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The Information Technology & Innovation Foundation (ITIF) lauds the Administration for taking the initiative to “develop a National Bioeconomy Blueprint detailing Administration-wide steps to harness biological research innovations to address national challenges in health, food, energy, and the environment.”¹

Because of the central role life sciences innovation plays in both the U.S. and the global economy, it is imperative that this “blueprint” development process reach a successful and early conclusion. ITIF has addressed these and similar issues several times, and we incorporate some of those comments into this letter by reference.² But in this letter we focus, particularly, on some of the low-hanging fruit, identifying policy changes that could quickly and dramatically enhance innovation to universal benefit.

The announcement soliciting public comments seeks input on a series of questions. Perhaps the one area in which input is solicited where easy policy changes could lead to the most dramatic and rapid positive results lies in the area of regulatory reform. Bringing regulatory oversight of innovative biotechnology products more into line with the level of potential hazard assigned by scientific analysis and experience would dramatically reduce the obstacles to commercialization these new products now face in two critical areas—biomedicine and agriculture.

The challenge of crafting policies to unleash safely the potential stemming from recent innovations in biomedicine is particularly complicated. The dramatic paradigm shift being ushered in by the age of personalized genomics has “changed everything but our way of thinking.”³ The situation is, nevertheless, rich with opportunity for improved efficiencies.

In an era where a fully sequenced individual genome will cost a thousand dollars or less, and proclivities for hereditary diseases and metabolic malfunctions can be mapped and deconstructed, it is reasonable to expect that more and more medicines will be specifically developed to treat more sharply focused, and smaller patient populations and even individuals. The era is waning in which a single blockbuster drug can be expected to produce profits sufficient to support 10,000 unsuccessful drug candidates at \$800 million to \$1.2 billion for each success. It is imperative to find ways to reduce the costs of R&D for new therapies and treatments. Perhaps the simplest solution would be to reconfigure FDA’s approach to the design of clinical trials. The current approach is rooted in brute force statistical methods dating to the 1950s and before. This model has considerable power to detect small increments in the safety and effectiveness of drugs and therapies. Its power is rooted in the use of large patient population sample sizes and rigorous double-blind testing. The disadvantage of this approach is that treating and following the clinical course of disease in large patient populations takes a great deal of time and money. This is one of the major drivers of the unsustainably high cost of new drug development. But it is not difficult to imagine a new paradigm that would decrease costs while at the same time increasing the potential for safety, efficacy, and economy.

The gene pool of *Homo sapiens* contains an enormous wealth of genetic diversity, affording our species a wide range of adaptability to different or changing environmental conditions and constraints. The biomedical consequence of this wealth of variation is that many drugs work better on some individuals than others, have differential impacts in different populations. Using this knowledge it is increasingly possible to sort patient populations into subgroups according to the heritable differences in metabolic pathways for different chemical substrates. If this is done it will be increasingly feasible to determine safety and efficacy of drugs in these selected sub populations with not just the same but with increased confidence by comparison with the classical, large sample size/brute force statistical approaches. This could reduce the need for sample sizes greatly, with concomitant savings. Part of OSTP’s blueprint for FDA should be, therefore, to instruct FDA to pursue the adaptation of clinical trial experimental design to the era of personalized genomics and drug sensitivity pre-screening at the earliest possible date.

The situation with respect to agriculture is, arguably, of even more fundamental importance, inasmuch as it is the bedrock of our entire economy, society, and civilization. The ability of agriculture in the 21st century to meet the demands of a growing world population for food, feed and fibre is not, at present, assured.⁴ But the potential for agricultural innovations to meet these challenges is real, and this is foreshadowed in the OSTP solicitation in two incarnations in the solicitation: in question 5, and in questions 13-15.

Question (5) What are the barriers preventing biological research discoveries from moving from the lab to commercial markets? What specific steps can Federal agencies take to address these shortcomings? Please specify whether these changes apply to academic labs, government labs, or both.

Question (13) What specific regulations are unnecessarily slowing or preventing bioinnovation? Please cite evidence that the identified regulation(s) are a) slowing innovation, and b) could be reformed or streamlined while protecting public health, safety, and the environment.

Question (14) What specific steps can Federal agencies take to improve the predictability and transparency of the regulatory system? (Please specify the relevant agency). Show citation box.

Question (15) What specific improvements in the regulatory processes for drugs, diagnostics, medical devices, and agricultural biotechnology should federal agencies implement? What challenges do new or emerging technologies pose to the existing regulatory structure and what can agencies do to address those challenges?

Perhaps the clearest example of regulatory obstacles to innovation that do nothing to improve safety while producing a major disincentive to the investment and innovation necessary to encourage a bio based economy is seen in agriculture. Regulations administered by USDA and EPA to crops and foods improved through biotechnology were promulgated under the “Coordinated Framework for Regulation of Biotechnology,” announced by OSTP in 1986.⁵

While a case was made for the regulations as originally conceived, in the intervening years implementation has clearly strayed from the original vision. Experience has shown that these biotech innovations are at least as safe as, and in many cases even safer than their conventional counterparts, which, for good reasons, generally undergo little or no regulatory scrutiny. Indeed, the brilliance of the innovations that produced these products has been recognized at the highest levels.⁶ However, the gap between the degree of *a priori* regulatory scrutiny applied to these products and any legitimate basis for such scrutiny in science or experience has grown into a chasm. The time taken by USDA to provide regulatory review before these products can clear the final hurdle to commercialization has grown from approximately 110 days in the 1990s (compared to the stipulated deadline of 120 days) to 2-3 years, presently. As such, Brazil has overtaken the United States among major agricultural exporters as having the shortest time for these products in the regulatory process.⁷ Although the record of safety and positive impacts from products regulated by EPA is no less impressive, EPA has recently proposed a dramatic expansion of the regulatory burden it would impose on these and related products.⁸ This follows a number of recent efforts by EPA to expand its regulatory oversight into areas traditionally covered by USDA, and without any demonstrated need or justification, and no resultant increase in safety of any kind. Industry groups have registered their concerns, which have fallen on deaf ears.⁹ Even more troubling, strong expressions of concern from the academic community have apparently been similarly dismissed.¹⁰

The harm from this regulatory irrationality can be easily identified. The U.S. Government database of “Completed Regulatory Agency Reviews” lists varieties of only 20 crops that have been approved for commercialization.¹¹ This category is enriched for crops grown on large acreages and for global, commodity markets (14 of 20) and contrasts dramatically with the wide range of crops being pursued in

innovative R&D in past years, when as many as 60 different crops were reflected.¹² Reviews of global R&D pipelines provide further corroboration of the erosion of the once uncontested U.S. lead in this area, as fully half of the innovations in new agricultural biotech varieties expected over the next few years are expected to come from research taking place now in other countries.¹³ It is widely recognized, particularly among academic researchers that this is in no small part due to the difficulties they face in securing the necessary regulatory clearance from regulators.¹⁴ What is to be done?

If the Administration is serious in its intent to encourage research and development essential to building a sustainable, bio-based economy, it must provide regulatory agencies with political leadership that will bring this to pass. Instead of increasing the regulatory burdens faced by innovators in this sphere, regulations that do not address credible hazards must be retired, and regulatory oversight must be refocused on areas where risks might in fact reside or significant uncertainty remains. This Administration has yet to provide such guidance, despite announcements of that intent.¹⁵ But announcements alone do not provide a sound foundation for sustainable economic growth. Specific, concrete remedies for these problems have been identified. However, until these and similar steps are taken the vision animating OSTP's efforts to develop the blueprint they seek will remain unfulfilled.¹⁶ Among the highest priority actions OSTP should direct be taken are these:

1. Reform the U.S. regulatory system. Regulations must be based in science and should be frequently updated to take into account the lessons gained from experience. The system should not seek zero risk as this is unattainable in the real world. Regulatory review should seek to establish that novel products are as safe as others in the marketplace. In making this evaluation regulators must take into account both the harms caused by present practices as well as opportunity costs, the potential benefits that would be lost by non-adoption. The degree of regulation should be commensurate with real risks and harms. Specifically:
2. The trigger for regulatory review should be the novelty of the introduced trait (introduced by whatever method) and not the process used to introduce the trait. The degree of scrutiny should depend on the relative risk associated with the phenotype and the host when it can be shown that the methods used do not add to the risk. The system should have clear guidelines that quantitatively specify timely decision making.
3. Exempt phenotypes from regulatory review if they could be accomplished through classical breeding methods. If a phenotype comparable to that under review could be produced by a variety of production methodologies (classical breeding vs. recombinant DNA modifications, for example) then there should be a strong presumption against any review process that would make it more difficult, for example, to see the rDNA product move into the field for R&D or commercial purposes.
4. Regulatory agencies must stop treating gene flow as intrinsically hazardous, and shift their focus to appropriate risk management/mitigation in the rare cases where genes so disseminated could, in fact, present a genuine hazard. Agencies must recognize that gene flow is a natural phenomenon and is nearly always irrelevant to safety. The potential for gene movement via pollen flow is a not, ipso facto, a cause for concern or regulatory intervention.
5. Shift to phenotype-based regulatory triggers. Agencies should transition from an event-based regulatory process to a phenotype-based process, as the hazard of a phenotype that is stably inherited has more to do with the distinguishing features of the phenotype than with the precise details of the process through which it was produced.
6. Enhance effectiveness, adaptability, and public confidence by accelerating regulatory updates and transparency. To unleash this technology and enable it to proceed at a pace dictated by the rate of scientific advance the remedy is simple: the new administration should insist on transparency and require prompt publication of proposed policy documents and regulatory guidance by responsible agencies, which must then be tasked with timely responses to public comment. This will

galvanize innovation not only in the animal biotech sector, which has suffered acutely in this regard, but broadly.

Regulators responsible for reviewing products of agricultural biotechnology today spend the vast majority of their time asking questions to which no conceivable answer could have any scientifically defensible impact on a decision for or against approval. This must not continue.

Endnotes

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3. Abraham Pais, *Subtle is the Lord: The Science & the Life of Albert Einstein* 2005 (Oxford, UK: Oxford University Press, 1983).
4. L. T. Evans, *Feeding the Ten Billion: Plants and Population Growth* (Cambridge, UK: Cambridge University Press, 1998).
5. USDA reg. 7 CFR 340; These crops and foods improved by biotechnology were commonly (and unscientifically) referred to as "genetically modified organisms" or "GMOs"; Published at 51 FR 23302.
6. United States Patent and Trademark Office, <http://www.uspto.gov/about/nmti/recipients/1998.jsp#heading-2>.
7. Observations on time taken for regulatory reviews are based on the personal experience of the author; "Analyst says overseas firms gain edge as U.S. biotech approvals lag," *Agri Pulse*, August 3, 2011, http://www.agri-pulse.com/uploaded/AgriPulse_reprint_08032011.pdf; and "Joao F. Silva, Agribulatural Biotechnology Annual: Brazil (report, USDA Foreign Agricultural Service, July 2011), http://gain.fas.usda.gov/Recent%20GAIN%20Publications/Agribulatural%20Biotechnology%20Annual_Brasil_a_Brazil_7-13-2011.pdf.
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10. Fedoroff, Nina, et al. "EPA's Proposed Biotech policy Turns a Deaf Ear to Science." *The FASEB Journal* no. 25: 2855-2857.
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13. Alexander J. Stein and Emilio Rodriguez-Cerezo, "the global pipeline of new GM crops: Implications of asynchronous approval for international trade," (JRC scientific and technical reports, JRC European Commission and Institute for Prospective Technological Studies, 2009), http://ftp.jrc.es/EURdoc/report_GMOpipeline_online_preprint.pdf.
14. Jamie K. Miller and Kent J. Bradford, "The regulatory bottleneck for biotech specialty crops," *Nature BioTechnology* 10, no. 28 (2010):1012-1014.
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