

Strauss presentation to NRC Committee on Biotechnology Regulations – June 2016

Dear Committee Members:

Thanks very much for the chance to speak to you. I have been working in transgenic plant biotechnology, with a focus on trees, for more than 20 years. I have conducted dozens of regulated, multi-year field trials, and consulted extensively with agencies and stakeholders about commercial regulatory approvals for trees. I have also written many commentaries about the scientific and legal basis of our biotechnology regulations in the USA. Many of these publications are available online, and two recent papers, a policy forum published in Science magazine about 8 months ago and a commentary published in Nature Biotechnology about one month ago, were submitted to Marilee and hopefully to the

committee. My comments today on the issues and new products regulatory agencies may face in the next decade or so will be a very abbreviated version of some of what is presented there. I will first talk about general issues in regulation, and then provide some thoughts on the traits that may come forward over the next decade.

I believe that the most important risk is that the large majority of innovations made possible by expanding science and technology, both in trees and crops, will not come before regulatory agencies at all. This is because of the costs, delays, and uncertainties inherent in today's predominantly method-based regulations. What are needed are smarter, more nimble ways to implement regulations based on product novelty and benefits. These should be made in the context of the extraordinary genomic and biochemical

variation that is inherent to conventional breeding and management but which has little if any federal regulation (nor seems to need it). Our papers give specific ideas for what such regulatory changes might look like. The ideas include regulation of gene products rather than insertion events, exemptions and much lower tiers of scrutiny for modifications to native genes and their expression (i.e., functional cisgenics and intragenics made with familiar markers), and allowances for adventitious presence of important, safe, and familiar products during routine research and breeding. Because of the time frame for breeding trees and other perennial crops, and their lower value and more primitive state of genetic technology (especially for forestry and biofuel applications), the costs and uncertainties of regulation have a particularly

damming effect as they add upon many other factors that retard investment.

Second, it will be critical to develop smarter processes for assessing the unintended effects of transformation. There seems to be a growing emphasis on evaluation of insertion sites, undirected omics studies, and whole food animal toxicology—which are costly, ethically questionable, and very difficult to interpret the significance of without extremely large studies. And, as pointed out by the NRC in its recently released GMO crop report, the unintended effects of breeding and environmental variation are being shown to generally dwarf the unintended effects of transformation. Regulators will need the authority to resist demanding such data except where the changes expected have a clear toxicological mechanism of concern compared to the variation inherent to conventional

breeding, and they will need to be competent to interpret, and not to over-interpret, what data they do review.

Third, regulations must be cognizant of the realities of today's rapidly changing world.

Due to climate change—which we know we cannot avoid in substantial degree—and also due to climate- and human-associated aggravation of plant pest impacts, crops and trees are badly in need of new and faster means for breeding. This is essential if production systems—and many wild ecosystems—are to remain functional over coming decades. Genetic engineering is clearly a powerful tool, but if regulated in the slow and costly way that it is done today, those tools will continue to be irrelevant, possibly at a high cost to us and our children. Can we evolve regulations, and evolve regulators, so that we evaluate applications with this

disturbing but undeniable new reality in mind? A reality where we recognize that there is no stasis, just rapid change, and we selectively use GE to help mitigate these changes? There are a number of cases for forest trees and for crops where transgenic approaches might provide powerful added tactics for combatting pest epidemics. But they will not even be studied, let alone developed, where every step of field research would require unknowable costs and delays due to method-triggered containment of every pollen grain. Extensive pre-commercial field studies are required to identify useful genes for complex 2nd generation GMO traits within relevant breeding lineages; they cannot be predicted based on computer, laboratory, or greenhouse studies. The freedom to conduct field research without undue costs and risks is essential to progress.

Turning to traits, I will cite three classes of traits in trees and biofuel crops that regulators might need to prepare for in the next decade.

First, genetic containment systems, such as engineered male and/or female sterility, may be used to help comply with regulations and other social forces that require avoidance of GMO presence. This topic is a major focus of research in my laboratory. But when is it really needed? How stable can it be assumed to be? How stable must it be? What if CRISPR is used to mutagenize floral genes? Is CRISPR removal essential (not so easy to do in long lived trees)? How does reproductive modification affect biological diversity, and are the impacts important compared to how conventional forest management impacts reproduction and biodiversity? We are just completing an in depth review of the effects of reproductive modification on biodiversity in forest trees and

have found that there is almost no research that explicitly addresses this area. Can decisions about approvals of such crops be made and learning/adaptation occur on the fly? Such “adaptive management,” as it is called in forestry, is the dominant mode of operation in most forestry research as a result of the long time frame and high costs for forest experiments. But how do we make this possible under today’s regulations for trees that grow for decades and whose pollen (and sometimes seeds) can travel for miles?

Second, biofuel crops with modified chemistry, or new chemical products as feedstocks, are likely to be increasingly deployed. How should these be evaluated in comparison to the extensive variation in chemistry and qualities in nature, and also under conventional breeding (which for intensively grown trees like poplars and

eucalypts often involves hybrids among species from all over the world). Tom Whitam at Northern Arizona University and his many coworkers have shown that natural variation in plant biochemistry in cottonwoods is extensive, and has large impacts on biodiversity in the wild. Perhaps comparative transcript- or metabol-omics can be helpful here, and might enable us to avoid studies of specific chemicals or insertion events, and instead focus on the relative magnitude of omics differences compared to wild and conventionally bred variation? How can we produce regulations, and regulators, able to make such decisions?

Third and last, regulators are likely to see the new technologies of gene editing and RNA interference more frequently. There is a great deal of research using these technologies, and we are starting to see more releases in trees

(such as the Arctic Apple and Honeysweet plum) as well as crops. (Though both of these approved products were initiated nearly two decades ago, so it's not clear how much will come forth new within a decade, with citrus a possible exception.)

There is much discussion of off-target effects from CRISPR and RNAi. However, although there is certainly more to learn, everything I have seen suggests that these technologies are far more precise and targeted than anything to come before them from conventional breeding or use of pesticides. Is the level of off-target effects a significant concern, whether for modification of internal gene expression or for pest control via HIGS (host induced gene silencing)? Can regulations evolve to make categorical judgements to justify exemptions or lower tiers of scrutiny, vs. requiring event-by-event

evaluation as though each insertion gave rise to a unique pesticide (as we do now for PIPs)? Is there a biological reason to treat HIGS as a pesticide at all given it's extraordinary specificity and use of natural pathways for gene suppression vs. the production of exogenous toxins? Can we create regulations and regulators who can act on this critical difference? For forest trees, where we rarely make use of Mendelian traits due to difficulty in breeding (a result of delayed onset of flowering and inability to inbreed/introgress), RNAi and CRISPR technologies could perhaps be game changers. But not in a world of regulatory uncertainty and unknowable cost and delay, where companies are forced by regulations and linked market forces to avoid rather than to embrace them.

In summary, with the growing power of genomic, physiological, and biotechnology

science the potential for new and more diverse types of GE products seems considerable. However, I believe it will take a revolution in regulation to produce an environment where companies or public sector scientists see fit to seek approval to market many of them. And nowhere is this more true than for trees and biofuel crops. While I understand that regulations are affected by public perception far more than science, and GMOs continue to be stigmatized by the market and social media in the USA and beyond, it is my hope that we can find a way to make regulations far more science based than we have today. And as you have heard, to me this means product-, benefit-, and familiarity-based, rather than method-based. In a world that needs all the technological help it can get, the opportunity costs of continuing on the current regulatory path seem irresponsible at best.

Good luck in your deliberations.