



# Getting Ready for Risk-Based GMPs

Patrick Clinton

**As FDA moves toward a new vision of GMP regulations, BioPharm International asked industry experts some key questions: What form will risk-based GMPs take? What are the benefits and costs for biotech? Will the change really encourage innovation? And, most important, can FDA leaders get field inspectors to buy into the new approach?**

In the sweeping program of change currently under way at FDA, perhaps no element has greater potential to transform the way companies do business than the agency's plan to move the regulation of good manufacturing practices (GMPs) in the direction of what FDA has described as "a science- and risk-based approach to product quality regulation incorporating an integrated quality systems approach."

Risk-based GMP regulation offers many potential advantages to the industry and the agency alike — including potential reductions in inspections, greater consistency, and coordination with international standards. But to date, for many in biotech, it is just a set of ideas that give few clues to what life under the system would be like.

For a better sense of what risk-based regulation promises — or threatens — we turned to a distinguished group of industry experts. Here is what they had to say:

## ONE PROGRAM, MANY MOTIVES

The first point to recognize about the risk-management initiative is that it has multiple motives. On one hand, it is designed to improve regulatory procedures and respond to industry

concerns. On the other, it is clearly meant to cope with a crisis of resources at the agency.

"You have to keep in mind that to a larger extent than many people realize the agency is diverted these days to a lot of bioterrorist-related initiatives and the reformatting of CBER into CDER," explains Michael Petty, an FDA veteran and a partner of the Washington, DC, office of the law firm of Ropes & Gray. "Even before that, the agency was crying of resource starvation. There are a number of areas where FDA doesn't meet the law. They're supposed to review citizen petitions within 108 days. They're supposed to inspect plants every so many years. There are all kinds of places where if it were industry doing what FDA is doing, they'd be under consent decree.

"But if you're going to assume that there are limited resources, and this is a serious issue for the agency today and going forward, you would have to prioritize based on something. Well, for a public health agency, what would be better as that 'something' than risk?"

Even if there weren't a resource shortage, there are still issues of efficiency, focus, and appropriateness, explains Ron Johnson, a 30-year FDA veteran, now executive vice president of Quintiles Consulting. "I think it's clear that FDA management is concerned that the energy the agency invests in enforcing GMPs may not be focused on the most critical issues," Johnson says. "A risk-based approach makes exquisite sense from the industry perspective, because it tries to separate the aspirin from the nitroglycerin, and that is something FDA historically has had a difficult time doing."

It's not that FDA has been unaware of risk, or that it hasn't already tried to build risk assessment into its operations, Johnson says. "If you ask anyone in FDA they will say, 'All of our planning has been focused and based upon risk.' If you look at the compliance programs, they identify high-risk things — sterile drugs, for example. But when it gets to the field office those priorities can get compromised. There are examples where FDA has spent enormous amounts of energy and effort on an over-the-counter pharmaceutical manufacturer. You have to wonder whether that's the most important thing in the world, because it probably is not."

If the point of the new approach to GMP regulation is largely to solve internal FDA problems, there is also a real focus on stripping away unnecessary regulation for the sake of consumers.

Sandy Weinberg, professor of biomedical entrepreneurship at Muhlenberg College in Allen-

town, PA, and head of the college's Biomedical Regulatory Tracking Project, follows regulation at more than a dozen agencies. He says, "There is incredible political pressure on FDA to find ways of reducing the cost of pharmaceutical drugs. You've basically got three kinds of costs. You've got the R&D cost. If you cut that, you end up without new products. You have profit, and although that sounds tempting to politicians, if you cut profits, capital flees to other industries, and again you have no new products.

"So you've got to find some way to cut production costs," Weinberg continues. "Most of production cost in the pharmaceutical industry is quality control, and you don't want to cut quality control where it counts — so FDA's new approach suggests a way to cut quality control where it doesn't count. The trend to consider cost as a factor in regulation is probably universal. This is the first time it's been applied in this industry, but it's been part of the process everywhere else."

For Don Burstyn, vice president for regulatory affairs at Alkermes, a publicly held biopharmaceutical company in Cambridge, MA, and a member of the PhRMA work group on GMPs, part of the point is to put science back in the driver's seat. "In manufacturing and setting up our systems we try to take a scientific, very rational approach to things. It makes good manufacturing sense as well as good business sense to have a scientific rationale for what we're doing. Today, unfortunately, we've gotten ourselves into a situation where many manufacturers as well as many inspectors, basically operate by dogma. They say, 'Things need to be this way because they've always been done this way' without thinking of the rationale behind it.' Those of us who have been in the business for a long time and have worked at the agency understand that there are multiple ways to approach the same problem. There are many right answers. We have to be sure that the answer we choose is right in the context of our overall operation, maintains product quality, and is efficacious."

As a result, the risk management concept seems to respond to multiple concerns at the same time. "I think the way the industry is headed and the way FDA is headed is to put more emphasis on good regulation through good science," says Tobias Massa, executive director of global regulatory affairs for Eli Lilly and Company and chair of the scientific steering committee for the Product Quality Research Institute (PQRI). "The GMP and inspection process evolved in response to various issues that have

arisen over time. The GMPs have served a very valuable purpose. But now we're saying, 'Look, everybody needs to understand that there's no such thing as zero risk. That being the case, how do you apply the best science to controlling risk?'

"We and FDA are saying that the answer basically relates to product quality and using the best current science to result in the best possible GMP program. It's true that to some degree this is the result of a resource issue, but I think it's more a response to the question: What is the best thing to do relative to how we regulate medicine?"

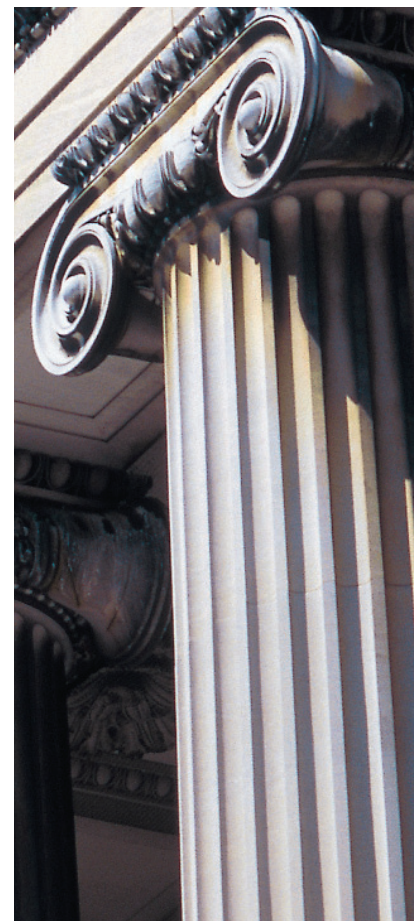
## MEASURING RISK

The big question now is how the new concept for GMPs will be implemented. Some experts are anticipating that a full implementation will take two to three years, including the time it takes to train inspectors. In the short run, FDA plans to meet with industry and others to gather information, beginning with a workshop scheduled to take place 22–24 April in Washington, DC.

"There is conceptual agreement among everyone involved — FDA, industry, and various segments of the industry — on where we're going on this whole concept of risk," says Gerry Migliaccio, vice president of global operations for Pfizer. "I think FDA has done a wonderful job of framing the discussion. And now that everyone is starting to use the same terms and understand the same concepts, we can start quantifying it. That is the task ahead."

For Migliaccio, who serves on PhRMA's GMP committee, that task is partly a matter of learning to work with data the industry already possesses thanks to technological developments in the past few years. "We have a significant amount of data on our products and processes," Migliaccio says. "We have analyzed the data. In many cases we understand the capabilities of our processes. And we're doing more and more of that as time goes on. To me, it's a matter of working with FDA to define the data set that's required to control risk. That is what we and FDA and academics have to develop jointly."

Working out the nuts and bolts of quantifying risk will be a substantial task. And in truth, there are probably still parts of the big picture that need to be filled in. "I don't think we've come to agreement on what we mean when we talk about risk," says Tobias Massa. "I think we have to look at risk from the perspective of what it means to the patient. As we do our jobs from the perspective of both the regulator and the regulated how are we viewing that? I think it's pretty clear



where we stand as an industry: When we talk about risk and quality, it basically means fitness for use. Are medications safe and effective? Are they available? Are the directions for taking the medication easy to understand? When we talk about fitness for use we're not talking about how well it meets minimum standards. We mean is a product safe, is it efficacious, is it readily identifiable, and is it easy to use?

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Availability may not be part of the conventional concept of risk, but it adds an extra dimension to the analysis. A patient can be harmed by the absence of a lifesaving drug just as surely as he or she can be harmed by an adulterated drug. And availability is a part of the risk picture that is heavily influenced by regulatory practice. "What does it mean if a product is not available to the consumer?" Massa asks. "Obviously that has to do with the intended use of the particular product. If you're talking about acne medicines, the risk is at one level. If you're talking about a lifesaving drug, your considerations are different. Those things need to be taken into account."

**GETTING INSPECTORS TO BUY IN**

The risk-based approach to GMPs is part of a sweeping campaign of reform at FDA, but that doesn't mean that the concept behind it is a new one to the agency. Risk management has been part of FDA's thinking for years. And some existing programs may well give a clue to how the agency plans to handle GMPs — and whether it is likely to succeed.

For a number of industry experts, the most compelling example of an FDA risk-based program is the approach to medical device manufacturing embodied in the Quality System Regulation (QSR), 21 CFR Part 820, which went into effect in 1997. Medical device manufacturers had been subject to GMP regulation since the early 1960s, but QSR brought a new set of ideas to the process. "I gave a speech to the Parenteral Drug Association seven or eight years ago, when I was still with FDA," says Ron Johnson. "I said if you want to know what your future is, look what's going on in medical devices. If I were betting, I would bet that the GMP for drugs will move in that direction."

Muhlenberg College's Sandy Weinberg explains how the system works: "Anytime you have any kind of submission for a medical device," he says, "you calculate the risk involved. You identify the predicate events that might tell you what kind of risks to expect, then you determine the severity and probability of those events, and based on that you classify them as high, medium, or low risk. Then, when you're filing an application, or when an inspector comes, you say, 'We determine this to be high, medium, or low risk. Here's why, and here's our standard for what we do to handle a high, medium, or low risk.' It's a pretty efficient system, and it really lets you put your dollars where they count."

But although many in the industry speak well of QSR, it hasn't been a panacea for the medical device industry. Larry Pilot, partner of the law firm McKenna, Long & Aldridge, and counsel to the Medical Device Manufacturers Association, has worked with medical device companies under the device GMPs and under QSR. He says that he hasn't really seen a reduction in the number of problems.

"It's the application of QSR by the agency through its inspection process that has caused difficulties," Pilot says. "The bottom line is at the district level. Do they really care about risk management? I can tell you that I've had experiences — past, recent, and current — where risk doesn't mean anything. If the district wants inspectors to put a gun to somebody's head, they'll put the gun to somebody's head. That's inappropriate, it's unfair — and it happens."

Pilot's experience raises an important issue in regard to FDA's current program of change — perhaps *the central* issue: Will the agency be able to change its own culture, right down to the crucial level of individual inspectors?

"The Achilles heel in any new initiative at FDA has always been at the worker bee level — the investigator on the street is the person that's got to get in tune with the new thinking," says Ron Johnson. "Historically FDA has not done a good job at corralling or managing its investigators, particularly those at the national expert level. That's going to be the real acid test. The managers and the Washington headquarters people can do all sorts of things, but it gets executed at the field level."

Part of the issue for individual inspectors is the ability to control the inspection. In theory, a risk-management approach is supposed to focus the inspector's attention on the highest-risk portions of a manufacturing process. But inspectors have





been known to balk at systems that seem to tell them what they should look at and what they should ignore. That emerged as a problem several years ago during a pilot program at the device center that used a Hazard Assessment/Critical Control Point (HACCP) approach as an alternative to the center's quality systems approach. "An FDA inspector wants to look at everything," says Johnson. "He doesn't want anything to be predetermined. In a HACCP program you're steered toward particular things, and I think some inspectors felt they were being denied access to information they needed to make a real evaluation."

At the same time, Johnson says, inspectors should understand that the agency is changing. "If they just look around at the rest of the agency, most other FDA programs, with the exception of biologics have moved on and have adopted current scientific principles, whereas the drug GMP has just stalled. Perhaps Janet Woodcock can drive that and Mark McClellan can drive it. And clearly this is an initiative that resonates with the administration."

In light of these concerns, some of the additional elements of FDA's plan — such as the decision to remove authority for warning letters from the district offices, or the new conflict resolution process — start to look like an attempt to manage a cultural change within the agency. "If the new initiative is successful, it will prevent some actions at the field level from coming to light," suggests Johnson. "A field observation will go through triage in Washington, and the Washington people will apply the risk-based concept and will be in a position to say, 'This is not a high-risk area, this is not a high-risk product, these practices are not high-risk. We're not going to permit you to do x, y, or z.'"

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If that is the plan, it offers its own set of challenges: Can Washington in fact manage this sort of triage? Can risk really be assessed away from the field? What will the impact be on the inspectors? But on the other side, there are real risks if FDA attempts to impose the risk-management system and fails.

"We're talking about a very big fundamental cultural change for both FDA and industry," says Tobias Massa. "The industry is basically a skeptical, captive audience here, and I think there are some folks who are saying in their own minds,

'We have seen quality efforts come and go, and yet we still revert back to the most conservative approach every time.' Maybe the industry fears that it will end up doing more things, but not see any change in how it's regulated.

"I don't think that's going to be the case. I think FDA has been very responsive to industry's concerns about consistency between the field and the center, consistency in the field, consistency in the centers. Industry has never said 'we don't want to be regulated.' I think what the industry has said is 'we want science-based regulations that are consistently applied.' If we don't achieve that, then both industry and FDA have failed to meet one of our fundamental goals."

## **CHANGING THE PLAYING FIELD**

Assuming that FDA can manage the transition to a new, more scientific approach to GMP regulation, there are still some important questions: Will a risk-based approach to GMPs create a two-tiered regulatory system, with some companies practically deregulated, while others bear an increased regulatory scrutiny? Will smaller companies be subject to a disproportionate share of FDA attention? Will the system encourage innovation, as it is intended to, or will innovation be perceived as intrinsically risky, and thus to be avoided? And will what looks like an effort to reduce regulation turn out to be something quite different — an offloading of responsibility and costs onto industry?

It's too soon to answer most of these questions, but some already seem reasonably clear. A two-tier system for instance? "I think my answer is yes, even though that's not FDA's intent," says Ronald Tetzlaff, president of the consulting firm KMI/Parexel. "FDA is going to intentionally inspect those facilities where noncompliance has the greatest risk to health, and of course biotechs certainly fall into that category for three reasons: FDA has listed three categories as being of special concern — sterile drugs, prescription drugs, and plants that have not previously been inspected — and biotechs typically fall into those categories. Second, many biotech products are proteins and by their very nature represent more of a challenge because they have relatively complex manufacturing processes and analytical methods, in addition to the fact that most biotech products by definition are derived from living cells that are themselves inherently more difficult to control. And biotech-derived molecules are often more difficult to characterize, because there are a lot more product attributes that potentially

pose hazards to patients. Because there's such a large number of facts that have to be addressed, and the scientific expertise necessary to evaluate those things is complex, you can expect FDA to give [biotechs] a lot more scrutiny."

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In principle, a two-tier system will come about because some companies will experience drastically reduced scrutiny, and no one will experience an increase in regulatory burden. That makes sense, says Michael Petty. "There's a continuum of products here. On one end, you've got risky prescription drugs with potential liver toxicity, 'black box' drugs, all those kinds of things. At the other end, you've got over-the-counter drugs (OTCs) that are not very problematic, and you're right on the line with cosmeceuticals or dietary supplements. You could probably make an argument that there are several OTC products that should really be in the same playing field with some dietary supplements, for instance, in terms of their risk."

Although biotech products will probably continue to be scrutinized more heavily, some will probably benefit from the new approach. "Not all biotech drugs are created equal," says Petty. "Look at the ones for which FDA is already working on monographs for quasi genericizing. They certainly think that they understand insulin and hCG. They've seen 12 different versions of them, and they all are safe and effective."

"Pharmaceutical companies are usually well established, and they have usually been in the business for a long time," says Massoud Lavian, assistant director for compliance for Clarkston Consulting. "They have gone through a lot of inspections. They are familiar with the basics. Biotech companies are generally smaller and often newer, so they are not as familiar with GMP issues, with documentation issues, with how to set up programs, and so forth. So yes, the emphasis will be on the biotech companies."

Does this mean that the new system will make life harder for young biotech companies? "In my opinion, no," says Lavian. "They are supposed to do the same things they did before. The amount of work stays the same. It just becomes easier for FDA to find out if they have done it or not."

There's even a case to be made that smaller companies will have some advantages in a changing regulatory environment. "Today a smaller company starting out has a better opportunity to

be 'compliant' than some of the larger companies," says Don Burstyn. "That's because CGMPs evolve. You look at a company that's been in business 30 years and has been doing things a certain way, it's very difficult to modernize or change things within the system. In addition they have baggage. Companies that have gone through many inspections end up with baggage, like one inspector finding something or asking them to change parts of the system. The systems become very cumbersome, and it's very difficult to maintain consistency. A small company starting out fresh, if it does things right, has the opportunity to put in best practices and scientific practices at the beginning."

Innovation is a more complex question. "In theory the new approach will allow companies to innovate if they choose to and if FDA is flexible as to how they interpret the GMPs," says Ronald Tetzlaff. "In the short term — the next two or three years — I think many companies will take a conservative wait-and-see approach. Many, if not most, will be unwilling to jeopardize their product approvals or invite delays in reaching market while waiting for FDA to interpret or approve an innovative approach."

"That will be especially true in the biotech industry where it's exceedingly complex, the science is very state-of-the-art, and it's going to be difficult to present the data in a manner that will satisfy all scientists. In the short term at least, prudent management will look to see if there are successful outcomes from other companies before they invest heavily in a novel approach."

At the same time, it seems clear that FDA understands that innovation may need support. Tobias Massa points to the Process and Analytical Technology (PAT) initiative. "PAT is probably the forerunner of the 21st Century initiative," he says, "because what PAT is looking at is continuous improvement and being able to introduce technologies into the manufacturing process."

To Massa and many others in the industry, continuous improvement and a quality systems approach are the real issues. "Quality systems drive you toward risk-based decision making," he says. "The whole effort here is related to product quality. If you look at FDA's material, they've renamed the program. It's no longer 'GMPs for the 21st Century,' it's 'Quality for the 21st Century.' FDA is saying we need emphasis on quality more than we need strict adherence to SOPs and so forth. Quality will drive everything else. If you have quality in the design and control of your drug process and your testing paradigm, good manufacturing practices will follow." **BPI**



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