

This article reviews the relationships between quality and regulatory practices, and the implications for business performers for suppliers of automated systems to the pharmaceutical manufacturing industry.

# Regulatory Considerations and Business Implications for Automated System Suppliers

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## Introduction

In the last decade, pharmaceutical manufacturers have seen a proliferation in the international regulatory expectations with regard to automated systems used in manufacturing. These expectations have been accentuated by the emergence and application of the FDA's 21 CFR Part 11 and by the increased focus by regulatory authorities on the lifecycle activities surrounding computerized systems. Although ultimate responsibility for automated system compliance lies with the manufacturer, suppliers also are greatly affected by the requirements. This article will review the multifarious regulatory practices that have become part of the *modus operandi* of suppliers. Research into the relationships between selected regulatory practices and supplier business performance is presented.

## Background

The regulation of the pharmaceutical industry has become increasingly rigorous and rigid over time due to a process labelled by some as 'regulatory creep' or 'regulatory spiral'.<sup>1</sup> Regulatory observations have been issued to manufacturers of drugs for such design related non-conformances as failure to adequately document software development, or failure to reliably manage changes to software. The FDA's Web site is filled with warning letters relating to computer system validation. While many of the deficiencies are related to manufacturer's responsibilities, some gaps cannot be closed without the involvement of the providers of the automated system in question. Hence, the regulatory reach is toward the supplier. The design, documentation, and control of automated systems must meet standards aimed at compli-

ance, almost from their conception. The Good Automated Manufacturing Practice (GAMP) Guide for Validation of Automated Systems has become almost a *de-facto* standard for management of lifecycle activities for suppliers.<sup>2</sup> The comprehensive scope of GAMP shows just how much supplier practices are affected by regulatory expectations. While many of the requirements can be fulfilled by adherence to good engineering practice and following software development standards such as the ISO series of publications, it would be difficult for developers to be successful in the pharmaceutical market without some working knowledge and experience of the minefield of the applicable regulations.

## So What's a Supplier to Do?

There are many activities in which a supplier must be engaged in order to compete successfully in the pharmaceutical world. The provision and availability of design documentation is important to the manufacturer as the basis for understanding and controlling their systems and also to allow testing of those systems to be performed against fixed specifications. Increasingly, manufacturers involve developers in their validation process and can leverage factory testing of systems into their own validation packages in an overall effort to prove fitness for use. Supplier's assistance with the provision of the relevant validation documentation might then prove vital for customer relations. Certain design features of the systems themselves may be necessary for compliance. The FDA's 21 CFR Part 11 is an obvious example of where built in software features can be essential for compliance. Many systems cannot be fully validated unless the system itself

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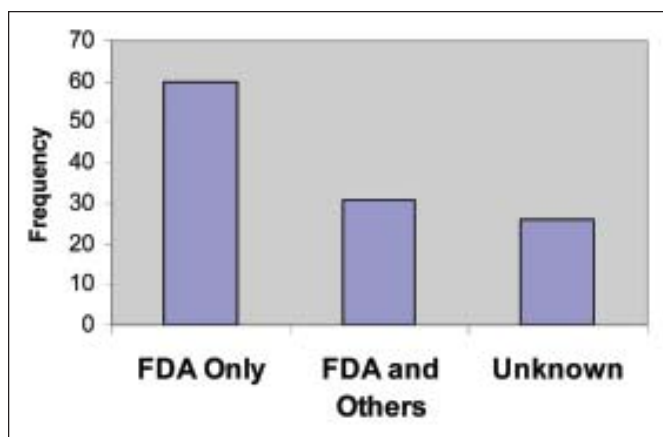


Figure 1. Distribution of respondents across regulatory categories.

allows the validation engineer to do so through appropriately designed interfaces and modules. Hence, regulatory compliance needs to be an early design consideration and developers need to be aware of, and trained in, the relevant Good Manufacturing Practice (GMP) regulations. Some software, such as embedded algorithms in subroutines, cannot be fully validated when the system is integrated. Therefore, it is imperative that such sub-systems are rigorously tested and that testing is documented before integration.

The quality management system operated by suppliers is subject to scrutiny by manufacturers during the selection process and periodically thereafter, and it might be wise for suppliers to have a quality system that has components that are geared toward regulatory requirements. The regulations themselves are subject to change and regular audits by the supplier of their quality systems and of their products to ensure that they continue to meet requirements could be advantageous. The use of the GAMP Guide by suppliers itself is a good indicator of commitment to compliance. Those providers who apply the principles of the Guide are highly likely to provide systems that meet many of the requirements for automated systems. Where the supplier's products have data processing capabilities, sound knowledge, and application of the rules for electronic records and signatures would be a fundamental requirement for business success in the pharmaceutical sector. From a manufacturer's point of view, important consideration must be given to the development strategy employed by the supplier and the mechanisms in place for control of code. In addition to this, the quality system environment itself must be in a fit state and effective to give maximum assurance to the quality of the automated system. Much has been written about the positive influences that quality management practices have on business success and will not be repeated here.<sup>3</sup> However, what has not been determined is the relationship between specific practices aimed at regulatory compliance and business performance. This article presents a first attempt at research in this field.

## Research Methodology

The research reported here was part of a broader project to establish the multivariate interactions between quality management practices, regulatory practices, and business perfor-

mance. In this article, only those elements pertinent to regulatory compliance are presented. A survey was conducted of 649 firms supplying automated systems to the pharmaceutical manufacturing sector worldwide. This sample was selected from industry databases and from advertiser indices from a series of prominent pharmaceutical trade and engineering journals.

## Selection of Regulatory Variables

As no such research had been conducted before in this area, the selection of important regulatory practice variables to be measured in the survey was extracted from themes in the wider trade and academic literature. Several criteria emerged from the literature as being important for suppliers of automated systems in order to achieve compliance as summarized below:

- extent of knowledge of the GMP regulations, and the ability to apply them to the development and delivery of their products
- the extent of use of the GAMP Guide (although it is not suggested that compliance cannot be achieved without it)
- availability of design and validation documentation
- extent to which validation features are built into systems
- extent of knowledge and application of Part 11
- extent of source code availability to manufacturers
- extent of use of regulatory design reviews for software

These regulatory criteria were used as variables to evaluate the extent of regulatory practices by respondents.

## Questionnaire Refinement

Once variables had been selected, questionnaire items were assigned to each regulatory practice variable. The questionnaire was extensively pre-tested and pilot tested before it was deemed complete. Pre-testing was done with the help of academic colleagues and a selected set of suppliers, which had shown a high level of interest in the study. Here, the pre-testers were asked to critique the questionnaire in terms of its simplicity, clarity, difficulty, ambiguity/specificity, burden, accessibility, relevance to study variables, and the feelings of the respondent regarding the completion of the business performance questions. The questionnaire was overhauled as a result of the pre-test. In particular, changes had to be made to the business performance questions. Here, subjective 'hard' measures of business performance were employed instead of objective hard financial measures. This meant that instead of being asked 'what was your percentage increase in sales last year?' Respondents were asked 'to what extent did last year's percentage in sales meet expectations?' There is much work in the literature to support the use of such subjective measures of business performance as reliable indicators of financial performance.<sup>5,6</sup>

Pilot testing was performed by selecting 41 random suppliers who had previously agreed to participate in the study. Unaware that this was a pilot study, they were asked to complete and return the questionnaire. Twenty nine re-

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sponses were received with no invalid questionnaires or negative comments regarding completion. The returned data was analyzed to ensure that statistical methods could be applied to it. As this was successful, no changes to the questionnaire were required, and the questionnaire was ready for the main administration.

Table A shows the relationship between the regulatory practice variables used in the study and the questions that were presented on the questionnaire to represent them.

## **Background Considerations**

As well as questions relating to regulatory practice variables, a series of qualifying background questions were asked which requested information about:

- the regulatory environments suppliers were producing for
- the complexity of the automation in their products
- the criticality of the respondent's most critical products to the manufacturer's drug quality

Other questions regarding company size, age, and quality management practices also were asked. The regulatory environments that respondents operate in had to be determined in order to ascertain whether differences existed between respondents in differing environments, and whether generalizations could be made. The same applied to the complexity level of the software used in the respondent's product, and how critical that software was to the end user's drug quality. That is, more complex or critical software may lead to more stringent controls and practices by suppliers. As complexity of software is a difficult thing for respondents to categorize, the time taken to develop software was used as an indicator for measuring complexity, where low complexity software was that which took in the order of a few months to develop, and high complexity software took many months or even years to develop.

## **Survey Administration**

The survey instrument was administered by electronic mail to each of the firms. The respondents could choose to use postal mail, a Web-hosted survey, or electronic mail return to respond. Each respondent in the sampling frame was individually invited by e-mail to participate, using a standardized e-mail text. Non-response was handled by a standard repeat mailing. Finally, 219 companies agreed to respond, although only 122 actually did, most citing internal resource pressures as the reason for non-response. 119 were valid. Where respondents failed to complete entire sections of the questionnaire, these questionnaires were considered invalid and were not used in the analysis. Typically for e-mail surveys, response rates of less than 10% are achieved;<sup>4</sup> therefore, the 18.9% observed in this work compared very favorably. The high response rate may have been in part due to the familiarity by suppliers of completing quality/regulatory related questionnaires at the request of drug manufacturers.

## **Factor Analysis and Cronbach's Alpha**

Factor Analysis involves reducing a group of indicators (questionnaire items in this case) to a much smaller group of indicators, or factors, to allow ease of analysis. It does this by finding underlying variance in the data common to a set of items, and grouping those items into a factor. In this case, when the set of 16 questionnaire items were subjected to factor analysis (Principal Components Analysis), three 'latent' factors resulted. Each factor was strongly correlated with a group of questionnaire items, and could be used to represent them. The actual questionnaire data for the group of questionnaire items represented by a particular question is summed together (this is called a summated scale) to give a factor value (i.e., a Direct Regulatory Involvement, Intrinsic Regulatory Compliance and Regulatory Documentation Availability score) for each questionnaire. A further test to ensure that all the questionnaire items linked to a factor actually vary together, and represent the same thing, is the internal reliability measure or 'Cronbach's alpha'. Here, a value of 0.7 or more shows that the summated scale is reliable. All factor derived scales in this study were found to be reliable as shown in Table B.

## **Data Analysis**

The responses were collated and a series of statistical tools was used to reduce the data into manageable subgroups, which could be more readily analyzed. Factor analysis - Sidebar 1 was used to detect underlying latent factors in the data and to build scales from which meaningful interpretation of the data could be achieved. From the data in this survey, three regulatory practice factors emerged. The first factor represented those questionnaire items that represented direct involvement by suppliers in regulatory related activities. The second concerned intrinsic regulatory compliance, by virtue of the supplier's activities (Table B), and the third represented availability of regulatory related documentation.

Each factor extracted represents a unique feature of the data and the summated scores within each factor can be analyzed as a single variable. That is, all the questionnaire items comprising the direct regulatory involvement factor could be used to form a scale. In survey research, the reliability of scales is an important concern. A standard measure of internal consistency reliability (meaning that all items in a scale actually measure the same feature) is Cronbach's alpha. An observed alpha value of greater than 0.7 represents a reliable scale.<sup>7</sup> For each of the regulatory practice scales in this research, Cronbach's alpha exceeded 0.7.

An identical process was followed to acquire data related to supplier business performance. Respondents were asked to state whether the following items had exceeded expectations:

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## Nonparametric analysis

Non-parametric techniques are useful for non-continuous data (that is, where 'gaps' appear between possible scores, such as with questionnaire answers where only five discrete levels can represent the answer), for where the distribution of scores is non-normal and for where there is a low number of respondents in a group. For the analysis in this work, Kruskal-Wallis H testing was used to detect significant differences across a number of categories (for example, was there a difference in regulatory scores across low, medium, and high complexity suppliers?). The Kruskal-Wallis test will not show which pairs within the groups cause the difference, it will just give an output that tells us that the three categories do not have the same mean scores in the population. Therefore, Mann-Whitney U tests were used to determine differences between pairs (was there a difference in scores between medium and high levels of complexity). This test is applied to each pair of categories and a 'significant' output shows that the mean scores for the pair of categories differ in the population. In this research, such techniques were used to ensure that assumptions of normality, continuous data, and number of respondents in a particular group were not required. This conservative approach leads to increased confidence in the findings.

- profit over five years
- sales over five years
- market share over five years
- current market share relative to competitors
- overall competitive position over five years
- new product sales over two years

A series of options were provided which could be used to determine whether expectations were exceeded, reached, or not reached. In all cases, the questions were directed to performance in the pharmaceutical market. After factor analysis, the data was reduced to two scales – one for profit and sales improvement against expectations and one for market share and competitiveness improvement against expectations. In each case, the Cronbach's alpha exceeded the 0.7 cut-off for internal consistency reliability. Table B shows the extracted factors and the corresponding scale items for both the business factors and the regulatory factors.

Thus, five new representative variables were created based on the summated scale scores for each factor.

## Analysis and Findings

### Statistical Methodology

Correlation and multiple-regression analysis were employed to determine the main relationships between the extracted variables. Non-parametric techniques (Sidebar 2) for hypotheses or 'difference' testing were then used to determine

whether background influences influenced scores for different respondent characteristics.

### Background Data

In looking at the background data acquired through the questionnaires, it was important to establish that there was representation from across the range of possible suppliers 'types.'

First, it was important to establish the regulatory background profile of respondents. Sixty of the 119 respondents produced for FDA regulated environments only. Only two respondents developed systems for the European Medicines Evaluation Agency (EMA) market alone with 26 others developing for both the EMA and FDA markets (combined with some others such as the Pharmaceutical Inspection Cooperation (Convention)/Scheme markets, which include 27 European and Oceanic countries, and those who produced to International Conference on Harmonization guidelines). Only one respondent claimed that they developed their products within WHO guidelines for GMP and the WHO were not considered further in the study. The data was summarized into three groups to ease understanding and analysis as can be seen in the bar chart in Figure 1. Here the regulatory environment was divided into 'FDA only,' FDA and others, and 'Unknown.' Twenty six respondents reported that they did not know their regulatory environments. From this, it can be seen that those who produced for the EMA market generally produced for the FDA market, but the converse cannot be stated.

With regard to the complexity of automation (based on a seven point scale determined by development resource required), 8.5% of respondents had low complexity automation in their products, 39.5% had medium complexity, and 52% reported delivering high complexity products. Using a similar scaling system, it was revealed that almost 14% had solutions that offered low risk to the manufacturer's drug quality (low criticality), 42% had medium risk solutions, and 44% of respondents had products that were highly critical to the quality of the pharmaceutical product.

In terms of how long companies were in business, 61% had been providing solutions for the pharmaceutical market for more than 16 years. The organization size distributions are

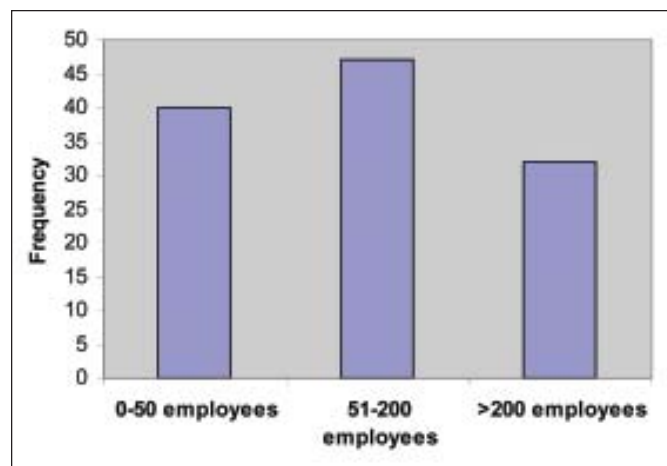


Figure 2. Distribution of respondent company sizes.

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Questions	Related Variables
To what extent is there a) high knowledge of 21 CFR Part 11 b) training provided on 21 CFR Part 11 related matters? To what extent are products and systems <i>designed</i> to be compliant to standards for a) Electronic records b) Electronic signatures c) Electronic records and d) security?	<b>Electronic Records / Electronic Signatures</b>
To what extent a) are design activities documented b) is design documentation made available to manufacturers?	<b>Provision of design documentation</b>
To what extent is validation documentation made available to manufacturers?	<b>Provision of validation documentation</b>
To what extent is a) GAMP used b) GAMP used rather than other standards?	<b>Use of the GAMP Guide</b>
To what extent a) are features designed into products to aid validation b) is validation considered early in the design process?	<b>Built in validation features</b>
To what extent are regulatory design reviews carried out?	<b>Regulatory Design Reviews</b>
To what extent a) are system developers knowledgeable of the GMPs b) is GMP a major design consideration c) do system developers have regulatory training d) is the quality system focused on the GMPs?	<b>Use of GMPs</b>

Table A. Regulatory practices by suppliers and the associated survey questions.

shown in Figure 2. Here, it can be seen that there was adequate representation in the study from small, medium, and large companies and from those companies operating less than 16 years, and those operating 16 years or more in the pharmaceutical market.

In terms of statistical validity of the findings, it was important that each company in the population had an equal chance of selection. The use of standardized mailings assured this. Examining the respondent profiles in terms of regulatory environments, size, time in business, complexity of automation produced, and criticality of automated products, it can be seen that a good cross section of possible respondent profiles were represented, which gives support to the 'external validity' of the study. This means that generalizations to the entire population of automated solution suppliers can be made from the study, based on the 18.3% response rate (119 valid questionnaires out of a population of 649 suppliers).

### Derivation of Relationships

Table C shows the correlation analysis between the regulatory variables and the business variables. Correlation analysis (Pearson's r) was used to determine whether a change in regulatory practice scores is connected to a corresponding change in the business performance scores. As shown, there were statistically significant levels of correlation between some variables (statistical significance is imperative in order to be able to claim that the relationships were likely to exist in the entire population). Some were significant at the p=0.01 level (meaning that there is less than 1% chance that the correlation does not exist in the greater population) and others

at the p=0.05 level. All other relationships were non-significant and hence, could not be generalized to the population.

From Table C, it can be seen that market share and competitiveness improvements have a low positive correlation with direct regulatory involvement, intrinsic regulatory compliance, and regulatory documentation availability. In addition, intrinsic regulatory compliance has a low positive correlation with sales and profit improvement. Changes in business performance are due to a variety of complex interrelated factors, but it would seem, that for suppliers of automated systems to the pharmaceutical market, that regulatory practices play a role. That is, from the correlations in Table C, it is clear that those companies who have better regulatory practices tend to have better business performance (above expectations). For example, a Pearson's r value of 0.38 between 'Intrinsic Regulatory Compliance' and 'Market Share and Competitiveness' indicates that there is a moderate correlation between actual regulatory compliance, and a higher than expected market share and competitiveness improvement. Therefore, suppliers who are 'better' in regulatory practice terms are likely to exceed their own growth expectations. Figure 3 illustrates the correlation between Intrinsic Regulatory Compliance scores and Market Share and Competitiveness (above expectations) scores.

### Uncovering Unique and Important Contributors to Success

Correlation analysis does not tell the full story. That is, the relationship between one regulatory variable and a business performance variable may not be true for all values of the other regulatory variables or for all background variable values. In order to assess unique contribution by the regulatory variables, stepwise multiple-regression was used. When all the regulatory variables were entered into the model, the direct regulatory compliance variable was found to offer a unique contribution to market share and competitiveness. This resulted in regression equation 1 below:

#### Regression Equation 1

Market Share and Competitiveness =  
1.620 + 0.353 Quality Related Factors + **0.222 Direct Regulatory Involvement** + e1, where e1 is the error term.

This meant that the Direct Regulatory Involvement variable was the strongest and most representative regulatory contributor to market share and competitiveness, and that although the other variables were related to this variable, direct regulatory compliance was dominant. That doesn't mean that the other regulatory variables were not important, in fact, they are all positively correlated to performance as shown in Table C. The R<sup>2</sup> value for a multiple regression equation tells us how much of the dependent (business) variable is caused by the independent components (regulatory, quality, and others) in the equation. Direct regulatory involvement added approximately 4% to the R<sup>2</sup> value for this regression equation; this means that 4% of the improvements in market share and competitiveness could be directly repre-

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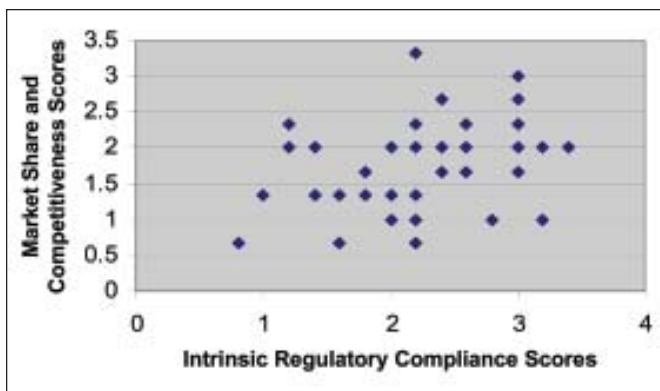


Figure 3. Correlation between Intrinsic Regulatory Compliance Scores and Market Share and Competitiveness Scores.

sented by direct regulatory involvement. Remember that this includes such practices as 21 CFR Part 11 competence, use of the GAMP Guide, and high awareness of the GMPs and their design implications. The total R<sup>2</sup> value for the equation was 20.1% and Regression Equation 1 was significant at the p=0.01 level (meaning that there is less than a one percent chance that it does not apply to the population as a whole.)

The research into quality practices (not reported here), and business performance in this sector showed that combining good quality practices and regulatory practices had substantial positive effects on business performance, as can be seen from the 20.1% R<sup>2</sup> value for Regression Equation 1. Quality practices were found to be significantly correlated with regulatory practices. The two sets of practices were found to be mutually beneficial, in that companies with high levels of quality practices also had high regulatory practice scores and vice versa. Therefore, while a 4% contribution to business performance from regulatory practice scores might not seem large, when combined with a sound quality system (high quality scores), the R<sup>2</sup> value for the regression equation was just over 20%. That is, by a combination of direct regulatory involvement activities and a good quality system, market share and competitiveness can be improved by 20% above company targets, which is a real business benefit and certainly worth the effort. It should be understood that as quality systems have been found to have been shaped by regulatory practices to some extent (as found in this research), then the overall contribution of regulatory practices to market share and competitiveness improvements can be seen to be substantial. That is, 4% of the improvement in performance is directly attributable to regulatory practices, and the remaining 16% contribution from quality practices is also partially due to regulatory practices influences.

When the regression model was applied to the sales and profit improvement situation, it was found that intrinsic regulatory compliance was the main player as shown in Regression Equation 2 below. Here it could be said from the R<sup>2</sup> value that 4.8% of improvements in profit and sales above expectations were due to activities focused on actual compliance with the regulations such as building in validation features into products, and actual application of the GMPs to the quality system and to products.

## Regression Equation 2

Sales and Profit Improvement =  
1.520 + 0.237 Intrinsic Regulatory Compliance + e<sub>2</sub>,  
where e<sub>2</sub> is the error term.

## Background Consideration – The Role of Software Criticality as a Predictor of Business Performance Improvement

In order to establish that the regression relationships were not spurious, it was important to control for background factors also. To do this, all the background variables were plugged into the regression model, including complexity of automation and criticality of product to end user drug quality, length of time in business, and company size. It was found that for both the market share and competitiveness and the profit and sales models that the regulatory predictor in the equation was replaced by the criticality to end user drug quality variable. This means that criticality considered on its own could be used to represent the gamut of regulatory practices, and as a key driver for them. That is, the business performance of any given supplier to the pharmaceutical industry is related to the risk their products pose to the manufacturer's products or processes. Suppliers providing higher risk products tend to have higher market share and competitiveness and also profit and sales improvements than those providing lower risk products. This finding is possibly related to the stringent processes used by pharmaceutical manufacturers to select suppliers for their higher risk applications. Also by their nature, specialist companies tend to be less in number than generalist companies, giving rise to an inherently greater market share.

<b>Direct Regulatory Involvement</b> Electronic Records/Signatures System Developers Know GMP GAMP used GAMP used over other industry standards GMP major Design Consideration System Developers Regulatory Compliance Training	<b>Alpha</b>      0.868
<b>Intrinsic Regulatory Compliance</b> Features Built In to aid Validation Validation Considered Early in Design QMS based on Regulatory Requirements Design is Documented Well Regulatory Compliance Audits	<b>Alpha</b>     0.749
<b>Regulatory Documentation Availability</b> Design Docs made available Validation Docs made available	<b>Alpha</b>  0.758
<b>Market Share and Competitiveness against expectations</b> Market Share Change over 5 years in pharma Market Share Relative to competitor change over 5 years Overall Competitive Position change over 5 years	<b>Alpha</b>   0.755
<b>Profit and Sales against expectations</b> Profit Level change over 5 years in Pharma sector Sales Volume Change over 5 years in Pharma sector New Product Sales to Pharma over 2 years	<b>Alpha</b>   0.755

Table B. Factors extracted from the survey data, the corresponding questionnaire items, and the reliability of the scale representing each factor.

## Differences across Background Categories

Further analysis was performed to establish categorical differences in regulatory and business scores between suppliers who operated in differing regulatory climates, had differing levels of automation complexity in their products, and whose products had differing levels of criticality to drug quality. Various statistical techniques were used to establish whether significant differences existed in the data, including the Mann-Whitney U test for two unrelated data sets and the Kruskal-Wallis H test for several unrelated data sets. Only statistically significant differences (at the  $p=0.05$  level or better) are reported here.

Looking at the regulatory variables, differences were found in terms of direct regulatory involvement. Differences were expected and found between those respondents who knew their regulatory environments and those who did not. Both the 'FDA only' and 'FDA and others' categories scored higher than for the 'unknown' category. If the respondent did not know their environment, it is unlikely that they would be adept at complying with the regulations. However, what was noticeable was that the FDA and others category scored significantly higher than for FDA only category. This suggested that an international view of the regulations was more likely to result in better application than a purely FDA focus. No significant differences were found between the categories in terms of intrinsic regulatory compliance. This can be explained by the strong relationships that the activities making up this variable have with general quality systems practices, which can vary from supplier to supplier regardless of regulatory environment.

The complexity of the software employed in respondent's products showed significant categorical differences with respect to both direct regulatory involvement and intrinsic regulatory compliance. The direct regulatory involvement variable showed an upward step change for each increase in complexity level from low to medium and from medium to high complexity. More complex systems are likely to be larger systems such as manufacturing control systems, manufacturing execution systems, quality documentation management systems, building management systems, SCADAs, distributed control systems, inventory management systems etc., which very often can have considerable impact on product quality. Therefore, to be competitive in the market, developers need to be in tune with the regulations. This is illustrated by GAMP which imposes requirements that increase in line with complexity and risk. In the case of intrinsic regulatory compliance, a difference in scores was detected between the low and medium complexity categories, but no difference was detected between the low and high, or medium and high categories so no useful pattern emerged. As an overall conclusion, from this study, it appears that companies operating with differing levels of complexity score differently in terms of regulatory practices.

Differences in criticality levels resulted in significantly different scores for the regulatory variables and the two business factors. Hence, a marked difference in business performance scores was evident, contingent on the criticality

	Market Share and Competitiveness	Sales and Profit Improvement
Direct Regulatory Involvement	0.31*	0.02
Intrinsic Regulatory Compliance	0.38*	0.24!
Regulatory Documentation Availability	0.22!	0.08
* Significant at the $p=0.01$ level		! Significant at the $p=0.05$ level

Table C. Correlation between summated scale scores for business and regulatory variables.

of the respondent's product to drug quality. The step increase observed in direct regulatory involvement, intrinsic regulatory compliance, and availability of regulatory related documentation scores is probably attributable to the two-way relationship between manufacturers and their suppliers. In order to be effective in the market, developers must be prepared to meet customer's requirements in terms of compliance, and also manufacturers must demand levels of quality and regulatory practices from their suppliers commensurate with the risk to their processes. Many manufacturers will require the quality systems and related regulatory practices of their suppliers to be of a standard that matches the risk to

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the product or to their compliance effort, i.e., the GMP criticality of the automated system. Developers supplying the higher risk products did in fact have this greater regulatory emphasis and the corresponding knock on benefits in terms of business performance.

## Summary

Adopting and enhancing regulatory practices for existing or prospective suppliers of automated products into the pharmaceutical market can have significant business advantages in terms of both market share and competitiveness growth, and profit and sales improvement, above expectations. That is, respondents who had better regulatory awareness and knowledge and who were more skilled at applying those regulations tended to report that their business performance in the pharmaceutical market was higher than their expectations. Although this general finding is true, it is not a case of one size fits all. The complexity of automation in the product and the risk the product poses from the drug manufacturer's perspective needs to be considered. Criticality plays a particularly important role in that companies that produced higher criticality products tended to have better regulatory practices, and enjoyed the corresponding knock on benefits in terms of business performance. However, high levels of regulatory awareness and application alone is not sufficient. There is a highly symbiotic relationship between general quality practices and regulatory related practices and both should be linked and harnessed for maximum benefit. The level of quality and regulatory practices should be matched to the risk that their systems can pose to the manufacturer's drug quality and to the complexity of the automation used in their products. This ensures two things, the maximum benefit to product quality and drug users, and maximized business performance for the supplier.

## References

1. Hancher, L., *Regulating for Competition: Government, Law, and the Pharmaceutical Industry in the United Kingdom and France*, Oxford: Clarendon Press, 1990.
2. GAMP® 4, *Good Automated Manufacturing Practice (GAMP®) Guide for Validation of Automated Systems*, International Society for Pharmaceutical Engineering (ISPE), Fourth Edition, December 2001, www.ispe.org.
3. Adam, E., L.M. Corbett, B.E. Flores, N.J. Harrison, T.S. Lee, R. Boo Ho, J. Ribera, D. Samson, and R. Westbrook, "An International Study of Quality Improvement Approach and Firm Performance," *International Journal of Operations and Production Management*, Vol. 17, No. 9, 1997, pp. 842-873.
4. Schuldt, B.A. and J.W. Totten, "Electronic Mail vs. Mail Survey Response Rates," *Marketing Research: A Magazine of Management and Applications*, 6 (1), 1994, pp. 36-39.
5. Pearce, J., Robbins, D., and Robinson, R., "The Impact of a Grand Strategy and Planning Formality on Financial Performance," *Strategic Management Journal*, Vol. 8, 1987, pp. 125-134.

6. Batory, S.S, W. Neese, and A.H. Batory, "Ethical Marketing Practices: An Investigation of Antecedents, Innovativeness, and Business Performance," *The Journal of American Academy of Business*, 2 (2005), pp. 135-142.
7. Bryman, A. and Cramer, Quantitative Data Analysis using SPSS 12 and 13. London: Routledge, 2005.

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