Response to Building a 21st Century Bioeconomy

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1. Identify one or more grand challenges for the bioeconomy in areas such as health, energy, the environment, and agriculture, and suggest concrete steps that would need to be taken by the Federal government, companies, non-profit organizations, foundations, and other stakeholders to achieve this goal?

Grand Challenges: The "Human disease-ome"

The National Institutes of Health (NIH) has invested billions of dollars in sequencing and studying the genome and determining how genes influence the many human biologic pathways. However, linkages between genes and human disease have been relegated to scientifically weak association studies whose results are often misleading and cannot be replicated. Lack of reproducibility of molecular targets for potential therapeutic interventions has been identified as a serious impediment that slows or prevents translation of the science to marketed products. The result is, in spite of all of this research, the number of new drugs approved by the FDA has remained at about 20-35 per year for over two decades. The major problem in clinical research is that the wealth of genetic disease data cannot be systematically linked to the patients and their diseases. Our scientists have sequenced the human genome, but we don't have the "disease-ome" that describes the natural history of diseases in ways that can be linked to genes, biomarkers and other mechanistic biologic probes. In the many subsets of the population, we need to be able to track the natural history of diseases characterized by the genes and thousands of biomarkers that have been discovered. We need efficient ways to obtain longitudinal data directly from patients using valid instruments, i.e. patient-reported outcome (PRO) measures. Once these data are available, we will be able to address the need for a more modern system to diagnose diseases and to replace the recently updated but completely outmoded ICD10 codes, a priority recently identified in a report from the National Academy of Sciences.

Another of the limiting factors holding back medical advances is our reliance on an outdated and dysfunctional clinical trial system. The Institute of Medicine's recent report found that the National Cancer Institute's clinical trials system to be unacceptably inefficient and several other IOM reports have repeatedly called for transformation of the clinical trial infrastructure.

We suggest a grand challenge to develop the human disease-ome. The first step would be to convene the clinical scientists and professional societies in order to define the common data elements needed to characterize and track the clinical course of patients with each known disease. This is feasible and the process has been begun by the FDA-designated international standards-setting organization, i.e. the Clinical Data Standards Interchange Consortium (CDISC).

CDISC partnered with the Critical Path Institute (C-Path) to form a public-private partnership that includes over 1000 scientists from 15 pharmaceutical companies, patient advocacy groups, FDA and NIH. These collaborators recently released to the public the final data standards for Alzheimer's disease clinical research and they are making progress on four other diseases. Once the common data elements were established, the companies pooled the control arm for 20 trials and placed data for over 5600 non-identifiable patients into the public domain. Using these data, quantitative disease progression models have been developed and are now available to support simulation of new clinical trials.

At the encouragement of the FDA, CDISC and C-Path have launched a new joint venture, the Coalition For Advancement of Standards and Therapies (CFAST). CFAST is prepared to begin work on 55 diseases identified as high priority by the FDA and they are in the process of gaining commitments from the biopharmaceutical industry to pool clinical trial data as was done for Alzheimer's. The goal of the grand challenge would be to have similar tools available for almost all diseases, beginning with the 55 identified by the FDA, but supplemented to include rare diseases, diseases of unmet medical need or special populations and diseases affecting global health.

The disease-ome could be started with data from clinical trials and then supplemented with data captured electronically from electronic health records. This would make the disease models "living," up-to-date descriptions of the spectrum of manifestations of diseases.

The ability to capture live data at the point of healthcare delivery will require the use of mobile device communications platforms with data privacy and confidentiality at a level now held only by the military.

2. Constrained Federal budgets require a focus on high-impact research and innovation opportunities. With this in mind, what should be the Federal funding priorities in research, technologies, and infrastructure to provide the foundation for the bioeconomy?

The first priority has to be the establishment of common data elements and links to the electronic health records so that we can truly have a "learning health care system."

3. What are the critical technical challenges that prevent high throughput approaches from accelerating bioeconomy-related research?

The major challenge in healthcare today is addressing our inability to link symptoms, behavior, and interventions to the outcomes of specific patients. Most systems today provide an average or mean response and almost all are plagued by late or incomplete data. For example, one third of prescriptions recorded in an electronic health record (HER) are never picked up at the

pharmacy, one third are not taken as directed and 40% of people are taking medicines that are not in the EHR because they were obtained from an unknown source (internet, another healthcare system or a relative). We must be able to track these and other metrics of care in a timely, unobtrusive and inexpensive manner if we are to ever have the ability to assess and improve healthcare.

4. The speed of DNA sequencing has outstripped advances in the ability to extract information from genomes given the large number of genes of unknown function in genomes; as many as 70% of genes in a genome have poorly or unknown functions. All areas of scientific inquiry that utilize genome information could benefit from advances in this area. What new multidisciplinary funding efforts could revolutionize predictions of protein function for genes?

The limiting factor is the lack of phenotypic data on the patients. Efforts described above would set the foundation for obtaining such data.

5. What are the barriers preventing biological research discoveries from moving from the lab to commercial markets?

A major impediment is the hodge-podge of university tech transfer systems that delay publication of new findings and interfere with commercialization by unrealistic demands for licenses and royalties. The nation needs to require that all data developed with public funds be posted and made public. IP should be declared and revenues to inventors determined after the technology has demonstrated value.
A second impediment is the antiquated and overly intrusive IRB system. Clinical research protocols should have an IRB of record and all Universities and others executing the protocol should be required to accept the approval of the first IRB's approval. Patients should be informed that additional research on their biological samples may be performed if approved by the IRB in the future and that their identity will be protected. Additionally, data from each trial should be made available to all participants from that trial as a way to enhance transparency and disseminate knowledge.

6. What specific changes to Federal Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs would help accelerate commercialization of federally-funded bioeconomy-related research?

Small businesses that are developing products for FDA approval should be better informed on the many precompetitive, critical path public-private partnerships established by Critical Path Institute and the FDA. These companies need to be better informed on how and when to utilize the newly developed tools for drug development, i.e. qualified biomarkers, PRO instruments and quantitative disease models.

7. What high-value data might the government release in the spirit of its open government agenda that could spur the development of new products and services in the bioeconomy?

De-identified patient level data from all NIH-sponsored clinical trials should be made public 60 days from completion of any trial so that it can be used by other scientists.

8. What are the challenges associated with existing private-sector models (e.g. venture funding) for financing entrepreneurial bioeconomy firms and what specific steps can agencies take to address those challenges?

All restrictions on the level of venture funding should be removed from SBIR awardees so that the very best technologies can be supported.

9. The majority of doctorate recipients will accept jobs outside of academia. What modifications should be made to professional training programs to better prepare scientists and engineers for private-sector bioeconomy jobs?

Doctoral students should be encouraged to work in the commercial sector for a period of time to gain experience in team work and the corporate world of timelines, deliverables and accountability. Corporations should be given incentives to offer more fellowships and internships.

10. What roles should community colleges play in training the bioeconomy workforce of the future?

Community colleges can train students to better perform important scientific roles such as biospecimen handling and preparation using Standard Operating Procedures to gain greater reliability of biomarker assays. Community colleges are a rich source of talented minority students. To produce the diverse workforce required for optimal health care research and delivery, these students should be encouraged through special programs and scholarships.

11. What role should the private sector play in training future bioeconomy scientists and engineers?

Encourage internships at companies that partner with universities

12. What role might government, industry, and academia play in encouraging successful entrepreneurship by faculty, graduate students, and postdocs?

Encourage and reward faculty and students when they participate in startup companies.

13. What specific regulations are unnecessarily slowing or preventing bioinnovation?

Not responding

14. What specific steps can Federal agencies take to improve the predictability and transparency of the regulatory system?

Food and Drug Administration: As discussed above, the FDA is responsible for approving most of the scientific advances that result from the nation's $100 billion annual investment in biopharmaceutical R&D. Since the passage of the Prescription Drug User Fee Act, the industry has offered to pay more and more money and in return has expected more and more certainty for the development process by asking the FDA to tell companies in advance what type of evidence will be required for approval of their products. This assumes that the FDA will have the expertise to provide reliable advice when in fact that level of expertise is often missing and the advice given is inconsistent, at best. In Europe this advice is provided by the best expert consultants available to the regulatory agencies and is perceived by the industry as superior to the advice provided by the Agency.

In 2004, the FDA recognized that the methods being used by the industry were outmoded and the Agency launched the Critical Path Initiative to create collaborations to identify, through consensus, the best methods to test new products. In 2007, part of the User Fee reauthorization (FDA Amendments Act, FDAAA) included a provision introduced by Congresswoman Gabrielle Giffords to create Critical Path Public Private Partnerships. The first and most successful of these has been the collaboration between the FDA and the Critical Path Institute (C-Path), a unique non-profit organization, based in Tucson, Arizona. C-Path was launched in 2005 by Governor Janet Napolitano with over $24 Million over 6 years in support from the Arizona community. While C-Path's current annual budget is only $8 million/year, it leverages this relatively small amount of funding from the FDA, the Arizona governments, community foundations and the Bill & Melinda Gates Foundation. Last year C-Path's 35 industry partners contributed and made public, data estimated at $350 million in value. C-Path has five drug development consortia in which over 800 industry scientists work closely with over 200 scientists from the FDA to identify more reliable, efficient and innovative methods for testing drugs. This is the most appropriate forum for reaching independent consensus on the most advanced testing methods. This process should yield the "independent" stamp of approval for innovative testing methods so that FDA reviewers can focus on their legislatively mandated role, i.e. determining whether a medical product has been found safe and effective. By directly influencing the sponsors' development plan, the FDA has placed itself in a position of perceived conflict of interest. How can the FDA's objectivity be assured when the FDA scientists are evaluating products that were developed according to their own recommendations? An independent process for certification of testing methods should be established by a neutral entity such as one of the critical path public private partnerships where all stakeholders can share precompetitive science, knowledge and expertise.

15. What specific improvements in the regulatory processes for drugs, diagnostics, medical devices, and agricultural biotechnology should federal agencies implement?

The FDA should move the Office of *In Vitro* Diagnostics into the Center for Drug Evaluation and Review (CDER) so that there can be greater efficiency and expertise in the review of companion diagnostics and drug-diagnostic co-development.

Secondly, there should be no restrictions on who can serve as advisors to the FDA. All conflicts of interest for advisors should be disclosed publically. Federal employees such as those at the NIH should be designated as consultants to the FDA for early determination of what type of evidence should be obtained in support of product approval. Product developers should be encouraged to use methods that have been independently certified by a scientifically rigorous, consensus-driven process.

16. What are the highest impact opportunities for public-private partnerships related to the bioeconomy?

The critical path public private partnerships created under FDAAA, should be given greater financial support and greater staff support from the FDA (see conflict of interest statement at the end of this document).

17. What are the highest impact opportunities for pre-competitive collaboration in the life sciences, and what role should the government play in developing them?

The greatest impediment to biomedical research is the lack of understanding of the pathogenesis of diseases. A greater focus on developing "read outs" for vulnerable pathways responsible for diseases would create opportunities for biopharmaceutical companies to develop effective interventions or preventions. As soon as NIH and French scientists identified HIV as a retrovirus, Burroughs Wellcome was able to develop AZT in 18 months. FDA scientists were involved directly and their review of the AZT NDA was completed in 6 weeks. The average development time for 9 HIV drugs was 3.3 years. No safety shortcuts were taken and all of these drugs are still in use today. The grand challenge described above can create the tools and the environment for replicating the HIV/AIDS successes. Government should require NIH and FDA scientists to work in precompetitive consortia and should share in funding the work. The SEMATECH experience with the semiconductor industry should serve as a prototype for how to support the Critical Path Public Private Partnerships.

Conflict of Interest Disclosure: Dr. Woosley is President of the Critical Path Institute, a recipient of a collaborative award from the FDA that funds a critical path public private partnership designed to reach consensus on improved testing methods and drug development tools. Dr. Woosley does not receive any personal income from any company that is developing or marketing a product that requires FDA approval and therefore has no personal conflict of

interest. Critical Path Institute does not receive funding for its core operations from companies that are developing or marketing a product that require FDA approval. The author acknowledges and hereby discloses that some of the statements and recommendations in this response to the RFI can constitute a conflict of interest. This conflict is mitigated by the fact that Critical Path Institute is a non-profit organization with a public health mission working in partnership with the FDA, industry and NIH to advance medical product development.

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