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**Risks and Regulation of Products of Synthetic Biology Products**

Dr. Gutmann, distinguished Members of the Commission:

Good morning. Thank you for the invitation to speak with you today. You've asked me to address the adequacy of the current biotechnology regulatory system as it might apply to the biosafety and environmental risks of first generation synthetic biology products. My comments here are drawn from an initial study on this question that I did last year for the Woodrow Wilson International Center for Scholars' program on synthetic biology. (A copy of this study is in your background reading packet.)

In general, existing laws and regulations that cover biotechnology would also apply to synthetic biology products. Since the first generation of synthetic biology products are likely to be relatively simple and similar to "conventional" genetically-engineered organisms, they are unlikely to raise novel risk assessment or risk management issues. But as the technology continues to develop and synthetic organisms become more complex and more artificial, it could become more difficult to assess the potential risks of organisms, particularly for those that are intended for use in the environment. Faced with uncertainty, regulatory agencies will be in a difficult position balancing benefits and possible harms under different laws.

**What's New about Synthetic Biology?**

As noted in the discussion yesterday, many of the issues before the Commission are strikingly familiar to the decade-long debate following the development of recombinant DNA transformation techniques in the 1970s. Concerns about biosafety motivated molecular biologists to convene at Asilomar in 1975 and led to the promulgation of the NIH research guidelines. Questions about the potential environmental impacts of a genetically engineered microbe in the early 1980s led the Environmental Protection Agency to assert its regulatory authority, ultimately leading to the development of a coordinated regulatory framework in the mid 1980s.

So while we may take some comfort from the fact that we have been at these issues for a quarter of a century and more, the recent announcement from the Venter Institute, along with other developments in the field of synthetic biology

and genomics, raises the question whether we have crossed some technological divide into novel territory.

In part the answer to that question depends on the further question, “novel compared to what?” Obviously, synthetic biology and synthetic genomics have been built on prior accomplishments in genetic engineering, systems biology, and information technology, and it’s hard to argue that this emerging set of tools represents a sharp break from what has gone before. Many practitioners see these new tools simply as the next logical extension of genetic engineering.

Yet simply because we can’t identify a sharp line between new and old does not mean that there are no significant differences between recombinant DNA technology and the emerging tools of synthetic biology. The most important difference is that genetic engineers are no longer limited to shuffling around the set of genetic sequences that nature has evolved over time or those that they can randomly generate through mutation and selection in the laboratory. Synthetic biology could give scientists the ability to design genetic code from the ground up, or to alter portions of an organism’s genome with entirely novel genetic code written in the laboratory. Above all, synthetic biology provides a new toolbox that makes genetic engineering much easier to do.

While there are therefore significant differences between older genetic engineering and the new toolsets of synthetic biology, the kinds of risks we are concerned about are largely the same. One issue is whether the technology can be used to inflict intentional harm by making it easier to develop more potent bioweapons. A second issue is biosafety, the risk that accidental exposure to an infectious or toxic engineered organism could harm laboratory workers or nearby communities. A third set of concerns is about environmental impacts, from both intended and accidental releases of an engineered organism into the open environment. Finally, there are concerns about the safety of final products (such as drugs) that might be produced using engineered organisms. Though the kinds of risk are the same, the relevant question is whether there is something about synthetic biology or synthetic genomics that changes the degree of risk or makes it more difficult to assess or manage. In this presentation, I’ll focus primarily on the issues around biosafety and environmental concerns.

### **Biosafety Issues**

Let me address first some of the biosafety concerns in a bit more detail.

The risks of working with pathogenic or infectious engineered organisms in a laboratory is not an issue limited to engineered organisms; researchers work with dangerous naturally occurring microbes all the time. Laboratory biosafety practices are designed to prevent exposure to lab workers and to prevent the release of such organisms outside a controlled environment through physical and biological containment measures. The NIH and the CDC issue biosafety guidelines for microbiological laboratories, and the Occupational Safety and

Health Administration regulates some blood-borne pathogens in some workplaces.

We generally understand the risk characteristics of known pathogens and can determine the appropriate level of biosafety protections. The particular challenge for novel engineered organisms is determining in advance how dangerous they are in order to know what level of biosafety precautions need to be taken. For recombinant DNA technology, the risk characterization is relatively straightforward, since one can identify the naturally occurring source of the engineered gene and determine its function. Synthetic biology makes this assessment more complicated. A synthetic microbe could be assembled from modified genetic parts taken from several different unrelated organisms or even from completely artificial sequences constructed in a lab. It's conceivable that the parts could operate in its new organism in unexpected ways: the engineered microbe could evidence emergent behavior. While unlikely, an engineered organism could have riskier characteristics than would be predicted from the understanding of its various engineered components.

For the last 30 years, the NIH's Guidelines for Research using recombinant DNA molecules have instructed researchers how to categorize the potential risk of engineered organisms and use corresponding measures of physical and biological confinement. As Dr. Patterson has told you, the NIH is working to amend those guidelines to apply them to the use of synthetic biology and synthetic genomics tools as well as recombinant DNA.

Those changes are commendable and will help ensure that research on the technology continues safely. The challenge, particularly as the technology develops and more complex organisms are developed, will be to develop guidelines that are sufficiently cautionary without imposing unnecessarily expensive and cumbersome containment requirements that could also stifle research. Ultimately, though, whether the guidelines work will depend on the institutional biosafety committees at universities and research labs that have the responsibility to implement them. We also need to understand whether research not covered by the NIH guidelines, such as entirely private-funded research, poses a significant problem.

### **Environmental Impacts**

The second area of concern again is not a new one: the potential environmental impacts of organisms that are intended for unconfined use, such as plants or microbes designed for bioremediation. There are a number of specific environmental risks:

- 1) An organism could directly or indirectly harm non-target organisms - beneficial microbes or insects or valuable plants and crops. An alternative scenario is that an initially benign organism could evolve virulence.

2) An organism could become invasive, reproducing rapidly and outcompeting other species and disrupting ecological balances.

3) An introduced gene could spread to a wild native population through horizontal gene transfer, resulting in widespread hybridization (what some have called “biological pollution”).

4) For traits intended to provide resistance (such as pesticides or antibiotics), the widespread use of the trait could lead to selective evolutionary pressure resulting in the development of resistance in the target population.

All of these scenarios depend upon an organism becoming established and successfully surviving in the environment. Most engineered microbes are unlikely to survive in the wild. Typically, the engineered trait exacts a biological toll on the organism, making it a feeble competitor. Most scientists believe that the more engineered or artificial an organism is, the less fit it is for survival in an open environment. Indeed, it has been the difficulty of getting an engineered microbe to retain its engineered trait and survive in the environment that explains the lack of successful genetically engineered microbial products intended for environmental use, such as oil-eating microbes.

But it is the concern about the potential irreversibility of an introduction of any new organism that argues for a cautionary approach. Unlike microbes intended for use in contained environments, such as bioreactors, synthetic organisms intended for uses in the open environment will have to be engineered to be hardy and fit for survival and to resist genetic drift.

In part for that reason, scientists have also developed a number of additional approaches to build in “biological leashes” that would kill the organism outside of a specific environment. While these risk management measures would make any establishment and subsequent harm highly unlikely, those risks are still not zero. (National Research Council) Such low-probability, high-consequence risk scenarios are notoriously difficult for making policy. Past experience suggests that it is not a strictly scientific question, and that policymakers will inevitably have to take into account the level of risk that is “acceptable” to society.

The NIH Guidelines generally address research in confined environments; commercial products intended for general use in unconfined settings are under the jurisdiction of the various regulatory agencies, as discussed below.

### **Product Safety**

The final set of concerns is about the safety of products developed through these new technologies. In some cases the final product would include the synthetic organism, but in most cases the organism would be used simply as a platform for the production of a conventional chemical or drug. Would food derived from crops engineered through synthetic biology be safe to eat? Would new industrial chemicals derived from synthetic microbes be safe to use? Would new drugs or biomedical devices or diagnostics using synthetic biology

techniques be safe and effective? While these kinds of questions as applied to genetic engineering have certainly generated much debate over the last decade and more, they are the kinds of questions that regulatory agencies such as the Food and Drug Administration and the Environmental Protection Agency have significant experience in addressing.

### **Adequacy of the Regulatory System**

So what is this the regulatory system for biotechnology and how well has it dealt with this same risks?

In the early 1980s, as genetically-engineered products began to emerge from research labs into commercial use, the NIH recognized that it had no regulatory or enforcement authority with respect to commercial and non-research uses. In response, in 1986 the Office of Science and Technology Policy led an interagency process to develop, the "Coordinated Framework for the Regulation of Biotechnology." The Coordinated Framework, which has guided US biotechnology policy since that time, developed three important policy principles. The first principle was that the process of biotechnology was not inherently more risky than other conventional breeding or production processes. The second conclusion was that regulation should be based on the final product, not by the process by which it was made. The third conclusion was that regulatory agencies using existing laws could adequately assess and manage the risks of any then-anticipated biotechnology products.

As a consequence, the United States has adopted a technology-neutral approach to product regulation. So, for example, drugs are regulated by the Food and Drug Administration, pesticides are regulated by the Environmental Protection Agency, and new plant or microbial varieties intended for general use are reviewed for potential pest problems by the Department of Agriculture.

Despite the general principle, the regulatory agencies have had to engage in good bit of legal legerdemain to fit biotechnology products into laws that were written with different products in mind. So, for example, the EPA has had to figure out how to regulate a corn plant as a pesticide, the FDA how to regulate a genetically engineered salmon under the new animal drug laws, and USDA how to regulate a herbicide-resistant variety of soybean as a potential plant pest. Each agency has had to rewrite - and in some cases are still rewriting - their regulations to address technological developments. While some of these creative legal interpretations could be open to legal challenge, the government's authority to regulate biotechnology products has not been contested to date in large part because the biotechnology companies have every reason to cooperate with rather than confront the regulatory agencies.

It's also important to note that as a result of a technology-neutral approach, biotechnology products receive widely different levels of regulatory scrutiny depending on their intended application. Our laws presume that a few products are inherently risky, and therefore place the burden on the manufacturer to prove to the regulatory agency that a product is safe before it can go to market.

Such mandatory pre-market approval laws apply to products like new human and animal drugs, pesticides, and food additives. Most new products, though, are not required to get safety approval before marketing, although of course the companies remain legally responsible for product safety. So a new dietary supplement developed through synthetic biology will get the same level of regulatory review as any other dietary supplement, which is to say, none.

Despite more than 30 years of experience, there continue to be strong differences of opinion about the adequacy of the U.S. regulatory system for biotechnology. A number of public interest groups and scientists continue to believe that the regulatory system should be more rigorous, particularly with respect to food safety. Other observers, including many plant scientists, believe equally passionately that biotechnology is highly overregulated, creating barriers to entry for beneficial new products.

Even if it is not the regulatory system one would design if one had a blank slate, the regulatory system has, in my opinion, worked reasonably well. Valuable new biomedical and agricultural products have been successfully introduced without any evidence of any public health or environmental problems. One could argue that we've just been lucky or that we haven't looked hard enough for evidence of harm, and there is some force in those points. On the whole, however, the system, however imperfectly, seems to be working.

As a practical and political matter, the U.S. is unlikely to reconsider the product-based approach to regulation using existing laws. So how adequate is the current system to deal with likely first synthetic microbes used to produce commercial products like drugs and biofuels?

The initial question is whether existing law gives regulatory agencies clear authority to cover those kinds of products. As noted previously, the agencies have already stretched the interpretation of their authorities to reach recombinant DNA products, and both EPA and USDA will likely need to revise their regulations to cover synthetic microbes intended for open environmental use. Laws that incorporate more "functional" definitions, such as FDA's drug approval laws and EPA's pesticide laws, are on a stronger footing. For the most part, though, existing laws are likely to provide agencies with sufficient legal authority to review new products developed through synthetic biology tools. The Food and Drug Administration, for example, has broad authority to review the safety and efficacy of drugs as well as the process by which they are manufactured.

But even if the existing system covers synthetic biology products, the more difficult and more important question is whether the agencies have the resources and tools they need to assess and manage their potential risks. There is no a priori reason to believe that microbes engineered through synthetic biology are any more risky than those produced through recombinant DNA technology or other engineering techniques. And the first microbes engineered with synthetic biology are not likely to be appreciably different than the kinds of engineered organisms that regulatory agencies have previously

reviewed.

As synthetic biology develops, however, we can expect to see more complex and more novel engineered organisms. The more that organisms differ from their familiar natural counterparts and become more artificially complex, the more challenging it will become to assess in advance their potential impact, particularly when they are intended for release into an open environment. Risk assessment is critical because it determines the levels of containment, controls or monitoring that will be required for commercial use. Getting the regulation right under such conditions of uncertainty – neither over-regulating or under-regulating – is a difficult task for any agency.

It may be particularly difficult for EPA given its limited authority under the Toxic Substances Control Act (TSCA), the law that would cover synthetic organisms used in the environment to produce fuel (such as algae) or bioremediation. TSCA is a hybrid statute. Congress clearly did not want to require the chemical industry to submit thousands of potential new chemicals for EPA's approval before going to market. Yet it also wanted to give EPA the authority to control or prevent the introduction into commerce of new chemicals that could pose public health or environmental risks. As a result, section 5 of TSCA requires chemical manufacturers to notify the EPA before putting a new chemical substance into the marketplace or introducing a significant new use of an existing chemical. However, the law places the burden on EPA to show that the new chemical presents an "unreasonable risk" before EPA can impose restrictions. Since the law does not generally require the manufacturers to test new chemicals, EPA often has relatively little data on which to make an "unreasonable risk" determination. The flaws of TSCA have been amply discussed in other fora, but the point here is simply that EPA may be limited in its ability to gather information and make an informed risk assessment about new synthetic organisms intended to be used in the environment. These are the organisms that are likely to pose the most questions since they will be engineered to survive in the environment.

Since risk assessment is likely to become more difficult, it is all the more important to have effective controls for preventing the unintended spread of synthetic microbes in the event of unanticipated adverse impacts. Moreover, such controls will be necessary in order to do field-testing. The experience of agricultural biotechnology has not been reassuring. There have been numerous cases where low levels of unapproved genetically-engineered seeds have been found in the seed supply, and there has been widespread gene flow from GM crops. Our experience to date suggests that the goal of achieving 100% segregation of biologically active materials is infeasible with current approaches. New approaches for biological containment must be developed and tested to give regulatory agencies a set of risk management tools. But it is critical that such tools be publicly developed and tested and widely shared to avoid some of the concerns that arose with "terminator" technology in the context of genetically-modified crops.

Finally, it's important to note that everything discussed in this presentation so

far is totally irrelevant to the potential biosafety risks of “do-it-yourself” synthetic biology. The federal regulatory system presupposes a regulated industry and research institutions who are knowledgeable about their obligations and motivated to comply. Researchers doing synthetic biology research outside of institutional frameworks are unlikely to be aware of legal or biosafety requirements. As the tools and technologies become less costly and more widely available, the potential for unintended harm is real. There are no clear regulatory models for addressing these issues. State and local permitting requirements may be an approach, but such agencies lack the technical capacity to assess the risks of any proposed research activities. Efforts to screen orders for genetic sequences are focused on biosecurity concerns and select agents that would not necessarily capture all of the biosafety concerns. While efforts to develop voluntary codes of safe conduct for the DIY synthetic biology community are laudable, they are unlikely to be satisfactory in ensuring the safe use of the technology.

### **Conclusion and Recommendations**

In conclusion, I would make the following recommendations for the Commission:

- 1) The Federal government needs to conduct a full and transparent review of the current biotechnology regulatory structure to ensure that regulatory agencies have sufficient authority, tools and resources with which to assess and manage potential risks of likely future products of synthetic biology and synthetic genomics. The recent DOE grant to the Venter Institute, on which I will also be working, hopefully can provide a process for beginning to do that.
- 2) Federal research funding agencies, including the NIH and the National Science Foundation, should fund robust programs of risk assessment methodology and risk research on synthetic microorganisms in order to provide regulatory agencies with independent information on which to make regulatory decisions, particularly on organisms intended for release in the environment. Funding is also needed to develop, test, and assess the effectiveness of biological containment measures. Having truly effective biological controls could allow for conditional releases of synthetic organisms even where the risk assessment may have uncertainties. Unless risk research keeps pace with the development of the technology itself, agencies are likely to respond to uncertainty by overregulation, potentially keeping beneficial products off the market. But such research needs to be done in an open and transparent way in order to provide credibility and public engagement.
- 3) The Federal government needs to assess the biosafety risks of “DIY” synthetic biology research and work with a broad group of stakeholders including state and local governments to develop appropriate responses.

Synthetic biology and synthetic genomics offer the promise of harnessing

**biology to address some of our most pressing environmental and public health needs. Having a credible, effective regulatory system in place when commercial products begin to move through the pipeline is a key part of ensuring that society receives the maximum benefit of the technology while reducing any potential risks.**

**National Research Council, Biological Confinement of Genetically Engineered Organisms, National Academies Press, Washington, D.C. 2005.**