ENGELBERG CENTER for Health Care Reform at BROOKINGS

August 1, 2013

Discussion Guide

Special Medical Use: Limited Use for Drugs Developed in an Expedited Manner to Meet an Unmet Medical Need

Introduction

While a number of regulatory reforms have been implemented to improve the efficiency of review for drugs that address serious or life-threatening conditions, concerns remain that the existing drug approval pathways are not optimized to support clinical development programs for some patient populations with unmet medical needs. The President's Council of Advisors on Science and Technology (PCAST) recommended in their 2012 report, *Propelling Innovation in Drug Discovery, Development, and Evaluation*, that the U.S. Food and Drug Administration (FDA) create a new "special medical use" (SMU) designation for the approval of drugs for subpopulations of patients with unmet medical needs.[1]

Sponsors have indicated that it can be difficult to study and seek approval for drugs that target high-risk subpopulations under the existing pathways due to uncertainty about what benefit-risk profiles are acceptable. As part of FDA's approval process, the Federal Food, Drug, and Cosmetic Act charged the Agency with weighing the potential benefits of a product against potential risks. PCAST commented that FDA has interpreted this statutory responsibility to include potential risks the product may pose to a broader population.[2] PCAST's recommendation is the most recent in a series of proposals which have sought to establish an approval pathway for products developed using limited clinical trial programs to accelerate innovation for specific patient populations.[3,4]

The PCAST recommendation outlined several parameters for the new designation, including that it be sponsor-initiated, voluntary, and conferred early in drug development for products targeting areas of unmet medical need. In order to receive the new designation, drug sponsors would need to demonstrate that clinical trials in a larger population of patients would require much longer time periods to complete or would not be feasible. While the new pathway would only require data from the patient subpopulation for approval, the same efficacy and safety standards as existing approval pathways (traditional or accelerated) would be applied. Special labeling and a logo would identify the product as approved through the SMU pathway, and would alert the health care community and patients that safety and efficacy has only been demonstrated in the indicated subpopulations. Following the initial approval, sponsors could apply to expand the indications to a broader population by conducting further clinical studies that demonstrate safety and efficacy in those populations. While product would have a restricted indication, the PCAST report also specified that it would not give FDA the authority to regulate the practice of medicine.

In response to the PCAST recommendations, FDA held a public hearing in February 2013 to gather stakeholder feedback on a potential new limited-use pathway for drugs developed in an expedited manner to address unmet medical needs. Public comments on the proposal included a broad range of views on the need for and utility of the new pathway. Many of the public comments were in favor of a

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[1] President's Council of Advisors on Science and Technology. (2012) Report to the President on Propelling Innovation in Drug Discovery, Development, and Evaluation. Retrieved June 25, 2013 from http://www.whitehouse.gov/sites/default/files/microsites/ostp/pcast-fda-final.pdf

[2] *Ibid*.

[3] Infectious Diseases Society of America. (2012). Limited Population Antibacterial Drug (LPAD) Approval Mechanism. Retrieved June 28, 2013 from http://www.idsociety.org/uploadedFiles/IDSA/News_and_Publications/IDSA_News_Releases/2012/LPAD%20one%20pager.pdf.

[4] Greenwood, J. (2011). Can a 21st century FDA accelerate biotech innovation to cure disease and save lives? *Food and Drug Policy Forum* 1(18):9-10. Retrieved June 25, 2013 from http://www.fdli.org/docs/default-document-library/fdli-policy-forum-18.pdf?sfvrsn=0.

limited-use pathway to address unmet need, but stakeholders requested more clarity on the characteristics of the proposal. Proponents of a new pathway asserted that allowing drugs to be studied narrowly in high-risk patient subpopulations could allow FDA to assess the drug product's safety, efficacy, and benefit-risk profile in a more targeted and efficient manner. This mechanism could support earlier access to innovative therapies for patients with the most pressing unmet needs by streamlining clinical trials and the approval process. This is also seen as a potential pathway to support the development of genomic and personalized medicines.

Multiple stakeholders requested more detail on the proposed pathway regarding evidence requirements and the acceptable balance of benefit and risk for patients with unmet needs. While many of the public comments reiterated the importance of ensuring safe use of these products, no consensus emerged on the effectiveness of special labeling and/or a logo to support appropriate prescribing and deter off-label use. Many comments noted that off-label use of drugs is a valuable and evidence-based practice in many therapeutic areas, and that restrictions on prescribing could be detrimental for patients. Suggestions to support appropriate use in the postmarket setting included educating prescribers, payers, and the public about products approved through this pathway. Groups indicated that restrictive labeling might also affect patients' ability to access or get coverage for these products in off-label or experimental applications. In general, stakeholders supported the need to monitor the safety and efficacy of these products in the postmarket setting. Finally, there were mixed reactions to potential restrictions on promotional activities.

Workshop Objectives and Overview

Under a cooperative agreement with the FDA, the Health Care Innovation and Value Initiative within the Engelberg Center for Health Care Reform at Brookings is convening an expert workshop to seek additional input on the potential utility and challenges of a limited-use approval pathway to expedite the development of products targeting unmet medical needs. This workshop will gather feedback from a range of stakeholders on how the proposed pathway may address regulatory gaps for unmet therapeutic needs, will explore potential tools that could be adopted to promote the appropriate prescribing of limited-use products, and will discuss mechanisms and systems to monitor use and generate evidence on the safety and effectiveness of these products in the postmarket setting.

Session I: The Special Medical Use Pathway Proposal

While the PCAST report broadly outlined features of the SMU pathway, additional discussion is needed to clarify how a new pathway could resolve current regulatory gaps to address areas of unmet medical need. This session will address the following questions detailed below.

What areas of unmet needs would be supported by a limited-use pathway?

A critical component of PCAST's proposed SMU pathway is that it would enable FDA to weigh the balance of benefits and risks in a more targeted manner to approve products for patient subpopulations. FDA is developing a structured benefit-risk assessment framework to support these assessments. The framework includes an evaluation of the product, any strategies to mitigate risks, and an assessment of the broader clinical context for the product, including the current state of knowledge regarding the condition, its severity, and existing therapeutic options.[5,6] Supporters of the limited-use designation assert that the framework could assist in identifying patient subgroups who may benefit from the proposed pathway, such as those highlighted in the PCAST report:

- patients with more serious manifestations of a condition (e.g., morbid obesity),
- patients at elevated risk for developing a serious condition,
- patients with a disease subtype (e.g., those found in breast cancer), or
- patients with no alternative therapeutic options (e.g., contraindications to standard therapies, highly-drug resistant serious infections).

[5] FDA. (2013). Food and Drug Administration Prescription Drug User Fee Act V Benefit-Risk Plan; Request for Comments. Federal Register / Vol. 78, No. 46 / Friday, March 8, 2013 / Notices. Retrieved June 21, 2013, from http://www.gpo.gov/fdsys/pkg/FR-2013-03-08/pdf/2013-05471.pdf

[6] FDA. (2013). Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making. Draft PDUFA V Implementation Plan – Fiscal Years 2013-2017. Retrieved June 21, 2013 from http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM329758.pdf

How would the potential pathway need to be designed and implemented to address the regulatory challenges?
The following questions about the characteristics of the pathway and how it might meet the needs of patients, regulators, and sponsors emerged from the public comment:

- How and when would products enter the pathway (e.g., sponsor- initiated, what stage in clinical or preclinical development)?
- How would this pathway interact with other pathways (e.g., Fast Track)?
- How should the proposed pathway be detailed to minimize regulatory uncertainty (e.g., guidance documents, increased contact with regulators, etc.)?
- Should the designation be seen as provisional?
- Should sponsors be able to conduct and submit postmarket studies to broaden the approved indications within the limited-use pathway? If so, how should these studies be designed and conducted?
- Are there conditions under which the designation could be withdrawn?

Session II: Implementation and Impact of Special Medical Use Products in Clinical Practice

FDA currently has a number of authorities to support appropriate prescribing of limited-use products once they enter the market, including authority over labeling and the ability to require sponsors to develop strategies to reduce risks associated with a product. A feature of the proposed limited-use pathway is special labeling and a logo to promote the appropriate prescribing of approved products once they entered the market. Some stakeholders expressed concerns that these steps may not be sufficient to ensure that products would be prescribed appropriately. Additional resources and tools may be needed to educate health care providers about limited-use products and their benefit-risk profiles. This session explores the following questions about how different stakeholder groups might support and promote the appropriate prescribing of limited-use products.

How can product labeling support appropriate use of limited-use products?
Product labeling serves as the primary method for communicating information about a product's safety and efficacy to prescribers. Approved labeling contains standardized information, including a list of the product's indications, limitations on use, pharmacologic class, and mechanism of action, as well as information on dosage, administration, and a contraindication(s) statement. Labeling also contains a summary of warnings and precautions, the most clinically significant adverse drug reactions, their frequencies, and how to monitor, treat, and report them. In addition, a number of other features may alert prescribers to safety concerns. However, product labeling may not include all information needed to prescribe a drug safely, but instead may refer providers to the full prescribing information. [7] A boxed ("black-box") warning may also be included or required as part of a risk evaluation and mitigation strategy (REMS) if the drug is shown to carry a significant risk of serious adverse effects.[8]

Advocates for the pathway contend that a prominent logo and labeling would be an added communication tool to reduce the likelihood that drugs approved through a limited-use pathway would be used in a broader patient population. The logo would identify the drug as a novel type of product with different evidentiary backing, which proponents believe could help signal to health care providers and other stakeholders that FDA considers the drug to be approved only for a narrow use.

Alternatively, some stakeholders have argued that relying on labeling and a logo alone to ensure appropriate prescribing will not be sufficient to influence prescribing behavior. They contend that labeling is unlikely to affect prescribing since physicians rarely see product labeling in inpatient settings. In addition, critics argue that physicians are typically trained on the use of a drug for a particular condition, but may be less familiar with nuanced indications relating to specific diagnostic criteria or population subtypes.

[7] Lal R and M Kremzner. (2007). Introduction to the New Prescription Drug Labeling by the Food and Drug Administration. *American Journal of Health-System Pharmacy* 64(23): 2488-2494. Retrieved June 11, 2013, from http://www.medscape.com/viewarticle/566885.
[8] FDA. (2011). Guidance for Industry: Warning and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biologic Products – Content and Format. Retrieved June 15, 2013, from http://www.fda.gov/downloads/Drugs/Guidances/ucm075096.pdf.

Although FDA does not have the authority to regulate the practice of medicine, it has worked extensively with manufacturers to restrict use of products through REMS. REMS may be required to ensure that the benefits of a product outweigh its risks, either as a condition of approval or if safety concerns arise post-approval, and can include medication guides, package inserts, communication plans to support implementation, and elements to assure safe use.[9] However, REMS are designed to mitigate known risks associated with a drug, and the PCAST report noted that it may not be an effective tool to promote appropriate use of products approved through a limited-use pathway that may have risks that are not well characterized.[10]

How can the broader health care community support appropriate use of limited-use products?
Supporters of this pathway suggest that promoting the appropriate use of these products may require a broad-based effort to enhance communication, education (e.g., continuing medical education or physician detailing), and cooperation across the health care system in both inpatient and outpatient settings.

Professional, national, and hospital clinical practice guidelines and formulary guidelines help shape prescribing patterns. Payer formulary guidelines, which are developed by insurance companies to indicate what products and uses of products will be reimbursed, may also influence prescribing, as can tiered benefit structures and prior authorization requirements. Although formulary and clinical practice guidelines are based primarily on FDA-approved indications, they may incorporate other evidence generated through clinical practice or postmarket trials related to off-label use of the drug, comparative- or cost-effectiveness research, or patient outcomes. Practice guidelines may also include restrictions on use or include requirements for monitoring. While not reflected in product labeling, guidelines based on these supplementary factors often shape prescribing practices and could potentially be used to support appropriate prescribing of limited-use products.

Other institutional policies may support more strategic prescribing practices. Stewardship programs for antibacterial drug therapy, for example, often create specific plans that allow for the escalation and de-escalation of therapy as the infection worsens or resolves. Antibacterial stewardship teams in hospitals (typically comprised of an infectious disease specialist and a clinical pharmacist) can also provide a system of checks and balances on prescribing by reviewing orders for antibacterial drugs, and providing guidance to prescribers to optimize treatment and minimize misuse. Institutions also periodically conduct reviews to assess prescribing patterns and the impact of changes in guidelines or policies.

Other suggested mechanisms to affect prescribing practices include specialized order and prior authorization forms, e-prescribing, and tools for clinical decision-making support. Hospitals often use special order forms for products with safety concerns or restrictions. Similarly, prior authorization may be required by payers for reimbursement of certain products. The use of computerized provider order entry, e-prescribing, and electronic medical records has facilitated these processes, and can also be used to support clinical decision-making. For example, software algorithms can prompt prescribers to select an approved indication from a drop-down menu, and indications can in turn be linked to checklists for diagnostic criteria. Ordering or prescribing a drug off-label could be discouraged, or could require additional inputs by the prescriber.

Economic factors influence the use of these products. Insurers may have more stringent restrictions on reimbursing expensive drugs, such as requiring providers to perform diagnostic tests to confirm the drug is being prescribed appropriately, or restricting coverage based on the product labeling. Cost-effectiveness of interventions may also be a factor. In a recent high-profile case, for example, a top U.S. cancer center decided not to use a new oncology drug that cost more than twice as much as comparable

[9] FDA. (2009). Draft Guidance for Industry: Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications. Retrieved June 12, 2013, from http://www.fda.gov/downloads/Drugs/Guidances/UCM184128.pdf.

[10] President's Council of Advisors on Science and Technology. (2012) Report to the President on Propelling Innovation in Drug Discovery, Development, and Evaluation. Retrieved June 25, 2013 from http://www.whitehouse.gov/sites/default/files/microsites/ostp/pcast-fda-final.pdf

therapies and appeared to offer no improvement in efficacy or safety.[11] Cost is less often a factor for prescribers in making care decisions, but may be raised by patients as a significant area of concern depending on their insurance coverage and ability to pay for treatment.

Session III: Postmarket Considerations to Promote Safe Use and Continued Evidence Development of Special Medical Use Products

Once products are approved by FDA, they continue to be monitored and evaluated for efficacy and safety. Postmarket surveillance and oversight is particularly relevant for limited-use products, as they will enter the market with more limited data on their safety and efficacy profiles than products approved through other pathways. This session will consider the following questions about potential concerns with limited-use products in the postmarket setting.

What limits or safeguards should be applied to advertising and promotion of limited-use products?
FDA regulates all advertising for prescription drug products, including direct to consumer (DTC) advertising. Any advertisement that names a drug product must also indicate the benefits and risks of the drug, and present them in a balanced manner.[12] FDA can require earlier review and approval of promotional materials (e.g., promotional labeling and advertisements) for some expedited pathway (e.g., Accelerated Approval).[13] Stakeholders have asked if these types of restrictions on promotional materials should be implemented for limited use drugs as it may be difficult to provide a "fair balance" of information about a drug's risks and benefits if the potential risks outside of the indicated subpopulation may not be well-characterized.

How can additional safety and effectiveness evidence be generated in the postmarket setting?
The PCAST recommendation proposed that sponsors should be able to gain FDA approval for additional indications by conducting clinical trials in a broader patient population in the postmarket setting. Multiple stakeholders supported the possibility of seeking approval for additional indications in order to drop the limited-use labeling and logo and earn traditional approval.

How can FDA utilize existing tools to monitor for safety concerns related to limited-use products?
Enhanced postmarket surveillance has been recommended by stakeholders as a component of a limited-use approval pathway to better monitor safety as products move from controlled clinical trial settings into clinical practice. FDA has a variety of tools to collect data on postmarket safety. The Agency maintains the FDA Adverse Events Reporting System (FAERS), which collects reports on adverse events, medication errors, and safety concerns from consumers, health care professionals, and manufacturers.[14] Data from FAERS can be used to initiate further evaluation of products, which can serve as grounds for regulatory action. FDA is also expanding its capacity to conduct active safety surveillance through the Sentinel system pilot, Mini-Sentinel. Mini-Sentinel utilizes routinely-collected electronic health care data to monitor the safety of FDA-regulated medical products and could be used to monitor limited-use products. To monitor products with potential safety concerns, the Mini-Sentinel's surveillance program has focused primarily on retrospective analysis of products.[15] The system is also being expanded to conduct prospective surveillance. It is expected that the Mini-Sentinel system will be able to prospectively monitor dozens of products at the same time, and complement other surveillance approaches, like spontaneous reporting, untargeted surveillance (data-mining), registries, and retrospective epidemiologic studies.[16]

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[11] Bach B, L Saltz, and R Wittes. (2012). "In Cancer Care, Cost Matters." The New York Times 14 October 2012. Retreived from web http://www.nytimes.com/2012/10/15/opinion/a-hospital-says-no-to-an-11000-a-month-cancer-drug.html?_r=0

[12] FDA. (2012). Basics of Drug Ads. Retrieved June 13, 2013, from http://www.fda.gov/Drugs/ResourcesForYou/Consumers/PrescriptionDrugAdvertising/ucm072077.htm.

[13] Applications for FDA Approval to Market a New Drug, 21 C.F.R. 314.550 (2013). Retrieved July 26, 2013, from http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=314&showFR=1&subpartNode=21:5.0.1.1.4.8.

[14] FDA. (2012). FDA Adverse Events Reporting System (FAERS). Retrieved June 22, 2013, from http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

[15] Platt R. "FDA's Mini-Sentinel Program to Evaluate the Safety of Marketed Medical Products Progress and Direction" (presentation, Sentinel Initiative Public Workshop, Washington, DC, January 31, 2013). Retrieved June 27, 2013 from http://www.brookings.edu/~/media/events/2013/1/31%20sentinel%20meeting/richard%20platt%20presentation.

[16] Mini-Sentinel. (2012). Statement of Work: Routine Prospective Safety Surveillance for New Drugs, Vaccines and Other Biologic Products. Retrieved June 12, 2013, from http://www.mini-sentinel.org/work_products/Assessments/Mini-Sentinel_Prospective-Surveillance-Statement-of-Work.pdf.