



## Reading the FDA Tea Leaves

By John Avellanet

**P**ublisher Henry Luce once wrote, “Business, more than any other occupation, is a continual dealing with the future; it is a continual calculation, an instinctive exercise in foresight.” When business mixes with regulation, foresight turns into regulatory agency anticipation.

As the 21st century drives forward, the turning of the U.S. Food and Drug Administration (FDA) to meet modern challenges is becoming clear. Of relevance to executives in industries regulated by FDA is the immediate impact, for the foreseeable future, of the trends shaping agency action, from guidance issuance, inspectional strategies and medicinal product approvals. The business executive has a simple question: “Will I, my firm or our products get caught in the crossfire of change?”



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The agency has been buffeted by eight large challenges since the 1990s: <sup>1</sup>

1. A rapidly escalating rate of scientific and technological advances and new medicines that increasingly require specialized knowledge to understand;
2. A continuing trend of globalization and market boundary erosion;
3. The growth of virtual organizations reliant upon a supply chain of goods and services stretching around the globe;
4. Demographic shifts compounded by intergenerational conflicting interests;
5. A widening gulf between the capabilities of technology versus the ability of regulations to change and adapt;
6. The industry’s cumulative regulatory weariness from all the regulatory agencies across the globalized marketplace;
7. The difficult economics of healthcare and valuation of human life, from pediatrics through geriatrics, in the globalized marketplace and

8. The increasing tension within the industry, within the agency itself and amongst compliance practitioners between the flexibility required in the 21st century and the 20th century's more typical command-and-control compliance program, expectations and rules.

These trends do not come with easy solutions, nor are they going away any time soon. Thus industry needs regulatory intelligence to forecast likely agency actions over the next 12-16 months. The first step is to explore the immediate environment within which FDA must operate.

### General Outlook for FDA

The next 12-16 months will be a time of self-defense for the agency. Between budget tightening and sweeping new implementation efforts required under the recently passed Food Safety and Modernization Act of 2010 (FSMA), the agency will struggle to maintain momentum.

First, FDA will suffer from budget constraints—if not cuts in name, then at least in fact.

FSMA is expected to cost the agency approximately \$280 million to implement in 2011 (and each subsequent year through 2015, up to maximum total of \$1.4 billion).<sup>2</sup> Congress eliminated the industry registration user fee originally expected to pay for all the new mandates on the agency, leaving much of the costs to be absorbed by FDA's current budget.<sup>3</sup> The result: de facto \$280 million budget cuts this year and next.

Funding for the agency will remain in limbo for the next few years as the Tea Party members and the Republican-led House of Representatives push for reduced federal spending across the board. Because the agency oversees approximately 25 percent of the U.S. economy,<sup>4</sup> FDA will avoid major cuts for now. Un-

fortunately, off-and-on spending freezes are likely, just as the agency accepts a plate of new food safety accountabilities.

Meanwhile, Congress—with no money to spend—will initiate more Congressional investigations of FDA. By the end of December 2010, three incoming Congressional committee leaders had sent letters to Commissioner Hamburg requesting more information and testimony on issues such as the recent Johnson & Johnson product recall, FDA's use of management consultants, FDA's handling of food recalls under the previous food safety statutes, the agency's approval of expensive new medical devices and so on. And in February, Fred Upton, chairman of the House Energy and Commerce Committee, and Joe Pitts of the health subcommittee initiated hearings on the current regulatory process for device approvals, a process that FDA has already begun modernizing.

### Industry Implications

FDA leadership, center directors and their staffs will be on the defensive throughout the next 12-16 months, regularly responding to Congressional requests for information, preparing for testimony and conducting directed internal investigations. This will limit the agency's ability to make strides on its 2011-2012 agenda, and imperil those firms counting on significant agency modernization progress.

During the Congressional committee meetings, FDA will likely step up its talking point pressure on industry executives to comply with current regulations. After all, or so the reasoning runs, if McNeil Healthcare executives and others who have recently received Warning Letters had complied with the current regulations and statutes in the first place, FDA would not need more money to conduct more inspections and the voting public would still be safe.

Expect FDA officials to expend significant time defending their need to keep staff, regulations and guidance documents up to date with continuing globalization and 21st century modernization trends. This may also play out in the snowballing need to update internal FDA systems and processes. All of this will add significant strain to current agency workload over the next few years. This, in turn, will only fuel the loss of internal knowledge and expertise as veteran FDA officials depart for retirement as soon as they become eligible, their specialized knowledge not to be replaced under a tight budget.

Bottom Line: For the next 12-16 months, expect an agency under fire, less able to proactively cooperate with industry stakeholders.

### Regulatory Revisions

The agency will continue its "regulation by guidance" when it comes to the Good Manufacturing Practice (GMP) regulations and the 510(k) device submission process. This is in addition to efforts currently underway to revamp some of the Good Laboratory Practices (GLPs).<sup>5</sup>

When it comes to the revised 510(k) process, the next six months will see the first efforts drafted and implemented; not until 2013 will the 510(k) revisions be complete. For now, the key changes to expect within the next 12-16 months are:

1. Creation of a fourth class of devices, "Class IIb." In 2009, the Government Accounting Office (GAO) hinted at a need for Class II devices to undergo more rigorous premarket evaluation as new device technologies are developed.<sup>6</sup> In 2010, FDA's own internal report on 510(k) improvements specifically recommended

the creation of an administrative subset of Class II devices to be known as Class IIb.<sup>7</sup> In addition, such a fourth class of devices would harmonize FDA with other global marketplace members, most notably the European Union and Canada.

2. Requirement of more pre-approval data as part of a 510(k) submission. This does not necessarily mean requiring formal clinical trials, but rather requiring a submission to have greater detail on overall device risk-benefits, as well as more safety and effectiveness data. As GAO noted, such information need not be clinically based.<sup>8</sup> Helping to drive this requirement is the societal push to contain healthcare costs (most noticeable in the new parallel review process announced by FDA and the U.S. Centers for Medicare and Medicaid in September 2010).
3. Adoption of a formal routine of pre-approval inspections similar to those conducted in the pharmaceutical and biotechnology industries. This will enable the agency to streamline its own internal processes by creating one set of application review factors that would trigger a pre-approval inspection (PAI) regardless of whether the application was for a drug or device. This will help the agency improve productivity while strengthening oversight.
4. Increased transparency of application review status, including publication of de novo decisions and internal agency review memos.

In terms of continuing GMP revisions, expect to see increased emphasis on controlling the supply chain and maintaining records that support a company's claim of consistent control. In January 2011, the Center for Drug Evaluation and Research (CDER) published its planned list of guidance documents.<sup>9</sup> Even a cursory glance at this list reveals the agency focusing on a mix of application specific guidelines such as "Non-Penicillin Beta-Lactam Contamination" to more general guidance such as general GMP expectations for anti-counterfeiting, components and supply chain control and oversight of contract manufacturers.

The agency will continue to reference International Conference on Harmonization (ICH) guidelines, particularly on good distribution practices, asking firms to use the storage expectations within such guidance documents as part of auditing programs for raw material and component suppliers. Although initially aimed at drug companies, tobacco and dietary supplement makers will want to pay close attention to these revisions as a portent of the future (as well as implicit expectations on the part of inspectors today).

### Implications

Component and raw materials revisions will require the auditing of at least critical suppliers as part of 21 CFR 211 compliance. Therefore, it is crucial to conduct risk evaluations of product and manufacturing processes, from raw materials contracting through distribution, to identify and prioritize audits to conduct. Companies should expect to complete their critical supplier audits within 18-24 months of the final guidance publication.

Many of the forthcoming requirements for GMP compliance are already

part of good quality systems—documenting training and its effectiveness, requiring internal audits and gap closures within a reasonable timeframe, performing periodic management reviews and so on. Familiarity with the ICH Q10 guidance on pharmaceutical quality systems and the European Union (EU) chapters 5 and 7 GMP changes for supplier oversight will allow easier compliance with next year's requirements.<sup>10</sup> Likewise, when planning for FDA's upcoming anti-counterfeiting expectations, executives will want to look directly at the World Health Organization's (WHO) recently revised good distribution practices guidelines (note that WHO is a charter member of the ICH).<sup>11</sup>

Increased pre-approval data requirements for the 510(k) submission process will set off alarm bells in some corners of the device industry worried about a broad mandate for clinical trials, affecting everything from pacemakers to tongue depressors. However, GAO explicitly commends FDA for instances when devices were approved solely based on good device engineering evidence rather than clinical data.<sup>12</sup> And an FDA initiative announced in April 2010 noted a growing concern by the agency around the lack of device testing in non-clinical settings without the supervision of healthcare practitioners.<sup>13</sup> This is the type of "voice of the customer" data that is routinely gathered in during new product development in other industries, has been documented as helpful to agency reviewers and is one of the additional types of data expected to be requested as part of any future submission under the impending 510(k) revisions.<sup>14</sup>

Finally, firms need to be careful to review all 510(k) submitted—and

supporting—documents to ensure that “confidential” is clearly marked where appropriate. Increasing transparency of the review process could easily lead to accidental disclosure of proprietary information if an overworked agency is unaware of the need to keep any particular information confidential. The recent FDA action plan, and its associated commentary, clearly denoted the information the agency wants the industry to mark as confidential and non-confidential in 510(k) submissions.<sup>15</sup>

**Bottom Line:** For the next 12-16 months, expect an agency sending mixed signals to the industry as it adapts last century’s regulatory requirements and medicinal product standards to 21st century realities.

## Guidance Outlook

In addition to revising regulations through guidance issuance, four emphases are emerging for future guidance documents across FDA centers:

1. Early clinical planning
2. Postmarketing surveillance
3. Consumer-friendly communications
4. Tobacco controls

Tobacco control guidance documents will be a big story throughout 2011-2012 as the agency finally completes its assessment of what its tobacco oversight allows. The agency also believes it now understands better how tobacco products are developed, produced and distributed. The result will be more scrutiny of the tobacco industry in three areas:

- Distribution through retailers
- Advertising and promotions
- Raw materials and components

Note that the last item—control of product ingredients—is why the author suggests that tobacco firms make time to review the upcoming GMP guidance documents on supplier control expectations, the recent EU changes to GMP chapters 5 and 7 and even the WHO good distribution and anti-counterfeiting guidelines.

Early clinical planning is the emphasis of at least six different planned guidance documents for 2011. One guidance to expect will cover development of nanotechnology-based devices (including co-development of combination devices using nanotech-scale elements). Firms developing (or partnering with) nanotechnology devices will also need to address the rapidly evolving Environmental Protection Agency (EPA) concerns regarding nanotechnology usage.<sup>16</sup>

Concurrently with FDA publication of its guidance documents, the agency will continue to point executives to recent guidelines from the ICH and the Global Harmonization Task Force (GHTF). For instance, although the agency has announced its intention to publish a unique device identifier (UDI) rule in 2011, FDA officials have spent the past year pointing device industry executives to the GHTF guidance on incorporating UDI’s into devices.<sup>17</sup> While critics like to lambast the agency for requiring industry to also pay attention to ICH and GHTF guidance documents, there is a simple reason for FDA’s stance: ICH and GHTF guidance cannot be interfered with or slowed down by Congressional meddling or industry lobbyists.<sup>18</sup>

Finally, the agency will continue its push for transparency and consumer-friendly communication by issuing guidance on using social media to distribute information and respond to consumers.

While many have expected the agency to issue formal guidance documents, the author suspects that the agency may take a newer tact: “guidance by FAQ.” Both the European Medicines Agency (EMA) and the UK’s internal health agency have begun publishing clarifications to guidance documents and to regulatory interpretations using question and answer formats posted on agency webpages. FDA adopted this approach recently in its “guidance” on avoiding moldy or musty odors in drugs.<sup>19</sup>

## Implications

Preclinical guidance continues to be a push for the agency as the means to a cooperative regulatory schema—better early stage clinical planning leads to faster and easier reviews of market applications as well as safer products (quality by design). Commissioner Hamburg stated in 2009 that she expects to see nearly all market applications for new medicines to incorporate quality by design elements within clinical trials and early stage production no later than early 2012.<sup>20</sup> Drug firm personnel should expect to be able to discuss critical quality attributes and critical process parameters with agency officials in an End-of-Phase II meeting.

Postmarket surveillance will also receive at least six different guidance documents next year. And these are in addition to the new ICH and GHTF documents expected, including a forthcoming GHTF guidance on the handling of recalls and field safety corrective actions. FDA will maintain an approach to postmarket surveillance and pharmacovigilance that will be harmonized with other regulatory member agencies in ICH. One tactic for industry executives to consider is reviewing the

forthcoming ICH Q11 Development and Manufacture of Drug Substances, a guidance due in draft form later this year. FDA had a significant hand in crafting ICH Q11, calling for a lifecycle approach to postmarket monitoring. Using ICH Q11, firms may want to draft a lifecycle control management strategy for any new product, and summarize it in the common technical document format section S.4.5.

**Bottom Line:** For the next 12-16 months, expect the agency to modernize regulatory requirements through agency guidances, website FAQs and international harmonization guidelines.

## Final Thoughts

Ultimately, FDA's growing reliance upon regulatory harmonization group guidance, as well as the newer approach of "guidance by FAQ," means that companies must have a proactive regulatory intelligence program in place as part of any effective 21st century compliance organization. For the agency to respond to the rapidly evolving global marketplace, with its dizzying array of scientific and technological advances, FDA will increasingly expect industry to adopt better premarket and postmarket controls. ▲

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2. Shilcutt, Katharine (2011) "Food Safety Modernization Act Passes, But at What Cost?" Houston Press, 5 January, [http://blogs.houstonpress.com/eating/2011/01/food\\_safety\\_modernization\\_act.php](http://blogs.houstonpress.com/eating/2011/01/food_safety_modernization_act.php) accessed on 9 March 2011.
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11. WHO (2010), *Good Distribution Practices for Pharmaceutical Products*, Geneva, Switzerland (Annex 5, Technical Report Series No. 957).
12. GAO (2009), *Medical Devices: Shortcomings in FDA's Premarket Review, Postmarket Surveillance, and Inspections of Device Manufacturing Establishments*, 18 June, Washington, D.C., p. 13.
13. Corbett Dooren, Jennifer, "FDA Pushes Oversight of Devices," *Wall Street Journal*, 20 April, <http://online.wsj.com/article/SB10001424052748704671904575194310283186290.html>, accessed on 7 March 2011.
14. For analysis of the role of voice of the customer data and FDA submissions, see John Avellanet (2010) Get to Market Now! Turn FDA Compliance into a Competitive Edge in the Era of Personalized Medicine, Washington, D.C.: Logos Press, pp. 121-134.
15. FDA (2011), *510(k) and Science Report Recommendations: Summary and Overview of Comments and Next Steps*, Washington, D.C., pp. 8-9.
16. See the EPA website at <http://www.epa.gov/opptintr/nano/>.
17. Trautman, Kimberly (2010) *The GHTF Document on Supplier Controls*, Speech to the FDAnews Supplier Quality Management Congress, 8 August.
18. Note that GHTF members have recently decided to reorganize the GHTF so as to make the industry representatives be advisory members only, much more in line with the ICH organization. The author believes this is a precursor to a longer-term move by the FDA to start citing GHTF guidance documents in warning letters and other regulatory enforcement actions, much as the agency started to do with ICH guidance in 2008.
19. See <http://www.fda.gov/drugs/guidancecompliance/regulatoryinformation/guidances/ucm192869.htm#5>.
20. John Avellanet, "Special Regulatory Outlook and Forecast for 2010," *Smarter Compliance* No. 36, Vol. 3, Iss. 12, p. 2.