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JANUARY 2009

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INDUSTRY OUTLOOK

FDA Forecast-2009

Nine recommendations to weather the new year.

By John Avellanet, Managing Director, Cerulean Associates LLC

This year will bring a tougher attitude toward drug, biologic and device makers by the U.S. Food and Drug Administration (FDA). Congressional critics, long frustrated by an agency seemingly more enamored with manufacturers than public safety, will push forward legislation encouraging a "tough love" stance that will last well into the next decade. The FDA will issue new regulations and update old ones to capture expectations that drug makers – and their suppliers – put a priority on public safety, product efficacy and policy compliance.

At a time when the global economy struggles, these changes will impact contract research organizations (CROs), contract manufacturers (CMOs) and pharmaceutical companies significantly. As the executives and business owner members of my SmarterCompliance™ regulatory intelligence peer advisory program have known since early last year, FDA changes for 2009 will impact their businesses' planned strategies, resource allocations and product development programs.

This article summarizes nine key takeaways SmarterCompliance™ members felt were most important in three areas:

1. Enforcement
2. Regulatory changes
3. Guidance issuance

Each anticipated change is outlined below along with a corresponding recommendation for you to consider in your business.

A note of caution: these recommendations are not as tailored as the ones in my advisory program since this format is not conducive to a personal knowledge of your business and the specific challenges you face; instead, I've tried to capture one key recommendation broadly relevant to most FDA-regulated businesses. As such, these recommendations should not be the sole basis upon which you make your decisions, particularly when it comes to staying off the FDA enforcement radar screen.

ENFORCEMENT

The FDA will increase its enforcement this year in three areas: direct-to-consumer advertising and marketing, overseas enforcement, and personal executive accountability.

1. *Personal Executive Accountability —* Working with the Department of Justice (DOJ), the FDA will continue its shift from overall quality systems compliance to pursuing individual executives and business owners for lack of effective oversight. A review of recent warning letters coupled with interviews with FDA inspectors and officials indicates that this trend to "ensure accountability at the top" will only strengthen.[1]

One specific example is the disconnect between senior management and line-workers, laboratory technicians and clinical staff that FDA and DOJ officials increasingly observe; this is especially troublesome given the rising reliance on contract labor or outsourced service suppliers (such as computer departments or CMOs). FDA officials have successfully targeted company presidents, legal counselors, scientific and medical officers, not to mention regulatory affairs and quality assurance executives. Indeed, in a recent webinar I gave, I pointed out that over the past 18 months, not a single warning letter mentioned anyone below "director" or "vice-president" by name.[2]

Recommendation: Among the many specific recommendations SmarterCompliance™ members have used with good success is a revision to the traditional response to non-compliance: more training. Clearly, given the FDA and DOJ's increasing frustration, the typical "more training" approach is not working. Instead, shift your training so that executives train middle management and supervisors only. Middle management and line supervisors are then responsible for training front-line workers, with senior management serving as coaches to middle management. This approach relies on the many studies over the past twenty years that show employees tend to trust their immediate supervisor, but distrust managers more than two layers above them. This twist on an old tactic also allows you to leverage your existing framework more effectively with minimal disruption.

2. *Overseas Inspections —* FDA inspections will increase as the agency stations inspectors in India, China, Latin America and Europe. However, few overseas inspections carried out by FDA are for routine Good Manufacturing Practice (GMP) reviews; most are pre-approval inspections. Any increase in GMP oversight by FDA inspectors will be short-term while the FDA trains its overseas counterparts on what FDA inspectors look for, previous experiences, and their logic.

Recommendation: If you have the funds, conducting your own mock FDA quality audits of critical overseas suppliers (such as CMOs, CROs and specific clinical sites) will lower your risk of getting caught up in any GMP-compliance sweep by FDA inspectors eager to demonstrate the effectiveness of the new overseas offices. However, if the global economic weakness has taken its toll on your budgets, consider prioritizing your critical suppliers based on their relative "closeness" to the patient or end product. Then, try to leverage other industry audits, certifications or accreditations like (such as the International Standards Organization – ISO – or the American Association for Laboratory Accreditation – A2LA) for those overseas suppliers you cannot personally inspect.

3. *DTC Advertising and Marketing —* I expect FDA to continue to pursue an increased oversight of DTC marketing – not only for drugs and biologics, but also for medical devices. 2007 alone saw a six-fold increase in warning letters issued around advertising and promotion; that trend continued in 2008 and will do so again this year. In part, this is due to increased FDA funding and resources, but also because of growing complaints from healthcare providers and mounting consumer advocacy pressure on the agency.

Recommendation: Executives and small business owners would be wise to ensure a regulatory affairs review of all promotional material. This review may rub marketing and sales personnel the wrong way if handled poorly, so make sure you are clear to all parties involved the intent (and limit) of this review: to ensure the company's promotional material accurately informs, and does not make exaggerated claims or make attempts to blur facts, hide poor trial results or gloss over critical academic studies.

REGULATORY CHANGES

Congressional action notwithstanding, this year should see the FDA tackle three thorny issues with regulatory changes: biotechnology generics, price controls and 21 CFR Part 11.

4. *Biosimilars —* I expect the FDA to pilot a regulatory pathway for biosimilars this year. There is simply too much money at stake. Business and their investors are struggling in the global economy and healthcare costs will rise as the growing elderly population lives longer and expects better medical care.

Recommendation: In February of last year, I recommended SmarterCompliance™ members start preparing themselves to compete with biosimilars by incorporating the voice of their customer into their product development and commercialization.[3] Customer information and preferences can be incorporated to help differentiate your product from generic competition. For instance, customer information could help you redesign packaging to be more user-friendly (a quick hands-on look at the current over-the-counter packaging for Tavist-D versus its generic competitor should give you some insights). This information is powerful in two ways – not only can this help you design a competitive edge into your products, but customer information like this has historically been seen as proprietary by the courts, and thus not open to review by a generic competitor.

5. *Price Controls and Efficacy —* Federal healthcare costs declined by 12% last year, driven in large part by the growing use of generics. As increasing numbers of baby boomers retire, costs will increase this year (and for the foreseeable future). This will put more pressure on the FDA (along with Health and Human Services and the Centers for Medicare & Medicaid Services) to factor in cost considerations. How this will play out is an increased emphasis on new drug, biologic or device efficacy. Slight improvements over existing versions (especially for drugs about to go off patent) will doom a newer version's chance for approval.

Recommendation: Significant or major treatment improvement are historically rare, and not something you should be counting on delivering. Instead, focus your development efforts on cost improvements. In my Quality by Design workshops, I work through data from the U.K.'s National Institute for Health and Clinical Excellence, the World Health

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Organization, and other not-for-profit agencies to factor out a maximum price per month a new drug or biologic can cost in the marketplace, and then help my client work backwards to derive a "not to exceed" development cost to stay under per month. In this way, a minor improvement in efficacy coupled with a significant decrease in cost can tip the FDA approval scales in your favor.

6. *21 CFR Part 11 —* Everyone's favorite bugaboo, 21 CFR Part 11, has finally been revised and is awaiting final center approval for publication. The release of the revised Annex 11 – Europe's version of Part 11 – put pressure on the FDA to complete its long overdue Part 11 revision. As I made clear to members of SmarterCompliance™ in May of last year, and then again in a September webinar, FDA's focus has shifted away from validation to electronic record integrity (e.g., long-term data integrity and quality).[4, 5]

Recommendation: To determine if your Part 11 efforts and monies are being spent on the right things, I advise you to do two things: first, review the EU's drafted Annex 11 revisions (and associated Chapter 4 revisions of the European GMPs); and then second, make sure you and your team know the answer to three simple questions:

* How long do "burned" CDs/DVDs last versus so-called "pressed" or manufactured CDs/DVDs?
* Why?
* How do I recognize a degraded CD/DVD on sight alone?

These and other questions – including the typical failure rates of backup tapes, and so on – are ones you can use to vet any Part 11, Annex 11 or validation consultant; those that do not know the answers are unlikely to be able to help you comply with FDA's new focus on data integrity and quality. The old "validate everything" misinterpretations will not help you prove record integrity.

GUIDANCE ISSUANCE

Along with new regulations and increased focus on executive accountability, 2009 should see the FDA release at least three new guidance documents covering process validation, third-party certification programs, and a Quality by Design guidance on design space.

7. *Design Space —* FDA guidance for design space is sorely needed by industry; far too much confusion exists. FDA's guidance will layout Quality by Design manufacturing concepts for drugs and biologics entering clinicals and for medicines already on the market.

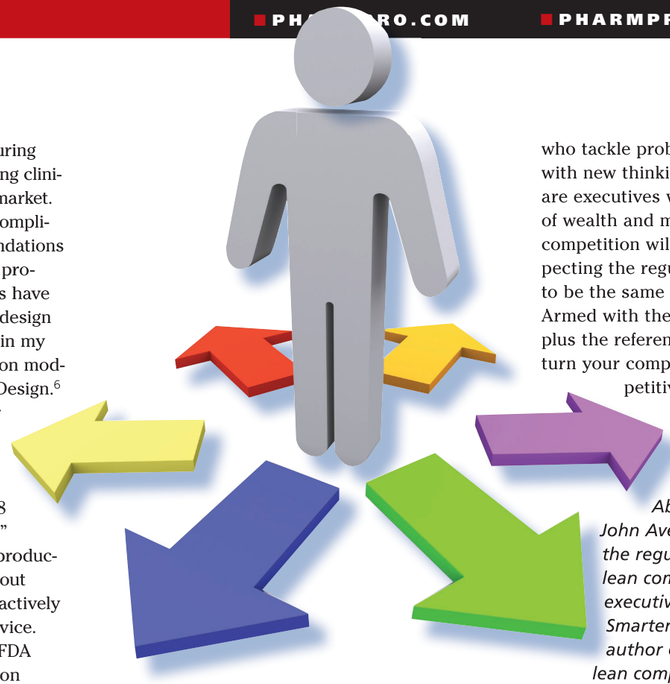
Recommendation: Design space is complicated, and among the many recommendations discussed in the SmarterCompliance™ program last year, were steps FDA officials have outlined when it comes to delineating design space. I spend significant time on this in my workshops and in my industry report on modern quality systems under Quality by Design.[6] You can get a good head start on your competition today by combining a review of my report with a study of the draft International Conference on Harmonization (ICH) Annex R to Q8 entitled "Pharmaceutical Development" (especially pages 3-5). Use your pilot production as a perfect testing ground to lay out design space, and do not forget to proactively contact your region's FDA office for advice.

8. *Process Validation —* The FDA will also release a major revision of its 1987 process validation guidance. Keeping in line with international efforts to harmonize and modernize quality systems and product development, the guidance will encourage increased emphasis on quality and compliance oversight of preclinical and Phase I clinical production and testing. Under the new guidance, the old approach of three batches is no longer acceptable.

Recommendation: If you have not already adopted a risk-based approach to process validation, now is the time; I expect 483s to be issued on this by the end of the year. Couple your risk-based priorities with a valid-statistical sampling and control strategy (download any of my recent "lean compliance" webinars for a detailed walk through on how to do this). The key is to make your approach consistent, straightforward, and systematic. Inspectors will expect to be able to follow your logic.

9. *Third-Party Certification —* The FDA is also set to release a guidance document that outlines its expectations for third-party certifications. This guidance is based in large part upon the ISO report guidance for device makers the FDA has been working on for the past year (that guidance allows device firms to voluntarily submit ISO audit reports to avoid an agency inspection).

Recommendation: There are two documents SmarterCompliance members have successfully used to craft their own policies around acceptance of third-party audits (particularly for suppliers and potential partners): Canada Health Agency's guidance for class II quality management systems accreditation and the Australian medical device guidelines (with their clarification of what is required in an expert report). Unless absolutely necessary, do not restrict yourself to just accepting ISO accredited audits; there are far too many former FDA inspectors and independent auditors who conduct excellent audits that may better represent your needs than just an ISO-focused audit report.



FINAL THOUGHTS

Other FDA initiatives to keep an eye on this year include a continuation of GMP modernization (think Quality by Design and ICH), the modernization of Good Laboratory Practices (think Quality by Design in preclinical and phase I clinicals), guidance on good importer practices, and a push by Congress to give FDA the power to force recalls. Much noise will also be made of splitting the agency into two – a food agency and medicinal agency – but do not expect anything to come of this over the next year.

Regulatory compliance has always been a necessary cost of doing business. Executives who continuously learn more about what regulators want in the very near future and who tackle problems in the here and now with new thinking and original directions are executives who will reap huge benefits of wealth and market position. Most of your competition will engage in stale habits, expecting the regulatory landscape of 2009 to be the same as that of the 1980's or 90's. Armed with the knowledge in this article, plus the reference materials cited, you can turn your compliance program into a competitive edge, leaving your competition, stuck in last century's mindset, mired in the mud. Are you ready? ■

About the Author:
John Avellanet is the founder of the regulatory intelligence and lean compliance program for executives and business owners, SmarterCompliance™. He is the author of more than 30 articles on lean compliance and quality systems, a co-author of a book on biotech business development, and a frequent speaker with FDA officials.
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