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The FDA In The Gottlieb Era: An Early Report Card

Evolving Regulatory Frameworks For Real-World Evidence (RWE) And Opioids And Other Pain Medications

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Realizing The Potential Of Real-World Evidence (RWE)

- The biopharma industry has long confronted the challenge of generating two, historically-distinct data sets
  - Clinical trial data set FDA uses to approve a drug/biologic/device
  - Real-world data set used by health-care systems and payors to inform and substantiate decision-making for healthcare delivery, coverage, and reimbursement
- Explosion of both data sets has fueled the interest in RWE
  - FDA openness to considering both data sets can help reduce development timelines and costs, accelerate medical products through the regulatory process, and better align FDA with payors
    - Evaluating both data sets in the regulatory process can facilitate coordinated evidence-generation strategies, where data can be leveraged to meet the needs of regulators, payors, and other healthcare stakeholders, with patients being the ultimate beneficiaries of streamlined approvals, enhanced patient access, and more informed coverage and reimbursement

So, What Is Real-World Evidence (RWE)?

- This somewhat-vexing question has been at the forefront of the debate over use of RWE in the regulatory context
  - RWE is comprised of real-world data (RWD) relating to patient health status and/or health care delivery (*e.g.*, recorded in EHRs, claims databases, registries, wearable technologies, etc.)
    - Generating RWE requires RWD, but RWD alone is inadequate
    - RWE is clinical evidence derived from RWD and analysis of RWD regarding usage, and potential risks/benefits, of a medical product
- In this era of "big data," supercomputers and other powerful tools have enabled the gathering, aggregation, and analysis of previously-incomprehensible RWD sets
  - Congress incentivized FDA to leverage these tools in the bipartisan 21st Century Cures Act (Dec 2016) and in PDUFA VI (FDARA), which set parameters for FDA's establishment of a RWE framework
    - Public workshops by end of FY 2018 and draft guidance by end of FY 2021 following public engagement with external stakeholders

Commissioner Gottlieb: "RWE Matters To Me"

- Commissioner Gottlieb is championing FDA's use of RWE
  - Under his leadership, FDA has sponsored two workshops at the National Academy of Sciences (NAS) (Sep 2017; Mar 2018), a meeting at Duke's Margolis Center (led by former-Commissioner Mark McClellan), and a third NAS workshop upcoming (Jul 2018)
    - The goal of the NAS workshops is to establish a standardized data set for RWD and RWE
    - The Margolis Center meeting produced a white paper outlining a framework for the use of RWE in the drug regulatory process
      - "The increasing availability of RWD, and the increasing desire to translate it into RWE useful for all stakeholders, represent a timely and important opportunity to enhance regulators' ability to leverage multiple types of RWE across a range of decisions. To make these regulatory applications a scientifically-sound reality that maintains FDA's long-held standards of ensuring the safety and efficacy of the medical products it regulates, a more nuanced approach to defining or categorizing RWE is needed." (Margolis Center White Paper, page 15)

Dr. Gottlieb Has Championed Use Of RWE (1)

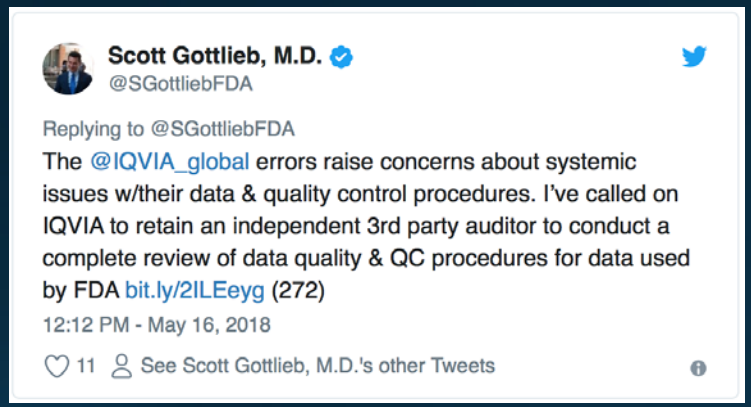
- Commissioner Gottlieb echoed these same themes in his presentation to the first NAS workshop (Sep 19, 2017):
  - "[A]dvancing the adoption of RWE in support of [FDA's] programs [is] a high priority of mine. We need to close the evidence gap between the information we use to make FDA's decisions, and the evidence increasingly used by the medical community, by payers, and by others charged with making healthcare decisions."
  - "[T]he rigor by which RWE is being collected is also gaining more precision. We're seeing the advent of more rigorous clinical registries. We're seeing electronic medical records (EMRs) being used in more effective ways to collect information at the point of care. As the breadth and reliability of RWE increases, so do the opportunities for FDA to also make use of this information."
  - "[W]e have a broader mandate as a public health agency to engage in the life cycle of how products are used. That means embracing the full continuum of evidence that informs their clinical use."

Dr. Gottlieb Has Championed Use Of RWE (2)

- Dr. Gottlieb's leadership is producing real-word results
  - FDA already has issued its first RWE Guidance: Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices (Aug 31, 2017)
  - "Since early 2015 alone, [FDA has] approved or cleared more than eight new medical devices and expanded the use of more than six technologies based on evidence derived from RWD."
    - Drug-eluting stents, transcatheter heart valves, technologies for spinal cord stimulation and esophageal atresia, and IVDs
      - "In these cases, we're using robust evidence that was generated in less time and at a lower cost than in the past, in some cases saving one to two years of development time."
  - FDA has launched various big data analytics initiatives
    - For example, the Oncology Center for Excellence is collaborating with Flatiron Health in the Information Exchange and Data Transformation (INFORMED) project to examine how RWD can be leveraged to gain insights into the safety and effectiveness of new cancer therapies

Opioid Addiction: A Persisting Public-Health Emergency

- Despite increasing heroin and illegally-manufactured fentanyl opioid-related overdose deaths in the US, some 40% of opioid-related overdose deaths involve Rx opioids
  - Rx opioids are increasingly seen as pathway drugs and commonly the first opioid patients encounter on a path to illicit consumption
    - A recent report by FDA's CDER emphasized that, in 2016, an estimated 11.5 million people misused Rx opioids, and each day an estimated 40 people died from an opioid-related overdose involving Rx opioids – stark statistics underscoring the need for vigilant action
      - As Dr. Gottlieb reminded IQVIA when it over-reported fentanyl sales by 20%, the accuracy of reported opioid statistics is equally critical – a key point in the context of the RWD collected in IQVIA's drug utilization databases



FDA's War Against Opioid Abuse Continues Expanding

- Under Commissioner Gottlieb, FDA has been very active in addressing opioid misuse and abuse as a top priority
  - As a clinician, Dr. Gottlieb is committed to ensuring appropriate prescribing for patients in medical need while sustaining coordinated regulatory and enforcement actions to curb addiction
    - As Dr. Gottlieb highlighted in January 2018 at one of many public hearings and workshops FDA has held/sponsored over the past two years, FDA is leveraging its Opioid Steering Committee (formed May 2017) and its Strategic Policy Roadmap, in conjunction with HHS' Five-Point Strategy, to prevent new addiction by
      - reducing exposure through REMS and provider education
      - changing packaging so physicians can tailor prescribing to medical need
      - driving more appropriate prescribing for shorter durations
      - encouraging development of abuse-deterrent formulations (ADFs), with 8 ADFs already approved with labeling on abuse-deterrent properties
      - supporting development of medication-assisted treatments (MATs) for opioid use disorder (OUD) and for management of opioid withdrawal symptoms (*e.g.*, Lucemyra (lofexidine hcl) May 16th)

Other Fronts In The War Against Opioid Abuse

- FDA's initiatives under Commissioner Gottlieb are part of a rising tide of concerted government/industry efforts
  - CMS' April 2nd Medicare Part D Rate Announcement allows Part D sponsors to limit at-risk beneficiaries' coverage for frequently abused drugs to certain prescribers and pharmacies and apply beneficiary-specific point-of-sale limits on amounts dispensed
  - Congress is pursuing multiple, bipartisan legislative initiatives addressing a range of issues (*e.g.*, expanded access to MATs, medical records privacy, evidence-based OUD program funding, and prescription drug monitoring program interoperability)
  - Payors and PBMs are initiating limits (*e.g.*, BCBS plans are limiting initial fills for first time Rxs, CVS Caremark imposes a 7-day supply restriction, and Express Scripts limits initial Rx fills to 7 days)
  - State AGs are pursuing new rounds of civil actions in state courts alleging various improper activities by opioid manufacturers, as the industry confronts a tidal wave of litigation initiated by individuals, cities, counties, states, and Native American tribes

The Regulatory Environment For Opioids & Pain Meds

- These initiatives inform/impact the regulatory framework
  - Recent developments reflecting potential limits on opioid marketing and evolving pain-medication review standards include:
    - In June 2017, FDA requested that Endo remove reformulated Opana ER (oxymorphone hcl) from the market, and a month later Endo did so voluntarily
    - In September 2017, FDA informed immediate-release opioid analgesic manufacturers that their products would be subject to the same REMS requirements as extended-release opioids
    - In January 2018, FDA required labeling changes for Rx cough and cold products containing codeine or hydrocodone and imposed limits on packaging for loperamide (Imodium)
    - In February 2018, a joint Ad Comm recommended against approval of a fixed-dose opioid combo of hydrocodone, acetaminophen, and promethazine (Hydexor) based in part on postmarketing data (RWD) on misuse and abuse potential of hydrocodone and promethazine
    - FDA's Opioid Policy Steering Committee continues pursuing initiatives to foster development of novel pain treatments
  - Further action within FDA's statutory authority can be anticipated

Thank You!

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