ENGELBERG CENTER for Health Care Reform at BROOKINGS

October 25, 2011

Meeting Summary

Understanding and Discussing the Implications of FDA's Sentinel Initiative

Background and Overview

With passage of the Food and Drug Administration Amendments Act of 2007 (FDAAA), Congress mandated that the U.S. Food and Drug Administration (FDA) develop a system for post-market risk identification and analysis using existing electronic health data. In response to this charge, FDA launched the Sentinel Initiative in 2008. Since that time, FDA has made significant progress in developing a system for conducting active surveillance of medical products and is on track to exceed its congressional mandate to be able to access data from 100 million patients by July 2012.

The Sentinel Initiative has made impressive strides during its first three years in building a system to support active surveillance. Much of this progress has relied on meaningful collaboration with a number of stakeholders outside of FDA, including data and analytic partners, patient groups, and safety scientists in academia. However, to date, medical product developers have not played a significant role in the development of the Sentinel System. Potential roles for them in the system are complex because while they are a rich source of expertise, they may also present both real and perceived conflicts of interest.

On October 25, 2011, the Engelberg Center for Health Care Reform at Brookings convened a meeting, "Understanding and Discussing the Implications of FDA's Sentinel Initiative," to explore questions related to engaging medical product developers in the Sentinel Initiative. This meeting provided an update to the medical product developer community on Mini-Sentinel's capabilities and FDA's vision for this system and considered issues related to potential medical product developer engagement in Sentinel. During the meeting, attendees considered proposals for involving this stakeholder group in safety surveillance activities. This document provides descriptions of these proposals and highlights additional issues raised by medical product developers.

A Proposal to Minimize Risk: Sentinel and Medical Product Developers

While part of Sentinel's success stems from FDA's ability to capitalize on expertise both within FDA and with external organizations, medical product developers may be another valuable underutilized resource. They are most knowledgeable about their products, and incorporating this knowledge into safety assessments may help to contextualize and interpret findings from the Sentinel System. They also have pharmacovigilance and pharmacoepidemiology expertise and experience with risk communications. Medical product developers in attendance emphasized that they share a common goal with FDA and the rest of the public health enterprise (including academia, practicing physicians) to maximize benefit while minimizing risks of any medical product or technology.

During the meeting, participants considered a proposal that includes Sentinel as a component of the existing risk minimization paradigm. In the current paradigm, during the pre-approval phase medical product developer review teams work with a variety of experts, including FDA's review team and data safety monitoring boards, to understand known and potential risks of a product and identify missing information. Once the product is on the market, data collection to refine understanding of risks continues, and if the data necessitates, medical product developers may work with other stakeholders to minimize risk (e.g., label changes, health care professional education, etc).

The proposal laid out a process, at the time a marketing application is submitted, for medical product developers, FDA, and other experts as deemed appropriate by FDA to meet to determine a plan for refining understanding of pre-specified risks, including the possibility of using Sentinel to complement existing post-market risk evaluation tools. During this meeting, the team of experts would identify which risks could be refined through Sentinel and which could not. For situations in which the use of Sentinel is deemed appropriate, the team could decide in advance whether rapid queries or protocol-based assessments are appropriate and agree upon details of assessments, triggers for conducting more complex assessments, risk minimization plans, and strategies to evaluate such plans.

The proposal laid out a similar process for refining unanticipated risks that emerge during the post-market period. Once a "new" risk is identified, medical product developers would meet with FDA and other experts as deemed appropriate by FDA as soon as possible to determine appropriate steps to evaluate and, if necessary, minimize the potential risk. Decisions at this point would be similar to the New Drug Application process and may include reviewing available information from preclinical and clinical data, determining what tools are most appropriate for evaluation (e.g., Sentinel), agreeing upon the pre-specified thresholds for concluding that risk is sufficiently clear to require a risk minimization plan, and developing details of that plan and strategies to evaluate the plan's effectiveness. If Sentinel is appropriate, the team would also agree upon the appropriate methodology and details of the protocol.

A Proposal to Support the Advancement of Safety Science

Meeting participants recognized the immediate need for more research in the area of safety science to better understand which methods are most appropriate and in what circumstances they should be used to conduct drug safety assessments. Another related priority is creating opportunities to train new scientists with the knowledge and expertise to conduct safety assessments with data from large electronic health care databases. Addressing both of these will require a variety of stakeholders to partner with FDA.

Participants considered two proposals for the creation of a public-private partnership (PPP) that oversees safety science methods research and development and science training in pharmacoepidemiology and pharmacovigilance. The PPP can support these priorities by obtaining a reliable and sustainable funding source, ensuring broad stakeholder collaboration, facilitating efficiency in methods research efforts, and maintaining close operational ties between the methods research agenda and the Sentinel System.

Medical product developers in attendance expressed an interest in participating in the PPP. The value proposition for developers includes allowing them to enhance their own scientific expertise through collaboration with scientists outside of industry and additional training opportunities, gaining synergy and efficiency in methods development, and gaining insight into other stakeholders' perspectives. While the current system for using automated electronic health care data is fragmented and lacks commonly accepted standards, developers expressed optimism that the PPP could pave the way to provide efficient access to a consistent system for using of electronic health care data for safety surveillance. The proposals are described below.

PPP Responsibilities

To advance methods research and development, and safety science training, the PPP's scope of work may include the following:

- Identifying research priorities based on the most pressing and important methodological needs;
- Creating an action plan and timelines to address the established research priorities;
- Establishing a network of investigators in both the public and private sectors that can address the research priorities (similar to the existing network of Mini-Sentinel Investigators, but could also include other investigators);
- Developing pathways to integrate parallel research efforts by groups outside of the PPP;

- Providing periodic updates and guidance on which methods are most appropriate and in what circumstances they should be used; and
- Establishing pharmacoepidemiology and pharmacovigilance training fellowships.

PPP Organizational and Financing Models

A strong governance structure will be important to ensure broad stakeholder input and representation while maintaining transparency and scientific and public credibility of the partnership. Meeting participants considered a governance structure that included two governing boards: an oversight board and a scientific advisory board (SAB). The oversight board would primarily be responsible for setting policies, while the SAB would provide strategic guidance on issues related to establishing and fulfilling scientific and training needs (e.g., establishing research priorities). Governance should include perspectives from patients, regulators, medical product developers, academia, and providers, and data and analytic partners and should also include a mechanism to manage potential conflicts of interest as necessary.

Beyond broad stakeholder representation on both boards, the partnership can benefit from input and contribution from groups including medical product developers, academic institutions, data and analytic partners, patient groups, and regulatory agencies. These groups might provide financial support, agree to host training fellows, and provide researchers who are willing to develop studies to address method research priorities.

An important function of the PPP is its ability to ensure sustainable funding streams to support the safety science enterprise, which will require developing a reliable financing model. Ideally, this model would fulfill the following needs:

- Provide a stable and sustainable funding source;
- Attract funding from a broad set of stakeholders (possible contributors include medical product developers, academia, FDA and other government agencies);
- Obtain funding in a manner that is equitable and fair to all contributors;
- Implemented easily by the PPP; and
- Maintain transparency.

Participants considered a number of potential funding mechanisms, but more consideration will be required to find a suitable model that satisfies the needs laid out above.

Potential Next Steps

Proposals presented possible next steps for the creation of this PPP. These include designating a host for the PPP and participants from previous meetings have suggested Reagan Udall Foundation as a potential host site; defining the scope of work for the PPP; establishing a selection process for the oversight board and convening the oversight board; and agreeing on an appropriate funding model.

Additional Issues Raised by Medical Product Developers

Medical product developers in attendance raised a number of other issues related to Sentinel's development and use.

- Managing expectations around communication of results: Meeting participants highlighted the importance of a predictable process for communication of results to medical product developers, patients, and providers. In particular, medical product developers indicated that they would like to know, preferably with some advanced warning ahead of the public, when FDA intends to conduct an assessment on their product. They also would like to know how FDA will use results generated from Mini-Sentinel.

- Utilization of the system: Currently, medical product developer-sponsored observational studies are conducted on a smaller-scale with claims data from one or two health plans. The Sentinel System's distributed data set links data from across multiple payers to allow FDA to access a data set that is unprecedented in scope for both FDA and medical product developers. Medical product developers, who have traditionally maintained the most data about their product, indicated that they would be interested in being able to utilize this larger data resource to conduct their own studies.

Medical product developers also raised some longer-term considerations:

- Signal generation: FDA is not currently using Mini-Sentinel to conduct signal generation, nor does the Agency have near-term plans to use the System for this purpose. Medical product developers were optimistic that signal generation would be useful to help identify potential risks. However, they also expressed concern about how this new capability for the system would align with their existing risk identification processes, and more dialogue on this topic will be required at a future point when Mini-Sentinel begins to develop its signal generation capacity.
- Devices: The Sentinel System is intended to monitor the safety of all medical products, including drugs, biologics, vaccines, and devices, but existing data sources are not yet well-suited for device monitoring. As device data becomes more accessible through advances such as registries and implementation of unique device identifiers, medical product developers expressed interest in learning how FDA and Mini-Sentinel will further incorporate device surveillance into Sentinel's capabilities.

Conclusion and Next Steps

The role that medical product developers can play in FDA's Sentinel Initiative is complex, representing both a valuable resource but also a potential conflict of interest. This meeting considered a number of factors related to their participation and proposals for engaging medical product developers in risk reduction and advancing safety science. Should they be involved in the Sentinel System, whatever role they take on will have to be appropriately managed to minimize conflicts of interest while still taking advantage of their unique product knowledge and valuable safety science expertise.