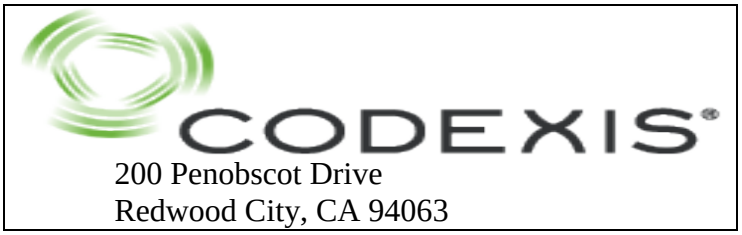

200 Penobscot Drive
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Response to 10/11/11 OSTP Request for Information

Introduction to Codexis

Codexis, Inc. (Nasdaq: CDXS) is an industrial biotechnology company, based in Redwood City, California, focused on developing biocatalysts that make manufacturing processes faster, cleaner and cheaper. Today, Codexis has 300 employees worldwide. Codexis is a two-time recipient of the EPA Green Chemistry Award for manufacturing processes for the blockbuster drugs Atorvastatin and Sitagliptin.

Codexis' key technology encompasses optimization of individual enzymes as well as entire host strains using the CodeEvolver™ directed evolution technology and developing integrated processes with these biocatalysts. Codexis serves major worldwide markets where clean technology can make a positive economic and environmental impact. The Codexis CodeEvolver ™ directed evolution technology accelerates development of high value sustainable products. Our focus is on the cost-effective conversion of renewable resources into transportation fuels, pharmaceuticals and biobased chemicals, and on the development of new technologies for effective air (*e.g.*, carbon capture) and water treatment. Codexis is also developing fatty alcohols for the detergent alcohol market that can also be processed into renewable diesel and jet fuel. Accordingly, all of Codexis' answers to this RFI are focused on the biofuels and biochemicals sectors of the bioeconomy.

Codexis thanks the Office of Science and Technology Policy ("OSTP") for this opportunity to offer our input on building the 21st Bioeconomy. If there are any questions about our submitted responses, or if Codexis can otherwise be helpful to the OSTP as it works to develop a National Bioeconomy Blueprint, please contact Jacques Beaudry-Losique, Vice-President, Corporate Development & Strategy, (phone) [redacted], (email) [redacted]

Question 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.

Considering that the United States has already developed the most advanced biomass-based chemicals and products technologies in the world, our country is well-positioned to lead the global economy in the bioproducts sector. According to the Biotechnology Industry Organization ("BIO") in testimony to the Senate Committee on Banking, Housing, and Urban Affairs on December 1, 2011, there are 1.42 million Americans directly employed in the

biotechnology industry. BIO has explained that "[t]he biotechnology industry has long been an engine for economic development and job creation across the country and our sector is working to add more high-wage high-skilled jobs to our workforce." As part of the biotech sector, the biobased products industry offers ample untapped growth potential. Sustained government support for near-term petroleum displacement through non-fuel bioproducts could create tens of thousands more jobs and high-value, exportable intellectual property to help revitalize the U.S. chemicals and plastics industry.

The potential for biobased products to help reduce our dependency on oil as well as deliver a better environmental future must be harnessed through a long-term commitment by the public and private sector. Some key incentives and policies Codexis would encourage the Federal government to commit to include:

(a) Maintain a strong Renewable Fuels Standard, implemented with continued vigor by the EPA.
(b) USDA programs (BCAP, others) which support a predictable second generation feedstock price, not to exceed a contractual level of $70/ton to the biofuels facility owners/operators.
(c) Easier Access to DOE National Labs expertise to support technology based commercialization bottlenecks, through quick turnaround contracts and attractive rates, with strong IP protections for the users.
(d) Availability of financial instruments to fund commercialization through a semi-private commercialization and development bank, on the model that exists in many other countries in the world (Brazil: BNDES), or even in the US (Ex-Im bank) for other uses.
(e) 10-years off-take supply agreements from DOD or GSA for both demonstration (2 million gallons per year or equivalent) and for pioneer commercial plants 20 million gallons per year or equivalent).
(f) Extend the $1.00 cellulosic tax credit expiring on December 31st 2012 for at least 5 years, and preferably 10 years.

Question 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?

There are two types of innovation opportunities to develop the bioeconomy:

(1) "Vertical" opportunities in which the government invests in end-to-end technology pathways that can produce specific outcomes or products, such as an innovative biological pathway to produce a specific fuel or chemical molecule from biomass feedstock, for example. This applied research consistent with the roles of EERE (lower risk approaches) or ARPA-E (game changing breakthroughs)..

(2) "Horizontal" or fundamental opportunities, in which the government could invest in technologies that facilitate innovation across the board, such as better characterization tools for micro-structures or enzymes – or in improving our fundamental knowledge of chemical catalysts. This is more the focus of the Office of Sciences or NSF, but these programs are often disconnected from the business reality of the private sector.

In the case of industrial biotechnology, we believe that many of the major bottlenecks to growing the bio-economy at this point in time are in the realm of applied research. However, a more cost effective approach would be to focus on specific high risk elements within pathways as opposed to funding entire pathways. As GHG and food concerns mandate a quick evolution of the industrial toward second generation feedstock such as agricultural and forestry waste and energy crops, we believe that a useful focus would be on the following elements:

Biomass pretreatment: the energy intensive biomass pre-treatment process, which treats biomass feedstock to make it easier of access by enzymes, involves a high quantity of solids, and is poorly studied and understood. As a result, replicability and reproducibility of the process are not at acceptable levels, and this drives higher capital, energy, and enzyme usage costs. This important process step, critical to the feasibility of using second stage biomass, has not benefitted from smart, focused government funding. We need better biomass pre-treatment predictive performance tools as well as industry access to a variety of scale-up conditions. We recommend a 5-years biomass pretreatment program designed in collaboration with industry.

Focus on big, large scale petroleum derived chemicals: While the government focus in recent years has been on biofuels, we would like the government to consider investing in applied research to fund new biological pathways to produce major hydrocarbon based chemicals such as ethylene, acrylic acid and some of the twelve major biobased "platform" chemicals identified by DOE National Labs in the past decade[1]. Not only would this displace a substantial amount of fossil fuels, but it would also speed up commercialization of profitable biochemicals, minimizing the long-term need for government support programs. Since biofuels compete in a cost-driven, high volume commodity market, they require far more initial government support than higher value biochemicals to become economically sustainable. Developing the biochemicals industry will also develop a supply chain nearly identical to that of biofuels, thus enabling to meet public policy objectives (energy security, climate change) at a far lower cost. Government investment should also be focused on technology pathways with the most promising LCA profiles, based on a full accounting, and discard investments on more "LCA-marginal" technologies and processes.

Focus on deployment: As hundreds of industrial biotechnology companies have emerged over the past five years, developing dozens of potentially attractive technology pathways, the government should now focus in integrating these technologies into the marketplace. The government could play a huge role by using its purchasing power (DOD, GSA) to provide long-term biofuels and bio-products off-take agreements (10+ years) to industry suppliers, enabling these companies to access financing sources.

Question 3. What are the critical technical challenges that prevent high throughput approaches from accelerating bioeconomy-related research? What specific research priorities could address those challenges? Are there particular goals that the research community and industry could rally behind (e.g., NIH $1,000 genome initiative)?

[1] Top Value Added Chemicals From Biomass, Produced by the Pacific Northwest National Laboratory (PNNL) and the National Renewable Energy Laboratory (NREL), 2004.

It is difficult to replicate biomass feedstock/pretreatment process combinations that deliver consistent substrates and compounds; thus, it is difficult to quickly validate our research approaches – because we are not getting reproducible results. Solids handling is also hard to scale and slows down our R&D throughput (see R&D recommendations in Question 2).

Another parameter that slows the scalability of second generation biomass is the presence of non-traditional sugars such as C5s. The C5 conversion rate is much slower than C6, because existing pathways are naturally C6 based. This prevents high performance, low cycle time end product production to occur, slows down scale-up efforts and drives higher capital costs.

Finally, the finishing steps of biofuels and bioproducts production require new product/impurities/water separation techniques which are complex, capital intensive and can reduce LCA benefits. This requires substantial applied research and engineering attention, and could also benefit from a 3-years DOE-industry research program.

Question 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?

Codexis does not agree with the premise of the question, with regard to industrial biotechnology, because sequence structure/function/production efforts are not the bottleneck to our commercialization efforts. We already have an excess of information to incorporate into our workflows. Codexis therefore recommends that what is needed is more multidisciplinary engineering-sciences collaboration to identify parameters need to be incorporated at lab level to ensure successful scale-ups.

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.

Codexis will focus on answers on industrial biology products, as opposed to pharmaceuticals or biotechnology products, which face a very different set of scale-up and regulatory challenges.

- The first challenge for biofuels and biochemicals is their competition with legacy pathways from fossil fuels or natural oils, whose production costs do not reflect their negative externalities (greenhouse gases, health, deforestation, *etc*.).
- The second challenge is the cost of R&D, driven by expensive equipment, specialized labor and extended development timelines.
- The third challenge is the cost of scaling up and demonstrating the technology, which can run in the tens of millions of dollars. Furthermore, even a successful scale-up only gives a firm the "option" to build a first-of-its-kind, highly risky pioneer plant.

- The fourth challenge is the lack of commercial project financing for biobased pioneer plants, which require hundreds of millions of dollars of equity and debt. This problem is compounded for second generation plants (from biomass) that require a capital-intensive pre-treatment and enzymatic "front-end", which adds to the cost and the risk of the facility. The only option for U.S. companies is to tap foreign countries with capital intensive development banks and location subsidies, at the price of locating their facility in a foreign country. This is why we see much of the industry locating their first facilities in Brazil and in Southeast Asia, instead of the U.S.
- The fifth challenge is the lack of built-in infrastructure for the new industry, be it for feedstock, or with regard to the finished product, especially with regard to biofuels. Legacy industries control the downstream infrastructure physically and contractually, based on investments made over the past century.

Question 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?

Not applicable to Codexis.

Question 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?

The Federal government could aggregate industry benchmark data on voluntary basis or on a mandatory basis (*e.g.*, with grant applicant or recipients). This would provide more performance transparency to the investment community as a whole. Such a list could include: feedstock type; conversion cost; enzyme cost; fermentation agent cost; LCA. The information would be sanitized so users could not determine the source of the information.

Question 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?

The two primary private sector models necessary to scale up promising bioeconomy firms are venture funding and project financing. While venture funding can bring an innovation to the verge of commercialization, it does not provide the capital resources needed to fund a first-of-its kind integrated biorefinery, which can cost in excess of $300 millions. Project financing is also a very difficult tool to apply, because it is premised on future cash flows, whose risks are mitigated by the presence of an off-take agreement for the product, a feedstock supply agreement, and a performance guarantee on the facility. Off-take agreements for fuels and chemicals do not have the terms length sufficient to support a long-term loan, and performance guarantees are impossible on "pioneer" plants because of the lack of historical statistical data on the technology performance.

The major steps that Codexis recommends that the agencies could take include:

- Use the government purchasing power to provide long-term off-take agreements (10+ years).
- Launch a quasi-governmental clean energy infrastructure bank with the authority to issue loans and loan guarantees to support the use of Project Financing.
- Protect the renewable Fuels Standards to ensure a government driven mandate to create market for biofuels.
- Look at developing a potential national labs role & expertise to validate new biofuels or product process technology and "certify" its potential performance. This information could be shared with prospective investors and lenders, but would not be available to the public at large.

Question 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

There is a huge scarcity of chemical and biochemical engineering graduates, and the government could help incentivize these disciplines by funding more internships. These internships would be very valuable as a preparation for private sector jobs. The government could also help foster more government-academic interactions.

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

Industry could use more hands-on research associates from community colleges, with current training in biotechnology, fermentation and engineering. These resources are very hard to find for the private sector.

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

The private sector needs to provide and invest in internal programs with discrete projects that could support a government sponsored internship program.

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

The national labs can encourage interactions between faculty, grad students and industry through creation of centers of excellence focused on bioenergy breakthroughs, such as the Joint BioEnergy Institute ("JBEI"). The JBEI is a San Francisco Bay Area scientific partnership led by Lawrence Berkeley National Laboratory. It includes the Berkeley and Davis campuses of the University of California, Sandia National Laboratories, the Carnegie Institution for Science, and Lawrence Livermore National Laboratory. JBEI's primary scientific mission is to advance the development of the next generation of biofuels — liquid fuels derived from the solar energy stored in plant biomass. See http://synbio.berkeley.edu/index.php?page=partners.

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.

In general, Codexis does not view regulations as a massive roadblock to bioinnovation. We believe that technology development and feedstock management or more critical path items pose the greater challenges. However, we provide the below list to demonstrate the kinds of regulations that impact Codexis bioinnovation activities and the implications of these regulations.

Clean Air Act RFS

Even though our biotechnology activities span beyond fuels to include chemicals and pharmaceuticals, we nevertheless believe that a strict interpretation of the RFS is the most important signal to investors that the Federal Government can provide. As a result, we support the strictest interpretation possible of the RFS within the language of the law. Furthermore, we believe that the RFS could benefit if it expanded from a strict focus on fuels production to a focus on the whole barrel of oil. For example, the production of chemicals from biomass that displace oil requirements are just as important for the nation's energy security and greenhouse gas emission balance than renewable fuels production. We believe that the RFS is a key tool to stimulate industrial biotechnology R&D activities, innovation and investment.

Clean Air Act Construction and Operating Permits

From an environmental permitting perspective, the critical path in permitting bio-refineries is the CLEAN AIR ACT Construction Permits. The federal government could show leadership and help the states by simplifying and expediting the review and approval of construction permits. This could be done without compromising air quality.

Codexis understands the requirements of New Source Review as a preconstruction permitting program. The applicable permitting requirements for Prevention of Significant Deterioration (PSD) requirements will depend on whether the proposed facility is a major or minor source and whether it is located in an attainment or nonattainment area. If the proposed facility is a major source, it will also require a Title V operating permit. We also understand that if our facility is in a Class I area, a Federal Land Manager (FLM) will have responsibility to review source impacts on site-specific air quality related values. Codexis also notes that in January, 2011, EPA announced that CO_2 emissions from biomass combusted at new and modified stationary sources will not trigger PSD permitting under the Clean Air Act for a period of at least three years. This has been made effective as of July 20th, 2011.

Clean Air Act New Source Performance Standards

It is important that EPA studies the impact of its New Source Performance standards on the permitting of biorefineries. Codexis understands that the New Source Performance Standards apply to new, modified, and reconstructed facilities in specific source categories identified by EPA that may apply to our downstream processing and finishing activities, such as hydro-treatment. A potential biorefinery, for example, would have to deal with permitting requirements for various components such as: Grain Elevator (Feed Handling); Stationary Gas Turbine; Small Industrial Steam Generator; Volatile Organic Liquids Storage; Sewage (Waste Water) Treatment; Petroleum Refinery, and VOC Emissions from Petroleum Refinery Wastewater Systems.

National Environmental Policy Act (NEPA)

Codexis understands that if a major federal action is involved in the siting of its proposed facility, NEPA requires that federal agencies have to assess the environmental consequences of their decisions before they undertake major federal actions that significantly affect the quality of the human environment. To help promote greater use of bioproducts, NEPA should be considered an integrated, expedited NEPA process to mitigate the financial and schedule risks to the applicants. Access to pre-permitted land on military or Federal Lands should be considered, as long as this does not add two or three years to the process, like the DOI Solar Programmatic EIS did with regard to Solar Concentrated Solar Power siting on Federal Lands.

Toxic Substances Control Act (TSCA)

TSCA regulates the manufacture and sale of chemicals. Of specific regulatory interest, Codexis uses genetically enhanced enzymes and organisms ("GMOs"), and may use feedstock derived from genetically modified seeds, approved for use in the United States. Codexis' plans for a first biorefinery project does not anticipate that such a project would have any changes to GMOs or other factors that would impact the ability to produce our bioindustrial products and/or biofuels at the projected volume and cost. Compliance with TSCA and other relevant requirements is a core component of Codexis' commercialization strategy.

EPA is considering reauthorization of TSCA. Although modernization of some of TSCA provisions are needed and generally recognized by industry and non-industry groups, these changes need to be done in a way that does not restrict innovation and does not compromise business confidentiality and intellectual property protection.

Energy Independence and Security Act (EISA), section 526

Section 526 requires that the life cycle green house gas ("GHG") emission of any fuel procured by the Federal government must be equal or below that of a conventional petroleum fuel. A lifecycle analysis ("LCA") of our green diesel fuel needs to be performed and compared to a baseline case of petroleum-based diesel. Codexis will use the GREET (Greenhouse Gases, Regulated Emissions, and Energy Use in Transportation) model that was developed at Argonne National Laboratory with support from the DOE's Office of Energy Efficiency and Renewable Energy.[2] There is still a lot of debate in the policy field on how to exactly do these LCAs and

[2] A very comparable study has been published by Argonne National Lab: ANL Report on Life-Cycle Analysis of Algal Lipid Fuels, August 2011. Download from http://greet.es.anl.gov/publication-algal_lipid_fuels.

make them comparable.[3] For instance, there are 13 studies on the LCA of fossil fuels and the GHG emission numbers that are reported in those studies differ by 30%. While we support the goals of Section 526, having more specific guidance from a government agency procuring fuel on how to address this issue in the response to a solicitation, and how the agency intends to evaluate responses in respect to compliance would be helpful.

Question14. What specific steps can Federal agencies take to improve the predictability and transparency of the regulatory system? (Please specify the relevant agency.)

Please refer to Codexis' response in Question 13 for suggestions regarding regulations. In addition, Codexis strongly recommends that having well written clearly stated and transparent processes for protecting intellectual property and business confidential information are key in providing the confidence to justify the large private sector R & D investments in biotechnological research. Without these assurances, we put our existing stakeholders' investments at risk and put unnecessary constraints on our ability to attract future investors. No one, of course, argues with the need for regulations to protect human health and the environment. This industry is based on reducing environmental impacts. However, to stimulate and encourage investment, the regulations need to be written and implemented in a way that supports innovation and protects intellectual property. Federal agencies have the opportunity to lead the way in this area.

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?

Codexis would respectfully suggest that Question 15 is not the right one and rather should be turned around to focus on the opportunities (vs. challenges) that new or emerging technologies represent to existing and proposed regulatory structures and the regulatory frameworks should be restructured to encourage these innovations. Existing regulations tend to be technology based on an emissions control approach. They are based on the assumption that there will be discharges to the environment and that adding controls at the end of the pipe is the way to reduce impacts to the environment. What if there was no "end of the pipes"? Regulations and the associated investment incentives could be written to encourage 'no discharge" technology and plant design. Regulations could also encourage biorefineries to be designed and built to produce multiple products such that the byproduct from one process in the raw materials for another, as opposed to strictly to penalize "discharges". Codexis suggest that there might be an opportunity for OSTP to work with regulatory agencies and convene stakeholders to "drill down" on potential new regulatory approaches.

[3]A description of LCA design is discussed in: AFRL-RZ-WP-TR-2009-2206 Advanced Propulsion Fuels Research and Development - Framework and Guidance for Estimating Greenhouse Gas Footprints of Aviation Fuels. Download from www.dtic.mil/dtic/tr/fulltext/u2/a513106.pdf.

Question 16. What are the highest impact opportunities for public-private partnerships related to the bioeconomy? What shared goals would these partnerships pursue, which stakeholders might participate, and what mutually reinforcing commitments might they make to support the partnership?

The Federal government needs to substantially increase its funding of R&D, and without picking "winners' and "losers", provide funds, national labs facility access and expertise to solve the scientific and technology bottlenecks that prevent the large scale production of bio-derived fuels and chemicals. These bottlenecks could be either identified through a series of workshops organized jointly by DOE, OSTP and NSF, or through RFIs and/or solicitations that would request private industry to identify major research projects around these bottlenecks, which could then be sorted by an expert merit review panel. For example, biomass pretreatment, as identified in our response to Question 2, is a critical bottleneck that the government could help address.

The Federal government has the ability to play a key role on infrastructure development, especially with regard to using second generation feedstock or biomass. The embryonic second generation feedstock market suffers from the lack of farmers' appetite for risk taking in an era of high commodity prices, the lack of collection and harvest tools for agricultural residues and new energy crops, and the lack of critical infrastructure, such as widened bridges and wider roads that are needed to accommodate the movement of millions of tons of biomass to the future biorefineries. Furthermore, investment in additional rail cars, loading and unloading docks, and pipelines will be necessary to accommodate the new production that will in large part come for biomass intensive regions such as the Midwest agricultural areas, the Great Plains, and the Southeastern and Western forestry areas. Codexis recommends a series of workshop on these topics involving DOE, DOT, USDA and OSTP, as a start. Further discussion on the role of CRP land would also be important, and should include entrepreneurs, farmers, NGOs and the Federal Government, especially the USDA.

Question 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? What can be learned from existing models for pre-competitive collaboration both inside and outside the life-sciences sector? What are the barriers to such collaborations and how might they be removed or overcome?

The industry supports the bioenergy center model funded by the DOE Office of Sciences, which work collaboratively through multidisciplinary partnerships to bring about new biobased products, methods and tools that the industry can use and other precompetitive elements of research. DOE established three Bioenergy Research Centers ("BRCs") in September 2007. The three centers are:

- DOE BioEnergy Science Center ("BESC") led by DOE's Oak Ridge National Laboratory in Oak Ridge, Tennessee.
- DOE Great Lakes Bioenergy Research Center ("GLBRC") led by the University of Wisconsin in Madison, Wisconsin, in close collaboration with Michigan State University in East Lansing, Michigan.

- DOE Joint BioEnergy Institute ("JBEI") led by DOE's Lawrence Berkeley National Laboratory.

Codexis highly recommends that these three bioenergy centers (JBEI, BESC and GLBRC) continue to be funded so that they can continue to inspire, support, and guide the biotechnology revolution.