# The "Business" of Risk Assessment in the World of Computer System Validation

By ***Emma Barsky and Len Grunbaum***

## INTRODUCTION

*In the highly competitive pharmaceutical industry, with increasing and increasingly stringent regulatory demands and an insufficient number of qualified personnel to achieve them, "risk assessment" has become more than a catch phrase; it is an essential part of doing business.*

Is risk assessment just another trend? Is it a regulatory requirement? We see it as neither. Rather, we believe that risk assessment is a necessary and practical business tool to help company management define and develop effective and efficient processes necessary to secure a marketplace position for the company through identifying, prioritizing, and remedying regulatory deficiencies in a stepwise, logical manner. Such a risk assessment approach is necessary to assure the future of a company and to maximize its profitability.

We will examine the subject of risk assessment in the world of computer systems validation from a business perspective. Defining risk, from a business perspective, as the "possibility of financial loss," we will outline the validation-related steps and scenarios that company management should consider in order to make sound assessments regarding the financial impact of regulatory deficiencies. Addressing any regulatory issue that represents a financial risk to the future of a company should be the highest priority and main responsibility of company management.

We are not the only ones to look at risk assessment through a business prism rather than a regulatory one. When you read the draft guidance documents issued by the Food and Drug Administration (FDA) in May 2004 dealing with pre-marketing risk assessment, development, and use of risk minimization action plans, and good pharmacovigilance practices and pharmacoepidemiologic assessment, you get a sense that the agency is thinking along these same lines. While draft guidance is for comment purposes only and not for implementation, and while the referenced drafts relate to "...risk assessment activities for drug and biological products" specifically, and do not directly relate to the subject of this article, the fact that the FDA is considering the risk assessment concept as a tool to improve the benefit-risk balance is, in itself, significant.

While we recognize that there may be issues outside the regulatory environment or the direct control of company management (e.g., war, economic conditions) that can affect company finances, we will concentrate on examining some of the regulatory risks and their respective symptoms that rise to the level of representing a direct threat to current or future company earnings. These, of course, must be remedied first.

Let us now take a look at how we, the industry, can embrace and adapt this approach to improve our internal practices and maximize our financial benefits.

## REGULATORY COMPLIANCE as a BUSINESS PRIORITY

The pharmaceutical industry, which employs us, has two facets. One is the humanitarian "face," with the noble cause of protecting and enhancing human

lives. It is that "face" that glorifies Noble Prize winners, nurtures discoveries, promotes innovation, and builds on knowledge. This "face" is about people and their welfare, scientific and technological progress, dedication and commitment. And we are all proud to be a part of it.

The other "face" of our industry is defined as highly competitive and pragmatic, with tough go/no-go decisions, strong pipelines, clairvoyant global vision, sales and marketing, revenues, and headline news. This is the face we all know as "business," although we are sometimes reluctant to acknowledge it. But, in all honesty, it is that which provides our employment, pays our bills, and permits us to buy things. It is this side of the pharmaceutical industry that ultimately places the company on the map, gives it recognition and the ability to leverage on its influence. And, it is this aspect of the industry that needs to be closely overseen by company management.

So, what does "business" mean in this context and how can one secure its success? In a nutshell, it is the firm's ability to have quality products on the market, at the least possible expense, in the shortest amount of time, and with maximum profitability. There are multiple and complex infrastructure components that contribute to this outcome, one of which is "regulatory compliance."

While many think of regulatory compliance merely as a means of supporting the "human" side of the industry through enforcing and ensuring safety, efficacy, and the quality of a drug product, it is equally important as a means to create, ensure, and build on business successes. "How?" you may ask. "Simple," we say.

The FDA perceives noncompliance with regulations as "lack of quality and controls." This results in the need to correct regulatory deficiencies. The outcome of such need signifies the loss of revenue and time, which translates into financial loss. Regulatory noncompliance, the unwillingness or inability to fix it, as well as the misinterpretation of the regulations, translate into increased material and labor costs associated with additional work, hiring costly industry experts, and troubleshooting, all of which can be avoided when quality is part of the process in the first place. Fixing regulatory noncompliance issues extends the timeline for completing all tasks, thus preventing companies from collecting revenues within anticipated timeframes.

Compliance, on the other hand, places your product ahead of some competitors, secures a good standing with the FDA, and results in cost savings at the end of the day through minimization of submission review times and the minimization of scrutiny associated with new product approval.

With the new FDA current Good Manufacturing Process (cGMP) initiative, FDA oversight is related to the degree of manufacturer product and process understanding, process significance to the safety of the product, product critical need or its significant public health impact, and the robustness of the quality system controlling the process. Furthermore, "...compliance status or compliance history of the manufacturer will continue to influence the intensity of FDA's oversight."[1] These factors will determine the frequency and scope of inspections, both of which, more often than not, interrupt normal business operations. Anything that directly affects profits or losses is a business priority. Thus, regulatory compliance is a business priority.

With this principle in mind, we will describe examples of regulatory conditions in the area of computer system validation that are conducive to financial loss. We will assess and quantify the possibility of such losses, as well as suggest ways to minimize these losses, or in other words, maintain and maximize gains.

We provide, below, a practical process for company management to follow. You may think that this is an unconventional approach to the risk assessment issue, but it surely makes sense from the business perspective.

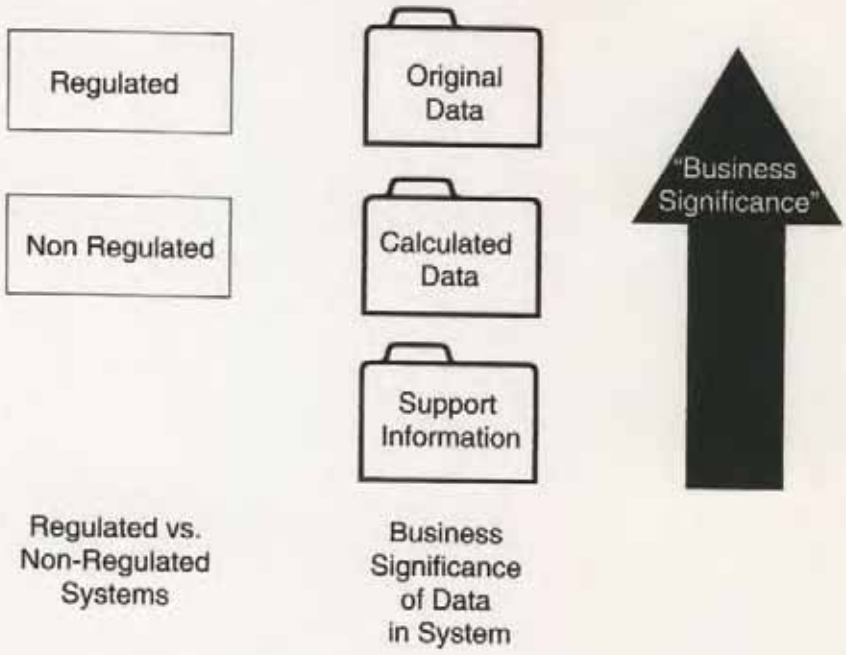
## OUR RISK ASSESSMENT MODEL

"Quality and productivity improvement share a common element - reduction in variability through process understanding (e.g., application of knowledge throughout the product lifecycle)."[2] To change it slightly, we hypothesize that regulatory compliance and business success share a common element: increased profitability at the end of the day.

Identifying compliance risks and determining how likely it is that these risks will become actual financial losses is certainly a start, but it is not enough. Company management also must determine what the dollar impact on the company will be should that

*Figure 1*

**Relative Business Significance of Systems and Data**




happen, how much money the company can afford to lose, and the steps to take to minimize potential losses. We boil this thinking down to four basic questions for company management to answer:

- How likely is financial loss?
- How much can be lost?
- How much financial loss are you willing to assume?
- How can financial loss be minimized?

## HOW LIKELY IS FINANCIAL LOSS?

The possibility of financial loss is directly related to the existence of regulatory deficiencies. The only true way to determine whether there exists the possibility of financial loss due to regulatory non-compliance is to measure company operations against applicable regulations. This is the traditional "gap" analysis, in which company processes are compared against regulatory requirements (e.g., 21 Code of Federal Regulations (CFR) Part 11 and pertinent predicate regulations), expectations as provided in guidance documents (e.g., computerized systems used in clinical trials) and inspector training materials (e.g., compliance program guidance manuals). Each gap, by definition, represents a potential regulatory risk.

In the world of computer system validation, the primary risks are twofold:

(1) The failure to validate when you should
(2) The failure to validate properly when you do

### *Failure to Validate*

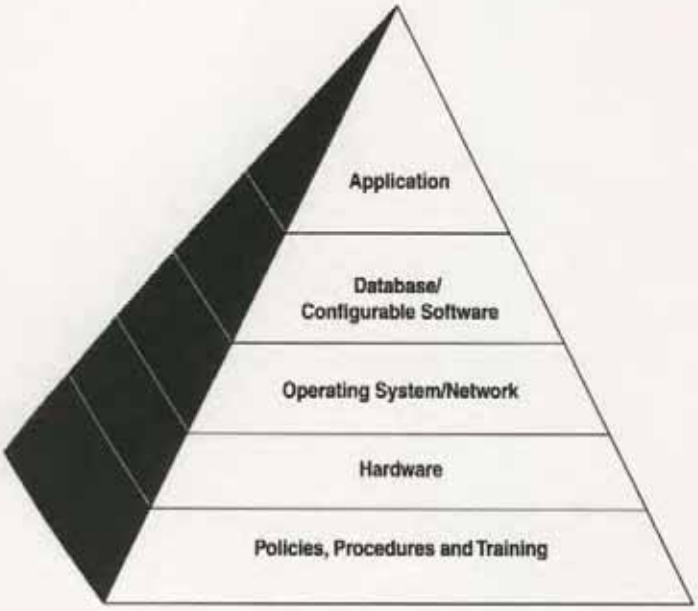
Failure to validate also has two manifestations:
(1) Systems are simply not validated
(2) "Wrong" systems are validated

Organizations will tend not to validate systems when management and staff lack an understanding of what validation is and why it is important. The following are symptoms of this condition:

- Lack of policies and procedures governing how systems are developed and deployed
- Because of the lack of policies and procedures, systems are developed and deployed

*Figure 2*

**Scope of Computerized Systems**




in an "ad hoc" manner, with no consistency between development or deployment efforts

- Documentation supporting development or deployment practices are inadequate, when such documentation exists at all

- Staff is not trained in regulatory or business needs to ensure that the system performs as intended and will consistently do so

These symptoms tend to show up more in small and start-up companies because these organizations may not have the infrastructure to accommodate quality practices, including validation. Additionally, company management may decide to apply resources to production operations that will more quickly generate revenue.

Organizations tend to validate the "wrong" systems when management and staff do not have an appreciation of the business significance of systems and data. An organization may have many computerized systems in its environment, but not all of them are subject to FDA regulations. For example, a clinical data management system or a toxicology system will be subject to agency scrutiny whereas a payroll system or financial modeling application will not. So, by definition, the business significance is greater for systems that FDA is interested in and might inspect as part of their mandate.

With respect to data, original data is most significant for business operations because one can always reconstruct, re-perform processes, or regenerate reports when the original data is available, easily retrievable, complete, and accurate. Calculated data (e.g., statistical analyses of safety and efficacy trends) is not as significant as original data because the original data to calculate with is needed in the first place. Should calculations be incorrect, required modifications can be made and the calculations re-performed so long as the original data is available. So, from a business standpoint, original data has increased significance when compared against calculated data.

Least significant, relatively speaking, is support information such as descriptive data, scheduling information, etc., that supports the original and calculated data. Support information has value, but is dependent on having the original and calculated data to support. So, by definition, the business significance is greater the closer one gets to the original data from which all subsequent operations stem. *Figure 1* illustrates the concept of the relative business significance of systems and data.

### *Failure to Validate Properly*

What happens when one does not validate properly? In our view, there are three basic manifestations of improper validation of systems:

(1) The scope of the validation is not appropriate.
(2) The evidence generated to support the validation is not adequate.
(3) The testing is not adequate.

Each of these presents a business risk.

### *Validation Scope*

With respect to scope, one must appreciate that a computerized system is comprised not only of the application (e.g., Clintrial, Documentum) that one uses to perform business operations. As is illustrated in *Figure 2*, Scope of Computerized Systems, there is much going on "below the surface."

The solid infrastructure "below the surface" starts at the foundation, which is composed of policies,

procedures, training, etc. Lack of this infrastructure means a lack of business processes and documentation that members of staff need in order to perform their respective functions. Next, come the hardware (e.g., servers) that the respective application resides on and the operating system (e.g., Windows XP) on a network that makes everything work. The business risk of not installing these components in a qualified manner (e.g., parameters not set properly) is that subsequent operations of all related software may be unreliable.

As with hardware and the operating system, the business risk of improperly installing database software (e.g., Oracle) and configurable software (e.g., SAS) is that the system may not be able to store data, develop custom programs, etc., in a reliable manner. Only after evaluating the status of all of the above items do you get to the application, and even here you must be careful to identify all pertinent modules as well as interfaces to other applications. The business risk of failing to address each issue according to this logic is that the system in use may not operate in the intended manner.

### *Validation Evidence*

What is "adequate" evidence? While there is no absolute answer to this question, there are criteria for what is inadequate. Inadequate evidence is lack of:

- User or functional requirements, which provide the business, performance, and regulatory requirements a system must meet
- Design and technical specifications, which provide the details of how the system is built and how it works (e.g., identification of programs, files, relationship of programs to files, error messages and what causes them)
- Policies and procedures that govern how systems are developed and deployed
- Policies and procedures that govern how systems are tested
- Documentation of traceability, from requirements to design documentation, to confirm that all requirements are included in the system
- Documentation of traceability, from requirements to testing, to ensure that all requirements are met
- Documentation that confirms that all hardware and software have been installed in a qualified manner
- Complete and current user and technical reference documentation, which provides required information for those who use and support the application to do so correctly
- Training documentation, to confirm that staff is qualified to perform the required activities
- Policies and procedures designed to maintain a validated state (e.g., change control, configuration management) and protect records (e.g., security, backup, recovery, contingency planning)

The business risk that results from inadequate evidence is that company management will not:

(1) Know the details of the processes used to support business operations.
(2) Be able to rely on effective or consistent operations.

Each of these conditions is an irresponsible business practice.

### *Validation Testing*

The third manifestation of improper validation is inadequate testing. In the business world, systems are continuously challenged with unexpected values and conditions, higher volumes than anticipated, unexpected run-time conditions, etc. Therefore, the system should be able to identify the "problem" and provide error and warning messages to the user, or at least not to corrupt data should the system abnormally terminate.

The nature and scope of challenges are dependent on the complexity of the system. The ability to define proper challenges is, therefore, dependent on the skill and experience of the tester (e.g., the larger and more complex the system, the more complex the challenges tend to be). A lack of adequate challenge

can result in structural problems within the system remaining undetected, a definite business risk.

The agency is planning to use statistical analysis to establish the correlation between various industry-related factors (e.g., product, process, facility, manufacture, etc.) and inspectional outcomes. Companies could use a similar statistical approach for prioritizing those regulatory issues that will result in the greatest business risk.

## HOW MUCH CAN BE LOST?

The answer to this question is two-fold. Sometimes the impact of the financial loss resulting from regulatory deficiencies is well defined and can be tangibly measured. In other instances, such financial impact may not be immediately felt because it stems from the "difficult to measure" intangibles associated with regulatory non-compliance. As we will discuss below, these intangibles may cause significant long-term problems for the business.

### *Tangibles*

Let us more closely examine the outcomes of some of the regulatory deficiencies identified above. The primary danger of having a poorly validated system results in using an incorrect or an incomplete set of data, as well as in a decision-making process that is based on erroneous information or assumptions. Lack of data integrity and quality results in rework or additional data retrieval, both of which can be quite costly and time consuming.

Validating the wrong system prevents concurrent and secure data access and increases the chances of deciding on conflicting solutions based on potentially inaccurate information supported by an unreliable database.

Inappropriate or incomplete system testing will not detect differences in the processes. Nor will it recognize the inconsistency in the shared database. Such deficiencies create the necessity of revalidating the process every time a new difference is identified and certainly will not support business needs in an efficient, quick, and easy manner.

At the regulatory level, these deficiencies can result in consequences ranging from 483s and Warning Letters (WL) to more serious consequences such as, but not necessarily limited to, consent decrees and even shutdowns in cases where a history of non-compliance exists. At the business level, these regulatory deficiencies may easily range from delayed or rejected submissions to potential lawsuits. Whatever the outcome may be it will significantly impact the financial health of the company because a revenue bearing operation will be interrupted.

While the actual dollar amount for each company will differ, the concept of the potential for financial loss being directly attributable to the significance of regulatory deficiencies is universal. What also must be kept in mind here is that whether we agree or disagree with FDA's conclusions, statements, and actions, the FDA is a vital and indispensable player within the pharmaceutical industry; its authoritative actions can directly affect the financial position of a company.

Besides the most obvious consequences, the validation-related risks described above may lead to disruption of customer service, which can result in customer loss, and information not supportive of company goals or strategies, both of which can put the company at a strategic or tactical disadvantage. In each case, re-doing processes or developing costly "workarounds" may be required. Either scenario (i.e., loss of customer revenue or failure to attain goals designed to increase profitability) increases the cost of doing business or, in other words, leads to financial loss.

### *Intangibles*

As mentioned above, there are also "intangibles" that company management must recognize. Enough publicized regulatory deficiencies will significantly dent a company's reputation not only in the eyes of the FDA, but also in the eyes of doctors, patients, the media, potential investors, and business partners with whom the company deals regularly and relies upon for support and services. The consequences of such negative "intangibles" present quite a gloomy picture for the future of any company:

- It will be difficult to hire and retain qualified staff. *Who will want to work for a company that may be in trouble or that has a reputation of flouting the law?*
- It will be increasingly difficult to market products. *Who will want to buy products from a company that has a reputation of not comply-*

*ing with regulations, which, in the public's mind, equates to compromising and jeopardizing the public health?*

- It will be difficult to maintain investor confidence in company stock. *Who will want to invest money in a company that is faced with decreasing revenues and increasing costs, not to mention going-concern issues?*

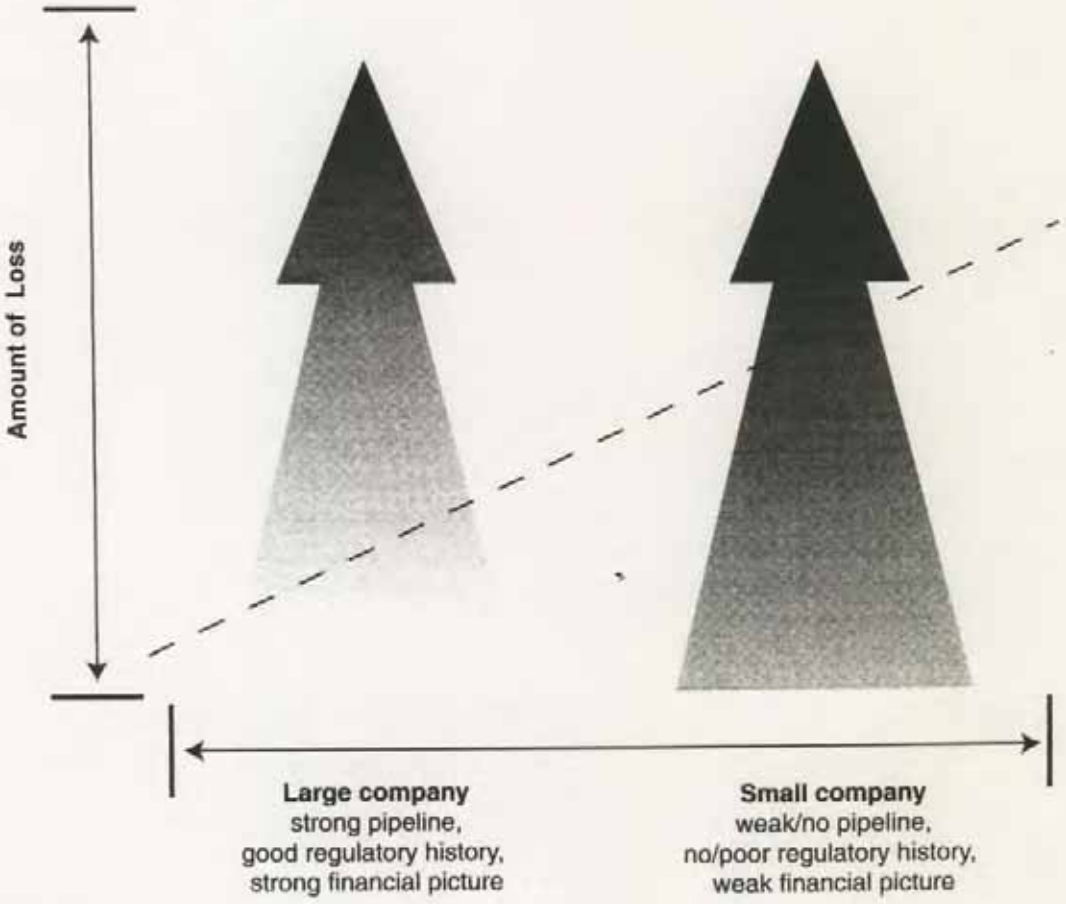
- The attractiveness of such a company as the focus of a potentially profitable merger or friendly take-over will be limited. *Who will want to merge with or take over a company with impending financial liabilities, such as those that may result from class-action lawsuits?*

- At the same time, the chance of such a company becoming the potential target for a hostile take-over would be greatly increased. *Predatory entrepreneurs often prey on firms in declining or tenuous circumstances to benefit from the sale of viable elements for their own financial gain at the cost of crippling the company and often of dissolving it totally.*

Ultimately, the answer to "how much can be lost?" is company- and situation-specific and must be considered when assessing company risk. It is not a simple calculation. However, company management must be willing and able to answer the question to become successful and profitable.

***Figure 3***

**How Much Loss Are You Willing to Assume?**



## HOW MUCH FINANCIAL LOSS ARE YOU WILLING TO ASSUME?

The amount an individual company can stand to lose before feeling the financial impact varies with its size and annual revenues. There is no single perfect solution for coming up with such a number, but the idealized answer is: "as little as possible."

The practical answer to the question above is as much a quantitative dilemma as it is a qualitative one because the immediate harm of the previously outlined negative intangibles is often difficult to measure in dollars.

*Figure 3* attempts to bring some perspective to the issue, and illustrates the following:

- A company can best afford to assume a financial loss to the extent that such loss is relatively minor and the company fits the following profile: large company, strong pipeline, good regulatory history with FDA, strong financial picture. As the amount of the potential financial loss increases or the situation of the company changes for the worse, company management will begin (or should begin) to "sweat about it."

- A company can least afford to assume a financial loss to the extent that the financial loss is relatively major and the company fits the following profile: small company, weak or no pipeline, no regulatory history or poor regulatory history, weak financial picture. Further, the amount of the potential financial loss need not be significant before company management begins (or should begin) to "sweat about it."

## HOW CAN FINANCIAL LOSS BE MINIMIZED?

Minimizing financial loss due to regulatory non-compliance depends upon quickly identifying the potential regulatory risk and then quickly remedying it. *Figure 4* provides a model for company management to use in achieving this objective.[3]

### *Management Control*

Company management must create a control environment that manages business risk through ensuring regulatory compliance. The ultimate asset of such an environment is people who are the most integral and valuable part of every process and every policy, people who are the driving force behind regulatory compliance or lack of it.

What are some of the main controls that management can implement to help their staff reduce or prevent regulatory non-compliance? A few are listed below:

- Policies and procedures for regulated processes must be approved, current, and available. They must be complied with and there must be evidence to confirm compliance. Deviations from approved policies must be brought to company management attention in a timely fashion and be resolved in an acceptable manner.

- Individuals responsible for conforming to these policies and procedures must be trained in a timely manner and the training must be documented. Only qualified individuals must be allowed to perform or have responsibility for regulated processes.

- Staffing levels should be appropriate and supported by an adequate degree of qualified supervision.

- Individuals must be held accountable for adhering to regulations relevant to their specific area of responsibility (e.g., department, study, function), and management must be ready and willing to replace individuals who do not perform to this standard.

### *Quality Assurance Audits and Inspections*

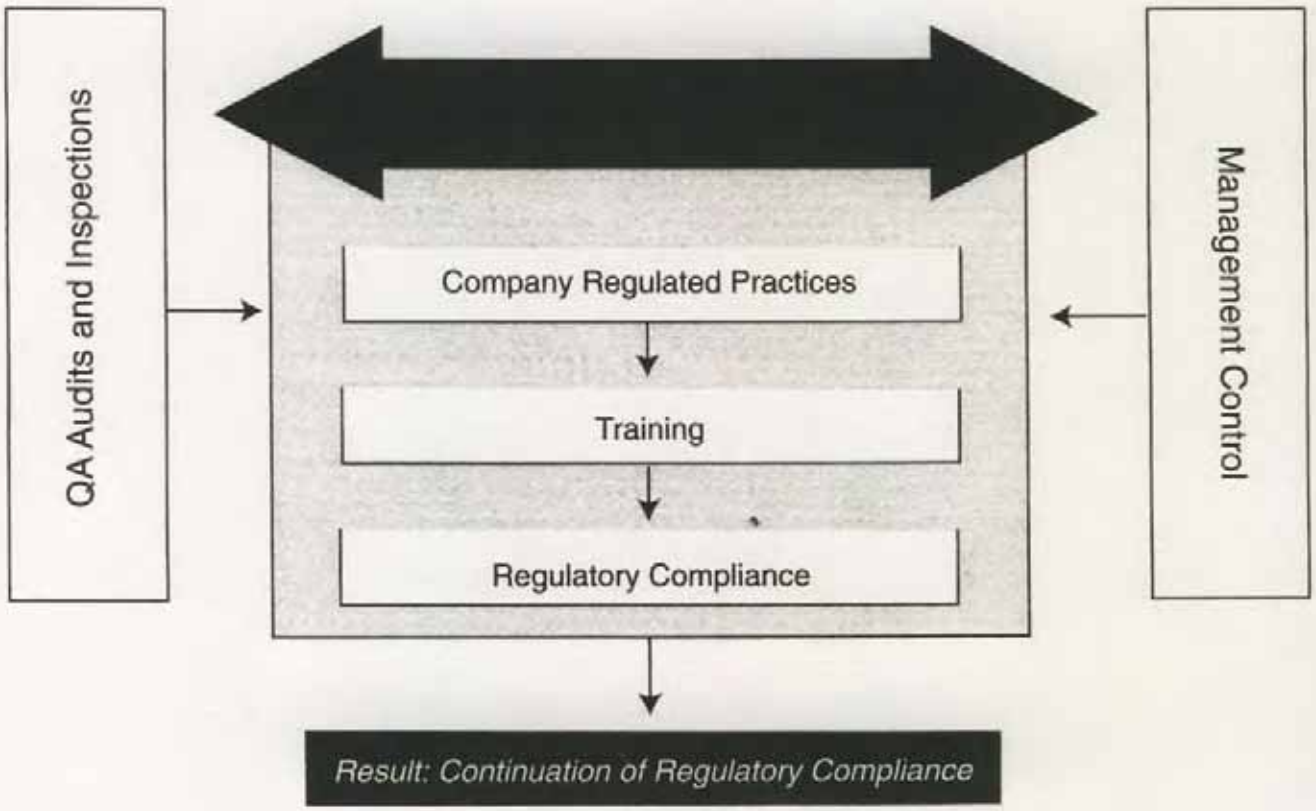
To realize its business objectives, the company should have an effective Quality Assurance Unit (QAU). While remaining separate and independent from the direction and conduct of the day-to-day business processes, the QAU staff must be held to the same quality standards as all other individuals who are expected to support compliance within the company. The QAU's main role is to ensure that policies and procedures are being performed properly and that regulatory compliance is being maintained. Furthermore, the QAU's job is to detect regulatory non-compliance in a timely manner, to bring issues to company management attention, to address potential impacts, and to assist with correcting the deficiencies before they become financial risks. In this context, the QAU is expected to:

- Have a working understanding of the requirements of the applicable regulations.
- Perform the requisite audits of processes and inspections of data to assess regulatory compliance.
- Report instances of regulatory non-compliance to company management in a timely manner.
- Provide practical resolutions to regulatory non-compliance issues and bring these issues to completion.

Anything less than a performance like that expected of the QAU will jeopardize company financial stability and should be questioned by company management.

***Figure 4***

**Business Risk Management**



***Feedback***

The infrastructure described above will allow company management to react to findings regarding regulatory non-compliance by enhancing existing controls, strengthening enforcement of existing controls, or instituting additional controls, as warranted. It will also allow company management to see trends vis-à-vis regulatory compliance, such as an increased frequency of regulatory issues in one area, with one individual or group, or with selected processes. As new or enhanced controls are implemented, the QAU is expected to assimilate them, not only into the master audit schedule, audit them as appropriate, and thereby provide continuous feedback to company management, but also into the way it assists the company to achieve its financial goals.

## PARTING THOUGHTS

For the FDA, efficient risk management is an approach that identifies the most important risks, continually analyzes the design, and conducts an evaluation of the agency's business processes. If this practical vision has become the model for the FDA, it makes even more sense for the industry to embrace and adapt the concept.

FDA's adaptation of risk management principles is focused on promoting and protecting the public health. Ensuring data integrity and quality through regulatory compliance is one way to achieve the agency's goals of implementing risk management, as well as maintaining a truly "good business practice."

What, then, should company management do to ensure that the risk assessment model works?

First of all, it should understand that regulatory noncompliance is usually expensive. To avoid unnecessary costs, issues should be prioritized based on business risks and benefits, focusing on the most important ones first. Costs and potential liabilities associated with status quo vs. addressing regulatory issues should be considered and evaluated. In addition, a strategy should be developed to incorporate regulatory compliance into the process.

To do that, there are a few factors that should be considered by all companies, regardless of their financial strength. The number of submissions pending approvals, product publicity, number of products in the pipeline, potential lawsuits, yearly revenues, stock performance, and increasing overhead are a few of these factors. The success or failure in managing these items will have a significant impact on the financial future of a company, as well as on its professional reputation.

The goal of every company is to maximize profits. The most logical starting point for this is to minimize financial losses, including the ones that are the result of regulatory deficiencies. Here are some tips to consider:

- Learn to interpret regulations and use common sense. These are two essential components.
- Exercise innovative thinking to achieve creative and practical approaches to stay in compliance.
- Acknowledge regulatory deficiencies and fix them based on the financial risk they present to the company.
- Utilize the knowledge and experience of technical and business experts.
- Define clearly the roles and responsibilities of each department.
- Establish a process methodology that defines what works best for your environment.
- Understand the time and effort required to complete different tasks. This will assist with setting realistically aggressive goals and objectives.
- Stay involved in the decision-making process and emphasize accountability for making decisions that negatively impact company finances. Such tactics will certainly decrease the chances of financial failure associated with regulatory deficiencies.
- Understand the importance of attracting and keeping qualified help.

In addition, establishing financial expectations for the company, having a clear business vision and a strategic plan in place, understanding the market, and knowing the competition are the direct responsibilities of company management. It is also their responsibility to understand the regulatory environment and, based on the information provided by qualified personnel, to assess the potential financial risks they present to the company. These simple, common sense principles apply to all company areas and processes and comprise the "ABC's" of a profitable organization. ❑

## ABOUT THE AUTHORS

*Ms. Emma Barsky is an Associate Director of Process Development/Product Formulation at Sankyo Pharma Development. She has over 17 years of broad pharmaceutical experience in the areas of analytical chemistry, CMC-related operations, QC/QA, outsourcing, project management, etc. She is currently handling multiple, complex, and timeline-driven global projects for the company, with the main objective of providing a quick and practical resolution to complicated technical and business issues. She can be contacted at 732.590.5049, or by email at ebarsky@sankyopharma.com.*

*Mr. Len Grunbaum is the President of META Solutions, Inc. In this capacity, Mr. Grunbaum is responsible for managing the company, and ensuring quality, timely, and cost-effective delivery of its consulting services. Prior to joining META Solutions, Mr. Grunbaum was the Principal of LAG Consulting, where he performed computer validation, computer security, and disaster recovery consulting activities.*

*Len is a recognized industry expert in the areas of validation and compliance with 21 CFR Part 11. He has written extensively on these subjects and has delivered numerous tutorials and training sessions to industry groups. In addition, he has provided validation and compliance training to FDA. He can be contacted at 908.791.1900 (x45), or by email at len.grunbaum@metasol.com.*

## REFERENCE

1 *Pharmaceutical cGMPs for The 21st Century - A Risk Based Approach; Final Report*; Department of Health and Human Services; U.S. Food and Drug Administration; September 2004; pg. 7.

2 Ibid., pg.5.

3 This chart and the accompanying explanation are based on an article by Len Grunbaum titled "Remaining in a 21 CFR Part 11 Compliant State," which was published in the *Journal of GXP Compliance*, April 2002.

### Article Acronym Listing

| | |
|---|---|
| CFR | Code of Federal Regulations |
| cGMP | Current Good Manufacturing Practice |
| FDA | Food and Drug Administration |
| QAU | Quality Assurance Unit |
| WL | Warning Letter |