is a fundamental requirement of current good practice with regard to achieving and maintaining regulatory compliance. Although the need to test computer systems is defined by certain regulations, the way in which computer systems should be tested is not defined in detail in specific regulations. However, supporting guidance documents issued by various regulatory agencies suggest good practice in a number of critical cases.

The nature and extent of computer systems testing should be defined and justified on a system-by-system basis, and this may be based upon a documented risk assessment. However, it is a basic regulatory expectation that GxP computer systems require some degree of testing.

Failure to test may undermine any validation case and the compliance status of the system. Where discovered during regulatory inspection, this may lead to citations and warning letters being issued and possibly a failure to grant new drug/device licenses, license suspension, or products being placed on import restrictions.

These regulatory expectations are based on the basic principle that computer systems are tested to confirm that user and functional requirements have been met, and in order to assure data integrity. These, in turn, are driven by a regulatory need to assure patient safety and health.

Validation of systems to guarantee accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records should be considered as part of the complete life cycle of a computer system. This cycle includes the stages:

- Planning
- Programming
- Commissioning
- Operation
- Modifying
- Specification
- Testing
- Documentation
- Monitoring
- Decommissioning

Before a system using a computer is brought into use, it should be thoroughly tested and confirmed as being capable of achieving the desired results.

Any modification should undergo risk assessment in order to determine the extent of the required validation and regression testing. Alterations to a system or to a computer program should be made only in accordance with a defined procedure, which should include provision for validating, checking, approving, and implementing the change. Change control procedures should maintain an audit trail that documents time-sequenced development and modification of any systems documentation.

There are other regulations which may impact the testing of GxP systems, e.g., health and safety legislation, environmental control.

Key Principles

This section outlines the key principles used in the planning and execution of GxP systems testing and builds upon the philosophy of risk-based validation established in *GAMP® 4*.

Use of Risk Assessment

General Principle: the scope of testing should be determined by a justified and documented risk assessment, taking into account both the potential effect on product quality and safety and the intrinsic risk associated with the method of implementation.

As defined in *GAMP® 4*, Appendix M3, risk assessment should be a fundamental part of the validation process. This can be used to determine the appropriate nature and scope of testing, as described in this article.

The GxP criticality of the requirements will provide one indication of the risk impact. This requires that the user understand and interpret the applicable GxP regulations. Combined with risk likelihood and probability of detection, this will provide an indication of risk priority for each requirement.

Consideration of the supplier audit and the maturity of the supplier's processes and product (in terms of history of compliance with an appropriate quality system, number of existing users, length of time in market, user satisfaction, etc.) will indicate an appropriate scope and rigor of testing. For example, in the case of an established supplier, only positive case acceptance testing may be required. Where the supplier processes or product are less mature, it may be appropriate to conduct additional testing (negative case testing, software module testing, etc.).

The same risk assessment process should be applied when changes are made to the system.

Testing and the GAMP® Life Cycle

General Principle: testing should be carried out as part of a formal development life cycle and test cases should be written and executed against documented requirements.

It is an assumption within this article that the system requirements have been adequately defined and documented and that an appropriate development life cycle is in place. This guidance concentrates on the testing required within that life cycle.

GAMP® 4 describes a framework for specification and qualification from the user's perspective.

The terminology used in the GAMP® 'V' model is based upon well understood industry qualification activities and their relationship to hierarchical specifications.

From a regulatory perspective, the responsibility for qualification activities resides with the user. In a practical sense, testing is usually a shared responsibility of both the supplier and user, which should be agreed at the start of the project.

Figure 3 (based upon *GAMP® 4*, Figure 8.2) shows the different types of testing associated with various requirements and design specifications. Software module and some levels of integration testing are usually the responsibility of the supplier (software vendor or system integrator) whereas the user is usually responsible for the functional, acceptance, and performance testing (qualification).

The use of the terms 'testing', 'verification', and 'validation' has often been a source of confusion and inconsistency. Within this article:

- 'Testing' is one form of verification activity that usually forms part of the validation process.
- 'Verification' is used to describe a means of confirming that one or more specific requirements have been met.

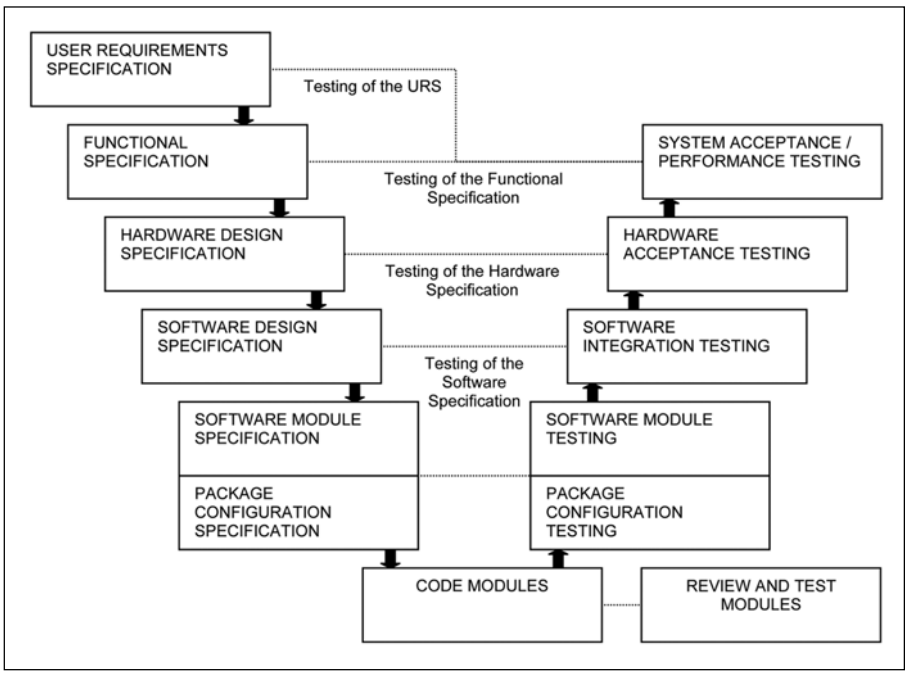

Figure 3. 'V-model' framework showing basic specification and test relationships.

- 'Validation' is used to describe an overall process.

This basic model is further developed for different software categories in the following sections and these may expand on the basic model shown above.

Testing Strategies

General Principle: testing should follow an agreed test strategy.

There are a number of points that should be considered when developing a test strategy. This may be as part of a separate test strategy document, or may be included in the Validation Plan.

Test Documentation

This section discusses the basic test documentation requirements, which are presented diagrammatically in Figure 4. For users, this test documentation, including any separate test summary report, will be summarized in the Validation Report (refer to *GAMP® 4*, Appendix M7).

Test documentation should be subject to independent review and approval. This is often conducted by a representative assigned by the relevant organization's quality function in accordance with their procedures.

When determining an appropriate test strategy, it should be kept in mind that the content of documents may be combined or included in another document, e.g., when testing small or simple systems:

- Although one-to-many relationships are shown in the diagram, in a simple system, a single document may include the test strategy, test protocols/test specifications, and test cases/test scripts, and a single test report may be all that is required.

- When testing small or simple systems, test inputs, test environment set-up, and expected results all may be covered within the test scripts, and a separate definition of test cases may not be required (this usually is the most common approach).

- The test strategy may form part of another planning document.

For larger or more complex systems the following also should be considered:

- Multiple test protocols or specifications may often be required. Each test protocol or specification should have an associated test report, and the test reports may be summarized into a test summary report (which is associated with a test strategy). It also may be useful to prepare test plans which will define:
  - location and timing of test phases
  - resources required for each phase
  - responsibilities for each phase
  - format of test references and incident references
  - planned coverage for each test phase (against established requirements)

- Test cases and scripts may be grouped into test groups or test sets (not shown) for ease of test planning, monitoring, and execution.

- Separate test cases may be prepared for some tests, which may describe:
  - complex test data sets
  - test methods
  - test input data
  - test environment set-up
  - expected results

In this case, test scripts may be used solely to document the sequence of actions (test steps) required to conduct a specific test. One test script may be used as the basis for conducting multiple similar test cases.

For all systems the test strategy should describe the use of appropriate test cases and/or test scripts, including test objectives(s), necessary pre-requisites, steps involved in performing each test, data to be recorded, evidence to be collected, and acceptance criteria.

Test Environment

There will typically be a test environment which is separate from the production environment and these environments may be separated logically, physically, or chronologically. The test strategy should consider the hardware, software, test data sets, user accounts, and reference documents that will be part of the test environment.

The test environment should be made as representative as possible of the final system. Differences should be documented and assessed for the level of impact introduced by the differences to allow additional tests to be planned for the final production system or environment if required.

The test environment should be documented and controlled to a level of detail that would allow it to be reconstructed if necessary.

Where test hardware/software/data/user accounts are applied to the final system, controls should exist to ensure that they can either be removed cleanly or be isolated from use within the final production environment.

Test Execution

When considering test execution, the test strategy should consider the methods used for manual test execution and the methods for automated test execution.

When automatic test tools are used, special care should be taken to assure they are fit for their intended purpose.

Test Results Recording and Reviewing

The test strategy also should consider the recording and review of test results, including the method for recording and filing passed and failed tests. The method for documenting, processing, and closing down test incidents and the requirements for test witnesses also should be addressed in the test strategy as well as the review of test results and associated documentation.

The witnessing and reviewing requirements should reflect the relative risk associated with the system element under test. For example, for testing of simple, low risk elements or for tests where actions and results are automatically captured, a single suitably qualified tester signing off a test may be appropriate provided that the final results are independently reviewed. For complex or critical functions, multiple testers from various backgrounds (e.g., supplier, engineer, and user production staff) may be appropriate.

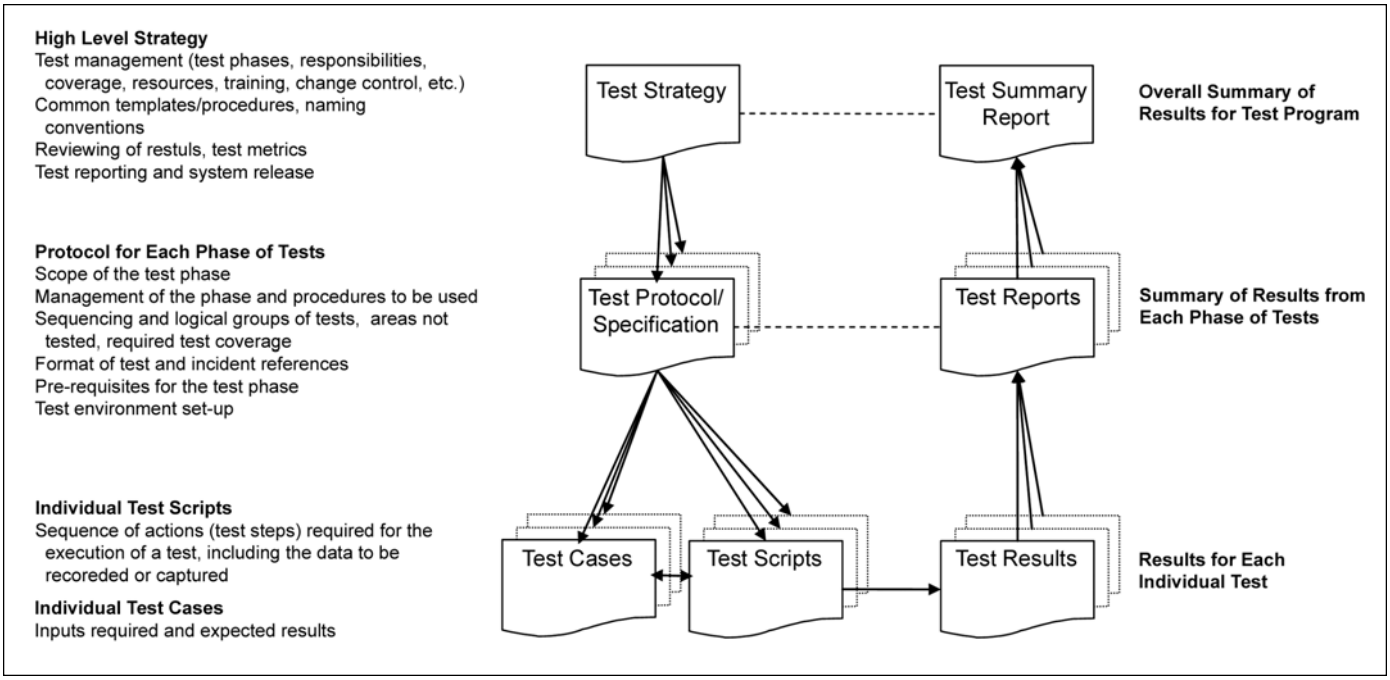

Figure 4. Basic test documentation model.

Test Reporting and System Handover

The test strategy also should define key considerations when producing test reports and planning to handover the system from one test phase to another, including the format of and responsibility for final test reports, the method of and authority for system handover, and any contractual implications.

The method for system handover may need to consider circumstances in which a conditional handover can be made – for example with workarounds in place, test incidents still open or tests still to be completed because they are not possible outside of the final environment.

The method also should be defined for ensuring that the baseline recorded at the end of one test phase matches the baseline recorded at the start of the next phase (e.g., to ensure that the software at the start of site acceptance testing is the same as that released at the end of factory acceptance testing).

Testing in the Operational Phase

Once a system has been implemented, there may be a need for future change. Depending on the scope of the change, there may be a requirement for developing a test strategy to define the scope and rigor of testing.

Test Metrics

Test metrics provide various measures of testing. These allow the test process to be assessed, and therefore, they may be adjusted in a managed manner. Testing often takes a large part of the software development life cycle, and consequently, making it as efficient as possible is important for good management. In the quality management cycle of:

- Plan
- Do
- Check
- Act

Test metrics provide a check on the effectiveness of testing.

Test metrics provide information that can justify, refine, and/or improve the amount and type of testing used or in certain circumstances to define that the system is of an acceptable quality for release. The metrics provide information that is fed into risk assessments and allow managers to manage the system qualification process.

Managers should decide what aspects of the life cycle and testing they would like to control and then look for suitable metrics for those features.

Testing and Hardware/ Software Categories

General principle: as with other validation efforts, the testing strategy should reflect risk to product quality, patient safety, and data integrity. The nature of the software and hardware is one factor affecting this risk.

GAMP® Hardware and Software Categories

Since the risk of system failure increases with the progression from standard software and hardware to custom (bespoke) software and hardware, a classification of system elements into categories can help support a risk-based test strategy. Categorization of hardware and software, as described in *GAMP® 4*, Appendix M4, is assumed throughout the remainder of this article.

Hardware and Software Maturity

In deciding the test effort required for a system element, the maturity of the hardware or software also may need to be taken into account with additional effort devoted to test elements that are not considered 'industry proven.' This

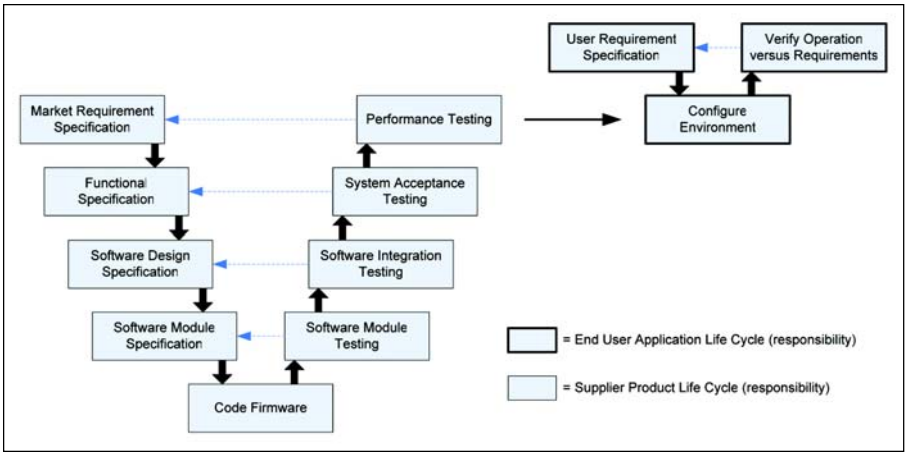

Figure 5. Test framework for GAMP® software category 2.

can apply both to the maturity of the standard elements within a supplier's product and to the maturity of custom elements re-used from one application to the next.

For example, where a user is unable to accept the standard functionality offered by a supplier and requests a modified module, additional testing of the differences between the standard offering and the modified module is likely to be appropriate. Conversely, where a custom module is re-used in further applications, a reduced test effort is likely to be appropriate.

Testing Responsibilities - Supplier and User

General principle: where possible, users should seek to benefit from supplier quality assurance processes and associated testing.

Where a supplier has been audited and their quality management system found to be acceptable, the user may benefit from the testing already carried out as part of the product development life cycle. This may reduce the need for additional testing carried out by the user.

Regardless of the categorization of the software acquired by the user, all software would at some stage have been written for the first time by the supplier and could be considered as customized code during development by the supplier (synonymous with GAMP® software Category 5). Therefore, it is appropriate to consider the supplier's development life cycle (and any integral testing) when considering the scope and nature of testing to be conducted by the User.

Therefore, the testing of the software (or system) is a combination of:

- testing conducted by the supplier during basic development of the standard product
- testing conducted by the supplier (or integrator) during application specific development
- testing conducted by the user

Where there is auditable evidence that supplier testing is appropriate to the risk associated with the software or system, the user need not repeat such testing, as long as an appropriate Supplier Audit has been conducted. This should include a review of general supplier test activities and a review of system, software, or release specific testing. User testing should then focus on customized, configured, and critical functions.

The examples that follow show supplier and user development and test activities and are based on the basic testing 'V-model' life cycle shown earlier in this article. Some suppliers may use alternative development life cycles other than those based upon the 'V-model.'

Alternative development life cycles may be perfectly acceptable - the important issue is to focus on the purpose, nature, and scope of the suppliers documented test activities and the veracity of the test results. Where these are appropriate to the risk associated with the users application of the software, these activities need not be repeated by the user.

The sections below describe the approach to testing various software categories. Note that most systems contain multiple categories of software, and the system specific approach to testing may be a combination of these models.

Operating Systems (GAMP® Software Category 1)

It is not necessary to specifically test operating systems, as these are qualified as part of the infrastructure and challenged indirectly by the functional testing of associated applications.

Firmware (GAMP® Software Category 2)

The creation of firmware typically involves code written by the supplier. Therefore, the supplier should gener-

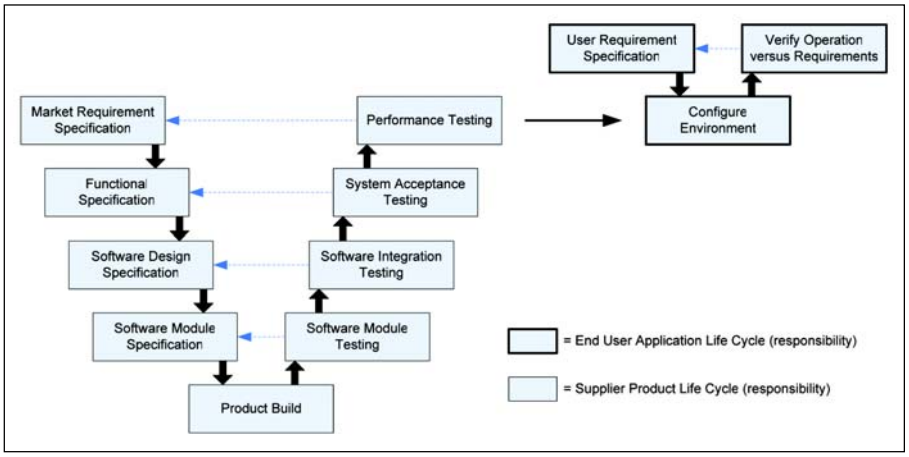

Figure 6. Test framework for GAMP® software category 3.

ally follow a full product development life cycle (either to the life cycle recommended for GAMP® software Category 5 or to equivalent standards).

On purchasing an item with embedded firmware, the user does not need to repeat testing already carried out by the supplier, assuming that the supplier has a suitable quality management system in place and that the firmware is 'standard' (rather than developed or modified specifically for the application).

The application life cycle verification activities can be limited to verifying the firmware version and that the parameters entered give correct operation as defined in the user requirements.

Standard Software Packages (GAMP® Software Category 3)

The creation of standard software packages typically involves code written by the supplier. Therefore, the supplier should generally follow a full product development life cycle (either to the life cycle recommended for GAMP® software Category 5 or to equivalent standards).

On purchasing a standard package, the user does not need to repeat testing already carried out by the supplier, assuming that the supplier has a suitable quality management system in place and that the package is 'standard' (rather than developed or modified specifically for the application).

The application life cycle test activities can be limited to verifying the installed software package version and that the parameters entered give correct operation as defined in the user requirements.

Configurable Software Packages (GAMP® Software Category 4)

The creation of configurable software packages typically involves code written by the supplier. Therefore, the supplier should generally follow a full product development life cycle (either to the life cycle recommended for GAMP® Category 5 or to equivalent standards).

In order to meet the requirements of the specific user, the software is then configured by the supplier, a systems integrator, or the user.

On purchasing a configurable package, the user does not need to repeat testing already carried out by the supplier, assuming that the supplier has a suitable quality management system in place and that the package is 'standard' (rather than developed or modified specifically for the application).

The application life cycle test activities can be limited to those which verify that the configuration has been correctly implemented such that the overall system performs as defined in the user requirements.

It is not usually necessary for the users to test functions within the system that the user does not intend to utilize and where:

- Supplier testing adequately demonstrates that unused functions do not interact with functions configured and utilized by the user.

- Supplier release notes adequately describe the extent of any interactions between functions that are and are not utilized by the user.

Custom (Bespoke) Software (GAMP® Software Category 5)

Where users (possibly working with their suppliers) develop a system that solely contains custom software, Figure 8 shows the users life cycle that will be followed. Note that because the system is not based upon a standard supplier product, there is no supplier's life cycle to be considered.

In the more likely case where custom development is required to modify or customize a supplier's standard product for use in a specific application, the full development and testing life cycle needs to be followed for custom modifications. In addition, the suppliers standard configurable software also will need to be tested as for GAMP® software Category 4.

Figure 9 looks at the development of custom modules to be added onto a standard product (for example to provide an interface to a separate third party software product). The life cycles given above can be followed for testing the standard package, but the custom modules require a full development and test life cycle of their own.

User Considerations

Ultimate responsibility for testing and confirming that the system meets its requirements lies with the user. It is likely that the user will be acquiring their system from one of two sources:

- Supplier: who is developing a product or a custom system

- Integrator: who is configuring a system specifically for the user

An integrator is simply a particular type of supplier. Their supply is likely to be based on commercial off-the-shelf products which they have configured for the particular user application.

Although the role of the integrator is highlighted in certain sections of this article, the general use of the term Supplier also includes integrators.

The user should be aware of how their application has been developed and of the methodologies adopted by the supplier and associated testing.

Depending on whether a supplier is developing a custom system or an integrator is developing a system based on configurable software, the user should confirm the approach being adopted. Custom development should follow a development life cycle appropriate for GAMP® software Category 5. Specification and configuration of commercial-off-the-shelf software should follow a development life cycle appropriate for GAMP® software Category 4.

General Considerations

The user can minimize the level of testing required by:

- avoiding unnecessary customization, e.g., by modifying the business process, if this is practical, to match an off-the-shelf application

- seeking to leverage the testing already executed by the supplier, or possibly by the user, on identical systems or pieces of equipment

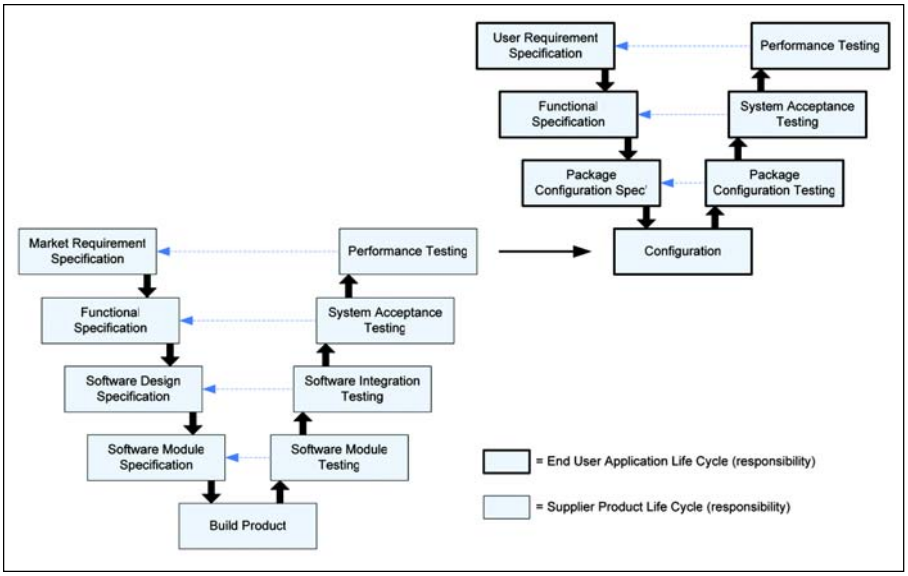

Figure 7. Test framework for GAMP® software category 4.

In an ideal situation, user testing may be reduced to a level which confirms that the system meets the user requirements and has been tested previously with existing documentary evidence for verification.

The user should confirm that the supplier can meet the requirements described in this article. This may be done by an audit process (see *GAMP® 4*, Appendix M2), but whatever process is used, it should be documented, and where shortfalls are identified, the user needs to assess and mitigate the risks on a case-by-case basis.

In cases where suppliers do not have a defined methodology for the testing of their systems, users should consider additional testing. Where additional testing does not appropriately mitigate the users risks, it may be appropriate that alternative products and/or supplier be sought.

Users should encourage suppliers to address any shortcomings in their testing processes and documentation in a systematic manner, possibly as part of a program of continuous improvement under a registered quality system such as ISO 9001:2000, TickIT, Software CMM (or CMMI), or an appropriate testing maturity model.

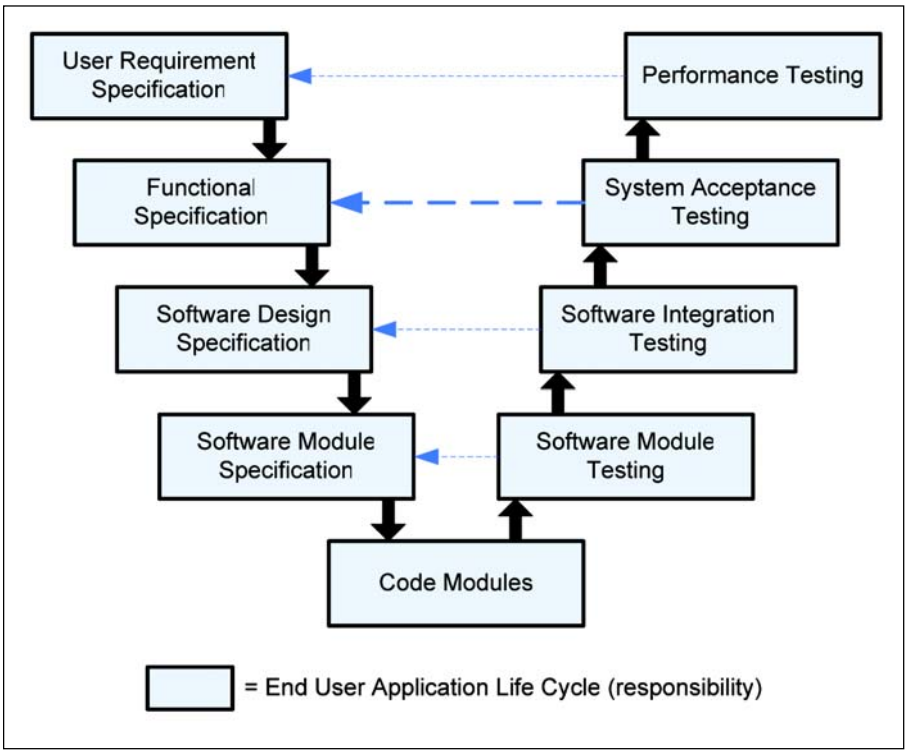

Figure 8. Test framework for GAMP® software category 5.

The discussion of supplier process maturity below, refers to a good track record within the healthcare industry and a history of compliance with an appropriate quality system. Product maturity refers to a history of good product quality with a high level of customer satisfaction in the healthcare industry.

Alternatively, any deficiencies may be addressed in a one-off product or on a project basis as part of a plan of corrective actions agreed between the user and supplier, and this may include additional user testing.

Users may consider that, where the systems are of a highly critical nature, it may be appropriate that corrective actions to the supplier's quality system have a suitable contractual basis. Should suppliers then fail to conduct or document appropriate testing agreed under such a contract, users may be able to reclaim the cost of additional user testing.

Products that are widely used in the healthcare industry are, generally, considered to be lower risk likelihood than new products or those developed for general markets and used infrequently in the healthcare industry.

Suppliers who are experienced in the industry pose a lower risk likelihood due to their greater understanding of regulatory requirements and the risk associated with certain user product profiles.

Users should seek to purchase low risk products and to do business with low risk suppliers. Market review and an initial Supplier Audit should establish the relative maturity of a product and/or supplier processes and this should include a consideration of supplier testing.

Regardless of the maturity of the product or the supplier processes, the same level of testing should be conducted by all suppliers and this should

be appropriate to the user's determination of risk. This level of testing should already be in place with an established supplier and this can be assured by initial Supplier Audit and routine surveillance audits.

Users may choose to select products which fall into the high/medium risk category, but this will usually result in an increase in audit or user testing to ensure that the increased risk potential is appropriately addressed (see *GAMP® 4*, Appendix M2 for further details).

Agreeing Roles and Responsibilities

Where the Supplier Audit identifies shortcomings, the user can define appropriate actions to mitigate the risks. These would often be detailed within the contract or project plan as agreed by all parties. The level of testing and responsibilities required from both the supplier and user depend on the category of system being supplied.

In cases where supplier and product maturity indicate a low level of risk, the user may determine that they only need to be involved in the execution of User Acceptance testing with all other testing conducted by the supplier. In cases where supplier and product maturity indicate a high level of risk, the user may determine that they may also need to witness supplier testing, conduct additional negative case testing, or repeat poorly documented supplier testing.

General guidance on appropriate user/supplier responsibilities for testing different software categories is described under Key Principles in this article.

Determining Appropriate Test Evidence

Users should define what level of test evidence should be in place before the system can be considered to be validated, and how long that evidence should be available. The value of such test evidence changes over time and the retention period and the appropriate level of test evidence to be retained can be determined by risk assessment.

The user should build on evidence of testing provided by the supplier and aim not to duplicate test evidence. Where supplier test evidence is relied upon to support the validation of the system, users should either request copies of the supplier test evidence, or should assure themselves that suppliers test evidence will be retained and available for the necessary period. This may be assured as part of the Supplier Audit, or specific contractual terms.

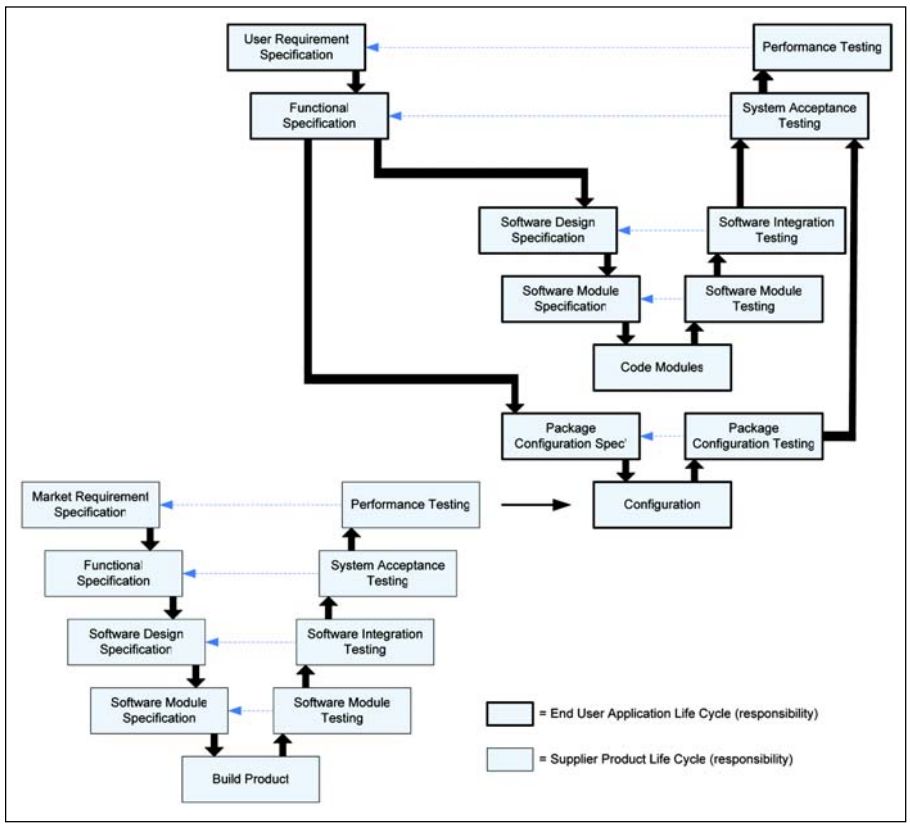

Figure 9. Test framework for GAMP® software category 4 and 5 (combined).

Supplier (Integrator) Considerations

The nature of the healthcare industry requires that systems are developed, documented, and tested following good engineering practices. Suppliers should seek to develop and supply systems in accordance with a defined methodology such as that described in GAMP® 4. Good quality testing conducted by the supplier is likely to allow reduced testing by the User.

Supplier Audit

For systems containing software Category 4 or 5 software (or highly critical software of Category 2 or 3), it is usual for a user to carry out an audit of the supplier's quality system. The supplier should make themselves aware of the areas likely to be covered by that audit (see *GAMP® 4*, Appendix M2, for example). Being aware of the requirements and preparing for the audit will assist both parties in determining any shortfalls and where specific remedial actions or testing may be required. The audit may be an important step in developing a long term relationship between the supplier and the user.

Use of Third Party Products

Where the supplier makes use of third party products at any stage of their product development they should consider the quality of their own suppliers and their suppliers' products when determining an appropriate level of testing. The *GAMP® GPG: Testing of GxP Systems* provides assistance to users in the healthcare industry as to how they should approach the testing of supplied systems. The same approaches need to be adopted by suppliers when they make use of third party products.

Suppliers should be in a position to verify that products they use have been

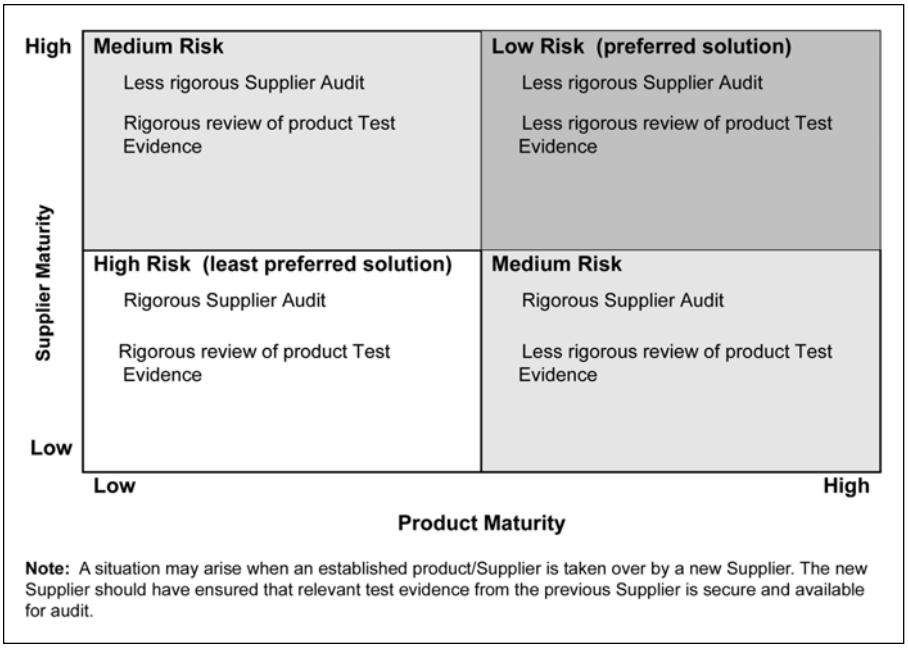

Figure 10. Supplier and product maturity model.

developed using good engineering practices and that they have taken all possible measures to ensure this. This may involve, but not be limited to:

- Audits of developers of the third party products, this may be restricted to a postal audit, but consideration should be given to carrying out a full audit and if not needed then the reasons for this documented.
- Specific testing of applications of these products, e.g., where specific configurations of automated test tools are used these should be tested and produce documentary evidence that the test tool does what it is supposed to do
- Where third party products are considered to be a "widely used industry standard" then suitable evidence to this should be available.

Similar to users, integrators should seek to leverage the testing already executed by their supplier(s), or testing conducted by themselves on identical systems or pieces of equipment.

Contractual Issues

Testing is often a milestone linked to a stage payment. Key points for success include:

- Agree and document early in the project the stages and scope of the testing required – (an assessment of the critical functions and risk to end-user can assist with this).
- Ensure the test script links back to the design specifications (possibly via the use of a traceability matrix).
- Involve the supplier and user personnel in the review and approval of test scripts that are relevant to them. This should ensure that all parties understand the test objectives and should limit the effects of subsequent changes.
- Ensure all equipment, including spare parts, are available prior to the commencement of testing.
- Ensure that time planned for document reviews factors in the expected size and complexity of the item to be reviewed.
- Ensure all personnel are available when required, including system developers, in case of a deviation occurring which requires a change to the system.
- Prepare contingency and recovery plans.

On completion of the testing, agreement on any outstanding actions or deviations should be reached between the supplier and user in order for the project to progress to the next stage.

Content of the SIG Guidelines

The *GAMP® GPG: Testing of GxP Systems* begins with material included in this article. Key principles are further considered and additional practical advice and guidance in the planning and execution of such testing are provided. This includes consideration of:

- Testing Policies
- Test Planning and Test Management
- Test Protocols, Cases, and Scripts
- Test Environments
- Test Execution
- Test Results – Recording and Reviewing
- Test Reporting and System Handover
- Testing in the Operational Phase

Case studies are provided, which apply the key principles to:

- Process Automation Systems
- Configurable IT Systems
- Analytical Instruments
- Desktop Applications
- Infrastructure and Interfaces

Templates and examples are included that should allow the less experienced reader to quickly develop a series of appropriate documents, suitable for planning, executing, and reporting on the testing of a GxP system.

Glossary

The following provides a definition of the specific terms used in this article. The source is listed at the end of each definition.

Acceptance Criteria - The criteria that a system or component must satisfy in order to be accepted by a user, customer, or other authorized entity. (*GAMP® 4*, IEEE)

Acceptance Test - Formal testing conducted to determine whether or not a system satisfies its acceptance criteria and to enable the customer to determine whether or not to accept the system. See also Factory Acceptance Test (FAT), Site Acceptance Test (SAT). (*GAMP® 4*, IEEE)

Firmware - The combination of hardware device and computer instructions and data that reside as read-only software on that device. (IEEE)

Functional Testing - Testing that ignores the internal mechanism of a system or component and focuses solely on the outputs generated in response to selected input and execution conditions. Also known as black box testing. (*GAMP® 4*, IEEE)

Hardware - (1) Physical equipment used to process, store, or transmit computer programs or data.(2) Physical equipment used in data processing, as opposed to programs, procedures, rules, and associated documentation. (IEEE)

Hardware Testing - Testing carried out to verify correct operation of system hardware independent of any custom application software.

Installation Qualification (IQ) - Documented verification that a system is installed according to written and pre-approved specifications. (*GAMP® 4*, PDA)

Integration - The process of combining software components, hardware components, or both into an overall system.Sometimes described as software integration and system integration respectively. (IEEE)

Integration Testing - (1) Testing in which software components, hardware components, or both are combined and tested to evaluate the interaction between them.(2) An orderly progression of testing of incremental pieces of the software program in which software elements, hardware elements, or both are combined and tested until the entire system has been integrated to show compliance with the program designed, and capabilities and requirements of the system. (IEEE)

Module Testing - Testing of an individual hardware or software components or groups of related components. (IEEE)

Negative Testing - Testing aimed at showing that software does not work. (BCS)

Operational Qualification (OQ) - Documented verification that a system operates according to written and pre-approved specifications throughout all specified operating ranges. (*GAMP® 4*, PDA)

Performance Qualification (PQ) - Documented verification that a system is capable of performing or controlling the activities of the processes it is required to perform or control, according to written and pre-approved specifications, while operating in its specified operating environment. (*GAMP® 4*, PDA)

Positive Testing - Testing aimed at showing that software does meet the defined requirements.

Qualification - The process to demonstrate the ability to fulfill specified requirements. (*GAMP® 4*, ISO)

Software - Computer programs, procedures, and associated documentation and data pertaining to the operation of a computer system. (IEEE)

System Testing - Testing conducted on a complete, integrated system to evaluate the systems compliance with its specified requirements. (IEEE)

Test - (1) An activity in which a system or component is executed under specific conditions, the results are observed or recorded, and an evaluation is made of some aspect of the system or component. (2) Determination of one or more characteristics according to a procedure. (*GAMP® 4*, IEEE), (*GAMP® 4*, ISO)

Test Case - A set of test inputs, execution conditions, and expected results developed for a particular objective, such as to exercise a particular program path or to verify compliance with a specific requirement. (*GAMP® 4*, IEEE)

Test Plan - A document describing the scope, approach, resources, and schedule of intended test activities. It identifies test items, the features to be tested, the testing tasks, who will do each task, and any risks requiring contingency planning. (*GAMP® 4*, IEEE)

Test Procedure - Detailed instructions for the set-up, execution, and evaluation of results for a given test case. (*GAMP® 4*, IEEE)

Test Script - Documentation that specifies a sequence of actions for the execution of a test. (IEEE)

Unit Testing - Testing of individual hardware or software units or groups of related units. (IEEE)

Validation - Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes. (*GAMP® 4*, FDA)

Verification - Confirmation, through the provision of objective evidence that specified requirements have been fulfilled. (*GAMP® 4*, ISO)