Four Proposed Grand Challenges, and Related Initiatives to Improve Healthcare Delivery in the 21st Century BioEconomy

Draft Document for Discussion

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Note: This draft document was developed on December 6, 2011, shortly before the submission deadline. As a result of the limited time available for preparation, only one literature reference has been included. Additional literature references may be made available upon request.

Proposal I: Pediatric Drug Development Fund (PDDF): An Expanded Pre-Competitive Public-Private Partnership to Discover, Develop and Commercialize Pediatric Drugs

I. Outline of Proposal
   a. Background and Overview: Pediatric Drug Development Fund (PDDF) would oversee prioritization of diseases, targets, and the most important drugs for development and commercialization for pediatric populations.
   b. Regulation: Change FDA regulations to allow companies to obtain exclusivity by contributing appropriate fees to Pediatric Drug Development Fund, without conducting pediatric trials. Allow pharmaceutical sponsors of high priority drugs to obtain exclusivity by developing drugs, in some instances with support from PDDF.
   c. Mission of PDDF: Fund and authorize PDDF to prioritize, develop, manufacture and distribute highest priority pediatric drugs.

II. Background and Overview

a. Pediatric populations continue to be underserved. Too few pharmaceutical formulations are tested in and optimized for use in infants and children. This creates a substantial burden on pharmacists, health professionals, payers, parents and children.

i. Commercial investment is hindered by:

1. small patient populations, highly fragmented due to different needs in different age groups;
2. different pharmacology and formulation and delivery needs in neonatal, infant/toddler, children, and adolescent populations;
3. ethical and operational issues in conducting trials, resulting expenses and other related barriers.

ii. Many legacy approved products lack the pre-clinical, pharmacologic, pharmacokinetic, safety, and efficacy data required to guide safe appropriate use in children.

iii. Some commercialized products are not available in the appropriate formulations to support use in one or more pediatric sub-populations.

b. Issues with Incentives Under the Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA)

i. Background: In order to obtain 6-month market exclusivity extension for adult markets, sponsors agree to conduct studies in children.

ii. Issues with trial requirement in exchange for exclusivity extension:

1. Critics and observers report that sponsors may not be motivated to seek commercialization of pediatric products.
    a. May result in investment of minimum resources necessary to meet the commitment in order to gain exclusivity;
    b. Studies may be conducted that are inadequately designed to produce interpretable efficacy and safety data. Such studies may simultaneously meet requirements for exclusivity, while failing to result in development and commercialization for pediatric populations, with robust safety and efficacy data from well-designed trials, and formulations optimized for infants and children.
    c. Critics allege that children are sometimes subjected to trials participation with its inherent risks, without the generation of interpretable data appropriate to guide drug development.

2. The incentive process is not designed to identify and support development of the most urgently needed drugs.
    a. The process only stimulates development of pediatric versions of new, branded drugs.
    b. Many needed drugs are generic, or low margin; their development and reformulation for children will not be stimulated by current exclusivity incentives.
    c. Some new drugs are simply not developed due to variables including market size and pricing, potential liability, time to market, and so forth.
3. Summary: The current system does not adequately prioritize and facilitate development of the most needed drugs for pediatric populations. It subjects sponsors to a requirement to conduct clinical trials in order to achieve an unrelated commercial objective of a 6-month extension of market exclusivity. While this incentive has resulted in increased commercial availability of some drugs for children, the process is alleged to result in substandard trial conduct, and is not designed to optimize identification and development of the most urgently-needed drugs and formulations for infants and children.

III. Recommended change in regulations:
- a. Offer sponsors the option to pay an appropriate multi-million-dollar fee in order to obtain 6-month additional market exclusivity.
- b. Fee designed to be substantial, but low enough to provide incentive for companies to pay fee.
- c. By paying this fee, they would obtain 6-month exclusivity extension, without incurring an obligation to conduct pediatric trials.
- d. Fees would be used by Pediatric Drug Development Fund (PDDF) to fund prioritization and development of the must urgently needed pediatric drugs.
- e. Sponsors wishing to obtain the exclusivity extension by developing and commercializing their <u>own</u> drug for pediatric populations, rather than by paying the PDDF fee, would be required to submit a proposal to the FDA outlining the need for the drug in children, and a plan for robust development, formulation, and commercialization. If the plan is approved, then the exclusivity extension would be allowed, contingent upon the sponsor actually obtaining pediatric labeling and making an appropriate formulation commercially available for pediatric use.
- f. Fees and exclusivity period could be increased or reduced depending upon the number of needed pediatric formulations commercialized (e.g. NICU, oral liquid formulation, and so forth).

IV. Role and Activities of Pediatric Drug Development Funds

a. Prioritization Process: Prioritize standard of care and unmet need, defining the most urgently needed pediatric medicines and formulations; draw from and collaborate with existing efforts (NIH, WHO and other organizations' lists of drugs needed for pediatric development).
b. Formulation Technology Platform Development
    i. Laboratory effort to develop improved formulation technology
    ii. Focus areas to include catalog of approaches for structural classes and delivery routes.
    iii. Specific Technologies: open source database and technology pool including solvents and excipients, algorithms, modeling software, and testing platforms.
c. Conduct pre-clinical and proof-of-concept studies in the highest priority areas:
    i. Outsourced through NIH, FNIH or other agencies, or funded via a direct grant-awarding function of the PDDF.
    ii. Clinical Development
        1. Develop improved clinical trial designs, instruments, and measurement tools for pediatric clinical studies
        2. Work with NIH and academics to organize an improved pediatric clinical trials consortium with patient registries
        3. Provide a state-of-the-art clinical trial management group
        4. Objectives:
            a. Prioritization process drawing upon published and primary comparative effectiveness research.
            b. Only medicines that are standard of care or will improve the standard of care would be developed.
            c. Medicines and classes shown to be ineffective or that do not have significant potential to provide substantial clinical or cost benefit over existing therapies will not be further tested in children.
            d. Study designs must be state-of-the-art, and designed to provide data needed to guide pediatric therapy.
d. Distribution: Organize a wholly owned Low-Profit LLC (L3C) or other subsidiary entity that will organize the manufacture and distribution of drugs developed by PDDF.
    i. produce low profits that can attract investment by foundations and other investors, while promoting the educational mission of the institute.
    ii. provide evidence-based information to pediatricians, patients and families;
    iii. direct profits back into PDDF to support its mission to develop, manufacture and distribute evidence-based pediatric drugs.

V. PDDF: Stakeholders likely to support initiative

a. Pharmaceutical sponsors: obtain exclusivity extension through a fee mechanism, avoiding the need to conduct costly and risk pediatric studies for drugs they do not wish to commercialize in children.
b. Payers, providers, hospitals:
    i. Benefit by having available the most urgently-needed pediatric drugs, with robust data packages;
    ii. Decrease the commercial influence on prescribing habits in pediatric populations:
        1. distribution would be performed by L3C responsible for carrying out the educational mission of the organization;
        2. profits resulting from carrying out the low profit manufacture, education and distribution function would flow into PDDF to further the mission.
c. Patients and families:
    i. Benefit by having drugs tested, formulated, reasonably priced.
    ii. Benefit by reducing unnecessary and poorly designed trials.
    iii. Benefit by gaining access to the most urgently-needed medicines, supported by robust evidence.
d. Government agencies:
    i. Food and Drug Administration (FDA), CMS/HHS, NIH, and related entities such as Reagan-Udall Foundation, Foundation for the NIH, and others benefit through making available to the public the most effective, safe, cost-effective drugs.
e. Philanthropic organizations and foundations benefit by meeting the healthcare needs of children.

Proposal 2: Put Pharmaceutical Marketing Reps and Allied Health Professionals to Work Promoting Evidence-Based Standards of Care, Including Use of Generic Drugs.

A. Develop marketing organization to detail standard of care and evidence-based medicine to physicians.
    a. Thousands of pharmaceutical marketing professionals have been laid off as industry has reduced costs.
    b. New sales force would promote best practices, including generics.
    c. Organization would analyze the cost versus efficacy and safety of new branded medications versus older generic medicines, educate physicians on the comparative data.
B. Infrastructure:
    a. Analysis center (immediately analyze new medications in terms of cost and benefit).
    b. Marketing center (create high quality materials and training)
    c. Sales Force
        i. Outreach to physicians and health professionals
        ii. Outreach to patients with balanced information
    d. CME Organization (conduce CME online, in office calls, and at professional meetings)

Proposal 3: Require Balanced, Standardized Presentation of Risks and Benefits for High Cost and/or Low Evidence Interventions funded by CMS.

1) Categorize CMS-funded procedures on the basis of cost versus evidence of efficacy. For procedures that are medium to low evidence, require that each patient to whom a CMS reimbursed procedure is recommended, undergo a standardized balanced presentation of risks and benefits prior to electing to undergo the procedure.
2) In one recent example, designed as one component of the Spine Patients Outcomes Research Trial (SPORT), patients to whom disk removal surgery was recommended, were required to view a video presenting a balanced discussion of the risks and benefits of the surgery. More than 50% of these subjects declined to undergo surgery, electing instead to undergo "watchful waiting" (Weinstein JN, Tosteson TD, Lurie JD, et al. *Surgical vs nonoperative treatment for lumbar disk herniation: the Spine Patient Outcomes Research Trial (SPORT): a randomized trial*. JAMA 2006;296:2441–2450).
3) Develop a series of standardized risk-benefit videos, and train/retrain appropriate health and allied professionals to present the videos.
4) Stakeholders: Those whose care would improve and/or costs would go down
    a. Academic Medical Centers and Hospitals/Delivery Systems
    b. Corporations: Large consumers of healthcare.
    c. Government Organizations funding healthcare.
    d. Patient groups consuming healthcare.
    e. NGOs

Proposal 4: Develop Central 2nd Source of Manufacturing for Critical Chemotherapy Drugs at Risk for Shortages; Create Shared Stockpile to Address Shortages