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Book Review
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BOOK REVIEW

***FDA in the Twenty-First Century: The Challenges of Regulating Drugs and New Technologies.* Edited by Holly Fernandez Lynch and I. Glenn Cohen (Columbia University Press, 2015. 568 pp.).**

FDA in the 21st Century is an excellent edited volume based on the Petrie–Flom Center's[1] 2013 Annual Conference.[2] The conference sought to gather thought leaders in academia, government, and private industry to evaluate the Agency and to make recommendations for Food and Drug Administration's (FDA's) future functioning. Peter Barton Hutt referred to it as, 'unquestionably the largest, comprehensive symposia on food and drug law literally that has ever been held'.[3]

Conference presenters (together with a few follow-on submitters) subsequently contributed essays to *FDA in the 21st Century*. The book's editors argue that their efforts are timely, given that the Agency is being faced with new challenges in the form of big data, personalized medicine, and increased globalization, together with longstanding problems related to funding, industry relations, and consumer access. Although, as a food and drug law aficionado myself, I do not think there is ever a bad time to have a book about FDA.

Of the book's 27 chapters, only one appears to have online open-access: the book's introduction by editors Holly Fernandez Lynch and I. Glenn Cohen (at SSRN).[4] The introduction describes each chapter's substance, so I will not attempt to reduplicate that content here.

The book's essays are on a diverse range of topics, although the editors have sorted them into broad themes. After the introduction, the volume starts with an engaging

1 The Petrie–Flom Center, *About Us*, http://petrieflom.law.harvard.edu/about/overview (accessed Oct. 22, 2015).

2 The Petrie–Flom Center, *The Food and Drug Administration in the 21st Century: The 2013 Petrie-Flom Center Annual Conference*, http://petrieflom.law.harvard.edu/events/details/petrie-flom-center-annual-conference-the-food-and-drug-administration-in-th (accessed Oct. 22, 2015).

3 Peter Barton Hutt, *Historical Themes and Developments Over the Past 50 Years (2013)*, https://vimeo.com/66653244 (accessed Oct. 22, 2015).

4 Lynch, Holly Fernandez & Cohen, I. Glenn, *Introduction to: FDA in the Twenty-First Century: The Challenges of Regulating Drugs and New Technologies*, in FDA IN THE TWENTY FIRST CENTURY: THE CHALLENGES OF REGULATING DRUGS AND NEW TECHNOLOGIES 1 (2015).

overview of FDA's history by Professor Hutt. The book subsequently groups chapters into seven parts, the descriptions for which I have copied directly from the text[5]:

(i) 'FDA in a Changing World', provide[s] a high-level review of major developments in the background context against which FDA must now regulate.
(ii) 'Preserving Public Trust and Demanding Accountability', highlights in particular FDA's role in encouraging transparency, as well as its enforcement approach when wrongdoing occurs.
(iii) 'Protecting the Public Within Constitutional Limits', offers a debate, of sorts, on the interplay between off-label promotion and the first Amendment.
(iv) 'Timing Is Everything: Balancing Access and Uncertainty', examines FDA's various categories of premarket approval schemes and post-market surveillance and also puts them in context of how other national and supranational regulators behave.
(v) 'Old and New Issues in Drug Regulation', starts with a historical perspective and then moves on to consider evolving issues in drug-safety communication and the oft-overlooked area of drug manufacture.
(vi) 'Regulatory Exclusivities and the Regulation of Generic Drugs and Biosimilars', considers some of the ways in which FDA encourages both advancement and competition, as well as some of the pitfalls and implications of the current approach.
(vii) 'FDA's Role in Regulating New Technologies', highlights some cutting-edge issues and ideas that are testing the agency's limits.

As a collection of essays from a group of writers, the book does not advance a particular thesis as much as it engages the reader in a thoughtful discussion of hot topics in food and drug law. Some chapters are more-or-less descriptive, such as those by Howard Sklamberg and Jennifer Devine, Deputy and then Associate Commissioner for Global Regulatory Operations and Policy at FDA. For those less familiar with how FDA functions and the Agency's current activities, these chapters are valuable resources. Readers can learn about, among other topics, how the Agency is adapting to an increasingly globalized supply chain and to ever-more engaged patient advocacy groups.

Other chapters provide predictions about future trends or normative claims about the kinds of activities the Agency should engage in. Many of these are by academic thought leaders: for instance, Theodore Ruger argues that FDA will cede some of its traditional predominance as the most important public health issues come to involve financing and consumption practices rather than abstract notions of safety and efficacy. Barbara Evans contributed an essay about the challenges FDA will face in trying to regulate prospective medicine, which she argues will involve very different issues than those related to most existing medical products. She argues convincingly that the Agency has broad powers under the Food and Drug Administration Amendments Act of 2007 (FDAAA) that allow it to require post-market studies related to a drug's efficacy as well as its safety.

5 *Supra* note 4.

The diversity of content makes the book a worthwhile read for anyone interested in FDA. The editors do not cover every FDA-related issue as 'there is only so much we can do with one book'. I am likewise unable to engage with all 27 chapters in a book review. But I do want to highlight a few chapters and arguments I enjoyed engaging with (without meaning to suggest those chapters are more important than the others).

Patrick O'Leary and Katrice Bridges Copeland have great competing chapters, in a sense, dealing with the issue of how FDA should best deter industry misconduct. Both chapters focus on going after corporate officers individually under the responsible corporate office doctrine, and both authors note that even multi-billion dollar fines do not seem to be adequately deterring misconduct. Copeland argues it is unfair to prosecute an executive without personal knowledge of misconduct and the intent for misconduct, and this fundamental unfairness should constrain the exclusion period associated with convictions. O'Leary argues that increasing the amount of fines is only likely to materially endanger a firm's financial well-being which in turn may reduce consumer access to products made by that firm, and that the solution lies in enhanced interagency coordination and prioritizing public health.

I was not convinced by Copeland's arguments that a three-year period of harsh limitations on an individual working with the government (and health care companies contracted with the government) is the modern day equivalent of 'civil death' for health care executives. Even assuming they are entirely unable to work in an industry that accounts for approximately 18 per cent of the US GDP, that still leaves plenty of employment opportunities. Likewise, while I agree that exclusion has a substantial and negative career impact, I was not convinced that its imposition 'is much more serious than the criminal penalties associated with a misdemeanor misbranding conviction', which can include prison time. I was also unconvinced by O'Leary's 'over-deterrent' argument about the size of fines, given that they are not large relative to the size of many pharmaceutical firms. I do agree with O'Leary that there is an important role for going after corporate officers individually, but most of his focus was on the practical and philosophical concerns related to the Park doctrine. It is unclear to me that his proposal for greater coordination among federal agencies and emphasizing a public health mission (and who can argue with that) is the solution for policing an industry with an unfortunate and continuing record of misconduct.[6]

The volume contains some exciting empirical research by Genevieve Pham-Kanter who analysed more than 15,000 votes by almost 1400 members of scientific advisory panels, a data set 10 times as large as prior studies in this area. Her research finds that panelists with a financial relationship with just the sponsor whose product is being evaluated are one-and-a-half times as likely to favor the product. However, she also finds that there is no increased likelihood of favoring a product where panelists have financial relationships with multiple companies. These are important findings, although (I did not see this disclosed in the book) the same research was published last year in The Milbank Quarterly.

I personally enjoyed the 'debate' in Part 3 on off-label use and the first amendment because I have written on this subject recently: Richard Epstein and I debated the

6 Epstein, Richard A. & Abbott, Ryan, *FDA Involvement in Off-Label Use: Debate between Richard Epstein and Ryan Abbott*, 44 Sw. U. L. Rev. 4 (2015).

appropriate role of FDA in policing off-label prescribing last year,[7] and Ian Ayres and I published an article about how the agency should adapt to a post-Caronia need for enhanced informational regulation.[8] Government regulation of off-label promotion by pharmaceutical companies is just as important a First Amendment issue now as it was a few years ago, and the book's content is still up to date.[9] The chapters in this part focus on the December 2012 decision by the US Court of Appeals for the Second Circuit in *United States v. Caronia*, which was the first time the FDCA's misbranding provisions were successfully challenged under the First Amendment. Christopher Robertson rightly draws attention to the fact that First Amendment challenges could extend far beyond regulation of promotional off-label speech. He also challenges the presumptions that off-label promotional claims are truthful and that the FDA is acting paternally to keep the truth out of the hands of consumers. Although, arguments that FDA restricts off-label use to promote research on off-label uses have been front and center before the courts in these cases. Ultimately, he proposes courts should impose a burden on drugmakers to prove their claims are true as an affirmative defense at a jury trial, and this seems like a very reasonable approach.

In her comparative piece, R. Alta Charo makes a strong case for FDA adopting the 'conditional approval' process of its European counterpart, the European Medicines Agency (EMA), to increase compliance with Phase IV trials and to speed the approval process.

Part 5 had with a fascinating historical account of the failed efforts of the National Academy of Sciences and the National Research Counsel to review the efficacy of the 4000 plus drugs that were already FDA approved in 1962.

Part 6 had great chapters by Arti Rai, as well as by Henry Grabowski and Erika Lietzan, on biosimilars. Those chapters provide insight into the differing intellectual property and regulatory challenges faced by generics and biosimilars. Rai argues compellingly that originator biologics firms may need less exclusivity than originator small molecule firms given the technical and regulatory barriers to entry faced by follow-on biologics. She suggests rebalancing US exclusivities along the lines of a European model which gives both branded biologics and small molecules the same term of exclusivity. Also, she argues that the Biologics Price Competition and Innovation Act (BPCIA) provides fewer opportunities than Hatch–Waxman for strategic behavior (such as reverse patent settlements) that would delay follow-on competition.

In the final Part, Nathan Cortez argues that FDA lacks a tailored regulatory framework for software devices, which is concerning given the ubiquity and importance of software in modern health care delivery. He suggests this risks the market being flooded by ineffective and unsafe software that can undermine consumer confidence. He convinced me that the Agency should be doing more in this area.

Finally, Andrew English, David Rosenberg, and Huaou Yan have a chapter on using e-prescriptions for post-market regulation. Their 'proposal would require physicians to

7 *Id.*

8 Abbott, Ryan & Ayres, Ian, *Evidence and Extrapolation: Mechanisms for Regulating Off-Label Uses of Drugs and Devices*, 64 DUKE L. J. 377 (2014).

9 Ryan Abbott, *Government Regulation of Commercial Speech: is Amarin Pharma's Breakout Moment? Bill of Health, Harvard Law*, http://blogs.law.harvard.edu/billofhealth/2015/09/07/government-regulation-of-commercial-speech-is-amarin-pharmas-breakout-moment/ (accessed Sep. 7, 2015)

specify on the e-prescription their treatment purpose for the prescribed medical product and would be called upon to report their knowledge of medical outcomes, both favorable and unfavorable'. It is an interesting proposal, but one I think that physicians would face a severe and untenable burden in accommodating. Not to mention that physicians often lack access to good outcomes data. The authors also do not acknowledge that much of what they propose is already being accomplished by the Sentinel Initiative, an active surveillance system now being operated by FDA. Sentinel has data on prescriptions and outcomes for over 175 million Americans by means of accessing data being maintained by insurers and health care provider organizations (like Kaiser Permanente).

In sum, *FDA is the 21st Century* is worth reading for anyone interested in FDA. All of the book's chapters provide insight into challenges facing the agency, and often provide thought-provoking proposals for change. The volume makes an important contribution to the growing academic literature about FDA.

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