

**FDA Compliance
For The Life Sciences**
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Trends, Issues and Analysis

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FDA compliance is at the heart of the Life Science Industries. The executive's dilemma is balancing compliance with the demands of the market and stockholders. This challenge is fundamental to the success of the Life Science enterprise.

Much confusion exists in the mid-market about those very regulatory issues. Key concerns include:

- How does the enterprise decide what compliance means to it?
- What strategy is right to balance risk with the compliance effort?
- What is the right balance between human and automated efforts?
- Who is responsible for compliance?
- Where does automation fit into the effort?
- What is IT's role in compliance?
- How do we select our automation partner?

This document is intended as a guide to addressing these questions for the mid-market Life Science executive.

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“...human and veterinary drugs are safe and effective; [that] there is reasonable assurance of the safety and effectiveness of devices intended for human use.”

–FDA’s Mission Statement

I. Compliance Defined

The FDA’s mission as a public health protector includes ensuring that “human and veterinary drugs are safe and effective; [that] there is reasonable assurance of the safety and effectiveness of devices intended for human use.”¹ Today, the need to audit processes concerned with human health has become even more critical in light of current bioterrorism fears.

The FDA has defined Good Manufacturing Practices (GMPs) to ensure that Life Science products are produced in a manner that supports its mandate. Originally, GMPs were based upon the best practices of the industry. As technology and practices improved, the GMPs evolved as well. GMPs for the U.S. drug industry were formally introduced in 1963 and were significantly rewritten in the 1970’s.

GMPs define a quality system that manufacturers use as they build quality into their products. For example, approved drug products developed and produced according to GMP are safe, properly identified, of the correct strength or potency, pure, and of high quality. At a high level, GMPs provide guidelines for:

- Properly designed, maintained, and cleaned equipment and facilities
- Documented Standard Operating Procedures (SOPs)
- An independent Quality unit (like Quality Control and/or Quality Assurance)
- Well-trained personnel and management

Good Manufacturing Practices (GMPs) are defined as regulations that describe the methods, equipment, facilities, and controls required for producing. These regulations are found in the Congressional Federal Register (CFR) 21 in the following parts:

- Human pharmaceutical products and veterinary products (21 CFR 210-211)
- Biologically derived products (21 CFR 600 and 21 CFR 620)
- Medical devices (21 CFR 820)
- Processed food (21 CFR 100)²

The set of regulations that are presently in effect are called Current Good Manufacturing Practices or “cGMPs”, emphasizing that these standards are dynamic.

¹FDA’s Mission statement, see - <http://www.fda.gov/opacom/morechoices/mission.html>

²see <http://www.fda.gov/cder/dmpq/cgmpregs.htm> for current regulations

The following parts are of special interest for pharmaceutical products:

- Part 210 Current Good Manufacturing Practice In Manufacturing, Processing, Packing, Or Holding Of Drugs; General
- Part 211 Current Good Manufacturing Practice For Finished Life Science Products
- Part 11 Electronic Records; Electronic Signatures

As automation began to replace paper-based systems, Congress feared a loss of documented control over safe pharmaceutical production processes. With an initial focus on medical devices and Life Science products, Congress mandated a verifiable, trackable plan that would allow digital signatures and automated audit trails to replace the volumes of regulatory paper work. This plan was published as 21 CFR Part 11 or simply “Part 11”. The impact of Part 11 on manufacturers will be as great or greater than the Y2K issue.

Part 11 is a loosely written regulation that intends to add a layer of security through audits and authorized sign-offs to the production processes of the Life Science industries. The implementation of Part 11 is not mandatory. It is called into play if a company chooses to use electronic records. A company may decide to stay with paper-based records and in that case, Part 11 does not apply.

GMPs change formally and informally. A formal change occurred when the U.S. medical device GMPs were completely rewritten, making them more compatible with the ISO-9001 quality document. The medical device GMPs were then renamed Quality System Regulation (QSR).

GMPs also change informally with the evolution of inspectors’ expectations over time. In the U.S., these changes are communicated through FDA Guides and Guidelines and by presentations and papers presented by FDA personnel. Industry personnel can also keep track of changes in expectations by watching the FDA-483s (inspectional observations³) and the Warning Letters⁴ issued to firms by the agency. More informally, cGMPs evolve as new practices become “feasible and valuable”. Life Science manufacturers will see increased attention to their systems as an estimated 700 FDA inspectors trained in computer systems and Part 11 become available.

Although the FDA sets forth thorough regulations, these regulations should be viewed as a set of guidelines, not as absolute statements of requirements. The FDA, compliance executives, lawyers, and others interpret the regulations differently depending on diverse factors including the product produced, the manufacturing processes used, and the risk involved.

³ <http://www.fda.gov/ora/frequent/default.htm>

⁴ (<http://www.fda.gov/foi/warning.htm>)

“Life Science companies should see Part 11 as an opportunity to improve business practices.”

II. Does It Impact Your Company?

Do cGMPs apply to you? If you manufacture human pharmaceutical products, veterinary products, biologically derived products, or medical devices, you need to understand and comply with cGMPs. If products are manufactured outside the US but marketed domestically, these rules will apply.⁵

Does Part 11 apply to you? Congress has mandated that the manufacture of drugs and medical devices—products with the potential of causing physical harm—require audit trails and digital signatures. Today nutraceuticals, biologics, companies involved in bone extensions, body part harvesting, blood banks, and skin grafts, and others are currently excluded.

Most assume that cosmetics, food and beverages will soon be added to the list of affected industries. Debate is ongoing as to the appropriateness of pharmaceutical regulations in food and beverage. The debate is not about the need for more control; the debate is about whether this is the right set of regulations.

For contract manufacturers of drug and medical devices, compliance should be regarded as a competitive weapon. Patent holders are exposed to risk from non-compliant contract manufacturers and will look more favorably upon sources that meet the patent holders’ definition of appropriate compliance.

III. Part 11: Opportunity Or Challenge?

Is Part 11 an opportunity or a challenge? It depends. If Part 11 is seen as a requirement that must be met, it will be a challenge. If Part 11 is seen as a way to improve your internal business processes, it will be an opportunity.

In permitting the use of emerging technologies to streamline record keeping and compliance, the FDA is encouraging manufacturers to take advantage of the benefits of technology. This technology can increase the usability of the information gathered and integrate both business processes and audit functions, without compromising the quality of regulatory compliance.

The opportunity can be significant. Life Science companies should see Part 11 as an opportunity to improve business practices. Benefits may include:

- Lowered cost of data collection
- Increased accuracy of data
- Increased abilities in data analysis

⁵For a list of regulated products, see http://lifesciencecioforum.com/products_regulated.htm

- Reduction in regulatory errors (for example, eliminating misfilings)
- Improved control over production, quality and other processes
- More rapid search of electronics records
- Improved information transfer between departments (for example, operations and quality)
- Improved information transfer between companies (for example - an external research organization and the sponsoring enterprise)
- Improved product recall

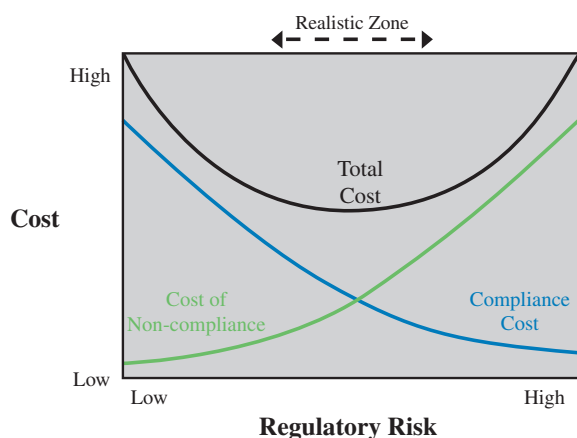
Why is Part 11 an opportunity? It allows a Life Science company to benefit from technologies that have been proven in other industries. It also can lower the long-term cost of compliance.

IV. Compliance Is About Risk

FDA compliance is not a fixed target. Compliance is a key objective for any regulated company, but what is required to meet these requirements is particular to each company, depending upon product, production processes and, perhaps most importantly, your tolerance for risk. Regulatory risk is the risk of being found out of compliance. If you are willing to accept very limited risk, your cost of compliance will be high. In accepting more risk, compliance cost is reduced but the potential cost of non-compliance increases.

Executive management has the responsibility of setting the organization's risk tolerance and allocating the required resources to satisfy that tolerance. Your compliance team

(quality, legal, etc.) needs to set the regulatory strategy for your company based upon its interpretation of the regulations relative to your specific situation, balancing the cost of compliance and the cost of noncompliance.



When reviewing compliance cost, we must think of the total cost of ownership. This includes the one time cost to initiate the system as well as on-going operational and maintenance cost. The one-time cost includes implementation, including training, acquisition of any equipment or software involved, and validation. On-going cost includes personnel cost, on-going training, maintenance of any hardware or software utilized, etc.

On-going cost also include the continuing effort to keep the compliance system in synch with evolving Standard Operating Procedures (SOPs). The automated component of the compliance system will need change with the SOPs. There are two ways that the ease with which the computer component can be altered has a major impact. The first is the cost of the effort itself—does a change take a day, a week, or several months of effort? The second, and perhaps more important, impact is the time lag between the decision to change the SOPs and the

system being ready to support the changed SOP. If this lag is significant, it can seriously impact your ability to improve operations.

The costs of non-compliance are those costs that would be incurred if you were found to be out of compliance, factored by the risk of being found out of compliance. The cost of non-compliance includes a range of penalties from the relatively minor—such as additional inspections, lost production time, or unsellable product—to more major costs—such as recalls, plant shut downs, company fines, or even jail time for executives.

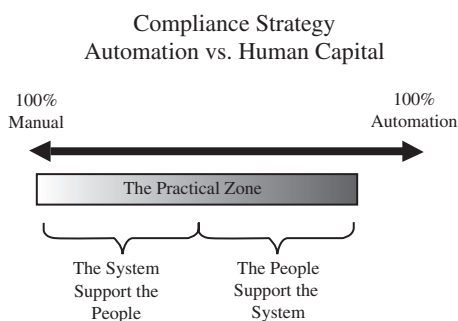
A difficult and significant cost can be public relations. The media may decide to feature your non-compliance, without regard to how serious any problem may actually be. How would this impact your brand and all the brand means to your success?

The financial effects of non-compliance on a mid-market business could be close to catastrophic, causing the small manufacturer to go out of business.

V. Strategy - People versus Automation

Compliance will always depend on a mix of automation and people. The proper balance of automation with paper records and human capital keeps cost under control and yields a flexible but controlled set of procedures. These two extremes each have their cost and characteristics.

Computers do a great job of handling repetitive tasks and organizing, storing and retrieving standard documents. People do a great job of handling exceptions. Evaluation of the characteristics of operations, products, etc. will reveal the mix of standard versus exceptional circumstances. The most effective procedures will allow computer systems to assist in repetitive operations while integrating manual or semi-manual approaches to exceptions. Exceptions should be captured in digital form to facilitate the storing and retrieving of documents where feasible.



Information systems can lower the people cost while generating their own cost. People cost and information systems cost must be balanced to yield the correct level of compliance at the appropriate cost. Remember, compliance is not about computers; it is about procedures that involve many elements, of which computers are only one.

At the extreme, the balance between automation and people could result in a compliance system that is 100% manual or 100% automated. The 100% manual option has been used for years and has proven acceptable in many cases. That option still exists and should never be ignored. Leveraging the strengths of automation can lower

the total cost of compliance however, and should be part of the compliance strategy. A compliance system that is 100% automated is neither achievable nor practical. The practical zone ranges from 100% people to a system that is automation-based with people feeding the system and handling exceptions.

The balance of people versus automation is a key decision when formulating your compliance strategies. Experience shows that the distribution of people and automation changes with the size of the Life Science company.

“The balance of people versus automation is a key decision when formulating your compliance strategies.”

Large

A large Life Science company needs a standardized approach that works across many plants and products. It wants centralized control and standard procedures to leverage its size advantage, lowering the overall cost of compliance on a per plant basis. Centralized control also lowers the overall compliance risk. Therefore, many larger Life Science companies have strategies that rely heavily on automation. In these cases, the people support the system. Given the realities of the larger Life Science company, this is a valid and effective compliance strategy.

Mid-Sized

A mid-sized company can leverage automation to handle normal and repetitive situations and rely on people for variations. Automation cost is often an issue with these companies; therefore we see trade-offs being made to allow automation to support people-based systems. For example, a fully automated system would have workstations at each step of the production process to record compliance information while a mid-sized company may rely on hard copy shop packets with compliance information captured on paper and selected information entered into an automated system at the completion of production. A mid-sized company typically pursues a strategy where the system supports the people.

Small

A small Life Science company typically does not have the financial resources to invest in automated systems. Its compliance strategy would be largely people based.

VI. Who Decides

The cost of compliance can range from acceptable to enormous. The cost to large companies will likely be in the hundreds of millions; these costs likely will have to be passed on to the consuming public, often via the current health-care system. To control and balance the potential cost of compliance, the company needs a compliance strategy, backed up with practical tactics.

Determining the strategy and tactics of compliance is a critical first step. Compliance is best thought of in holistic terms. Fragmented approaches add to the total cost and create gaps in the compliance structure and integration.

A high level (VP's or Directors), cross-functional team should recommended compliance strategy with the final decision reserved for top management. Members are recommended as follows:

Quality

A key contributor in determining the strategy and tactics of compliance, especially when the position includes careful tracking of regulatory compliance. When somebody in this position is tied in with the FDA (and often lobby groups) he can better ascertain the timing of impacts and the degree of compliance necessary to “pass.”

Legal

Compliance regulations are open to interpretation and non-compliance has severe legal impacts. Therefore legal representatives must be on the compliance team.

Production

Compliance impacts production capacity, efficiency, and budgets. Production must contribute to create compliance strategy and tactics that can be successfully implemented. Within production, plant maintenance should also have a voice.

IT

Today many internal processes run with the assistance of computers. IT must contribute to ensure that the plan is practical.

Finance

Compliance costs money. Calculating the cost of compliance is the responsibility of Finance.

Marketing

For contract manufacturers, compliance is a competitive weapon. The balance between internal compliance plans and the expectations of patent holders must be considered.

“Determining the strategy and tactics of compliance is a critical first step.”

VII. Where Does It Impact The Business?

Regulations call for the business to be “in control”. In the broadest interpretation of the regulations, this requirement could mean every part of the business being in control and even being reviewed by the FDA. Thankfully, this is not expected to be the case, but compliance can still have a major impact on the entire infrastructure of the business. Within the production arena, the areas directly impacted include:

Procurement

Only approved materials can be purchased for production purposes.

Inventory

Lot control is central to compliance and must be fully integrated with all transactions that impact inventory.

Manufacturing

The manufacturing work order, automated or paper-based, is a primary control document.

Quality

From receiving materials to shipping end product, quality controls the acceptability of materials and processes.

Sales order processing

What product/lot is sold to which customer is controlled by the sales order processing system.

Other regulations impact these areas of the business. Perhaps most important is Adverse Event Reporting. When the manufacturer receives information on an adverse effect from outside sources (patients, pharmacies, medical professionals, etc.), the manufacturer is required to report this information to the FDA, using form 3500A. This is an example where other regulations should be integrated into the above systems. In this case, the 3500A should be integrated into other compliance systems to assist in investigating the incident.

While important to your business, non-operational areas like Finance, much of Human Resources, and Sales and Marketing are not impacted by compliance considerations. Note that all R&D functions, HR and marketing are impacted by other regulatory considerations.

“Evaluation for a Life Science company is very much about regulatory strategy.”

VIII. IT Impacts

With any automation being introduced as part of the compliance strategy, IT plays a key role in execution. IT systems are impacted as follows:

Security

The regulations suggest security requirements that exceed those accepted in non-regulated industries. For Part 11, additional security is required to ensure the integrity of electronic signatures. For FDA audits, the security details of electronic signatures have proven to be an area of great interest.

Procedures

Regulations require documented procedures. These procedures may include IT procedures like granting security profiles, back up, testing, etc.

Information storage

Compliance can accumulate very significant storage requirements. The information must be kept in a secure fashion, be organized for later analysis and retrieval, and be administered to avoid performance impacts.

Analysis

Utilizing the volume of compliance information for the benefit of the business can be a challenge. Analysis tools must be available to mine the compliance information for both compliance objectives and operational improvements

Proof

The regulations demand proof of compliance. The compliance system must be extended to address this objective. Information must be located and presented in a way that satisfies the needs of the FDA.

Audit

If automated systems are part of the compliance strategy, audits will include inspections of the IT system including security, procedures and storage efforts.

“...compliance is not about computers. Compliance is about operations.”

IX. Selecting a Technology Partner

Who decides on a technology partner? Evaluation of application software is about business processes. Evaluation for a Life Science company is very much about regulatory strategy. Evaluation of application software for a regulated company must focus on the operational applications. Although the non-operational applications (financials and human resources, for example) are important to your overall business, these applications vary little in any meaningful way across the vendor landscape for most companies. Since the focus of the evaluation should be operations, the leader and the majority of the decision-making team should come from operations. Other functions, such as finance, supply chain, etc., should be represented. IT must play a key role since software will be a major part of the resulting business processes and the IT impacts (see above) are important to your compliance strategy.

Assessing potential automation vendors should focus on key compliance issues. The decision team should test both the product and the knowledge and dedication of the vendor to the regulated industries. Suggested questions include:

Q - Is your software validated?

This is a test. It is impossible for any vendor to offer a turnkey compliant system. The FDA does not validate computer systems; it validates the operations of a specific manufacturer, which may include a computer system. Any vendor who makes such a claim is incorrect and proves it does not know your issues.

Q - Can you guarantee that we can be validated with your system?

This is another test. No vendor can guarantee compliance. Compliance requires both procedural controls (i.e. notification, training, SOPs, and administration) and administrative controls put in place by the user, in addition to the technical controls that the vendor can offer. The vendor can offer an application containing the required technical requirements of a compliant system. Although it is the responsibility of the Life Science company, a vendor with the right experience can assist in implementing the system such that it can be validated.

Q - Can the system work in a semi-automated world?

Your compliance strategy will utilize both people and automation. For the mid-sized Life Science company, the people part of the equation is often more dominant than the automation part. Will this product permit you to use any combination of people and automation that is right for your business? Will the system allow for changes in the mix of people and automation, or will it limit your flexibility?

Q - What is your Part 11 strategy?

Part 11 is a key compliance and audit issue. Since the definition of compliance is not set but rather is interpreted for a specific company and product, we see great variation in the need for Part 11 control procedures. Vendors have differed on their approach to Part 11. Many vendors have taken an application approach wherein they identify the specific application points where Part 11 will be implemented in their package. To accept this approach, you need to be satisfied that the vendor's decisions match your compliance needs. You also must be satisfied that your needs will not change.

Alternatively, some vendors have taken an architectural approach to Part 11. These vendors build a universal Part 11 routine that can be placed anywhere in the system. This allows you flexibility in deciding where Part 11 control is required, and the freedom to evolve those decisions. For example, one company decided that Part 11 control should exist over the security procedures used to build and maintain security profiles. While this level of control may seem excessive to many, the fact that this decision was not limited by the control points built into the vendor's product allowed the company to define compliance as it best suited its situation.

Q - How can your company help us with validation? What is your experience with validation?

The ultimate test of the compliance strategy is validation. Vendors with validation experience may assist in many ways. The assumption that the location will be audited must be a consideration from the first day that the implementation is planned. Testing must go beyond that which is normally carried out in non-regulated industries to ensure that regulations are met. Since on-going efforts will impact the system, vendors who are focused on the Life Science industries usually offer on-going tools, like test cases, which can lower the long-term cost of compliance.

X. Summary

Most Life Science companies will be impacted by existing and new FDA regulations. Executive management must determine a strategy that balances the trade-offs of risk and cost, while satisfying the needs of the market, the FDA and the shareholders. Executive management must decide if the company will see compliance as an opportunity to improve the business or a challenge to meet regulations.

In making these decisions, executive management must consult with a wide range of operational and administrative management while maintaining the latitude to develop the strategies and tactics that are right for the business as a whole.

Information technology will play a key role in compliance, but it must be remembered that compliance is not about computers. Compliance is about operations. The manner in which IT is involved, the role of technology providers, and the degree of automation implemented are critical success factors. The use of technology has both short-term and long-term implications on compliance, cost, flexibility and operational effectiveness.

About the Author

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