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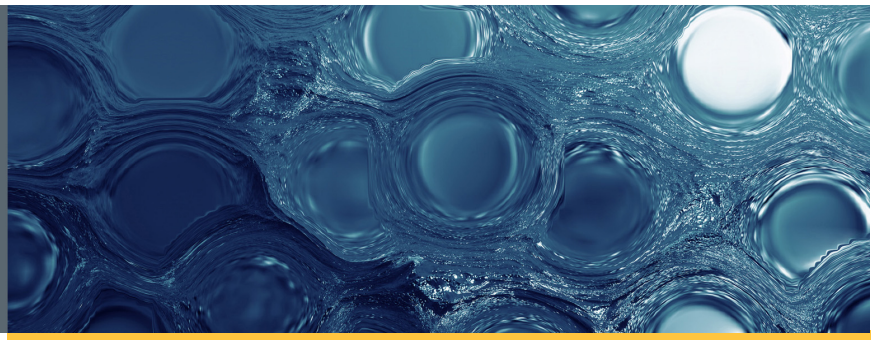

December 2013

FDA Deputy Commissioner Details Agency's Priorities in Recent Speech

In this Issue:

Deputy Commissioner of the FDA, Sally Howard, recently spoke on the topic of "FDA at the Crossroads" at a presentation to the Bioresearch Central Summit in Kansas City, MO. Topics included the scope of the FDA, recent public health and innovative program successes, and a roadmap of high-priority future initiatives. Key points and additional details about FDA's current programs are highlighted here.

I. Snapshot of the Agency: FDA -regulated products

- Products Regulated by FDA Include:
  - Human Drugs
    - Rx, OTC, Generics
  - Vaccines, Blood Products, and Other Biologics
    - Blood supply
  - Medical Devices
    - Newly emerging Mobile Medical Applications to heart pacemakers
  - Electronic Products
    - Microwave ovens, tanning beds
  - Foods
    - Food safety, food additives, Nutritional information
  - Dietary Supplements
    - Cosmetics
  - Veterinary Products

- ♦ Livestock feeds, pet food, use of antibiotics in animals
- Tobacco Products

- FDA-regulated products represent about 20 cents of every consumer dollar spent in the U.S.
- FDA is responsible for regulating over $2 trillion in medical products, food, and tobacco
- Around 14,000 full time employees located around the world
- FY 2014 budget of $4.7B
  - ~ 45% ($2.1B) of budget provided by industry user fees
- There are over 15,400 prescription drug products approved for marketing
- FDA has oversight of at least 5,900 different medical device product categories
- There are at least 1,600 FDA-approved animal drug products
- There are approximately 300 FDA-licensed biologics products
- These products are manufactured or handled at more than 183,000 registered facilities, more than half of which are overseas

II. Recent Public Health Milestones

- Family Smoking Prevention and Tobacco Control Act
- Patient Protection and Affordable Care Act
- Nutrition Labeling of Standard Menu Items at Chain Restaurants
- Biosimilars
- Establishment of Office of Minority Health
- Food Safety Modernization Act
- Food and Drug Administration Safety & Innovation Act
- Tobacco Control Act (TCA) - ushered in a new era of tobacco control, giving FDA the authority to regulate the manufacture, distribution, and marketing of tobacco products to protect public health; and recognized that almost all new users of tobacco products are under age 18. (June 22, 2009)
- Affordable Care Act (ACA) - (March 23, 2010)
  - Section 4205: Nutrition Labeling of Standard Menu Items at Chain Restaurants: ACA requires restaurants and similar retail food establishments with 20 or more locations to list calorie content information for standard menu items on restaurant menus and menu boards. Also requires vending machine operators who own or operate 20 or more vending machines to disclose calorie content for certain items.
  - Sections 7001 – 7003: Biosimilars- Amends the PHS Act to create an abbreviated licensure pathway for biological products that are demonstrated to be "biosimilar" to or "interchangeable" with an FDA-licensed biological product. (also referred to as the BPCI Act- "Biologics Price Competition and Innovation Act of 2009)
  - Section 10334: The FDA Office of Minority Health

(OMH) was established in 2010, as mandated by the ACA. OMH serves as the principal advisor to the Commissioner on minority health and health disparities.

- Food Safety Modernization Act (FSMA) - the most sweeping reform of our food safety laws in more than 70 years, aims to ensure the U.S. food supply is safest by shifting the focus from responding to contamination to preventing it. (January 4, 2011)
- Food and Drug Administration Safety & Innovation Act (FDASIA) - provides critical resources the Agency needs to support regulatory science, improve patient access to new and better treatments and alleviate drug shortages. It also includes a robust enhancement of FDA's inspectional authorities. (July 9, 2012)
- "Drug Quality and Security Act", Public Law 113-54 - allows large-scale compounders that register with the FDA and meet good manufacturing practices to be exempt from certain regulatory provisions that govern the production of traditional pharmaceuticals. (December 4, 2013)

III. Innovative Programs at FDA

A. FDA has a number of programs intended to speed the availability of promising new therapies to patients with serious and life-threatening illnesses.

- There are four FDA regulatory mechanisms or approaches for expedited approval of drugs.
  - It is FDA's view that drug developers should have a clear understanding of all of FDA's expedited development and review tools. To help industry better understand each of these mechanisms, including when the tool can be used and the features of each, in June 2013, FDA published a draft guidance for industry entitled "*Expedited Programs for Serious Conditions—Drugs and Biologics.*"

1. Fast Track and 2. Breakthrough

- For a new drug directed at a serious condition that provides early evidence for fast track; or early clinical evidence -- for breakthrough -- of benefits over available therapy. These drug applications receive:
  - Meetings and early advice to optimize development
  - Rolling review of new drug applications (submit completed parts)
  - Priority designation, as appropriate
  - For Breakthrough applications -- an FDA organizational commitment to involve senior FDA managers and experienced review staff or a cross-collaborative, cross-disciplinary effort.

3. Priority Review

- For a new drug that appears to provide -- before full review -- a significant improvement in safety and/or efficacy over available therapy for a serious or life-threatening illness such as:
  - Greater efficacy
  - Reduction of important adverse reaction(s)
  - Better and documented patient compliance
  - Safety and efficacy in a new subpopulation
- FDA will review and act on Priority applications within

6 months of filing instead of 10 months for standard applications.

4. Accelerated Approval

- For a new drug that provides a meaningful therapeutic benefit over existing treatments and relies on a surrogate endpoint, or an intermediate clinical endpoint, to predict the drug's ultimate anticipated clinical endpoint.
- Drugs "reasonably likely to predict a benefit" may receive Accelerated Approval. Examples of clinical endpoints may include tumor shrinkage for cancer or short-term reduction of HIV viral loads for HIV treatments.

B. Pediatric & Rare Disease Initiatives

- PREA improves the safety and effectiveness of drugs, biological products, and medical devices intended for pediatric populations
  - FDASIA made permanent the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA), and authorized certain funding associated with pediatric device development.
- Priority review voucher provision encourages development of new drugs and biologics for prevention and treatment of rare pediatric diseases
  - The rare pediatric disease priority review voucher provision encourages development of new drugs and biologics for prevention and treatment of rare pediatric diseases. This program, like the neglected disease voucher program on which it is modeled, is designed to provide financial incentives to sponsors of products to treat these diseases
  - Since sponsors are unlikely to ever benefit financially from the sale of these products (because the number of patients likely to benefit is too small to recoup the financial investment in research and manufacturing), the concept of the voucher is to reward the sponsor with a voucher providing priority review for another more lucrative product application
  - The voucher is awarded only if the rare pediatric disease application (or neglected tropical disease application) is approved
  - FDA has already designated one drug product as a drug for a rare pediatric disease and is reviewing several other designation requests.
  - FDA expects to publish Draft Guidance about the Rare Pediatric Disease Priority Review Voucher Program in the future
- Orphan Products Grants Program funds clinical trials involving rare disease
  - The Orphan Products Grants Program funds clinical trials involving rare diseases; i.e., diseases that affect less than 200,000 people in the United States.
- Humanitarian Device Exemptions allow sponsors to seek approval by demonstrating reasonable assurance of safety, not effectiveness.
  - To encourage the development of medical devices intended to benefit patients in the treatment and diagnosis of rare diseases, certain devices for rare diseases or conditions may be granted a Humanitarian Device Exemption (HDE), which allows

the sponsor to seek FDA approval for the device by demonstrating only a reasonable assurance of safety and not a reasonable assurance of effectiveness.

C. Drug, Biologics & Device Innovation

1. Antimicrobial Resistance - LPAD

- The decline in antibacterial drug research and development (R&D) as serious antibacterial resistant infections rise is a tremendous public health and patient care problem. FDASIA included several provisions intended to spur the development of antibacterial and antifungal drugs to treat serious or life-threatening infections in humans, including five additional years of exclusivity and fast track and priority review status (GAIN Act).
- FDA is working on several clinical trial design guidance documents to facilitate product development. In addition, proposed legislation, the Limited Population Antibacterial Drug (LPAD) pathway, provides for approval of antibacterial drugs.
- The proposed legislation also includes a LPAD designation on the label which would alert the healthcare community that such drugs should be reserved for use in the indicated sub-population.
- Consideration of LPAD is part of a wider effort to develop new, more innovative clinical trial designs, an effort that FDA is collaborating on with NIH, and hope will also include academia and industry. Antimicrobial Resistance is one of the biggest public health threats we face and it will take collaboration between the USG, researchers in academic settings and within industry, and the commitment of biotech companies and pharmaceutical companies to develop new drugs to meet this threat.

2. New Animal Drug Innovation Initiative

- Many of the pharmaceutical companies which make animal drugs are located in Kansas and the director of the Office of New Animal Drug Evaluation has traveled to Kansas to present how the Center will work with sponsors of new and innovative products to put together a clear review pathway that addresses the uniqueness of each product.

3. Vaccines

- CBER's regulatory science program supports the development of regulated products by enabling the use of innovative manufacturing methods, providing tools to assess product safety and efficacy, and contributing to animal models that may be used to study new therapies and product testing methods. Some recent examples of this work include the development of an animal model to help facilitate development of next-generation pertussis vaccines; development of a new testing method that could speed up potency testing of influenza vaccines; work on a potential "universal" influenza vaccine; and development of a simple and rapid poliovirus test to speed evaluation of vaccines and support the global polio eradication campaign.

4. Mobile Medical Apps

- The issuance of this Guidance on 9/25 is a great example of FDA's recognition that it must be ready and willing to enter a new "space" to keep pace with technological advances, foster (not stifle) innovation, and provide clear, predictable, and reasonable clarity regarding Agency expectations. The Guidance lays

out, with examples, FDA's intention to regulate mobile medical apps based upon functionality and risk by focusing its oversight on medical mobile apps that meet the definition of device in the Federal Food, Drug, and Cosmetic Act and are intended to: transform a mobile device into a medical device regulated by FDA; or be used as an accessory to a medical device regulated by the FDA. It also provides clarity regarding the specific types of apps for which the Agency intends to exercise enforcement discretion. Importantly, FDA intends to stay current with the expertise needed to evaluate mobile medical apps for which safe use and accuracy are critical to public health.

D. Advancements in Clinical Trials

- FDA has long recognized the need to maintain flexibility in applying its safety and efficacy standards to address unmet medical needs and new treatment options without compromising the golden seal an FDA approval represents. Towards this end, the Agency has strengthened and streamlined its approach to clinical trials so that they are conducted in a safe, efficient, least burdensome and cost-effective manner, while maintaining appropriate patient protections.

1. Non-Randomized Clinical Trials (aka external control groups)

- An externally controlled trial compares a group of subjects receiving the test treatment with a group of patients who are not part of the same randomized study as the group receiving the investigational drug.
- The control group could be a well-documented population of patients observed at an earlier time or a group treated during the same time period but in another setting.
- External control groups are used rarely but when they are, it is most frequently in cases where disease progression is well understood and there is rapid, high mortality such as with cancer that does not respond to treatment or serious rare diseases. A recent example of a drug approved using this method is:
  - Carbaglu: Approved in 2010 for the treatment of the rarest form of urea cycle disorder, a disease afflicting less than 10 people in the U.S. Approval was based on a control group of 23 patients treated in Europe.

2. Streamlined Medical Device Clinical Trial Framework

- CDRH, like CDER, often accepts non-randomized trial designs in support of marketing applications, as well. CDRH is also developing a clinical trial framework that allows decision-making tailored to the type of study, incorporates a benefit-risk decision -making approach, and incorporates patient-specific factors such as tolerance for risk.

3. Use of Open Source Data

- FDA appreciates the potential for innovative applications of open source data about medical products and recognizes that quality data are available from published studies, as well as other sources. For example:
  - CBER works closely with sponsors and does consider data from these sources when submitted as part of a Biologics License Application (BLA). An example of CBER's efforts in this area is the approval of BLAs for cord blood. These products had been used widely prior to licensure, and CBER staff knew data existed regarding their use which

had not previously been submitted to the agency as part of either Investigational New Drugs (INDs) or BLAs. Therefore, CBER established a docket to which sponsors and health care practitioners submitted information regarding safety and effectiveness, which FDA evaluated and used in support of approval of the these types of products.

- CDER, too, is willing to consider the submission of open-source data in applications, clinical trials, etc. Generally, the type of data and its purpose will determine what type of quality control or assurance is needed. For example, genomic data from the NIH Human Genome Project is well established and has known and widely accepted quality controls.

- To further demonstrate its commitment in this area, on June 4 2013, FDA issued a Federal Register Notice seeking public comment on a proposal to make available de-identified and masked data derived from applications for drugs, biological products, and devices. The Notice stated that making data from premarket applications available could make an important contribution to regulatory science "by providing scientific data that may be of value in the generation of new knowledge to facilitate innovation in the development and evaluation of critically needed medical products. The contribution of patients who participate in clinical trials should be maximized for the benefit of society." FDA extended the comment period for this Notice on October 1, 2013.

IV. Cross-FDA Alignment Initiatives

1. Alignment by Program Area:

- On 9/6, the Commissioner appointed and charged the senior leaders from every Center, Directorate and ORA to identify and develop plans to modify FDA's functions and processes to meet the challenges facing the Agency from scientific innovation and advancing product complexity, globalization, and expanded statutory authority. The Group was tasked with clarifying roles and responsibilities and promoting better operational and program alignment to maximize Agency performance including: (1) Transitioning to commodity-based, vertically-integrated programs that cut across Agency units; (2) Establishing coherent policy and integrated strategy development; (3) De-layering management structures; and Streamlining management decision making and accountability. The Group is expected to report back to Dr. Hamburg with its plans and timing to address these issues.

2. Continued Transparency

- Medical Device Pivotal Clinical Investigations

- Examples of Continued Transparency:

  - CDRH - Through its Case for Quality Initiative, CDRH is looking at ways to leverage the broad array of quality-related data it receives from recall and adverse event reports and inspection results. In addition, on 11/6, CDRH released a final guidance document, Design Considerations for Pivotal Clinical Investigations for Medical Devices. This is the first time the FDA has provided guidance containing specific examples of pivotal clinical study designs and principles to guide medical device manufacturers in the selection of a particular design. Improving the quality of data obtained through pivotal studies will lead to timelier FDA approval or clearance of

premarket submissions, and speed U.S. patient access to new devices.

- CBER and CDER – As required by the FDA Amendments Act of 2007, FDA posts action packages for original biologics license applications (BLAs) and new drug applications (NDAs) within 30 days of approval. The action packages include a great deal of information related to the review of an application, such as a summary review that documents conclusions from all reviewing disciplines, product labeling, and decision documents.

3. Compliance with ClincialTrials.gov Databank

- ClinicalTrials.gov
- Enforcement of CT.gov: FDA, in cooperation with NIH is initiating efforts to notify companies and investigators about missing clinical trial registration and results information from the ClinicalTrials.gov database as contained in the NCT record. Companies/Investigators are asked to be sure to voluntarily make any necessary submissions or corrections of clinical trial information to avoid potential regulatory action in the future. Submissions should be up to date and current so that ClinicalTrials.gov can continue to serve as a one-stop, web-based resource that provides patients, their families, health care providers, researchers and the public with easy access information to publicly and privately supported clinical studies.

V. Policy Initiatives Underway

1. CDRH

- Patient Preferences Initiative
- Case for Quality Initiative
  - The Case for Quality Initiative is a fact-based initiative which shows that firms that manage risks by driving quality organization-wide are more productive, have fewer complaints and investigations per batch, and often have smaller quality units with lower quality-related costs than their competitors. Through this initiative, stakeholders operate collaboratively with FDA, and independently to continuously improve quality practices and strive to produce the highest levels of device quality. Device makers allocate resources to activities that are producing quality outcomes. Consequently, FDA can focus on outliers that produce low-quality devices, while continuing some surveillance of firms with demonstrable controls over quality.
- Medical Device Innovation Consortium
  - The Medical Device Innovation Consortium (MDIC) is a novel opportunity for FDA to work in partnership with patient, medical device manufacturers, thought leaders, non-profits, and clinicians to address some of the most vexing regulatory science challenges facing the medical device pipeline. FDA is joined in this effort by sister agencies NIH and CMS.

2. CBER

- Continued utilization of PRISM
  - To evaluate vaccine safety signals, FDA now utilizes the Post-Licensure Rapid Immunization Safety Monitoring (PRISM) system, which is the

vaccine safety component of the FDA's Mini-Sentinel Program. PRISM is the largest vaccine safety surveillance system in the United States (U.S.), with active observation of a representative subset of the general population. Because PRISM has access to historical information for over 100 million people, FDA is able to identify and analyze rare health outcomes that have previously been challenging to assess. With PRISM, FDA has greatly advanced vaccine safety surveillance.

- Pandemic and Threat Preparedness

3. CDER

- Enhancing Drug Quality
    - Quality is the foundation of assurance of drug performance – and FDA is not as good as it needs to be in preventing or predicting problems.
    - Too many patients are unable to access life-sustaining drug treatments because of drug shortages and too many more are exposed to undue risks from medications that do not perform as described in the drug label.
    - CDER is responding to these needs by creating a single Office of Pharmaceutical Quality (OPQ) dedicated to overseeing quality throughout the lifecycle of a drug. The new office will integrate the review and compliance aspects of good manufacturing practices (GMPs) and enable CDER to get a better handle on the state of the inventory. OPQ will sharpen our focus and strengthen our resources around pharmaceutical quality.
- Changes in Generic Drug Labeling
    - Acquired safety information. FDA would also post information on its website about proposed labeling changes to facilitate access by healthcare professionals and the public during FDA's review. FDA would make a decision on approval of proposed changes to both generic and brand drug labeling at the same time to ensure that both products have the same FDA-approved labeling.
- Drug Shortages
    - On 10/31, FDA took two actions to further enhance the Agency's ongoing efforts to prevent and resolve drug shortages. The release of a Strategic Plan, as called for in FDASIA, outlines FDA's efforts to improve the Agency's response to imminent or existing shortages, as well as the longer term approaches for addressing the underlying causes of shortages. FDA also issued a proposed rule requiring all manufacturers of certain medically important prescription drugs to notify the FDA of a permanent discontinuance or a temporary interruption of manufacturing likely to disrupt their supply. Since the President's 2011 Executive Order on reducing drug shortages, the number of new shortages in 2012 was 117, down from 251 in 2011.
- Proposed Hydrocodone Reclassification
    - FDA is challenged with balancing access of opioid products to those patients who rely on continuous pain relief while addressing

concerns about abuse and misuse.

- On 10/24 FDA announced its intent to recommend to HHS that hydrocodone combination products should be reclassified to a different and more restrictive schedule. This determination came after an analysis of scientific literature, review of public comments, and several public meetings, during which FDA received input from a wide range of stakeholders.
- By early December, FDA plans to submit our formal recommendation package to HHS to reclassify hydrocodone combination products into Schedule II. FDA anticipates that the National Institute on Drug Abuse (NIDA) will concur with our recommendation, leading to a final decision by DEA.
- FDA has also published draft guidance to assist industry in developing new formulations of opioid drugs with abuse-deterrent properties.

4. CVM

- Unapproved veterinary drugs
  - CVM has serious concerns about the widespread use of unapproved drugs in veterinary practice including compounded products. Although animal drugs are no longer included in the Pharmacy Compounding Bill, CVM recognizes the need to put together a strategy to address the use of compounding. Options that are being considered include a revised Compounding CPG and other regulatory and enforcement tools.
- Continued pharmacovigilence and adverse event collection

For More Information

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