Legal & Regulatory Update

The FDA's Quality Revolution

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ABSTRACT

Let it be said that the spark that ignited the flame was when FDA leadership asked, "Do we know enough about the quality of drugs that are sold in the United States."

In 2009, the FDA announced its Safe Use of Drugs Initiative. The theory being that one way to make drugs safer is to ensure that they are used as directed. The main strategy was education and the agency's efforts were (and are) aimed at physicians, nurses, pharmacists, and patients.

Earlier this year, the agency announced not just an office, but a Super Office of Pharmaceutical Quality, further underscoring that the FDA operates not under a two-dimensional system of safety and efficacy, but a three-dimensional approach that includes quality … with a capital (indeed a "super") Q.

Since there is no such thing as a safe substandard product, the agency is putting time, resources, and the use of the bully pulpit to go beyond cGMPs, API and excipient sourcing to develop a risk-based approach that includes data gathered from a variety of sources including manufacturing inspections, adverse event reporting, and substandard pharmaceutical events as evidenced in the agency's bioequivalence- driven actions with bupropion in 2012, metoprolol in 2014, and methylphenidate in 2015.

So, in many respects, pharmaceutical quality is both a pre and post-licensure endeavor and, like Safe Use, a scientific and educational enterprise that requires close coordination with many stakeholders. And it won't come easily or inexpensively. As Aristotle said that, "Quality is not an act, it is a habit."

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Let it be said that the spark that ignited the flame was when FDA leadership asked, "Do we know enough about the quality of drugs that are sold in the United States."

So said, CDER Director Dr. Janet Woodcock during the webinar, *"Understanding CDER's "Super" Office Of Pharmaceutical Quality and Its Effect on You."* Dr. Woodcock was joined by Dr. Lawrence Yu. I was honored to moderate the FDA News-sponsored session. (Janet is the acting director of the OPQ and Lawrence is the acting deputy.)

Let's put the new OPQ into some historical context.

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I began the interview by asking Dr. Woodcock, "how is the FDA going to make pharmaceutical quality a habit?" She responded by sharing her belief that industry must "own" quality – and must be able to measure it. As the saying goes, that which gets measured gets done. The CDER Director was blunt:

"We think industry should own quality. And to own quality you need to measure it, because you can't improve anything that you haven't measured. We would really like to see companies have quality dashboards to understand for themselves the state of quality in their facilities, and also have companies submit quality metrics to us to facilitate the uptake of this attitude within the industry."

"After a number of years of us working with the industry on these quality metrics and submission of some of them, we'll be able to incorporate them into our risk model and thus be better able to answer the question *what is the overall state of quality in the United States, of drugs marketed in the United States*? And also to decide where we should do our inspections, where we should spend our limited resources and put that into the model of risk-based inspection program we're developing."

On the postmarket side, according to Dr. Woodcock, "the real question is, *what is the state of quality of manufacturers for drugs that are marketed in the United States?* I have asked this question many times of the staff. What is the overall state of quality of the drugs that people are taking, and how do we know? And the answer is our programs did not allow us to know. And so now we are going to try very hard to be able to give the American public an assurance that we understand the state of quality of drugs are marketed in the United States."

Woodcock continues, "There are two things that go into this, and this has to do with the functions of the Office of Surveillance. The first is what is the inventory of facilities that are contributing to drugs that are marketed in the United States, no matter where they are in the world. How often have we inspected them, and what do we think about their state of quality, and what other information do we have about state of quality in that firm, say, from other regulators and other sources we might have as well as our own inspections?"

"The second piece is another source of information that we will be seeking from companies, which is quality metrics that have to do with the quality of manufacture, how well they're achieving their aspirational goals, making their specs, being able to reliably make product and so forth."

The OPQ philosophy is more than just about NDA/ANDA parity. It's not just a "promotion" for quality – it's a quality revolution that goes from top to bottom. But, as Audre Lorde reminds us, "Revolution is not a onetime event." This adage should be inscribed on the wall at OPQ.

Dr. Woodcock stressed the need for the FDA to treat the issue of quality from a much more senior-level perspective. The immediate result will be the creation of a separate policy function for quality issues within OPQ.

(She was wisely noncommittal on whether or not the agency would be requesting additional funding for OPQ via PDUFA VI.)

I asked her how the agency's evolving OPQ strategy would inform and influence the agency's regulation and especially its pharmacovigilance practices regarding biosimilars? She responded that, "biosimilars and other complex generics have many similarities in the sense that we're doing a lot more is the quality science. These aren't ordinary comparisons that we do. These are very intensive scientific activities that are performed within the quality organization. We can't underestimate how difficult this is going to be for the agency in the biosimilar world. I think the OPQ reorganization will really help in that regard."

And what about the relationship between the OPQ and the Office of Safety and Epidemiology (OSE)?

Woodcock, "We have long wondered and not known fully when and whether quality problems lead to adverse events. Now we're forming a very good relationship with OSE, and I think we've already worked on and identified various quality problems that actually can or have perhaps led to either complaints or problems that are reported to OSE. There's a very bright future for a seamless safety net that includes quality problems as well as inherent properties of the drug."

One of the pillars of quality, of course, is inspection. Dr. Yu made it clear that, in the new OPQ era, the FDA would be going "beyond documentation." In other words (to borrow a phrase from the arms control lexicon), "trust but verify." As Dr. Yu commented, "The purpose of doing this is that we want our reviews focused on assessment, focused around evaluation, not simply documentation."

An immediate result is a new paradigm for inspections and reports that will advance pharmaceutical quality. The new standardized approach to inspection will include:

- Data gathering to inform "quality intelligence" of sites and products
- Risk-based and rule-based process, using expert questions
- Semi-quantitative scoring to allow for comparisons within and between sites
- More common inspection report structure
- Positive behaviors recognized and rewarded where facilities exceed basic compliance

OPQ is, as both Janet and Lawrence said, about having the agency speak with "One Quality Voice." Specifically:

Put patients first by balancing risk and availability

- Ensure clinically relevant quality standards
- Integrate review and inspection across product lifecycle
- Maximize efficiency by applying risk-based approaches
- Strengthen lifecycle management by using team-based processes
- Effectively apply staff expertise to enhance quality regulation
- Encourage innovation by advancing new technology and manufacturing science
- Enhance cross-disciplinary interaction, shared accountability, and joint problem solving
- Build collaborative relationships by communicating openly, honestly, and directly

Whether an innovator medicine, a generic drug, or a biosimilar, per Dr. Yu, "We want to ensure the clinically relevant quality standards … All human drugs must meet the same quality standards to safeguard clinical performance … The same terms of equivalence, especially related to impurities and dissolution. We want to ensure the same quality standards for new and generic drugs, to ensure the generic drugs and new drugs are truly equivalent. In the future we want to see dissolution much more *in vivo*. The goal is to try to achieve a parity of new and generic drugs."

Another significant development is a clinically relevant specification. Dr. Yu, "The key is quality standards based on performance. In other words, our subject is the patient instead of, for example, regulatory specifications based on the evaluation of batches. I want to make very clear that our specifications are based on product performance for the patient, not on evaluation of a batch we observed. This is a significant evolution."

Dr. Yu, "OPQ will use a risk-based approach to understand any change's impact. Specifically now within the Office of Pharmaceutical Quality we have a special unit devoted to API, whether it's new drugs or generic drugs. Their function is assessment for API. We are forming a team for excipients."

And further, "For some generic products we see some issues and pharmacovigilance comes into play. We saw a pharmaceutical quality problems and we see the link. What we want to do is systematically evaluate pharmacovigilance data with our surveillance information to see if there's any relationship between quality and safety or efficacy in terms of pharmacovigilance."

And the major foundation is product quality informatics. In the "knowledge is power" category OPQ recognizes that enabling an efficient science-driven assessment requires significant transformation in how they collect, evaluate, and learn from the product quality data. Specifically:

- Core areas of Product Quality Informatics: Structured data submission and collection
- Knowledge management and communication Established conditions
- Risk mitigation
- Post-market surveillance and quality monitoring
- Intelligent data analysis

Both Janet and Lawrence underscored the importance of cross-office cooperation (via "program alignment agreements") and specifically mentioned working with the Office of Surveillance and Epidemiology to better understand how pharmacovigilance signals can inform the agency's actions on quality problems.

What about the OPQ and the evolving agency view on bioequivalence?

Dr. Yu, "When we change the policy for bioequivalence standards we'll also change the policy related to quality, because they go hand in hand. When we beefed up the standards for bioequivalence they also impacted all quality standards. We beefed up bioequivalence standards, and Office of Pharmaceutical Quality will make efforts to make corresponding changes to ensure the quality standards are consistent."

"I want to emphasize that quality is the underpinning of safety and efficacy."

Drs. Woodcock and Yu also spoke to the urgency of a more regular and risk-based approach to changes in API and excipient sourcing, as well as more systematic monitoring of bioequivalence. Both she and Dr. Yu agreed that the agency's new respect for quality would influence their views on both the review and post-marketing surveillance of both biosimilars and non-biologic complex drugs (NBCDs).

Make no mistake — the Office of Pharmaceutical Quality is a regulatory revolution, Drs. Woodcock and Yu are regulatory revolutionaries and (as Abbie Hoffman quipped), "the first duty of a revolutionary is to get away with it."