

Regulatory Agency Perspective
Steve Gutman, M.D., M.B.A.

DR. TEUTSCH: Steve, let me welcome you. Again, thank you for all your service to FDA and to the Committee in so many ways, and not only this Committee but our predecessor. Thanks so much. You will be talking to us a bit about the regulatory agency perspective.

DR. GUTMAN: I can't think of a better swan song than to stumble across this topic, so I thank you.

FDA has a longstanding interest in standards. In fact, the original regulations in FDA for our primetime submission, the 510(k), which is what we use for me-too devices, call for the use of standards in equivalency decisions.

In the early '80s FDA initiated development of standardized, traceable methods and expected thresholds for both glucose and hemoglobin, took them to the public, and I guess they weren't ready for primetime yet because we couldn't make the sale.

So what we resorted to -- and in fact the regs were subsequently changed to accommodate for the nascent life of standards in the '80s -- is we changed the regs to call for special controls.

Our program is largely based on two operative terms for me-too devices: showing that they are substantially equivalent to a predicate and, for novel, high-risk devices, showing that they are de novo, safe, and effective. Neither of these regulatory submissions actually calls for or requires identification of either standards, traceability, or performance against standards. I would argue that that is a weakness in our regulatory toolbox.

That has, of course, not been a deterrent to our renegade workgroup. We continue to rail for standards. FDA was a founding member of the CLSI. We are an active member of the ISO Technical Committee 212, an active member of the IBD Subgroup of the Global Harmonization Task Force, and an early proponent of the CDC's Standardization Program. So the lack of standards does not demonstrate a lack of enthusiasm on the part of our workgroup.

In fact, if you bother to look at our webpage, you can see that when we write guidance we frequently reference standards. When we develop special controls, we frequently reference standards. In fact, if you look at our decision summaries, the more "with it" companies will in fact reference standards.

We also have an interest in the material standards that NIST is developing. We always attempt to identify usable standards, whether they are NIST, whether they are CDC, whether they are WHO, or whether they come from other legitimate sources. We have experience with the use of material standards in both pre- and post-market programs.

In terms of the formal process, there is a formal recognition process, at least for methods standards. About two dozen members of my office participate actively. We have recognized a number of CLSI standards and a smaller number of ISO standards. They are all, again, found on our webpage.

There is a formal process that these standards, once recognized, can be used in the context of pre-market review. There is a particular entity called the abbreviated 510(k), where companies can

actually conform to standards. That increases the certainty and decreases the negotiation between FDA and the sponsor submitting that particular standard.

In point of fact, there is usually partial rather than complete conformance. The CLSI standards are an interesting hybrid, some more geared towards laboratory practice and manufacturing practice. It would be fair to say the abbreviated 510(k) is not a perfect program.

I would also point out that informal use of standards is very frequent. Often pedigreed materials, sometimes from CDC, sometimes from WHO, sometimes from other sources, may actually carry a floundering company over the threshold in terms of pre-market review. While our pre-market review has, I think, weak regulatory tools, the quality system regs that are part of our post-market compliance program do in fact have very beguiling portions of the regs that might speak to. If FDA were aggressive in the pursuit of those regs, the use of standards. So there are interesting tools to look at in the future if there was a call for better standardization products.

There certainly are incentives to do this. The IVD directive in Europe very explicitly calls for the use of standards. Our transparent posting of decision summaries provides a reward for use of standard materials or methods because it becomes a matter of public information. I would argue the STAR*D initiative and other efforts to provide clinical standardization will only be as good as the ability to have an underpinning of analytical standardization as well.

That being said, there is a long journey ahead. The truth is the status quo for routine assays -- PSA, troponin, d-dimer are three of my favorites -- is absolute noncongruence. If you look at proficiency testing surveys, you will be astounded by the laboratory and company differences. You can get a heart attack simply moving from one ER to another.

The status quo for new assays is worse because there is no proficiency testing. There is no QC material. It is gratifying to see that NIST is starting to move forward, but there is a mountain of new assays, some of them protected by IP, that might make it very difficult to create cross-lab standards.

This has all been further complicated by the fact that in the year 2009 we actually get it in terms of the complexity of sample procurement and the whimsy of pre-analytical systems in terms of impacting the results any particular system might generate.

At the end of the rainbow, there is a pot of gold. I think Mike may talk about this in more detail.

There is a shift towards evidence-based medicine, even laboratory medicine.

Thank God, because there is an escalation in healthcare costs that laboratory medicine could help or could hinder which is not sustainable. In fact, consumers are increasingly interested in quality. That being said, there is no free lunch. All of this will take a lot of work.

Fortunately, there is free literature about standards, literature written, usually by dark poets, often poets who died young like Dylan or Plath. I will let her have the final word.

"Cold worlds shake from the oar.

"The spirit of blackness is in us, it is in the fishes.

"A snag is lifting a valedictory, pale hand;

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"Stars open among the lilies,

"Are you not blinded by such expressionless sirens?

"This is the silence of astounded souls."

This is the path forward for standards. Thank you.