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Faster, More Efficient Innovation through Better Evidence on Real-World Safety and Effectiveness

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Background

Many proposals to accelerate and improve medical product innovation and regulation focus on reforming the product development and regulatory review processes that occur before drugs and devices get to market. While important, such proposals alone do not fully recognize the broader opportunities that exist to learn more about the safety and effectiveness of drugs and devices after approval. As drugs and devices begin to be used in larger and more diverse populations and in more personalized clinical combinations, evidence from real-world use during routine patient care is increasingly important for accelerating innovation and improving regulation.

First, further evidence development from medical product use in large populations can allow providers to better target and treat individuals, precisely matching the right drug or device to the right patients. As genomic sequencing and other diagnostic technologies continue to improve, postmarket evidence development is critical to assessing the full range of genomic subtypes, comorbidities, patient characteristics and preferences, and other factors that may significantly affect the safety and effectiveness of drugs and devices. This information is often not available or population sizes are inadequate to characterize such subgroup differences in premarket randomized controlled trials.

Second, improved processes for generating postmarket data on medical products are necessary for fully realizing the intended effect of premarket reforms that expedite regulatory approval. The absence of a reliable postmarket system to follow up on potential safety or effectiveness issues means that potential signals or concerns must instead be addressed through additional premarket studies or through one-off postmarket evaluations that are more costly, slower, and likely to be less definitive than would be possible through a better-established infrastructure. As a result, the absence of better systems for generating postmarket evidence creates a barrier to more extensive use of premarket reforms to promote innovation.

These issues can be addressed through initiatives that combine targeted premarket reforms with postmarket steps to enhance innovation and improve evidence on safety and effectiveness throughout the life cycle of a drug or device. The ability to routinely capture clinically relevant electronic health data within our health care ecosystem is improving, increasingly allowing electronic health records, payer claims data, patient-reported data, and other relevant data to be leveraged for further research and innovation in care. Recent legislative proposals released by the House of Representatives' 21st Century Cures effort acknowledge and seek to build on this progress in order to improve medical product research, development, and use.[1] The initial Cures discussion draft included provisions for better, more systematic reporting of and access to clinical trials data;[2] for increased access to Medicare claims data for research;[3] and for FDA to promulgate guidance on the sources, analysis, and potential use of so-called Real World Evidence.[4] These are potentially useful proposals that could contribute valuable data and methods to advancing the development of better treatments.

What remains a gap in the Cures proposals, however, is a more systematic approach to improving the availability of postmarket evidence. Such a systematic approach is possible now. Biomedical researchers and health care plans and providers are doing more to collect and analyze clinical and outcomes data. Multiple independent efforts – including the U.S. Food and Drug Administration's Sentinel Initiative for active postmarket drug safety surveillance, the Patient-Centered Outcomes Research Institute's PCORnet for clinical effectiveness studies, the Medical Device Epidemiology Network (MDEpiNet) for developing better methods and medical device registries for medical device surveillance and a number of dedicated, product-specific outcomes registries – have demonstrated the potential for large-scale, systematic postmarket data collection. Building on these efforts could provide unprecedented evidence on how medical products perform in the real-world and on the course of underlying diseases that they are designed to treat, while still protecting patient privacy and confidentiality.

These and other postmarket data systems now hold the potential to contribute to public-private collaboration for improved population-based evidence on medical products on a wider scale. Action in the Cures initiative to unlock this potential will enable the legislation to achieve its intended effect of promoting quicker, more efficient development of effective, personalized treatments and cures.

What follows is a set of both short- and long-term proposals that would bolster the current systems for postmarket evidence development, create new mechanisms for generating postmarket data, and enable individual initiatives on evidence development to work together as part of a broad push toward a truly learning health care system.

Enhancing Drug Innovation through Improved Postmarket Evidence

The Sentinel Initiative is an example of how FDA can support private-sector collaboration to develop better postmarket evidence.[5,6] Sentinel has become an integral tool in FDA's activities to obtain timely evidence on the safety of drugs and biologics. Approaches like Sentinel could be expanded from their use of insurance claims data to increasingly incorporate electronic clinical data and patient outcome data to develop better real world evidence (RWE) on safety and effectiveness through two short-term steps: promoting an FDA-led effort to develop and apply methods for real-world evidence, and providing in-kind and financial support for public-private collaboration to create a virtual postmarket network to produce this evidence.

Improving Real World Evidence Development

The initial draft of the Cures legislation includes a provision on real-world evidence that requires FDA to develop and issue draft guidance on the "appropriate standards and methodologies for the collection and analysis" of RWE as well as its potential application in development and regulatory review. This is an important step toward establishing methods and mechanisms for using the often messy, nonrandomized data developed in the postmarket setting to produce evidence relevant to understanding risks and benefits for particular patient populations and additional uses of a treatment. The current draft requires draft guidance outlining FDA's RWE program within 12 months of enactment and final guidance six months thereafter.

However, as work with the data used for safety studies in the Sentinel Initiative has shown, laying out best practices for collecting, analyzing, and incorporating RWE into biomedical innovation is a major undertaking, one that is unlikely to be effectively completed in this short timeframe. Further Cures discussion drafts requiring FDA and stakeholders to work toward a better system for harnessing RWE should give this effort more time to take shape, perhaps through a stepwise approach. Given the methodological complexities involved and the need for collaboration with a wide range of stakeholders to produce and use real-world data effectively, the legislation should also provide more opportunities for stakeholder feedback, forums, and workshops, along with clearer expectations about progress to improve postmarket evidence on drug safety and effectiveness.

A process by which FDA works in a public-private collaboration with stakeholders to establish a general framework for implementing an RWE program would be much more likely to overcome the major hurdles to using a RWE system effectively. This would allow for broader input and stakeholder support and would better focus the goals of an RWE program. The framework should include information describing the current sources of RWE data, the gaps in current data collection activities, and the current standards and methodologies for collection and analysis of such data. It should establish priority areas, remaining challenges, and potential pilot opportunities that an RWE program will need to address. The collaborative process for establishing this program framework should be completed within 12 months.

Under this proposal, FDA would implement the RWE program as originally envisioned by the early Cures language, but with a stronger foundation and focus. The program should ideally be given two to three years to explore collection, analysis, and regulatory applications of RWE as outlined by the framework. A downstream guidance document or formal report should still be included in updated legislative proposals in order to create a mechanism by which the RWE program disseminates its findings.

Funding and Resources for Enhanced Postmarket Evidence on Drugs and Biologics

A clearer framework for developing and using RWE will only have an impact if it is accompanied by effective ways of producing much better data for use in RWE studies. A much more robust virtual infrastructure for generating that evidence is possible, but is not yet part of the Cures legislation. Existing building blocks for such a system include the Sentinel Initiative and a range of other private and collaborative activities, many of which have benefitted from data standards and methods developed by Sentinel. The Sentinel Initiative itself is a potentially useful model of the virtual, public-private collaboration that is needed: it enables an increasingly broad range of participating data partners to contribute information related to postmarket safety evidence while protecting the confidentiality of individual data, and it has begun to contribute to RWE development for other public health purposes outside of drug surveillance.

In conjunction with a multi-stakeholder process like that described above, limited but meaningful extensions of Sentinel's data capabilities could enable faster and more effective RWE development on treatment utilization patterns and outcomes, which could be used not only to address issues related to safety and effectiveness of drugs and biologics, but potentially other issues related to improving public health and the use of medical technologies. These additional uses of the same virtual infrastructure could bring in additional resources and expertise for RWE, leading to better support and better evidence on the safety and effectiveness of medical products.

To enable these improvements in RWE to be realized, Cures legislation could provide clear authorizing language for complementary use of Sentinel System infrastructure and capabilities including linkages with a broader range of data sources and for other RWE uses beyond drug safety surveillance. This language would be framed as a parallel effort to the RWE program outlined above, and would allow for Sentinel extensions to include effectiveness and other types of public health evidence. Without dictating exactly how FDA and private-sector collaborators could implement this enhanced postmarket infrastructure, the legislation could highlight the key elements that need to be addressed to build on existing and emerging systems. This includes establishing governing principles for collaborations to use these data, and transparency around methods used and public reporting of results.

Public funding for initial pilots and seed funding to sustain activities alongside private support would accelerate the development and implementation of a shared and sustainable plan for substantial improvements in active postmarket safety surveillance. Any legislation should provide authority for the Secretary to enter into contracts with public and private entities to fulfill such requirements. Together, these proposals would enable use of postmarket systems like Sentinel for broader public health purposes than drug safety, and would enhance the use of a growing range of data sources available for postmarket evidence on safety and other public health priorities.

Active Postmarket Surveillance for Medical Devices

Better postmarket evidence is at least as critical for medical device innovation as it is for drugs. The design of medical devices are typically revised and improve with actual use over their life cycle. In addition, surgeon or operator skill matter for devices, and premarket studies of the long-term safety and effectiveness of implanted devices are difficult to undertake in the premarket setting. To improve postmarket device surveillance, Congress enacted legislation in 2012 mandating FDA to expand the Sentinel system to include medical devices.[7] To date, however, Congress has not directed specific resources to support this work. Moreover, additional steps are needed to create and sustain the needed infrastructure for a robust system of medical device surveillance in the U.S. For example, unlike drugs, specific medical device information has not been routinely captured in electronic health insurance claims, complicating the ability to use claims data to track devices. Without such a system in place, it is very difficult to implement a truly "life-cycle" approach to device development and regulation, leading to less certainty about the risks and benefits of medical devices, less investment, and slower development.

Recently, the National Medical Device Postmarket Surveillance System Planning Board released recommendations on how such a system could be implemented as a partnership between FDA and the private sector.[8] Convened by the FDA to address these critical challenges, the Planning Board was composed of a broad range of stakeholders, including leading medical device experts, clinicians and hospital representatives, patient representatives, and device industry leaders. The Planning Board noted that improved medical device surveillance is a public health and national priority and that the most effective way to address this priority is to build a medical device-focused multi-stakeholder public-

private partnership with broad participation. The Planning Board made a set of recommendations for the implementation of such a system. We build on the Planning Board's recommendations for a two-stage approach here.

Establishing a Short-term Project to Design a National Medical Device Postmarket Surveillance System

In order to lay the groundwork for a National Medical Device Postmarket Surveillance System (MDS), Cures legislation could mandate that FDA work with external stakeholders to establish a specific implementation plan for the MDS. This could be accomplished over the course of three years, and could include targeted pilot programs to begin to implement the national system.

This implementation plan should, at a minimum, include recommendations to develop the core system capabilities. It should define the framework for MDS's implementation, including the organizational structure, core tasks, and supporting authorities, and identify key partner organizations, role(s), and mechanisms for recruitment and collaboration. The plan should propose mechanisms to ensure appropriate patient protections and data privacy requirements, and identify and prioritize pilot projects to initiate in early implementation of MDS.

The implementation plan should also include logistical recommendations for implementing MDS through a public-private partnership. This would include mechanisms for selecting the MDS leadership, such as a Governing Board and Executive Committee, as well as a management and operational framework that outlines staffing and information technology needs. Financial projections, an estimated budget, and a list of potential funding sources (e.g., appropriations, potential membership fees, service fee structures, in-kind contributions) will be an important component of early-stage MDS planning. Finally, the implementation plan should include guidance on transparency and communications strategies.

Overall, the implementation plan should seek to create an efficient, public-private collaboration with sufficient capabilities, partnerships, and resources to conduct effective and meaningful medical device surveillance. Wherever possible, the plan should rely on external expertise and resources to accomplish MDS's mission through partnerships that leverage resources and reduce burden. Pilot activities identified and potentially initiated within the incubator project should help create a foundation for establishing these ongoing partnerships.

Based on the scope of work and the Planning Board's recommendations, this legislative provision should provide approximately $6 million in funding for the three-year project. The funds would include support for a small number of short-term pilot feasibility studies. Legislation laying out requirements for the MDS implementation plan could be accompanied by provisions mandating its actual creation, outlined below. Both legislative proposals would replace the FDASIA language that mandated device information be incorporated into Sentinel.

Implementing the Long-Term MDS Plan

Based on the MDS plan developed by a partnership involving FDA and other stakeholders, Congress should support the full implementation of a national postmarket medical device surveillance system. This commitment would provide added momentum to the development of the MDS, in turn enabling other provisions aimed at improving medical device development and regulation to work more effectively. For example, the MDS could support a multi-pronged approach to ensure widespread adoption and use of Unique Device Identifiers (UDIs) in electronic health care data.[9] It could make important contributions to ongoing efforts to minimize the burden of postmarket data capture and

sharing, or policies being developed to ensure the protection of patients and their privacy. In short, full-scale implementation of the MDS would provide lasting value to a broad group of stakeholders.

Until more detailed information about the long-term development of the system is in place, it is not possible to specify with certainty the level of funding needed to support MDS in the first five years of the implementation. However, without some commitment of initial seed funding enabling active FDA engagement, it will be difficult to sustain the momentum necessary for other stakeholders to fully engage in the development of MDS. Based on other activities with similar missions and scope, the Planning Board roughly estimated that the cost to implement and maintain the system over the first five years will be approximately $200–250 million in combined federal and private sector funding.

As a point of comparison, the Sentinel Initiative launched the 5-year Mini-Sentinel pilot program in 2009 with approximately $130 million. This funding supported the development of Sentinel's core staffing and data infrastructure, as well as the execution of FDA surveillance activities. In parallel, the Agency for Healthcare Research and Quality provided $100 million over 3 years to develop a separate infrastructure needed to collect quality indicators from clinical care and use electronic health data for comparative effectiveness research. It is estimated that that MDS will require funding comparable to the total of both initiatives. MDS should seek to partner with existing systems like Sentinel and PCORnet that currently do not capture medical devices, but have extensive data networks, partners and methodological capabilities. The hope is that MDS costs will be reduced by leveraging the resources of existing systems. Even with these systems, MDS will need to map and efficiently link new data sources and will likely need to include more data partners in order to conduct medical device surveillance.

As stated above, legislative language outlining implementation of the MDS could be introduced as a follow-on to language requiring development of the MDS implementation plan. These proposals could be incorporated in the same section of FDASIA that mandated device information be incorporated into Sentinel. Other ways of incorporating this activity in legislation may also be possible.

Establishing Pilot Opportunities for Capturing Unique Device Identifier Data

A current stumbling block to fully realizing active medical device tracking and safety surveillance – and an integral part to ultimately achieving the aims of better evidence and more efficient development and use of medical devices – is the incorporation of UDI information into electronic data sources. A range of proposals have been developed for such UDI collection for major devices such as implants as part of claims data, provider administrative systems, and electronic health records.[10] While there is considerable support for implementing UDIs, providers and other stakeholders also want to make sure that UDIs are implemented so that the benefits clearly outweigh the administrative costs and other burdens. To speed progress, pilots for UDI implementation into payer claims and other data sources should be implemented in conjunction with the incubator project for postmarket device surveillance.

To make progress toward integration of UDIs into routine data sources like electronic records and health insurance claims, legislation could support pilot studies and smaller-scale UDI implementation efforts. These should be clearly linked to demonstrating benefits for payers and providers who must report the UDI information. Without clearly identified benefits for patients, mandates to collect and report UDI run the risk of appearing to stakeholder groups as an overly-onerous data collection burden that does not merit the up-front investment in changes to data capture and reporting. We therefore propose two initial efforts that could make clear the link between incorporating UDI into claims and generating real benefit for patients, clinicians, payers, device manufacturers, and additional stakeholder groups.

Require CMS to amend the HIPAA-adopted administrative transactions. This could be accomplished by developing a field in the HIPAA-adopted electronic ASC X12 837I Claim Form for the UDIs of implanted devices during the next scheduled revision post-enactment. The field would be tied to the implantation procedure as a situational rule and initially used in a pilot study. Over time the field would be used for more widespread capture of UDI information for major implantable devices. The schedule and scope for implementation would be developed in a stepwise manner, requiring that benefits significantly outweigh costs.

Require UDI collection pilots as part of the MDS program. As the MDS implementation plan provess outlined in (h)(2)(A) above begins to implement pilot studies and develop large-scale systematic capability for integrating UDI into claims (a necessary component of realizing the full potential of MDS), the program could dedicate at least one pilot activity to testing UDI integration and collection in administrative transactions, and another pilot for collection in hospital electronic health records and/or other hospital management systems. Legislative language could be modified to include such pilots as a mandate. This language could focus specifically on direct UDI capture for a small subset of medical devices, such as high-risk implantables.

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[1] 21st Century Cures Act Discussion Document. January 27, 2015. http://energycommerce.house.gov/sites/republicans.energycommerce.house.gov/files/114/Analysis/Cures/20150127-Cures-Discussion-Document.pdf

[2] Title II, Subtitle F

[3] Title II, Subtitle F

[4] Title II, Subtitle G

[5] Behrman RE, Benner JS, Brown JS, McClellan M, Woodcock J, Platt R. Developing the Sentinel System—a national resource for evidence development. *N Eng. J. Med.* 364(6), 498-499 (2011).

[6] Platt R *et al.* The U.S. Food and Drug Administration's Mini-Sentinel program: status and direction. *Pharmacoepidemiol. Drug Saf.* 21 Suppl 1, 1-8 (2012).

[7] 21 USC 360i

[8] Strengthening Patient Care: Building an Effective National Medical Device Surveillance System. The Brookings Institution. February 2015.

[9] Unique Device Identifiers (UDIs): A Roadmap for Effective Implementation. The Brookings Institution. December 2014.

[10] Unique Device Identifiers (UDIs): A Roadmap for Effective Implementation. The Brookings Institution. December 2014.