Turn FDA Compliance into a Competitive Edge

GET TO MARKET NOW!

John Avellanet

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Turn FDA Compliance into a Competitive Edge in the Era of Personalized Medicine

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Introduction

Today's compliance and quality systems, with their emphasis on standardization and prescriptive rules, are rooted in a command-and-control philosophy from the 1900s. As we move forward in the 21st century into an era of medicines customized to individuals and particular patient populations, how well served are we with a one-size-fits-all mindset?

To foster innovation and medicine personalization, we need compliance infrastructures—from regulatory affairs, quality systems, and corporate policies—that work alongside our research and development programs as partners, not policemen.

For biopharmaceutical and device organizations to succeed in the coming decades, executives need a compliance program that is flexible and cost-effective, a regulatory strategy that balances rule-adherence with risk-taking, and a quality system that helps scientists and engineers build in safety, efficacy, and quality from day one. And, as I will show in this book, many executives have already started and many industries have faced similar challenges. Your advantage lies in being able to review their experiences and to pick and choose tactics that best suit you and your organization.

One thing is certain: executives who select a "wait and see" strategy will watch as their chances to successfully adapt and profit in the era of personalized medicine shrink with each passing year. The average time to bring a new drug or biologic to market is now almost 13 years; to bring a new device to market requires at least eight.[1] To adapt even some of the strategies and tactics in this book to new medicinal product development and regulatory compliance structures, executives need to start right now. The sooner a firm begins, the better its results, the faster its new product time to market, and the lower its costs.

These lessons are also relevant beyond individual companies and executive teams. Our industry needs new ways of thinking about regulatory compliance, quality systems, and medicinal product development that reflect the changing reality of the 21st century. And we need to start adopting those new strategies *now*.

WHO ARE THE EARLY ADOPTERS

As I will show in the pages that follow, companies, along with their executives, are trying to adapt to the challenges of personalized medicine by restructuring their research and development (R&D) programs and their compliance infrastructures to be more in synch.

A number of these early stage adapters already exist:

- Husseini Manji, a vice-president in Johnson & Johnson's global research and development group, is committed to integrating personalized biomarkers and diagnostics tools as early in development as possible. This in turn is making their entire research and development process more efficient and more effective.[2]
- Mark Fishman, head of Novartis AG, has led his company's large investment (in 2002 alone, over $4 billion) in genetics-focused medicinal research. The result: a June 2009 approval for Novartis' new genetic-based drug, Ilaris, ahead of market expectations.[3]
- AstraZeneca's vice-president of oncology research, Alan Barge, is scrutinizing the genetics of cancer to discover drugs that target those genetic profiles, establishing a model of future biologics and pharmaceutical drug development with the potential to dramatically reduce side effects and earn AstraZeneca strong patient loyalty.[4]
- Sanofi-Aventis CEO, Chris Viehbacher, has introduced Sanofi's new model of drug research and development that looks first at patient needs, and then regional healthcare issues, before tackling the science; as a result, medicine development is increasingly patient focused.[5]
- Precision Therapeutics, a small Pennsylvania company, has demonstrated the use of predictive diagnostic modeling to identify how a patient's genetic makeup

> will respond to various available treatments. The result: cancer patients have a 40% greater chance of survival and a 300% greater likelihood of cancer-free survival. These results alone have netted the company $42 million in investor funding.[6]

And there are dozens more examples of companies adopting tactics espoused in this book to develop personalized drugs and device products.

WHAT ARE THE FORCES AT PLAY

Underlying the need for changes in R&D and compliance infrastructures are powerful forces at play in the early 21st century, including:

Knowledge Specialization

Over the past twenty years, our scientific and technical knowledge has dramatically increased, from decoding the human genome to mastering the building of nanoscale materials. As a result, professional expertise has dealt with this revolution of knowledge and technological ability through an increase in specialization, sub-specialization and even sub-sub-specialization. Toxicologists have begat neurotoxicologists who have begat proteomic-neurotoxicologists.

Specialization adds two significant problems in any organization:

1. Each specialized professional vies for his or her share of limited company resources, thus reducing the amount for everyone else
2. Ever more narrowly focused information makes it more difficult to see patterns and linkages

These two problems alone make coping with the complexity of personalized medicine challenging. Additionally organizational politics and personal egos can frustrate integration of disciplines and knowledge-sharing; because knowledge is power, executives frequently have little incentive to share information.

The result: without careful shepherding, new medicine development, regulatory compliance, and quality systems programs become

mired in organizational politics and silos of specialization.

Virtual Companies

Beginning in the 1990s, a new type of company emerged: the virtual corporation. Virtual companies depend heavily on the Internet, computers, and telecommunications. They are made up of contractors, freelancers, part-time workers, and multiple suppliers and partners. They take advantage of their virtual structure to keep costs low and drive product development through outsourcing most or all of their research and development functions; these are not physical, "brick and mortar" companies you can visit in order to resolve a problem.

As globalization and technological capabilities have grown, the prevalence of virtual companies has also grown, including in the biopharmaceutical and device sectors.

While regulators expect biopharma and device executives to "own" their suppliers, those same executives are facing increasing challenges trying to bring complex new medicines to market using a chain of outsourced company functions, independent contractors, and virtual vendors around the world. How does one enforce rules or inspect a company whose only tangible physical presence is a website?

Generational Factors

Much has been written about the generational challenges companies face trying to juggle retiring baby-boomers, rising Gen-Xers, and the new Gen-Y or Millenials now entering the workforce. The implications for product development, quality systems, and compliance are significant.

Senior scientists, engineers, and compliance professionals are watching their hard-earned knowledge and expertise become obsolete. Their expectation of doing things "the company way" is being replaced by Gen-X and Gen-Y professionals who are much more willing to try new technological tools, take risks, and ignore convention. They are, in other words, more entrepreneurial. This mindset shift is good news for increasing innovation, but how does this work when it comes to creating new medicines? How does one take highly entrepreneurial people and tell them to innovate, develop, and design in a tightly controlled environment in constant compliance with regulatory rules, boundaries and expectations?

Consider that Gen-Ys have never known a time without computers, without the Internet, without wireless access, without file-sharing and swapping sites, and without pocket-sized cell phones. Gen-Ys see no difference in working with someone halfway around the world whom they only know by an alias and in working with someone the next desk over. And they certainly struggle with why they shouldn't ignore current copyright regulations and download music and software created and owned by others. Thus, not only do executives need to worry about how these new workers will innovate new medicines under current regulatory expectations and their firm's standard operating procedures, executives also need to consider how to protect nascent intellectual property *before* the company lawyer is even aware there is something new to patent!

Economics and Healthcare

Our global population is simultaneously aging and expecting better healthcare that is customized and tailored to the individual. But personalizing such cutting-edge medicine comes at a cost.

In my workshops on speeding personalized medicine development, I frequently note that we have less of a "healthcare crisis" in the world than we have a "healthcare funding crisis." Proof lies not in all the detailed statistics but rather in a simple question that I pose to each of the executives in my workshops:

> *Today, we have the technology and the drugs to keep you alive deep into your 100's—in fact, I'd be willing to bet, we could probably keep you alive almost forever. Now, admittedly, you'll spend your time lying in your hospital bed hooked to more machines than you have organs, and you'll get pumped with chemicals and biologics continuously, but we can keep you alive. So… here's the question: who will pay for you?*

To the aging population around the globe, add the declining birth rates in the Western world, the increasing cost of developing a new medicine, and a vacillating global economy, and biopharmaceutical and device executives are left with a conundrum: the population who can afford to pay for expensive new treatments is shrinking while the demand

for new, customized treatment is growing.

How will firms lower costs, improve personalization, and make a profit selling smaller amounts of new medicines to ever-smaller subpopulations? Part of the answer comes from increasingly relying on cutting-edge information and technology, and yet this also comes with its own perils.

Diversion of Technology and Regulation

The US Food and Drug Administration (FDA)—along with its international counterparts—is modernizing the regulations under which firms develop and bring new medicines to market. However, government efforts are too slow compared with the speed at which business must act to stay afloat.

In 1997, the FDA published a regulation laying out its expectations and rules for companies adopting electronic or digital signatures and/or records (instead of paper and ink). This regulation, Title 21 of the Code of Federal Regulations Part 11 (21 CFR Part 11 or "Part 11"), quickly grew out of control in its scope and its application—not because of the agency or the industry, but because of a growing gap between technological realities and regulatory expectations.

New computer-based products emerge every month. Moore's Law states that every 24 months computing power and capability double. Apple's iPhone contains more computing power than all of the computers worldwide in 1990. So why are we still using medicinal development methodologies developed before 1990 as our default strategies? It is no wonder then that new drugs and devices take so long to develop, and that keeping them safe, efficacious, and compliant costs so much.

How quickly do regulations evolve to accommodate technology that doubles in capacity and capability every two years? At the time of writing, the FDA's Part 11 has still not been updated or revised after more than twelve years.

Imagine a company not buying any new computers or software until the FDA had published its final version of the revised 21 CFR Part 11. Would such a company still exist by the time the agency published its new rules? This growing gap between regulatory expectations and marketplace capabilities is only accelerating. Despite the FDA's best efforts, the agency is not expected to complete its first pass at modernizing the regulations until at least 2012. At such a pace, "modernized" regulations

risk obsolescence before they've been approved for publication. Given the long timeline required to bring a new drug or device to market, one can hardly afford to wait to explore new technologies and processes until the FDA has finished its regulatory revisions.

Globalization

At the beginning of this century, regulatory agencies around the world began pushing to align their rules and regulations with each other. Through international working groups such as the International Conference on Harmonization (ICH) and the Global Regulatory Task Force (GHTF), regulations and expectations have been harmonized to standardize much of the regulatory requirements for drugs, biologics and devices. Ironically, because these changes necessitated compromises and reinterpretations by the FDA, this harmonization has made many biopharmaceutical and device compliance and quality systems out of date.

If the 20th century's industrial-based compliance systems are struggling, the question becomes, what will work? And how much will it cost? A simple economic analogy can clarify this. Think of your organization as a microcosm of the overall economy. Your regulatory affairs and quality management systems are part of your organization's service sector (along with other support functions such as information technology, human resources, finance and accounting, legal, and so forth). What then are your manufacturing sectors?

Most people draw the conclusion that an organization's "manufacturing" sector is its production areas (*e.g.*, factories and production lines). And in the 20th century, that would have been correct. By 2003, however, 85% of the average company's value was based not on goods produced by its factories and production lines, but on intangible intellectual property produced in offices and laboratories.[7] *The Economist* completed an analysis showing that for US companies alone, 75% of their value was solely based on intangible information and services.[8] In the 21st century's economy, an organization's "manufacturing" sector is its laboratories, clinical sites, engineering departments, etc.; the areas of the company that produce the intellectual property which production lines turn into pills, gels, defibrillators, and parenterals.

These cutting-edge, knowledge-creation "factories" require an advanced, dynamic quality system and compliance infrastructure to keep

up with them and help guide them.

Increased Compliance Burden

Thirty years ago, approximately 100 clinical trials were held in the US in an average year. Today, more than 41,000 clinical trials occur annually worldwide, with 4,000 – 6,000 in the US alone.[9] As we customize medicines to fit patient profiles, the number of clinical trials will continue to rise, perhaps doubling or tripling within the next 12–17 years.

With increased medicine customization will come increased liability for the executives involved; patients will claim that companies should have done a better job testing for and optimizing their new medicines based on genetic profiles. Is there any doubt that this will further increase the need for multiple clinical trials?

As the number of clinical trials increases, the overall cost to bring a new medicine to market will increase. Even if clinical trials become smaller as they multiply, the in-depth analysis work will increase as compliance, medical affairs, and quality management executives will be forced to juggle multiple trials and objectives, where before they might only have faced a single trial at a time.

Long before a company needs to figure out how to manufacture and distribute a personalized medicine, executives need to determine how to allocate resources to shepherd personalized medicine candidates through the development pipeline, into the marketplace, and into post-market monitoring.

In the era of personalized medicine, one drug or biologic trade name may need multiple variations and approvals to cover multiple drug versions, each tailored to a specific genetic population. The years ahead promise significant upheaval for quality systems predicated on single formulations, single production runs, single procedures, and single products.

Overly Rigid Quality Systems

Many standard operating procedures (SOPs) and policies make business adaptability all but impossible. We are all familiar with seemingly inane procedures that had to go through lengthy change and approval processes just to adapt to a minor business condition or technology change since the SOP was first crafted. In the era of customized medicine, the more SOPs and policies that have outlived their usefulness, the farther

behind a company will fall.

Business flexibility is a vital survival mechanism, and so some companies routinely ignore their own rules, or write memos to the file to get around their SOPs, or engage in round-the-clock SOP-revision projects. Inevitably, this sloppiness results in regulatory agency enforcement actions. And, at least in the US, FDA Form 483 observations and warning letters are the least of a company's problems: more and more quality system and compliance failures are causing financial declines, investor lawsuits, and bankruptcies.[10] Lawsuits (investor-led, or based on product-liability claims) against companies and executives citing their failure to adapt the firm's product development, quality systems, and compliance plans are expected to continue to increase in the decade ahead.

COMPLIANCE AS A COMPETITIVE EDGE

To succeed in the global era of personalized medicine, executives need to make it easy for regulators to approve a new product; to make it easy for consumers and patients to understand why they should buy that new medicine over competing products; to make it easy for prospective partners, collaborators, and investors to understand why working with the company improves their odds of success and return on investment; and to make it easy for employees and suppliers to comply with the regulations and company quality system expectations.

Executives can achieve compelling results by developing a flexible, cost-effective compliance infrastructure that builds safety, efficacy, and quality into new medicines from day one. Such a proactive program is vital for having effective discussions with investors and healthcare reimbursement agencies, fast-tracking a new medicine's development, negotiating with regulators, launching the new medicine ahead of industry expectations, and competing successfully in a globalized marketplace.

Given the landscape challenges we face over the next decade, compliance as a competitive edge will be both complex and demanding. Bringing together quality management, scientific development, regulatory compliance, and a host of different company sub-cultures, and then expecting them to work cooperatively and cross-functionally from preclinical research through post-market monitoring and improvements will be an immense challenge.

You can succeed by using a wide portfolio of tactics, tools, and strategies—many of which I've outlined in the pages that follow. Taken indi-

vidually, these techniques—virtualization, voice of the customer, rapid prototyping, intellectual property espionage protection, defensible documents, quality by design, and others—are not new. It is their unique combination under a holistic framework that provides the results.

The more strategies and suggestions in this book that you adopt, the more innovative, more agile, and ultimately, more successful you, your colleagues, and your organization will become. Compliance as a competitive edge will help you develop your potential, taking you to the next level where few of your competitors will be able to follow.

GETTING STARTED

This book is organized into two parts:

> Part one—chapters one through four—summarizes the landscape today, including the traditional models of medicinal product development and the roles of regulatory compliance and quality systems, and then looks at the larger landscape in which compliance and product development must exist, from the rise of the informed patient to the increase in executive liability. Throughout, I blend current analyses with forecasts for how these trends and factors will evolve over the next decade.
>
> Part two—chapters five through ten—lays out the strategies, tactics, and techniques to cope with, adapt to, and succeed in the decades ahead to bring safe, efficacious personalized medicines to market, stay compliant, and turn a profit.

At the end of each chapter, I have also added a "to do" checklist to either reinforce the takeaways or provide a step-by-step review to simplify implementation.

To strengthen the book's practical, "how to" mindset, I have created a dedicated website (http://www.Get2MarketNow.com) with bonus material, downloads, and supplemental information, including:

- Free articles
- Checklists and templates
- Sample policies and standard operating procedures
- Subscription forms to my blog and newsletter
- Information about new events and publications
- Free mini-seminars

TWO QUESTIONS

When I speak to organizations and executives about these topics, two questions almost always arise:

- *Why are you discussing drugs, biologics, and devices altogether as if they are similar?*
- *Why do you use terms like "compliance," "quality systems" and "quality management" interchangeably?*

For the latter question, consistently stating "*regulatory affairs, quality assurance, quality control, quality management, quality systems, quality management systems, records and document controls, computer security, electronic information integrity controls, corporate policies, and so on*" seems more than unwieldy. As a result, I try to use the phrase "compliance infrastructure" or "compliance programs" to encapsulate all these different aspects of medicinal product compliance. You will need to tailor these terms to your environment. When I do specifically describe a particular strategy component to be carried out by your "regulatory affairs department" or your "quality department," I do mean those specific groups.

In terms of conflating drugs (including biologics) and devices (including diagnostics), there are six reasons to consider these together as I lay out a proactive, holistic compliance framework:

- FDA officials have repeatedly stated that "we got it right with device regulations" and their desire to make drug regulations more aligned with the device regulations
- Genetic segmentation of potential patient populations increasingly relies on incorporating diagnostics into treatments—in other words, blending devices and drugs
- Biologics account for more and more of the new drugs

on the market, and because of the problems associated with taking biologics orally, these new drugs often rely upon devices for administration
- Many of the trends in the 21st century regulatory landscape affect drug, biologic, and device firms similarly
- A majority of the tactics and strategies in this book apply equally to firms that develop new medicines, be they drugs, biologics, devices, or combinations thereof
- Increasingly, both innovation and compliance rely on the convergence of technologies such as data sharing and telemedicine

I will show the details of each of these as the book unfolds.

Additionally, while this book uses FDA requirements and expectations as its baseline, the compliance strategies, tactics, and tools I outline are designed to meet, with some degree of modification, regulatory agency expectations in Europe, Japan (and other parts of Asia), Australia, Canada, and elsewhere. A book like this cannot hope to fully address every regulatory requirement worldwide, so you will need to judge the specifics to be tailored to your organization, its products, and the environments you face.

NEXT STEPS

From reading this book, I hope you take away two key realizations:

- Without a flexible, cost-effective, proactive regulatory compliance infrastructure covering the preclinical through the postmarket product lifecycle, companies cannot hope to bring a personalized drug, biologic, or device to market at a sustainable cost
- The combination of this type of flexible, cost-effective, proactive compliance infrastructure with an adaptive, customer-oriented medicinal development program is required if a company is to compete effectively—and survive—in the coming decades

These realizations reflect the growing gap between our 21st cen-

tury knowledge and our 20th century, industrial-era mindset. And this gap presents enormous vulnerability, but also historic opportunities. Readers of this book will have access to many of the strategies and tools to capitalize on these opportunities. This book will give you the techniques and tactics to enable 21st century competitiveness while still adhering to regulations, rules, and interpretations largely laid down in the previous century.

If this book merely provokes discussions amongst your colleagues and company, the book is a disappointment. My humblest hope is that you will adopt at least some of the tactics and tools in this book to help speed your time to market with new medicines over the next decade.

My challenge to you is to map out your own timeline for adapting as many of the strategies and suggestions in this book as possible so you can bring your new medicines to market now.

1 — Today's Regulatory Landscape

This book is about the future of drug, biologic and device compliance—whether in terms of quality systems, records control, or regulatory affairs—and its role in enabling innovation and new medicinal marketplace success.

In this chapter, I describe the major changes in the regulatory landscape. Each of these changes has traditionally been seen in isolation by outside observers specializing in one particular compliance aspect. With a broader view, we can see the evolution of the larger landscape to which we must adapt our development plans, regulatory approval strategies, and quality systems programs. Not only can we then stay compliant, but we can give ourselves a chance to be proactive with the ultimate result of gaining a competitive edge.

Executives have already started reacting to the dramatic transitions in drug, biologic, and device development that has unfolded over the past few decades. However, without a holistic strategy, firms have been left to struggle forward in a confused manner.

To provide a clear framework for success—one that you can adopt and adapt to your specific needs—I will look first at the four major regulatory compliance trends placing companies and their new medicine development plans in significant jeopardy:

1. Evolution of onerous safety, efficacy, and quality expectations from regulators
2. Rising role of reimbursement concerns in new drug or device marketability
3. Increasing emphasis on records, document, and data integrity controls
4. Declining levels of experienced compliance personnel

SAFETY, EFFICACY, AND QUALITY EXPECTATION EVOLUTION

To shed light on the new landscape, the first step is to summarily review how regulatory oversight from the US Food and Drug Administration (FDA) has evolved since the 1980s.

Role of the FDA

While regulation of drugs started back in the days of the Lincoln administration, the FDA as we think of it today began with the 1938 Food, Drug and Cosmetic Act (FDCA) during the Franklin Roosevelt administration. The legal statutes of the FDCA and subsequent acts of the US Congress provide the basis for the FDA and its authority over drugs, devices, and biologics. In terms of actual requirements for how these medical product sectors should comply with the law, these statutes only cover the high level requirements (*e.g.*, do not produce unsafe products). Instead, Congress has left it to the FDA to create practical rules. And for executives and investors in the industry, it is these rules that matter most.

To achieve the mandates of the legislation, the FDA has crafted a series of regulations or rules under Title 21 of the Code of Federal Regulations (21 CFR). These regulations, covering various activities involved in the discovery, design, development, testing, production, sales, and distribution of drugs, biologics, and devices, lay out the minimum requirements for life sciences organizations. Depending on the types of activities undertaken, a company may be subject to just a few parts of 21 CFR (*e.g.*, the manufacture of drugs is specifically governed by 21 CFR Parts 210 and 211), or the full panoply of FDA regulations and expectations.

In the 1980s, critics of the FDA claimed that this ever-escalating set of regulations was inadvertently impeding innovation—the more a company tried to move innovative ideas through its research and development (R&D) pipeline to market, the more regulations it had to comply with, thus driving up costs and diminishing incentives. Despite the ongoing need for some level of protection for consumers from unsafe products and/or unscrupulous executives (*i.e.*, the 1950s Thalidomide tragedy and the more recent push by some pharmaceutical executives to hide or downplay poor clinical studies results), criticism that medical

innovation was at risk did not fall on deaf ears at the FDA.

Beginning in the 1990s, the agency held a series of meetings with executives from other industries that had faced the dilemma of balancing public safety and product reliability with innovation and business profitability. Executives from industries as diverse as aerospace, automotive, semi-conductor, telecom, and information technology met with the agency and reviewed their struggles and achievements. In 2002, the FDA released a concept paper on 21st century Good Manufacturing Practices.[11] With the assistance of several biopharmaceutical firms, pilot programs were started to explore the viability of revising 20th century regulations to meet 21st century demands.

In conjunction with this 2002 concept paper, the FDA tackled another concern of critics and agency personnel: the growing difficulty of adhering to FDA regulations in the US while also developing and making products for other markets around the globe. Each nation's regulatory agency governing medicinal products was different enough to cause major headaches both for companies and for agencies trying to coordinate inspections and compliance from medicine manufacturers based overseas. As part of its deliberations for the 2002 concept paper and in subsequent progress reports, the agency referenced its work with other regulatory agencies in Japan and the European Union to harmonize scientific standards and regulatory operations on medicine quality.[12]

Meanwhile, the FDA had struggles of its own. Budget limitations and the exploding rate of scientific knowledge (the human genome was decoded in June 2000), meant the agency was forced to make tradeoffs—not every product could be analyzed, not every manufacturer or researcher could be inspected. Originally, the FDA had focused on keeping unsafe medicines off the market; as the agency's own inspection manuals simply stated, the FDA's mission was "to prevent the distribution of unsafe or ineffective products."[13] By the early 2000s, however, the agency had increasingly shifted into prioritization mode. In the 20th century, inspections of companies were done in a prescriptive manner, with checklists drawn from a line-by-line comparison of the regulations. By 2004, according to Helen Winkle, Director of the Office of Pharmaceutical Science, and Thom Savage, Director of the Office of Regulatory Compliance, FDA inspectors started to be trained to assess a company less on a black-and-white adherence to specific regulatory wording and phrasing, and more on the firm's ability to maintain—and demonstrate—a consistent "state-of-control."[14]

This mindset shift coincided with the publication that same year of two FDA reports, "Introduction or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products,"[15] and "Pharmaceutical cGMPs for the 21st Century—A Risk-Based Approach."[16] The reports identified many of the challenges facing the biopharmaceutical sectors in the era of globalized medical product development and manufacture. The FDA followed its reports with discussions of steps the agency would take over the next decade to ensure medicinal product safety, efficacy, and quality while still fostering innovation in the industry. While much of the resulting reports revolve around internal agency dynamics and activities, for biopharma and device executives, four major components stand out:

1. The revision of current regulations to incorporate new scientific knowledge and techniques
2. The increased level of international harmonization with other non-US health agencies
3. The adoption of a risk-based philosophy of oversight and inspection
4. The push for companies to design quality, safety, and efficacy into their new medical products as early as possible (*e.g.*, quality by design)

Medical device and diagnostics executives familiar with 21 CFR Part 820 Quality Systems Regulations (QSRs) who review these two FDA papers will be pleasantly surprised at the similarities with Part 820. Indeed, at a 2007 pharmaceutical industry conference, FDA official Kim Trautman expressly conducted a cross-comparison between the regulations governing devices and those governing drugs and biologics, concluding, "We got it right with the device QSRs."[17]

More recently, in publications and speeches (some of which are discussed in this chapter), regulatory officials have argued that not only do life sciences companies need to make fundamental changes by 2020 to get to market with new medicines, but also that life sciences executives "do not have the option to go slow."[18]

As I will show throughout the rest of this book, there should be little doubt that FDA regulations governing pharmaceuticals and biologics will look increasingly like the regulations governing medical devices and diagnostics, with an emphasis on risk-based controls, quality by

design, and international cooperation. Several of these initiatives bear similarity to long-held philosophies of other national health agencies such as the European Medicines Agency, and were clearly influenced by the FDA's involvement in two international regulatory alignment groups starting in 1990: the International Conference on Harmonization and the Global Harmonization Task Force.

Role of the International Conference on Harmonization (ICH)

The FDA, along with the European Union's European Medicines Agency and Japan's Ministry of Health, Labor and Welfare (MHLW), became a founding member of the International Conference on Harmonization (ICH) in January 1990. Other members include the major pharmaceutical trade groups in each of these three regions, plus Health Canada and the World Health Organization.

The ICH essentially drafts harmonized regulatory guidelines covering biopharmaceutical quality, safety, and efficacy. A miscellaneous category of guidelines also exists, tackling items such as common medical terminology and a common technical document format (the CTD) for regulatory submissions, thereby streamlining the submissions process in all member states.

Each ICH guideline goes through multiple revisions before it is published in final form by the ICH and released by its respective national health agency (*i.e.*, the FDA in the US) as a formal regulatory guideline for industry. Of critical importance to biopharmaceutical executives was the announcement in 2007 that the FDA was going to start enforcing ICH guidelines by the end of 2008. And in April 2008, the first warning letter was issued citing failure to comply with an approved ICH guideline.[19]

Role of the Global Harmonization Task Force (GHTF)

In 1992, the FDA also became a founding member of a similar harmonization effort, this time for medical devices and diagnostics, the Global Harmonization Task Force (GHTF). Other members include health agencies from the European Union, Canada, Japan, and Australia.

Like the ICH, the GHTF has broken down guidelines into categories designed to be harmonized across all regions. The GHTF has organized its categories around the position of the medical device in its overall

lifecycle—development ("clinical safety/performance"); submission for approval ("premarket evaluation"); production and distribution ("postmarket surveillance and vigilance")—plus operational considerations ("quality systems" and "auditing").

At the time of writing, FDA officials are debating whether to enforce GHTF guidelines. FDA inspectors are being trained in GHTF expectations and rules.[20] It seems certain, given increasing pressure on the agency to strengthen medical device requirements, that compliance with GHTF guidelines is inevitable. While compliance may only initially be limited to firms in the device, diagnostics, or combination product marketplaces, as we will see, in the era of personalized medicine, few executives will be able to win an argument claiming complete exemption from GHTF compliance.

Long-Term Implications

Harmonization will continue as regulatory oversight agencies confront the realities of overseeing a global marketplace. No regulatory agency has the necessary staffing, expertise, and budget to inspect every purveyor of medical products. International cooperation is a necessity. As the regulations are increasingly harmonized, I expect a commiserate increase in joint inspection and oversight responsibilities; inspections by Health Canada or the European Medicines Agency will be accepted by the FDA and vice versa.

For the drug, biologic, or device executive, experience with FDA regulations is no longer enough. Even for a firm planning to develop and market its new medicine in the US only, FDA regulations only make up half the required device or drug rules. Compliance with ICH or GHTF (or both if a company is developing a combination drug and device) is now a necessity.

Three key implications can be drawn from this reshaping of the regulatory safety, efficacy, and quality landscape. First, hiring of personnel and outside compliance experts with only FDA expertise puts firms at a disadvantage in an internationally harmonized regulatory environment. Second, medical product development plans and compliance strategies need to incorporate—and design controls around—building quality, safety, efficacy, and harmonization as early as possible. And third, the traditional approaches to compliance-related issues, from FDA enforcement responses to the submission of applications to market a new drug

or device, are increasingly out of date. Executives who fail to adapt their 20th century philosophies to the new realities of the 21st century regulatory landscape will find the odds increasingly stacked against them.

MEDICINAL REIMBURSEMENT AND MARKETABILITY

Most of the industrialized world has some form of government-sponsored healthcare. These government agencies play a significant role in controlling drug prices. In the US, the Centers for Medicaid and Medicare Services (CMS) accomplishes price regulation indirectly; in the U.K., the National Health Service is more active through its National Institute for Health and Clinical Excellence (NICE), and in the rest of Europe, the Committee for Medicinal Products for Human Use (CHMP) controls prices with its emphasis on risk-benefit ratios.

Roles of NICE in the UK and CHMP Elsewhere in Europe

Under the UK's national health insurance program, biopharmaceutical firms must submit their product's cost-effectiveness information to NICE for analysis and review. Part of this effectiveness information includes the quality-of-life-adjusted-year (QALY) tool that analyzes how a prospective treatment affects patient quantity of life (*e.g.*, how much does it extend life?) and quality of life (*e.g.*, how much better is a person following treatment?). Typically, NICE takes approximately 18 months to assess a new drug or biologic. If NICE determines that claims of effectiveness are not supported—for instance, the cost of the new drug is 30% more than a drug already on the market in the UK but the new drug's effectiveness is only 5% greater than the existing drug—NICE will not approve coverage of the drug.[21] In other words, proof of efficacy *and* proof of cost-efficiency are required for reimbursement and sales in the UK.

The European Medicines Agency has a similar framework, although because each member state has different reimbursement mechanisms, Europe's CHMP focuses on the risk-benefit ratio in regards to effectiveness and safety data.

How does this play out in terms of personalized medicine? Consider the example of Amgen's cancer drug Vectibix. In May 2007, the CHMP refused to grant approval based on clinical trial data that did not dem-

onstrate a clear level of effectiveness. Amgen promptly appealed. In its appeal, Amgen provided a biomarker analysis of its previous Phase 3 study plus a Phase 3 extension study. Amgen showed that patients with a *KRAS* gene mutation were resistant to the drug (approximately 35% of prospective patients).[22] By excluding those patients with the genetic mutation from any effectiveness conclusions, Amgen was able to demonstrate that its biologic had a significantly improved risk-benefit ratio. In other words, for patients with the non-mutated *KRAS* gene, Vectibix was highly effective and cost-efficient. The European Medicines Agency then granted Amgen marketing approval for patients with the non-mutated *KRAS* gene.

Whether it's an analysis of the risk-benefit ratio or a review of comparative cost-effectiveness, NICE and CHMP serve as gatekeepers in their respective markets to control healthcare costs.

Role of CMS in the US

In the same way that decisions by CHMP and NICE are reviewed by other health reimbursers throughout Europe, so too do private health insurers in the US take their cues from the reimbursement levels assigned to new medications by CMS.

CMS's underpinnings for reimbursement categorization can be confusing—indeed, an entire cottage industry of reimbursement consultants has arisen to help executives sort through the confusion of CMS (*e.g.*, how to appeal financial rulings and private insurer decision-making). An understanding of reimbursement expectations is critical for new medical product development and innovation. While US regulatory approval and marketplace launch may not be impacted directly by CMS reimbursement classification, a company's sales and marketplace success are impacted. Private insurers look to CMS reimbursement rates and set their own reimbursement rates accordingly.

Therefore, the earlier that reimbursement classification estimations can be defined, the sooner biopharmaceutical and device executives can start to gather data supporting reimbursement goals.

Role of Venture Capitalists

In addition to regulatory healthcare agencies, venture capitalists also play an increasingly influential role in new medical product innovation. Gone are the days—if they ever truly existed—where venture capitalists

would provide money to a scientist or biomedical engineer with simply a "good idea." Increasingly, venture capitalists are experienced in the realities of new medical product development, from the poor chances of success to the enormous costs involved and to the long timelines.

A 2009 University of Maryland study found that venture capitalists pay little to no attention to the academic credentials and scientific research successes of medical product scientists and engineers who want to become entrepreneurs.[23] Instead, since 2000, venture capitalists have focused more on commercial execution rather than research credentials, providing more and more funding to those startups planning to develop the new molecule, biologic or device *up until* it can be licensed or sold away.[24]

Today's venture capitalists have an average time horizon of approximately 3 years in which to obtain a return on their investment.[25] Indeed, the number one question that life science entrepreneurs are asked is "What is your end game?" In other words, the venture capitalists understand that the odds of a nascent company independently launching a new medicine is extremely unlikely. So is the strategy to focus on research and license the intellectual property? Or to bring the new drug/device through early clinical trials and then license, sell, or partner?

Unless a company can provide compelling evidence that a new product is marketable—including laboratory testing results, clinical results, comparative product analyses, and reimbursement likelihoods—company executives are going to run out of time and money. The pressure for both financial returns and R&D productivity has only increased with the rising number of biotechnology and device entrepreneurs all around the world, from China and India to Europe and Latin America. Excluding long-time biotechnology industry observers, few scientists and entrepreneurs realize that less than a third of all biotechnology firms are in the US.

Long-Term Implications

For the drug, biologic, or device company executive, being able to appropriately factor in reimbursement realities and financial trends with compliance and development strategies is now an essential skill. Failure to adopt cost-efficiencies within regulatory compliance, quality systems, and medical product development strategies will put firms, shareholders, investors, and prospective patients in jeopardy.

Over time, I expect some form of the UK's NICE and Europe's CHMP to expand into other English-speaking nations such as Canada, Australia, and India, not to mention other countries such as China and Brazil. NICE has already consulted on a non-profit basis with more than 60 countries on how to ensure affordable medicines.[26] The US will not be exempt from this. As I noted in the introduction, we have the technology and science available to extend life considerably; what we do not have are the resources to match; trade-offs are inevitable.

The FDA also plays a role in helping determine cost-efficiencies of new medicines. In August 2008, the agency issued a procedural guidance document entitled *Integrated Summary of Effectiveness*.[27] This document laid out the specific expectations of the FDA for comparisons and analyses of efficacy results in clinical trials, including any comparative effectiveness data between competing products. While the FDA currently cannot use cost-effectiveness information in its approval decisions on new medicines, by encouraging companies to develop this type of specific information in their clinical packages, the FDA fosters the creation, and ultimately the awareness, of this information. Whether such information then directly or indirectly influences CMS or private insurer reimbursement is unclear; however, executives would be wise not to discount the possibility.

Analysis of further financial issues impacting medical product development falls beyond the scope of this book. Such financial examinations require a depth of analysis that goes well beyond the boundaries of regulatory compliance, quality systems, and regulatory affairs, and so I will briefly touch upon further financial impacts and trends only insomuch as they help illustrate observations or recommendations in the book. Readers looking for more in-depth analyses of the behind-the-scenes financial details can find these in some of the resources listed in the bibliography.

RECORDS MANAGEMENT AND DATA INTEGRITY

Executives must keep in mind that the pressure to produce compelling evidence of new product marketability increases the temptation to skirt the rules. Fraudulent clinical and laboratory results have been on the rise over the past few years, and the FDA trains its inspectors and reviewers to spot records fraud.

Since 2006, more than 95% of FDA enforcement actions and deni-

als of marketing approval have been motivated by inadequate records integrity.[28] Whether it is the integrity of data in a regulatory submission, or the ability to control the documentation and information in your own company, it seems that regulatory approval is predicated upon the ability to control the reliability and quality of records.

The increasing importance of new medical product innovation and compliance emphasizes three crucial needs:

1. Intellectual property protection
2. Data integrity
3. Records controls

Intellectual Property Protection

Intellectual property protection is typically left to lawyers; unfortunately, this assumption unintentionally endangers discoveries, proprietary processes, and other forms of intellectual property.

As I have written before, "Intellectual property is the greatest asset of any company; it must be thoroughly protected and secured."[29] Whether a discovery in the lab, a revelation from patient research, an engineering blueprint, or a unique production method, intellectual property forms the core of the 21st century drug, biologic, and device company. The medicine itself is really just a tangible form of the underlying intellectual property.

In the context of traditional FDA compliance professions—regulatory affairs and quality management—the goal of the former has been to bring this medicinal intellectual property to market successfully in a compliant manner, while the goal of quality management personnel has been to ensure this medicinal intellectual property was produced and maintained in a controlled manner.

Understanding that confidential information encompasses far more than patented intellectual property—that it includes drug interaction data, internal quality audit results, biologics production processes, critical manufacturing control parameters, and so on—gives us opportunities to incorporate controls throughout the product lifecycle. Quality management, regulatory affairs, and other compliance executives are perfectly poised to easily incorporate intellectual property (IP) controls into any compliance program.

Executives who ignore the interplay between intellectual property,

regulatory compliance, and quality systems do so at their firm's peril. In December 2008, Pfizer was penalized US$38.7 million for stealing clinical drug interaction and comparative-use data on the drug Bextra. Pfizer had obtained this confidential information through a former employee of another organization.[30]

The intricacies of intellectual property and its protection are beyond the scope of this book. However, as I will show in chapter five, there are several steps that quality management, regulatory affairs, and other compliance executives should be taking on a regular basis to help protect their organization's intellectual property.

When I speak to organizations on preventing theft of their intellectual property and trade secrets, I start by asking attendees to list basic questions they might consider incorporating into their internal quality audits or due diligence reviews of new suppliers and partners. A few, tentative suggestions—typically involving some variation of "ask the lawyer"—are voiced. I follow by offering two simple questions every compliance-based due diligence or internal audit should include:

1. Are visitors required to sign in with specific information, such as which company they are from and whom they are visiting?
2. Does the lab director or the clinical investigator enforce a clear desk policy regarding confidential information?

These two examples alone tend to spark thoughtful discussions by attendees on what each member of a due diligence or internal audit team could do better to improve the security of their firm's intellectual property and confidential information. Given that quality, regulatory affairs, and other compliance executives are at the forefront of due diligence and internal audits, those who do not include at least some assessment of intellectual property controls unwittingly place their company and their investors at undue risk.

Data Integrity

Not long ago, quality of data integrity was judged by how well a firm managed its laboratory notebooks and batch production records. The sooner a researcher's notes and test results were reviewed, witnessed, and signed off by his/her supervisor, the better the integrity.

As paper notebooks have given way to electronic lab notebooks and laboratory information management systems, data integrity is no longer about who witnessed what when. Electronic information is time and date stamped the moment it is created, and again when it is saved. Today's uncertainties center on the amount of integrity inherent in any given information set. Have the data been tampered with? Are all the data present, or have negative results been omitted or obscured? Whether it is production batch records, analytical lab test results, or adverse event reports, regulatory officials increasingly scrutinize a company's records and documents for integrity… or a lack thereof.

To FDA regulators, medical product and compliance records are reliable and trustworthy if they are accurate, legible, attributable to a particular individual, original, complete, and contemporaneous (*i.e.*, the information was recorded at the time of the actual activity, such as a lab test or production run).

In 2007, FDA directors revealed that agency inspectors had been receiving specialized training on "uncovering data integrity, data manipulation and fraud."[31] A year later, Edwin Rivera-Martinez, of the agency's Office of Compliance, noted that one-third of all pre-approval inspections—the FDA onsite inspections conducted prior to granting approval for a new medicine—are initiated because of record integrity issues.[32] And whistleblowers who allege data manipulation and fraud increasingly find a receptive outlet in the FDA.

Data integrity issues become increasingly difficult considering how long much of the information needs to be retained. Different types of product safety, efficacy, and quality information may be required, by regulation, to be retained for more than two decades. Paper records, when properly maintained, last at least several hundred years. No one knows how long digitally-stored information will last. So far, most forecasts have fallen dramatically short. Compact discs (CDs), for instance, were supposed to last indefinitely. Then it was determined that a typical lifespan might be 20-25 years. Today, we know that the chemical reactions that occur when you record information onto a CD degrade far more rapidly than originally thought, causing the CD to fail regardless of how it is cared for and stored. A recorded CD will last, on average, only 8-10 years. Given the long horizon involved in new medical product development, the retention of product safety, efficacy, and quality records is yet another new aspect of the regulatory landscape of the 21st century, and one to which we will return in chapter nine.

Records Controls

The integrity of information can be maintained, intellectual property can be protected, and proof of a new medicine's safety, efficacy, and quality can be demonstrated as long as your company's records are controlled. Records are your proof. They either support your assertions, or they reveal the invalidity of your claims.

Analysis of 294 warning letters made publicly available since 2007 reveals that 271 of the 294 letters cite firms for records control-related issues such as "firm was unable to provide documentation"[33] and "firm does not keep adequate records to determine each batch, lot, or unit is manufactured in accordance with the Quality Systems regulations."[34]

Establishing standard operating procedures, and training personnel to employ them, is only the beginning. Unfortunately, for many executives accustomed to 20th century expectations, the bar has been raised; simply having a written procedure and holding a training session to explain it is not enough. Records must exist that prove that the procedure was followed, and those records must be maintained over time. To establish and maintain that proof, requires records controls.

Each FDA regulation has a subsection within it spelling out the types of records the agency expects companies to retain and control. From laboratory notebooks and clinical investigator reports, to production lot files and adverse event reports, each record type has different retention periods and requirements. As such, companies need to set up records retention schedules and define governing policies and controls procedure.

Compliance executives are natural leaders for these efforts. After all, it is their responsibility to ensure that the company has defensible documents. Such defense goes far beyond simply having a standard operating procedure. Defensible records require controls. Executives who ignore the expectations encapsulated in the recent warning letters cited above, and who try to define their role in the context of last century's regulatory expectations, do so at their peril.

Long-Term Implications

For the drug, biologic, or device executive, familiarity with basic good records management and control practices is a must. Just as medieval knights lived and died by the sword, today's executives succeed or fail by the record.

While the stock prices of firms rise and fall by as much as 40% based on public FDA enforcement actions[35], many of us have also seen the conviction of executives and firms in the court of public opinion in the news of court cases involving GlaxoSmithKline, AstraZeneca, Merck, Wyeth, Boston Scientific, Bristol Myers Squibb, and countless others. In each of these cases, documents and records that reflected poorly on these companies and their executives were disclosed in the courtroom. In the case of embarrassing public exposure such as this, an FDA warning letter may be the least of a company's concerns. Financial penalties, bad publicity, and ruined careers linger far longer than FDA Form 483 observations and wounded pride.

I expect records integrity to continue to dominate the regulatory landscape in the 21st century. Development of personalized medicine is complicated, with subtle differences having significant impacts on safety, efficacy, and quality. Records are your proof that you understood these risks, put in place appropriate controls, and have maintained both effective controls and suitable documentation. When inspectors arrive at your facility, few will be interested in hearing about how wonderful your processes are. Instead, expect to be asked to "prove it."

CHANGING COMPLIANCE EXPERTISE

At the same time that all of these shifts are occurring in the regulatory landscape, the ability of companies to cope with these shifts is at risk. Demographics are working against the industry.

US Regulatory Affairs and Quality Management Demographics

A 2006-2007 survey by the University of Southern California (USC) found that two-thirds of experienced compliance professionals in the US—those with more than 10 years of experience—are preparing to retire between 2015 and 2020.[36] Some of these individuals will stay engaged in the field through speaking and advisory roles, yet how interested will these semi-retirees be in accumulating the substantial set of new skills required to navigate records controls, reimbursement strategies, and the globally harmonized, stricter regulatory expectations of personalized medicine?

As a part of preparing this book, I conducted a topic review of the

various industry certification programs and graduate degree programs available to rising professionals within quality systems and regulatory affairs. To date, within these programs each of the major trends I identified above—the need to incorporate reimbursement elements within regulatory strategies, the changing expectation of FDA to incorporate quality by design and regulatory harmonization, and the criticality of records integrity—is given minimal attention, if they are discussed at all.

The implication that compliance personnel are not being developed with the requisite skills necessary for success in the 21st century is borne out by the USC study. More than 48% of companies express difficulty in filling compliance positions with personnel who have experience beyond the traditional textbook view of regulatory affairs and quality systems.[37]

FDA Personnel Shifts

Concurrent with this loss of private industry expertise, the FDA is set to experience its largest knowledge transfer, with the retirement of nearly 50% of its workforce by 2020.[38] The significant loss of tacit knowledge, just as the agency is revising its regulations might be disconcerting, were it not for the shift noted above of increasing global harmonization and cooperation. As a result, while industry struggles to adapt to all the shifts in the regulatory landscape, FDA officials can rely on assistance from their colleagues in other regulatory agencies around the world. The result will be more international harmonization, more multinational inspections, and more knowledge sharing between regulatory health agencies, just as companies are confronting a dearth of knowledge and expertise.

Witness the industry's frustration with the UK's NICE. Because of growing reliance upon non-FDA agencies to offer advice and expertise on regulatory requirements, I expect officials from non-traditional medical product oversight agencies such as NICE and CMS may obtain greater say over which products will be approved and which products will not. The rising influence of healthcare reimbursers on approval decisions is one reason why medical product effectiveness so easily correlates to cost-effectiveness. If healthcare reimbursement agency personnel question a new medicine's effectiveness, expect doubts to creep into the FDA reviewers' minds as well.

Long-Term Implications

For the drug, biologic, or device executive, there are several lessons to be gleaned from this trend of declining expertise. In the short term, company development programs will need to make up for the inability of industry and educational certifications to keep up with the knowledge required in the 21st century. This can be accomplished with formal employee development programs, or executives can look at and adopt the recommendations in the second half of this book to provide compliance personnel with practical frameworks in which they will naturally develop crucial knowledge. Ideally, a company will adopt both, providing a robust system to ensure development of effective compliance personnel.

As global harmonization proceeds, companies will increasingly have the opportunity to outsource basic regulatory affairs and quality systems activities. Outsourcing basic tasks is something that other industries have adopted, and there is little doubt that device makers and biopharmaceutical firms will also proceed down this path. Today, regulatory agencies are actively harmonizing their submissions formats for requests to market a new medicine. If a regulatory submission is largely similar regardless of whether it is for the US, Canada, the EU, and so on, then companies can quickly and easily gain efficiencies by outsourcing the bulk of such work to regulatory affairs professionals in India, Australia, or China and then complete minor amendments for the US, Canada, or the EU. This is one way I expect companies to adapt to declining compliance expertise in the US. That such outsourcing also dovetails with the outsourcing of clinical trials and manufacturing overseas only supports its inevitability.

In the 21st century compliance roles will be split between those more easily outsourced because the work is relatively operational with a high degree of consistency due to regulatory harmonization (for instance, CTD formatting, supplier due diligence auditing, and regulatory training) and those compliance roles less easily outsourced because the work is unique to a company and its products (for instance, developing a clinical regulatory integrated strategic plan for a newly created medicine, ensuring that the reimbursement, efficacy, and safety characteristics of a new medicine are verified under a compliant quality system, and so on).

SUMMARY

As I noted at the beginning of this chapter, there are four trends shaping the regulatory landscape today:

1. Declining expertise in compliance
2. Increasing emphasis on records controls and integrity
3. Globalized expectations to incorporate safety, efficacy, and quality in new medicine development
4. Increasing relevance of reimbursement issues

These four trends cover large, structural, systemic evolutions. And not a single one was evident throughout most of the 20th century. Executives who do not change how their compliance infrastructures and strategies support new medicine development and launch are not likely to succeed in the 21st century landscape.

A company's quality systems and regulatory compliance infrastructure for the 21st century must include reference to, and be compliant with, ICH guidelines and/or GHTF guidelines. The FDA, along with other regulatory agencies around the world, has moved away from proscriptive oversight to a more principled approach that focuses on looking at the justifications that prove your controls meet or exceed expectations. As I will show you later in the book, the wise executive can use this to his or her company's advantage.

Developing a new medicine is highly regulated with rewards increasingly controlled by public healthcare agencies with considerable interests in equating medicinal price with efficacy. Because clinical development and medical product production are intimately involved with efficacy, regulatory affairs and quality systems executives will be increasingly asked to incorporate elements of reimbursement strategies in any compliance strategy; this is yet another aspect of using compliance as a competitive edge.

And determining how to gather, organize, and control all of this proof is a core consideration in your product development and regulatory compliance strategies. Quality systems and regulatory affairs have not traditionally tackled records management issues. In this century, executives unwilling to expand outside of traditional compliance roles will lead their companies and product development efforts to failure.

Understanding these trends allows us to grasp why companies are

increasingly having difficulty hiring regulatory, quality, and other compliance personnel who are able to think beyond the traditional landscape, and why such companies are increasingly at risk. To stay current, more outsourcing of compliance-related tasks is inevitable. And to succeed in launching a new medical product, executives will need to blend their newfound flexibility of compliance with an understanding of the trends shaping new drug, device, or biologic development; topics which are covered in the next chapter.

EXECUTIVE'S CHECKLIST FOR CHAPTER ONE

Understanding the major trends impacting the regulatory compliance landscape in which new medicines are developed is the first step toward success in the 21st century. Here's a step-by-step to-do list:

- ☐ Download and review the FDA's reports on its Critical Path initiative and Quality by Design (copies of these can be obtained from the FDA or from the book's website at http://www.Get2MarketNow.com)
- ☐ Visit the ICH and GHTF websites to determine which rules apply to your organization (links to these websites, plus to those of the FDA, the European Medicines Agency, Health Canada, and other agencies, are on the book's website and in appendix two)
- ☐ Update any consultant and personnel selection and hiring processes to clarify that familiarity with ICH and/or GHTF are mandatory
- ☐ Decide what comparative effectiveness data you will plan to assess during development
- ☐ Read Chapter 5, "Improving Innovation," on ways in which you can incorporate basic intellectual property protection mechanisms into your compliance and medicinal product development activities
- ☐ Verify you have an effective and up-to-date records retention program that defines, at minimum, how long all FDA and ICH/GHTF required record types are retained
- ☐ Read Chapter 9, "Driving a Holistic Compliance Framework," to learn how to put in place a compliant

records management program
- ☐ Review due diligence and internal audit questionnaires with your legal department to identify which corporate espionage controls you should be regularly assessing
- ☐ Ask your colleagues to assess their level of comfort with ICH and/or GHTF requirements
- ☐ Map an ICH and/or GHTF professional development program with your human resources/personnel department

About the Author

John Avellanet is the founder of Cerulean Associates LLC—a private FDA compliance and quality systems consultancy. In addition to writing this book, he was a contributing author to the book *Best Practices in Biotechnology Business Development* (2008), is a compliance columnist for three international journals, and has written over 100 articles on lean regulatory affairs and FDA quality systems compliance. He serves on the advisory boards of several trade associations, and is a frequently requested speaker for industry events, business schools, and corporate workshops.

Prior to founding Cerulean Associates LLC, Mr. Avellanet was a *C*-level medical device and biopharmaceutical executive who created, developed, and ran a *Fortune 50* subsidiary's records management and information technology departments to meet FDA, ISO, ICH, and GHTF compliance requirements. In 2006, he was awarded lifetime membership in the Who's Who of top executives in the pharmaceutical and life sciences industry. And he has been interviewed in print and on radio programs such as *Tomorrow's Business* and *My Technology Lawyer*. He currently lives in Williamsburg, Virginia.

Through his firm, Cerulean Associates LLC, Mr. Avellanet offers a range of independent consulting services and compliance products, all of which are based around the ideas outlined in this book. More information on Cerulean and Mr. Avellanet can be found on the website www.Ceruleanllc.com

Mr. Avellanet would love to hear any feedback on the concepts and advice offered in this book. Contact him through the book's website at john@Get2MarketNow.com