The Art of Compliance
Turning Compliance into Sustainable Business Advantage

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# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>4</td>
</tr>
<tr>
<td>The Traditional Compliance Approach: Complex Procedures, Point Solutions</td>
<td>5</td>
</tr>
<tr>
<td>Moving up the Compliance Maturity Curve</td>
<td>7</td>
</tr>
<tr>
<td>Case Study: Moving up the Compliance Curve</td>
<td>12</td>
</tr>
<tr>
<td>Summary</td>
<td>13</td>
</tr>
<tr>
<td>About the author</td>
<td>14</td>
</tr>
</tbody>
</table>
Introduction

The art of compliance is more than just meeting regulatory requirements for a new drug, biologic or medical device. It is the ability to elevate compliance beyond execution to achieve strategic advantage. Its insight-based solutions facilitate quick and appropriate response to rapidly changing conditions.

The last few years have presented extraordinary regulatory and quality compliance challenges for pharmaceutical, biotechnology, and medical device companies charged to do more with less as a result of consolidation, restructuring, and economic uncertainty. Without the right attention, these challenges can permit systems and processes to weaken, domain and critical thinking expertise to erode, and core quality principles to be neglected, leaving companies vulnerable to compliance lapses and enforcement action.

In the wake of the financial markets collapse in 2008, global regulatory agencies that oversee all industries are increasing their muscle, and those overseeing the healthcare products industry are no exception. As Margaret Hamburg, M.D., Commissioner of the U.S. Food and Drug Administration (FDA), explained in a major announcement intensifying FDA enforcement policies in 2009, “the FDA must be vigilant, strategic, quick and visible.” As the medical products industry now knows, Dr. Hamburg’s vision for a strong FDA that enforces the law has been coming to fruition. For example, the number of FDA warning letters issued between fiscal years 2009 and 2010 increased by more than 40 percent. Several well-known multinationals have endured the dreaded “consent decree of permanent injunction” – which typically involves factory shutdowns until problems are fully remediated – as well as years of vigorous FDA oversight, monetary penalties, and significant intangible effects on brand credibility to healthcare providers, patients, and investors.

Companies can no longer afford to take a traditional compliance approach in this heightened regulatory environment. In the traditional compliance approach, Quality Assurance and Compliance are backroom cost centers, the internal police or “sales prevention” departments perceived as piling on non-value added requirements that detract from the company’s ability to innovate and be profitable.

However, good leaders realize that quality and compliance are the “tickets to play” in the healthcare products space. Enlightened leaders know that best-in-class compliance is an opportunity for market differentiation. By applying systems-based thinking and aligning compliant quality systems with key business processes – practicing the art of compliance – even greater rewards are possible. Such strategies facilitate sustainable compliance as well as systematic, data-driven medical product development.

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Number of FDA Warning Letters*
FY 2008  445
FY 2009  474
FY 2010  673

Good leaders realize that quality and compliance are the “tickets to play” in the healthcare products space.
Enlightened leaders know that best-in-class compliance is an opportunity for market differentiation.
The Traditional Compliance Approach: Complex Procedures, Point Solutions

A traditional compliance approach is often distinguished by a complex array of quality policies, standard operating procedures and work instructions that in practice may bear only passing resemblance to the way work actually gets done. Procedural complexity escalates as new businesses with legacy systems are acquired and not integrated or as new facilities or product lines with seemingly unique requirements are established. Although the good manufacturing practice (GMP), good clinical practice (GCP), and good laboratory practice (GLP) regulations require the establishment of some 200 procedures, it’s not atypical for biopharmaceutical companies to have thousands of such procedures, each requiring periodic review, revision, and training. Paradoxically, while a complex network of procedures is designed to compel consistency and compliance, without careful attention to the practicality and relatedness of these procedures to business needs, procedural complexity is more likely to result in non-compliance and inefficiency.

Another traditional compliance approach is to rely on reactive, point solutions to address problems that surface. Point solutions typically flow in the following manner: find a problem, add a procedure and fix only that problem. Historically, the prescriptive nature of the biopharmaceutical approval and GMP requirements inadvertently reinforced the reluctance of biopharmaceutical manufacturers to make systemic changes to their products or systems, favoring the use of more focused point solutions. But point solutions tend to fix symptoms rather than systemic causes. They similarly falter when they do not address the same or similar issues that may be present elsewhere in the company.

The confluence of point solutions with complex procedures that don’t reflect the way that work gets done makes it impossible to achieve sustainable compliance (i.e., interlinked processes and systems that help an organization respond to problems, maintain compliance, and prevent non-conformities from occurring). Furthermore, companies that have not achieved sustainable compliance are vulnerable to enforcement action, as illustrated in this excerpt from a 2010 FDA warning letter:

“...despite past assurances that previous enhancements would control this problem, deviations continue. Your firm failed to implement sustainable corrective actions to prevent [this problem] as well as other continuing problems. As a result, we have concerns regarding the failure of your firm, including the [quality control unit], to act proactively to ensure compliance with SOPs and the CGMP regulations. Please indicate how you intend to implement, support, and sustain a comprehensive quality system that is consistent with CGMP. Be advised that FDA expects that your corporate management will undertake a comprehensive evaluation of manufacturing operations to ensure compliance with CGMP.”

Regulatory Compliance
Adherence to rules and requirements, as mandated by governing regulatory bodies.
Assurance that processes, practices and products are developed and maintained in compliance with established guidance and regulations.

Process Optimization
The discipline of adjusting core business and scientific processes to improve outcomes, reduce variance, and ensure consistent execution.
The most common goals are to minimize cost, maximize throughput and/or efficiency, and increase predictability.

Sustainable Compliance
Interlinked processes and systems that help an organization respond to problems, maintain compliance, and prevent non-conformities from occurring.
FDA’s approach to sustainable compliance evolved with the agency’s initiative to modernize pharmaceutical GMPs with a less prescriptive, more robust quality systems approach like that in effect since the mid-1990s for medical devices. In the draft guidance, “Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations,” FDA noted that “the central goal of a quality system is the consistent production of safe and effective products and ensuring that these activities are sustainable.” Figure 1 highlights the characteristics FDA identified as necessary for an effective quality system.

Figure 1  
8 PILLARS OF AN EFFECTIVE QUALITY SYSTEM

- Science-Based Approaches
- Decisions Driven by Understanding of Intended Use of Product
- Identification and Control of Potential Process Weakness
- Responsive Investigation Systems Leading to Timely Remediation
- Sound Methods for Assessing & Reducing Risk
- Well-Defined Products & Processes: Throughout the Product Life Cycle
- Systems for Careful Analysis of Product Quality
- Supportive Management: Philosophically & Financially


FDA’s focus on supportive management as one of the eight pillars of an effective quality system underscores a principle implicit in the current philosophy of global regulatory bodies. In the same guidance document, FDA noted:

“Modern robust quality systems models call for management to play a key role in the design, implementation, and management of the quality system. ...Management has ultimate responsibility to provide the leadership needed for the successful functioning of a quality system.”

Consequently, it is both a strategic and sustainable compliance imperative that management teams of today’s healthcare product companies fully engage in their organization’s quality management and compliance activities. An initially painful but effective approach implemented by a top 10 pharmaceutical and medical devices manufacturer is for business leaders, not quality staff, to present the operating unit’s quality performance at quality management reviews with the CEO. With a deep understanding of what goes on “under the hood” – warts and all – a leader can legitimately claim the engagement and ultimate responsibility for quality performance that regulators require. A leader should both understand and drive actions to correct key metrics for their business including:

- Which CAPAs are open and late, and why
- How many devices are under recall in the field that have not yet been corrected
- How many adverse events were reported late, in which countries, and why
- What quality and regulatory problems are causing shipment holds

Moving up the Compliance Maturity Curve

How does a company move compliance from a traditional approach to a fully effective quality system that is not only compliant but efficient and integrated to key business processes? Think of this in terms of a compliance maturity curve, with four stages of maturity (see Figure 2).

At Stage 1, companies with complex, ineffective and impractical quality systems are typically broken and are (or will soon be) in fire-fighting mode. Stage 1 companies are reactive and continually remediating processes that don’t work.

Companies at Stage 2 are slightly ahead on the curve. They are more likely to make timely and effective fixes, but all too often slide back down the curve as their processes get increasingly complex or their solutions are not sufficiently systemic.

At Stage 3, a company has an effective, fully functioning and compliant quality system like that advocated in FDA’s systems-based quality systems framework. Stage 3 is a laudable accomplishment, yet Stage 3 performers have not fully achieved the degree of efficiency and business value that is possible. When done right, the same methodology used to achieve Stage 3 compliance can be taken to Stage 4, a process-driven and sustainable compliance framework integrated with business processes to facilitate business effectiveness, efficiency, and innovation.

Stage 4 is distinguished by applying critical systems and process approaches not only to quality systems, but to other key product development activities and business decision making. Management input and oversight are critical to ensure Stage 4 success because Stage 4 solutions by definition address key organizational strategies and objectives.

Figure 2  ASCENDING THE COMPLIANCE MATURITY CURVE

- **Stage 1**: Broken
  - Minimalist Quality Approach
    - Increased FDA scrutiny
    - Fire-fighting
    - Always on defensive

- **Stage 2**: Point Solutions
  - Expected Approach
    - Well-defined Quality System
    - Sufficient staff, skill sets
    - Adequate data processing

- **Stage 3**: Fully Engaged
  - Sustainable Compliance
    - Efficient data capture
    - Fast, effective quality decisions
    - Continuous self-improvement

- **Stage 4**: Process Driven Compliance
  - Performance
To ascend the maturity curve and reach Stage 4 sustainable compliance, companies must practice the art of compliance utilizing a three-step approach involving Assessment, Solution Design, and Implementation as shown in Figure 3 and described further below:

1. **Assessment**

Begin with an objective, rigorous assessment of the current situation. Enlist the best critical thinkers and problem solvers in your organization. If this skill set is unavailable, get experts to help. The assessment should include the following categories:

**Identify and Prioritize Gaps**

- Regulatory requirements are constantly changing, especially in emerging markets. Identify the risk areas where processes are not sufficiently robust to consistently meet regulatory requirements. Anticipate reasonably foreseeable regulatory changes – perhaps based on changes already afoot in some regions – that could be proactively addressed.

- Prioritize the key gaps compared to the regulatory requirements based on compliance risk and strategic imperatives. Short-term and long-term goals will vary based on the company’s current stage of the compliance maturity curve. For example, Stage 1 or Stage 2 companies may require short-term remediation and validation before tackling the longer-term, more proactive objectives.

- Ask whether all key processes are adequately staffed. Does management make quality a priority – in words and actions?

**Examine Systems and Root Causes**

- Assess what matters most for the product and customer. How does work currently get done? What are the detailed activities, drivers and owners? Which activities provide no added value and could be eliminated?

- Undertake a critical analysis of the root causes of past problems. What system(s) have failed and why? Enlist proven techniques like “the 5 whys,” causal factor tree analysis, failure mode and effects analysis, fishbone diagrams, contradiction tables, and design of experiments to systematically get to the root cause of a problem.

- Examine all quality subsystems with special focus on typically vulnerable processes such as change control, validation, and complaint handling. Consider the entire product life cycle to identify challenges and opportunities where systems or processes are either absent or lacking.

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Figure 3
Determine Opportunities

- Define performance improvement opportunities. How do the current quality system and business processes align with industry-leading practices and organizational models?
- Examine whether communication and decision making linkages between geographies, business units (especially acquired units that may not be fully integrated) and functions are sufficiently strong.

Assess Critical Drivers

- Identify the key drivers for product development “stage-gates” used to make decisions on project viability and continuation. What information is needed in order to “fail fast” or maintain funding? What are the logical linkages between product development processes and quality system processes?
- Ask whether metrics are established that are both meaningful and attainable to drive performance and assess effectiveness. How do key performance indicators compare against industry benchmarks? How should quality data feed into business processes?
- Explore how engaged business leaders are. Do they convey a consistent philosophy throughout their organizations?

2. Solutions Design

Develop the future-state operating model and optimized quality system. Addressing sustainable compliance requires a comprehensive solution, taking into account the company’s strategic priorities, goals, and objectives and typically encompasses the following steps:

- **Establish a multifunctional steering committee** chaired by a high-level process leader.
- **Facilitate strategic design workshops** to get insight and buy-in from key stakeholders about the current state and proposed solutions.
- Systematically **develop proposed solutions** using techniques like sequential design of experiments to optimize every step of the process.
- Simplify, and where appropriate, **reduce the number of procedures and processes** that reflect how work actually gets (or will get) done.
- **Drive internal control ownership and accountability.** Tie updated processes to individual job responsibilities.
- **Take a broad approach.** Focus on the organization as a whole and not silos; on global harmonization and not individual facilities or product lines. Keep in mind that regulators view companies, including large multinationals, as monoliths, not loose federations of unrelated divisions. Regulators increasingly expect solutions to be applied systemically throughout the organization.
At the same time, balance the need for consistent compliance against the temptation to apply a “one size fits all” approach. What works for one geography, division or product area may not be effective or possible for another. If customization is necessary, develop and apply umbrella corporate procedures to all geographies and business unit locations, and allow individual units the flexibility to develop compliant procedures within the umbrella. A different yet still compliant approach is better than forcing a single paradigm that cannot or will not be consistently followed.

3. Implementation

Never underestimate the importance of a properly planned and executed implementation plan, especially if the solution is transformative in nature. Former Honeywell CEO Larry Bossidy and noted business consultant and author Ram Charan note below in Execution: The Discipline of Getting Things Done that:

“No worthwhile strategy can be planned without taking into account the organization’s ability to execute it. ...Execution is a systematic process of rigorously discussing hows and whats, questioning, tenaciously following through, and ensuring accountability. ...In its most fundamental sense, execution is a systematic way of exposing reality and acting on it. Most companies don’t face reality very well.”

Key areas of focus for implementation include:

- **Change management.** Involve key stakeholders during the process to ensure engagement. Communicate throughout the organization at appropriate intervals to keep staff informed and in step with the transition. Personnel impact may be multifactorial, including changes to job responsibilities, day-to-day work processes, performance expectations, and metrics. Effective execution is possible only when these changes are appropriately managed.

- **Continued engagement and regular communication by senior leadership.** Consider broadening participation in key review boards (e.g., for CAPA, product safety and quality management), to keep quality and compliance issues visible to business leaders.

- **Delivery and process transformation.** Allow for staged transition from the current to future state.

- **Judicious use of technology.** Provide the tools, knowledge repositories, and management support infrastructure to transition from tribal knowledge to fully integrated quality systems and business processes. Utilize dashboards, scorecards, and other analytical tools to provide staff the ability to see at a glance which procedures and processes apply to them, and to access the same performance and effectiveness metrics that will be used by leadership.

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- **Evaluate effectiveness.** Even routine corrective actions must be evaluated to ensure a correction is effective. Apply the same principles to evaluate major structural changes to the quality system and business processes. Consider a design of experiments approach to systemically evaluate the effectiveness of new processes. Expect changes to be needed, both initially and over time. Think of a Stage 4 sustainable compliance system as a living organism requiring regular care and feeding to remain healthy.

![Figure 4: Where is your company on the compliance maturity curve?](image)

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<thead>
<tr>
<th>Maturity Level</th>
<th>People</th>
<th>Process</th>
<th>Technology</th>
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<tbody>
<tr>
<td>Level 1: Broken</td>
<td>Insufficient staff in both number and skills</td>
<td>Poorly written SOPs, lack of synchrony with actual practice</td>
<td>Manual records, loosely connected legacy IT</td>
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<td>Level 2: Point Solutions</td>
<td>Temporary resources to augment staff and regain basic compliance</td>
<td>Overhaul, rewrite of SOPs for critical processes</td>
<td>Establish initial basic IT architecture, new tools</td>
</tr>
<tr>
<td>Level 3: Fully Engaged QS</td>
<td>Staffed to deal with required operations plus quality problems</td>
<td>Well-constructed, well-executed SOPs</td>
<td>Accurately-configured IT, well-trained users</td>
</tr>
<tr>
<td>Level 4: Sustainable Compliance</td>
<td>Optimized staff, balanced with outsourcing of key quality tasks</td>
<td>Business processes integrated and mapped to quality requirements</td>
<td>State-of-the-art predictive data, real-time decision-making on quality data</td>
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CASE STUDY: MOVING UP THE COMPLIANCE CURVE

A mid-sized specialty pharmaceutical company was mired with a disjointed collection of some 4,500 procedures across their global R&D organization. Despite the procedural and country-specific focus, the company lacked alignment with regulatory requirements, found it difficult to execute global projects due to varying business processes, and was replete with inefficient, non-value added activities. The company was operating at Stage 2 on the compliance maturity curve – functioning, but at risk of sliding to Stage 1 and into trouble.

Starting with a global, top-down regulatory assessment, the company developed a global quality system with activity-based procedures and processes focused on regulatory compliance. As a result, the number of procedures was reduced 96% from 4,500 to less than 200, with equally significant reductions in procedure maintenance and training requirements. All staff now operate under the same procedures, wherever they go in the company. Responsibilities for critical processes involving regulatory risk, such as pharmacovigilance, were modeled and are now clear and fully integrated. These changes were managed through extensive involvement of affected stakeholders, development of a web-based portal for employees to see at a glance all of their quality and compliance related responsibilities, and visibility to key performance metrics.

Talking points were developed for presentation in regulatory audits so that staff could clearly explain how 96% of the procedures in the former quality system were eliminated without sacrificing compliance. Moreover, the company was able to demonstrate how quality and compliance were enhanced by sharing improvements in meaningful quality indicators and metrics. The company passed two stringent regulatory inspections with no observations noted, and is currently evaluating how the same model can be applied to other types of regulatory requirements, including financial, labor, environmental, and data security.

These improvements brought the company not only to a fully compliant state, but also achieved greater rewards because of the critical attention given to align quality processes with the product development cycle. R&D concurrently aligned to a stage-gate governance model driven by meaningful metrics that support pipeline

How to Support Sustainable Compliance

Ensure that every member of the organization has a basic understanding of what regulations are intended to accomplish

Establish systems – interlinked sets of processes and procedures – that help the organization respond quickly when things don’t go as planned and that prevent those situations from recurring

Establish reliable and thorough information pathways that keep management informed of the various aspects of a product’s life cycle

Maintain a knowledgeable staff commensurate in number and skill level with the products you make and market

Ensure that every individual in the company understands a few fundamental concepts: change control, corrective and preventive action, root cause and validation

Establish and maintain a simple, logical and complete documentation program

decision making. By focusing on science-driven development supported by the incorporation of key metrics designed to facilitate “fail fast” strategies, the company is innovating more quickly. By deconstructing processes into detailed activities, drivers and owners, new processes are in place for key disciplines supporting product development, such as Medical Affairs and Medical Safety. Moreover, by eliminating unnecessary procedures and tasks, the organization was poised to return to its core mission: to focus on science and the development of products addressing unmet needs. The company’s pipeline has never been more robust. Product quality and credibility with regulators has improved. Sustainable compliance has been achieved.

Summary

Quality problems or enforcement actions may drive a company to begin its journey up the compliance maturity curve, but the best time to take action is before such problems surface. Timely and proactive efforts to drive sustainable compliance minimize the risk of quality problems or enforcement action (see Figure 4). Importantly, when not distracted fighting fires, leaders have the relative luxury to practice the art of compliance – to think more strategically and design and implement a Stage 4 solution.

Sustainable compliance is the art and science of managing a business with a clear view of the regulatory requirements that govern all businesses in this industry. It is a fundamental part of the healthcare industry – and one that can profoundly affect the financial health of the enterprise. It is a component of the business that deserves as much attention to excellent planning and flawless execution as any other. Done well, it provides competitive advantage, growth and financial health for the shareholders; done poorly, it can mean interruption of supply to customers, long-term decline of a firm’s credibility and the ultimate demise of the business enterprise. Understanding compliance as a core business process and integrating it into the way the organization lives and breathes is the way to success.³

The time is now. Regulators typically take enforcement action against a company when they see quality and compliance lapses that lead the agency to conclude the company is “just not getting it.” But they also take action against entire industries – with additional and more onerous requirements – when they view the industry as a whole as having eroded quality principles, weak systems, and with top leadership giving more attention to the bottom line than to fundamental quality and compliance. In this current era of heightened enforcement, it’s more critical than ever for the entire healthcare industry to get it right. This is especially timely given the upcoming five-year re-evaluation cycle of the Food, Drug and Cosmetic Act as the Prescription Drug User Fee Act (PDUFA) and the Medical Device User Fee Act (MDUFA) come before Congress for reauthorization in 2012. Sustainable compliance is not just nirvana for the process gurus, it’s an imperative.

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For 32 years, Bob Rhoades has held positions in Quality for FDA-regulated industries advising senior pharmaceutical and medical device executives on compliance and its impact on corporate direction and strategy. A skilled practitioner of both the Quality System Regulation (QSR) and the pharmaceutical CGMPs, Mr. Rhoades has designed and implemented compliance improvement initiatives for major manufacturers in the U.S., Europe, China and India.
