by James N. Czaban, JD
Chair, FDA and Medical Products Regulatory
Group DLA Piper LLP (US)

IS FDA REGULATORY FLEXIBILITY AN OXYMORON?
The title of this column poses a critical question that goes to the heart of Precision Medicine’s prospects to revolutionize medical care and improve health outcomes for millions of people in the United States and worldwide. This question was also the topic of a lively and insightful discussion at a panel I was privileged to moderate at the Precision Medicine Leaders Summit in San Diego in August. The panelists’ insights, as discussed below, were particularly timely in light of recent regulatory developments at the Food and Drug Administration, and the emerging trend under FDA Commissioner Scott Gottlieb, M.D., to develop new pro-innovation approaches for the FDA’s review, approval and regulation of novel therapeutic and diagnostic products.

The question posed above is broad and goes more to institutional and organizational issues than to specific examples of how FDA reviewed and approved (or refused to approve) any particular product(s). Thus, the following two sections will lay the foundation for two key issues: (i) institutional, organizational, and cultural factors that make it difficult for FDA to change the status quo (one possible definition of “regulatory agility”); and (ii) how, from the standpoint of FDA’s Congressionally-granted authority, the FDA has more than sufficient discretion and flexibility in how it reviews and approves drugs and devices to make significant “agile” changes if it so desires. Following that background is a sampling of key takeaways offered by the Precision Medicine Leaders Summit panel on these and other related topics.

Do FDA’s History and Organizational Environment Prevent Regulatory Agility?

The general case that FDA is institutionally unable to apply rational regulatory flexibility in the review and approval of therapeutic products can be articulated based on general principles of organizational psychology, the structure and history of the Federal Food, Drug, and Cosmetic Act (FDCA), and the political realities faced by FDA in pursuit of its core mission.

First, large organizations, and especially large governmental bureaucracies, are prone to inertia and an excess of caution. Indeed, scholars have even cited regulatory flexibility as a causative factor in such bureaucratic inertia. See, e.g., Congleton, R., A Model Of Asymmetric Bureaucratic Inertia And Bias, Public Choice (Kluwer Academic Publishers 1982) (arguing “that the mere existence of bureaucratic discretion is sufficient to allow both bureaucratic distortion of policy (bureaucratic bias) and resistance to changes in official policy (bureaucratic inertia).”).

Second, the historical legislative evolution of the FDCA is one of repeated reaction to medical crises, tragedies, and emergencies, resulting in Congress enacting new and more restrictive (i.e., less flexible) requirements applicable to the approval and general regulation of FDA-regulated products.

The Pure Food and Drugs Act of 1906 was a reaction to the horrific portrayal of the meat packing industry in Upton Sinclair’s book, The Jungle, and prohibited the interstate sale of adulterated food or drugs. It did not, however, impose a pre-market review process for drugs. The Federal Food, Drug, and Cosmetic Act of 1938 was a reaction to the tragic deaths of more than 100 people from the drug Elixir Sulfanilamide, and mandated the submission of safety data (but not efficacy data) and a limited process of governmental pre-review for new drugs. The 1938 Act did not, however, require affirmative FDA approval of a new drug application – if the agency did not object to the safety data within 60 days, the drug was automatically deemed to be approved with no further FDA action required.

The 1962 Kefauver-Harris amendments to the FDCA mandated the submission of supporting data and the affirmative FDA approval of drugs for both safety and efficacy, in reaction to the emergence in Europe of an epidemic of children born with shocking deformities due to their mothers’ use of the drug thalidomide during pregnancy. Thalidomide had not yet been approved in the U.S. due to the resistance and delays imposed by the novice FDA medical reviewer assigned to the application, Dr. Frances Kelsey. The repeated requests for additional safety information and the resultant delays in approval were enough so that once the thalidomide-birth defect association was identified the sponsor withdrew the New Drug Application and Dr. Kelsey was hailed as a hero for saving countless American children from a similar fate. President Kennedy awarded her the President’s Award for Distinguished Federal Civilian Service, and after her retirement from FDA (she retired in 2005 at the age of 90!) the agency created the annual Frances O. Kelsey Award for Excellence and Courage in Protecting the Public Health. Thus, the 1962 amendments, and Dr. Kelsey’s revered status within FDA, illustrate, and have significantly influenced, the FDA’s strong institutional bias toward precautionary principles in the review of new medical technologies for the past 50 years.

Third, FDA management and line personnel are under constant public and political scrutiny, and any time unexpected injuries or deaths arise that are attributed to an approved drug or device, critical media coverage, and often Congressional inquiries, come raining down on the agency drawing unwanted (and often unfair) attention on individual FDA officials. This creates an atmosphere of natural and understandable stress in connection with the
review and approval of any new technology whose safety and efficacy characteristics may not be fully understood.

A natural human response to such stress in the context of FDA’s product review and approval function is, as noted, to rely heavily on precautionary principles by, for example, requesting more and more information, consulting internally on potential questions of safety, taking a hard line on clinical endpoint or other protocol issues, seeking to scale back or limit the scope of the requested conditions of approval, and so forth. In the age of User Fee legislation and the tight FDA review commitments involved, much of this de-facto inquiry and review has been pushed forward into the product development stage before FDA even receives a marketing application for a product.

Thus, a confluence of powerful big-picture factors can certainly lead one to conclude that FDA has no meaningful prospect of adopting a more flexible, or more “agile,” approach to new medical technologies. Whether that proves true or not may well be made clearer by the end of Dr. Gottlieb’s tenure as FDA Commissioner, but as described in the following section, as a matter of statutory authority, the FDCA leaves FDA with tremendous room to maneuver if it wishes, and tries, to become a more “agile” agency.

FDA’s Authority is Sufficiently Discretionary to Allow for Rational Regulatory Flexibility

While the foregoing discussion may offer critics of FDA some handy explanations to support the view that FDA is too slow, inflexible, and lacking in regulatory agility, those factors are not themselves specific objective evidence to prove such conclusions. Moreover, this background begs the question of whether FDA has the legal tools and scientific discretion to in fact be an agile regulatory actor. Looking at the actual statutory requirements for FDA approval of a drug, or approval or clearance of a medical device, one finds a decidedly high level of generality in terms of what Congress has mandated. For example, the FDCA mandates that FDA “shall” approve an NDA if “none of the grounds for denying approval specified in subsection (d) applies.” 21 U.S.C. § 355(c)(1).

Subsection (d) lists only six safety- or efficacy-related grounds for FDA to refuse to approve an NDA. Specifically, FDA may only refuse to approve a new drug if one of the following is true all emphases added:

- The submission does “not include adequate tests by all methods reasonably applicable” to prove safety
- The data “show that such drug is unsafe for use under such conditions [described in the proposed labeling] or do not show that such drug is safe for use under such conditions
- The manufacturing of the drug is “inadequate to preserve its identity, strength, quality, and purity”
- There is “insufficient information to determine whether such drug is safe;”
- “There is a lack of substantial evidence” of efficacy; or
- “based on a fair evaluation of all material facts, such labeling is false or misleading in any particular.”

The statutory criteria for FDA to refuse to approve a premarket application (PMA) for a Class 3 device are similar but more streamlined, and the clearance criteria of “substantial equivalence” for 510(k)-eligible devices and diagnostics arguably is even more flexible. See, 21 U.S.C. § 360e(d)(2) (PMA approval criteria); 21 U.S.C. § 360e(i)(1)A (“substantial equivalence” definition).

Thus, while “safety” and “efficacy” are themselves already inherently subjective terms, additional statutory approval criteria such as reasonably applicable,” “inadequate,” “insufficient information,” “substantial evidence,” or “fair evaluation, introduce additional subjective concepts that FDA has wide latitude to define or re-define in the context of its therapeutic product review and approval processes. In other words, Congress did not grant FDA such discretionary authority merely as a means to allow the agency to require that every ambiguity and potential risk be identified, analyzed, and eliminated as a possibility before a drug could be approved. The line drawing, in other words, has been entrusted to FDA, and the agency can use that authority to make the product development and approval processes more, rather than less, agile.

Thus, the FDA optimists can argue, FDA can exercise its inherent statutory discretion in ways that are both agile, and protective of the public health.

The Expert Panelists Weigh In

With the foregoing as background, the following commentary of the panelists at the Precision Medicine Leaders’ Summit provide thoughtful, concrete, and current insights into the “regulatory agility” question. As the moderator of the panel, I can say without fear of contradiction that the panel members represented an incredibly impressive mix of FDA and industry perspectives. The panelists were:

- Elizabeth Mansfield, Ph.D. (who served at FDA for 15 years, much of which involved leading and developing the agency’s regulatory approaches to Precision Medicine);
- Edward Abrahams, Ph.D. (president of the Personalized Medicine Coalition, comprised of more than 220 member entities from industry, academia, and elsewhere);
- Paul Billings, M.D., Ph.D. (Founder of Fabric Genomics and other precision medicine companies);
- Katlin McKelvie Backfield, Esq. (who served in various legal roles within FDA for 10 years).
The following quotations illustrate both varying and consensus views of the panelists, but to spark readers’ curiosity and open-mindedness about these perspectives, I have deliberately chosen not to attribute the quotes to the specific panelists. A full video of the panel discussion will be made available online by the sponsor in the near future and readers are encouraged to view it in its entirety.

**On the issue of whether FDA is institutionally constrained from being “agile”...**

- **Panelist:** “FDA has to operate within a statutory framework...that form the boundaries for what FDA can do...so if you’re wondering why isn’t FDA doing something...it may because they simply lack the statutory authority to do that.”

- **Panelist:** “One of the things FDA tries very hard to do...is to not create internal precedent conflicts where one activity by one Center or on one product creates a precedent that will then make huge implications that are unwanted for another product or other Centers and that’s actually quite complicated and getting more complicated all the time.”

- **Panelist:** “FDA has a terrific challenge in keeping up with the science... I think they do the best job in comparison to other agencies...but it’s always a losing battle because the science moves so fast and it changes the paradigms with which we work so quickly.”

- **Panelist:** “Not entirely clear to me that FDA is well positioned to agily adapt and empower consumers to be their own directors of their own [health]care.”

**Has FDA been agile enough given its institutional or other constraints?....**

- **Panelist:** “The central core of FDA is safety and efficacy and those are notions that have a history: what was safe and efficacious 100 years ago and what our notions of it are now might be quite different...It’s kind of an evolving notion.”

- **Panelist:** “[I’d] like to see more real-world assessments of efficacy and pooling of data...a more adept FDA at trying out things and letting things be proven in terms of the efficacy side in the real world as opposed to the safety side.”

- **Another Panelist’s response to efficacy comment above:** “I think scientifically people would probably be somewhat uncomfortable with that at this point...[but] FDA is part of the government and the government is supposed to do what the people want...so should the people decide this what they want... [and are] willing to take a drug or diagnostic that may not help them...who [is FDA] to tell the people they can’t do that? But I have not heard a lot of clamoring to ‘let me operate my own healthcare, let me be my own mechanic’... not clear to me the people are completely ready for that.”

**On the ongoing issue of FDA regulation of LDTs....**

- **Panelist:** “One area where FDA could have done a better job...is the regulation of laboratory-developed tests; it’s inconceivable we have two agencies doing that; leads to enormous confusion in the market and one might argue one of the challenges for the diagnostics industry is that they can’t figure it out and therefore there’s less investment in diagnostics than we would like because of this.”

---

**Conclusion**

Asking if FDA can perform with “regulatory agility” is meant to be thought-provoking and indeed it is a bit of a loaded question, but neither this column, nor the Precision Medicine Leaders’ Summit panelists, actually defined what “regulatory agility” means, or should mean. That lack of a definition is both inevitable and by design, as one can only assess such “agility” in highly subjective and otherwise imperfect ways; for example: by comparison to one’s own personal (or business) preferences and expectations; by comparison to other regulatory agencies’ performance on very different regulatory tasks; and/or in a retrospective manner using post-decision data and experience to judge how fast and flexibly FDA could have or should have acted with respect to a particular product or technology based on facts that did not exist at the time FDA had to make a decision. What can be said objectively, however, is that FDA is taking Precision Medicine very seriously, and is applying sophisticated scientific and regulatory skill sets in its efforts to appropriately regulate Precision Medicine within the bounds of its legal, political, and public health mandates and constraints. And thus, the debate about FDA’s “regulatory agility” can continue indefinitely in ways that hopefully can advance all stakeholders’ shared objectives.

---

James N. Czaban, is a Partner and the Chairman of the FDA and Medical Products Regulatory Practice Group at the international law firm DLA Piper LLP, in Washington, D.C. In nearly 25 years of private practice, Jim has focused on counseling pharmaceutical, medical device and diagnostic, and other life sciences clients on a broad range of complex regulatory strategies and compliance matters, and regularly represents such clients in legal, public policy, and enforcement matters before the FDA, other administrative agencies, and in the federal courts. Jim has been deeply involved in the law and regulation of Precision Medicine since mapping of the human genome was completed more than 15 years ago.