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Food Safety and Inspection Service
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SUBMITTED ELECTRONICALLY VIA REGULATIONS.GOV

RE: Docket No. FSIS-2018-0036 for FSIS-USDA and FDA Joint Public Meeting on the Use of Cell Culture Technology To Develop Products Derived From Livestock and Poultry

Thank you for the opportunity to submit comments to the U.S. Department of Agriculture's (USDA) Food Safety and Inspection Service (FSIS) and the Food and Drug Administration (FDA) (collectively, the Agencies) on the safety evaluation, inspection, and labeling of cell-cultured meat derived from livestock and poultry.[1] We are grateful to FSIS and FDA for engaging stakeholders in a robust and open dialogue on these important issues. We appreciate the Agencies' commitment to enabling innovation and technological advances in the food sector while ensuring the safety of the resulting products and support the Agencies' commitment to clarify science- and risk-based regulatory policies to advance innovation and increase regulatory predictability.

As organizations committed to working toward the safe and efficient introduction of cell-cultured meat to the U.S. marketplace, we are heartened that FSIS and FDA are cooperating to clarify a pathway to market for cell-cultured meat under the Agencies' existing statutory authorities. We took great interest in the Agencies' recently announced plan to share oversight of these products in accordance with each agency's area of expertise in regulating cell-culture technology and livestock and poultry products.[2] We are confident that this plan can ensure that cell-cultured meat is safe and truthfully labeled.

Our comment first addresses the framework for oversight that the Agencies proposed on November 16, 2018 and then turns to the specific questions on which FSIS and FDA have requested comments, discussing how the Agencies can address hazards, provide adequate inspections, and ensure fair labeling. We recognize that the Agencies have requested comments

[1] Other commonly used terms include "cell-based meat," "cultured meat," and "clean meat." We use the term "cell-cultured" here to describe these products because it is the term the Agencies have used, but our comment should not be read as an endorsement of this particular term or as purporting to tell the Agencies which term is preferable for regulatory purposes.

[2] *See* Sonny Perdue & Scott Gottlieb, Statement from USDA Secretary Perdue and FDA Commissioner Gottlieb on the Regulation of Cell-cultured Food Products from Cell Lines of Livestock and Poultry (Nov. 16, 2018), https://bit.ly/2RBv4FT.

specific to food products made from livestock and poultry cells, but in light of the Agencies' expressed goal of reducing duplicative and inefficient regulation, where relevant we also address seafood created through cell culture technology (sometimes called cellular aquaculture), which generally would be under the sole authority of FDA.[3]

I. FSIS and FDA's Proposed Framework for Sharing Oversight of the Production of Cell-Cultured Food Products Derived from Livestock and Poultry Can Ensure Consumer Safety and Confidence.

We support the pledge made by FSIS and FDA to do right and feed everyone through technological innovation and the safe production of food.[4] As Secretary Sonny Perdue stated at the Agencies' October 23-24, 2018 joint public meeting "It's important that we have a framework that encourages innovation and new technology while we provide the responsibility of a public, safe, wholesome, and nutritious food supply."[5] These vital goals can be accomplished through the recently announced framework for shared oversight, under which FDA "oversees cell collection, cell banks, and cell growth differentiation" and FSIS oversees "the production and labeling of food products derived from cells of livestock and poultry."[6]

In our submission following FDA's July 12, 2018 public meeting, we outlined the reasons for the substantial public interest in cell-cultured meat.[7] These include lower environmental impacts and increased efficiency, vastly decreased risks of microbial contamination, and the avoidance of prophylactic antibiotics that contribute to the evolution of antibiotic-resistant pathogens, with a final product that is the same in its basic nature, essential characteristics, and composition as conventionally produced meat. American consumers deserve to have access to the healthy and sustainable dietary choices that cell-cultured meat, poultry, and seafood products can provide,

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[3] 21 C.F.R. § 123.3(d); *see also* FDA, Seafood Guidance Documents & Regulatory Information, https://bit.ly/2ti1f5x (last visited Dec. 14, 2018); *but see* Food, Conservation, and Energy Act of 2008, Pub. L. 110-246, § 11016(b), 122 Stat. 923, 21030-31 (2008) (placing farmed Siluriformes, or catfish, are under USDA jurisdiction). Further, it is worth noting, that FDA would also have jurisdiction over any products cultured from non-amenable land species not identified in the Federal Meat Inspection Act and the Poultry Products Inspection Act as well as any products created for consumption by pets, which at least one company is currently developing.

[4] *See, e.g.*, Transcript of FDA Public Meeting: Foods Produced Using Animal Cell Culture Technology, Docket No. FDA-2018-N-2155, 14, 24 (July 12, 2018), https://bit.ly/2PI10XO (hereinafter "Transcript of July 12 FDA Meeting").

[5] *See* Elaine Watson, *Cell-based Meat Cos: Please Stop Calling Us 'Lab-grown' Meat… and We Don't Use Antibiotics in Full-scale Production*, FoodNavigator-USA (Oct. 25, 2018), https://bit.ly/2q9ABHx.

[6] *See supra* note 2; *see also* USDA, *USDA-FDA Joint Public Meeting, Day 1, Morning*, YouTube (Oct. 23, 2018), https://bit.ly/2EmAErV (beginning at 0 mins. 51 secs.) (hereinafter "Joint Meeting Day 1 Morning Video").

[7] *See* The Good Food Institute (GFI), *Comment from The Good Food Institute, et al*, Docket No. FDA-2018-N-2155-0467, 2 (Sept. 25, 2018), https://bit.ly/2A0MaGF. We incorporate that comment in this submission by including it as Appendix A. On consumer interest, *see generally* Faunalytics, *Messages to Overcome Naturalness Concerns in Clean Meat Acceptance: Primary Findings* (July 2018), https://bit.ly/2D6MW8Z (Appendix B).

which is why a transparent and predictable regulatory path to market for these products is essential.

FSIS and FDA's plan for shared oversight lays the foundation for this path. This framework would establish FDA as the point of entry to the regulatory system for all cell-cultured meat products. This is consistent with the recommendation of a 2017 report published by the National Academies of Sciences, Engineering, and Medicine, that urged regulatory agencies to develop a single point of entry into the regulatory system for cell-cultured meat in order to streamline their regulatory approval process.[8] As we discuss below, FDA is well suited to conduct premarket safety evaluations of cell-cultured meat, poultry, and fish.

FDA additionally has the necessary expertise and experience to ensure the safety of the development of cell-cultured meat products through oversight of cell growth, cell banks, and cell proliferation and differentiation. FDA currently oversees facilities that produce food through cell culture and, as the agency has pointed out, it has extensive experience ensuring the safe production of microbial, algal, and fungal cells generated by large-scale culture in food.[9] As GFI's Director of Science and Technology Dr. David Welch explained in his comments to FDA's Science Board on October 22, 2018, the potential hazards associated with the production of foods using animal cell culture technology are not significantly different than those associated with the other forms of food production and processing that FDA already regulates, and there are well established controls to effectively mitigate against any risks to consumers.[10]

FSIS in turn has expertise under the Federal Meat Inspection Act (FMIA) and the Poultry Products Inspection Act (PPIA) to ensure the safety and accurate labeling of the meat and poultry products that result from the cell-harvest stage of cell-cultured meat production. Through inspection of processing and packaging facilities and review of labels for cell-cultured meat and poultry products, FSIS can ensure consumer safety and transparency while also ensuring, in the words of Secretary Perdue, that these products are "treated in the same fashion as . . . past products."[11]

II. FDA Is Well Suited to Oversee Premarket Safety Evaluations of Cell-Cultured Meat Products.

An effective and efficient way to ensure consumer safety and confidence without imposing unnecessary or duplicative regulatory barriers is for FDA to serve as the single point of entry to

[8] Nat'l Acads. of Scis., Eng'g, & Med., *Preparing for Future Products of Biotechnology*, 9, 141-44 (2017), https://bit.ly/2MG2Jes (Appendix C).

[9] *See* Appendix A at 3, n.8 (citing Transcript of July 12 FDA Meeting at 23; FDA, Notice of Public Meeting, Request for Comments, 83 Fed. Reg. 28238, 28238-39 (June 18, 2018)).

[10] *See* Dr. David Welch, *The Current State of the Cell-Based Meat Industry*, GFI (Oct. 22, 2018) (presentation slides) (Appendix D).

[11] *See* Joint Meeting Day 1 Morning Video.

market for all cell-cultured meat products, as the Agencies have proposed.[12] The Agencies already work together under a Memorandum of Understanding (MOU) to ensure the safety of ingredients used in the production of meat and poultry,[13] as well other MOUs similarly intended to coordinate the agencies' efforts, avoid duplication, and foster collaboration.[14] For ingredients that fall under the meat and poultry MOU, including those derived from meat and poultry as well as plant-based sources, FDA generally evaluates safety under its food additive authority or, if applicable, its color additive authority, pursuant to the Federal Food, Drug, and Cosmetic Act, while FSIS evaluates the suitability of the ingredient for its intended use under the FMIA or PPIA.[15]

As FDA is well aware, many new whole foods and ingredients enter the American market under the Agency's premarket program for food additives or foods that are generally recognized as safe (GRAS).[16] For example, Quorn (mycoprotein) is sold as "meat-free burgers and fillets and prepared meals (e.g., stir-fries, curries, and pasta dishes in which mycoprotein is the central component)" and received a "no questions" letter under FDA's GRAS program.[17] Similarly, foods derived from new plant varieties developed using biotechnology have entered the market under FDA's premarket consultation program, pursuant to FDA's food additive and adulteration

[12] *See* Biotech. Working Grp., 2017 Update to the Coordinated Framework, 7 (2017), https://bit.ly/2GoXilX (amending Office of Sci. & Tech., Exec. Office of the President, Coordinated Framework for the Regulation of Biotechnology, 51 Fed. Reg. 23,302 (June 26, 1986)) (hereinafter "the Coordinated Framework"). Such an arrangement would also be supported by the Coordinated Framework, which encourages federal agencies to coordinate to use their "existing statutory authorities and regulations to ensure the safety of the biotechnology products for their intended applications." *Id.* at 7. Although the Coordinated Framework is focused on products of genetic engineering or the targeted or in vitro manipulation of genetic information of organisms—not new substances created without genetic modification—the independent review conducted by the National Academy of Sciences on future biotechnology products repeatedly references cell-cultured meat, so it would be reasonable for agencies to look to this guidance in their approach to all cell-cultured meat. *See* Appendix C.

[13] *See* FSIS & FDA, MOU between FSIS and FDA Regarding the Listing or Approval of Food Ingredients, MOU 225-00-2000, 65 Fed. Reg. 33,330 (Jan. 31, 2000), https://bit.ly/2CnT1LQ.

[14] *See, e.g.*, AMS & FDA, MOU between AMS and FDA, MOU 225-75-4002 (1987), https://bit.ly/2rBcKBs (establishing procedures for the exchange of information and the coordination of activities so as to avoid duplication of effort in inspecting and sampling dry milk product plants); AMS & FDA, MOU between AMS and FDA, MOU 225-73-2007 (1973), https://bit.ly/2QO4E6D (outlining cooperative efforts between these two agencies regarding the inspection, sampling, and examination of imported raisins so that the responsibilities of both agencies can be efficiently carried out).

[15] *See* 21 U.S.C. §§ 348, 379(e), 434(g), 601(m); *accord* MOU between FSIS and FDA, *supra* note 13.

[16] *See, e.g.*, 21 U.S.C. § 321(f) (providing exceptions for GRAS substances, pesticides, and foods sanctioned for use prior to 1958); 21 U.S.C § 348; Linda S. Kahl, Ctr. for Food Safety & Applied Nutrition, FDA, Experience with GRAS Notices under the 1997 Proposed Rule, Docket No. FDA-1997-N–0020 (Nov. 4, 2010); Food for Human Consumption and Animal Drugs, Feeds, and Related Products, 57 Fed. Reg. 22,984 (May 29, 1992) (explaining the statutory framework for new foods and food ingredients particularly within the context of foods derived from new plant varieties); FDA, Microorganisms & Microbial-Derived Ingredients Used in Foods (Partial List), https://bit.ly/2PCzxX5 (listing certain foods and food ingredients derived from microorganisms that have been approved by FDA as food additives or generally recognized as safe) (last updated Jan. 4, 2018).

[17] FDA, Agency Response Letter to GRAS Notice No. 000091 (Jan. 7, 2002).

authorities.[18] FDA's guidance explains that when an ingredient normally derived from nature is produced by a new process, producers are encouraged to consult with FDA to determine "whether the resulting ingredient still falls within the scope of any existing food additive regulation applicable to the original ingredient or whether the ingredient is exempt from regulation as a food additive because it is GRAS."[19] Drawing on its extensive experience with food safety evaluation, FDA, in cooperation with cell-cultured meat producers, can effectively and efficiently ensure that these products are safe for consumers.

Finally, FSIS need not impose any premarket notification requirements, such as a new technology notification,[20] which would undermine the Agencies' shared goal of avoiding duplicative and inefficient regulation of establishments and products under both Agencies' jurisdiction.[21] As FDA has made clear, "the key factors in reviewing safety concerns should be the characteristics of the food product, rather than the fact that the new methods are used."[22]

III. The Potential Risks Associated with the Production of Cell-Cultured Meat are Well-Understood and Can Be Adequately Addressed by FSIS and FDA.

In their request for comments, FSIS and FDA raise several questions regarding animal cell culture technology relevant to an evaluation of safety, particularly related to foreseeable hazards and preventive controls. The core technology used for the production of cell-cultured meat is well understood and is described in detail in our previous submission to FDA.[23] In this section, we address the specific questions that the Agencies posed in their request for written comments.

A. There Are Well Established Controls to Effectively Mitigate Against Any Risks That May Be Associated With Cell-Cultured Meat.

The Agencies requested comment on the potential hazards related to cell-cultured meat. Fortunately, this production process poses no novel hazards. Safeguards already used in FSIS-

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[18] *See* Food for Human Consumption and Animal Drugs, Feeds, and Related Products, *supra* note 16; FDA, Guidance on Consultation Procedures Foods Derived From New Plant Varieties (June 1996, revised October 1997), https://bit.ly/2zM3vD2.

[19] *See* Food for Human Consumption and Animal Drugs, Feeds, and Related Products, *supra* note 16.

[20] *See* FSIS, FSIS Procedures for Notification of New Technology, 68 Fed. Reg. 6,873, 6,873 (Feb. 11, 2003).

[21] *See, e.g.*, *id*.

[22] *See* Food for Human Consumption and Animal Drugs, Feeds, and Related Products, *supra* note 16, at sec. I; *see also* FDA, Guidance for Industry: Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances, Including Food Ingredients that are Color Additives, 13 (June 2014), https://bit.ly/2OxQzWP (stating "[t]he manufacturing process of a food substance is considered for the purposes of safety assessment only insofar as it may affect the properties and safety of the finished product").

[23] *See* Appendix A.

and FDA-regulated facilities can mitigate risks and ensure the safe production of cell-cultured meat.

The primary potential hazard for cell-cultured meat is the introduction of adventitious agents, including bacteria, fungi, and viruses, through culturing components, human workers, or food packaging. Cell-cultured meat cell lines will be similar to those used in applications with FDA oversight, for which existing FDA guidance documents provide guidelines and well-established tests for adventitious agent detection.[24]

As we explained in our previous submission to FDA, closed-containment bioprocess designs developed for other industrial biotechnology applications, including those used to produce food processing aids like recombinant enzymes, in conjunction with stringent operational protocols, could be used to adequately minimize the risk of contamination.[25] Further, materials that come into contact with the cells during cultivation should be evaluated for suitability for food, just like any other processing aid or packaging material used in the food industry.[26]

Another potential hazard is that the cell culture process and conditions in the bioreactor might cause cells to create substances at levels different from those in an intact animal. Examples include: growth factors and other molecules produced by intra- and inter-cellular signaling; production of unintended or abnormal levels of metabolites; genetic and epigenetic drift that could alter protein expression levels; and endogenous retroviruses or other species-specific viruses, although any risk from such viruses is very unlikely.[27] These potential hazards are well understood and can be adequately mitigated through the use of preventive controls and monitoring methods. In particular, as with components of cell culture media and scaffolds, well-established and documented controls and assays — including polymerase chain reaction (PCR), chromatographic, and immuno-based assays — exist to detect abnormal levels of such substances and ensure that such deviations are brought back to suitable levels. Screening

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[24] *See, e.g.*, FDA, Guidance for Industry: Cell-Based Products for Animal Use (June 2015), https://bit.ly/2A4H8c4; FDA, Guidance for Industry: Content and Format of Chemistry, Manufacturing and Controls for a Vaccine or Related Product (Jan. 1999), https://bit.ly/2GxZKXL; FDA, Points to Consider in the Characterization of Cell Lines Used to Produce Biologicals (1987, revised July 12, 1993), https://bit.ly/2xGbuPY; FDA, Guidance for Industry: Characterization and Qualification of Cell Substrates and Other Biological Materials Used in the Production of Viral Vaccines for Infectious Disease Indications (Feb. 2010), https://bit.ly/2OsdbvB; FDA, Guidance for Industry: Enzyme Preparations (Jan. 1993, revised July 2010), https://bit.ly/2NINx0r; Int'l Conference on Harmonisation of Tech. Reqs. for Registration of Pharms. for Human Use, ICH Harmonised Tripartite Guidance: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products, 63 Fed. Reg. 50,244 (Sept. 21, 1998), https://bit.ly/2rMMR1O.

[25] *See* Appendix A.

[26] *Id*.

[27] *See, e.g.*, Marion Koopmans, Inst. of Med., *Food-Borne Viruses from a Global Perspective*, Improving Food Safety Through a One-Health Approach (2012), https://bit.ly/2HiYa70; Merten O.W., *Virus Contaminations of Cell Cultures - A Biotechnological View*, 39 Cytotechnology 91 (2002), https://bit.ly/2CpBsLi.

methods already exist to ensure the cell line you are using does not pose such a threat (upstream) and to detect such adventitious or oncogenic viruses should they arise (downstream).[28]

Thus, the potential hazards related to cell-based meat are not novel. While some commenters at the October 22, 2018 FDA Science Board meeting and the Agencies' joint public meeting raised concerns about purported genetically-modified cell lines used in meat production exhibiting characteristics of cancerous cells,[29] these claims are unfounded. There is no evidence that any potentially cancerous cells that might present in cell-based meat would pose a hazard. But even if there were, there are well-established controls and monitoring methods for oncogene expression that could be employed during the production process. To the extent that the Agencies wish to reduce or eliminate consumption of meat that contain expressed oncogenes,[30] they can test for oncogene expression during the manufacturing process, allowing for easier and more effective monitoring than would be possible with the conventional production of meat from animals.

B. Inspections under Each Agency Should Be Conducted in the Same Manner and with the Same Frequency as Other Facilities under Their Oversight.

The Agencies also asked about the type and frequency of inspections at cell-cultured meat facilities. Because the Agencies have decided to share oversight of cell-cultured meat and poultry in accordance with their areas of expertise, and because no aspects of cell-cultured meat production present unique risks or hazards not present in other forms of food production and processing under the Agencies' purview, it makes sense that each agency would inspect cell-cultured meat and poultry facilities in the same way it would similar kinds of facilities.

Each agency already requires producers to implement sufficient preventive control procedures to assure the safety of foods subject to the agency's respective oversight. Both agencies require analyses of hazards, plans for mitigating or preventing them that must be in place prior to beginning operations, recall plans, and recordkeeping to demonstrate compliance. Each agency also has specific expertise in its areas of oversight under the shared framework.[31]

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[28] *See, e.g.*, Points to Consider in the Characterization of Cell Lines Used to Produce Biologicals, *supra* note 24.

[29] *See* Neil Stephens et al., *Bringing Cultured Meat to Market*, 78 Trends in Food Sci. & Tech. 155 (2018), https://bit.ly/2B2SQ6L (calling for more research "to confirm or dispel uncertainties over . . . the safety of ingesting genetically-modified cell lines, as these lines exhibit the characteristics of a cancerous cell which include overgrowth of cells not attributed to the original characteristics of a population of cultured primary cells"). For references to this article in public comments, see oral remarks from Amanda Starbuck (Food and Water Watch) and Michael Hansen (Consumers Union). USDA, *USDA-FDA Joint Public Meeting, Day 1, Afternoon*, YouTube (Oct. 23, 2018), https://bit.ly/2EnUh33 (appearing at 39 mins. 10 secs. and 25 mins. 41 secs., respectively).

[30] To be clear, there is a significant difference between a cell expressing oncogenes and a cancerous lesion or tumor. An oncogene has the potential to create a tumor, but the presence of an oncogene does not indicate a cancerous lesion or tumor.

[31] USDA and FDA have worked to reduce redundancies, such as for dual-jurisdiction facilities. *See, e.g.,* 80 Fed. Reg. 55,907, 55,988 (Sept. 17, 2015). It is our hope that the agencies will work together to harmonize requirements for cell-cultured meat facilities as well.

FDA has extensive experience evaluating products produced using cell culture technology and inspecting the facilities in which these products are manufactured. With this experience, FDA can carry out the ongoing oversight of cell collection, cell banks, and cell growth differentiation of cell-cultured meat subject to the Hazard Analysis and Risk-Based Preventive Controls (HARPC) requirements. In particular, cell-cultured meat facilities would be manufacturing or processing[32] food, and they therefore would need to register with FDA[33] prior to beginning production and renew their registration every other year.[34] As registered facilities, they would thus be subject to HARPC. Compliance with HARPC for these facilities would require that they develop a written food safety plan, including preventive controls and procedures for their implementation.[35] Facilities will also need to comply with current good manufacturing practices in FDA regulations, especially related to contamination and allergen cross-contact.[36]

At cell-cultured meat and poultry facilities conducting pre-harvest stages of the cell-culture process,[37] HARPC requirements should be enforced through inspections carried out with the frequency determined by the Food Safety Modernization Act (FSMA).[38] During inspections of physical facilities, FSMA requires that inspectors verify compliance with regulatory requirements and current good manufacturing practices, and the wholesomeness of incoming source materials. They must also check processing procedures, the food safety plan, the supply-chain program (as applicable), records, and other compliance under HARPC.

Questions were raised at FDA's October Science Board meeting regarding the technical specifics of the bioreactor stage of cell-cultured meat production. As explained in our previous submission to FDA, the process of cell proliferation and differentiation will likely take place within large bioreactors. The two main types are stirred-tank and perfusion bioreactors.[39] Differentiation can be triggered by factors in the cell culture medium or by characteristics of scaffolding. Generally, transferring cells from a stirred-tank bioreactor to a perfusion bioreactor (with or without the addition of scaffolds and in combination with different medium components) will coincide with the differentiation from stem cells to differentiated cells. While stirred-tank bioreactors presently

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[32] *See* 21 C.F.R. § 1.227 (definition of manufacturing/ processing).

[33] 21 C.F.R. § 1.225.

[34] 21 C.F.R. §§ 1.230(a)-(b).

[35] *See* 21 C.F.R. part 117, subpart C.

[36] *See* 21 C.F.R. part 117, subpart B.

[37] Although FDA will also oversee facilities carrying out all stages of cell-cultured fish and seafood production, fish and seafood are subject to 21 C.F.R. part 123 (HACCP and other requirements) and are exempt from HARPC (21 C.F.R. part 117, subparts C, G).

[38] Furthermore, any cell-cultured meat or poultry facility that also processes or packages cell-cultured meat products post-harvest will additionally be subject to the significantly more frequent FSIS inspection schedule.

[39] Stirred-tank bioreactors are already widely used for large-scale suspension animal cell cultures. Tissue perfusion bioreactors, which permit cell retention during continuously perfused medium flow, will require additional engineering for scale-up.

allow for cells to take up approximately 1 to 5 percent of volumetric space, several other bioreactor types[40] could fundamentally increase the available surface area of cells to grow, which would allow for greater densities.[41]

Following cell proliferation and differentiation, cells will be harvested from bioreactors, the resulting tissue will be washed (to remove excess media), and any non-edible scaffolds will be removed. This final stage, when the cell-cultured meat has been harvested and any remaining traces of the culturing process have been removed, is the most logical point for the transition from FDA oversight to FSIS oversight for cell-cultured meat and poultry products.[42]

FSIS should ensure the safety of the products through enforcement of its Hazard Analysis and Critical Control Point (HACCP) requirements. Similar to the requirement that facilities register with FDA, any facility processing or packaging harvested cell-cultured meat and poultry products would first need to apply for FSIS inspection.[43] To receive a grant of inspection, facilities generally would be required to develop written Sanitation Standard Operating Procedures (SSOPs) to comply with FSIS's regulations on sanitation, which are similar to FDA's current good manufacturing practices, and require facilities to address grounds and facilities, equipment and utensils, sanitary operations, and employee hygiene[44] and to keep records (available to FSIS) to document compliance and corrective actions.[45] Facilities must also take corrective action when SSOPs fail to prevent direct contamination or adulteration of products.[46]

Next, the facilities would be required to develop HACCP plans, starting with a hazard analysis "to determine the food safety hazards reasonably likely to occur in the production process and identify the preventive measures the establishment can apply to control those hazards."[47] The facility also will need to validate their HACCP plans conduct ongoing verification activities, and reassess the plans at least annually.[48] Additionally, each facility would be required to "prepare and maintain written procedures for the recall of any meat, meat food, poultry, or poultry product

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[40] These include packed bed bioreactors and hollow fiber bioreactors, as well as microcarrier methods.

[41] Based on current technological capabilities, it is estimated that a 20,000 liter stirred tank bioreactor could produce approximately 3500 kilograms of cell-cultured meat per batch. However, current research in cell-culturing technology promises to increase that yield even further.

[42] Cell-cultured fish and seafood would remain under FDA oversight.

[43] *See* 9 C.F.R. §§ 304.1(a), 381.16.

[44] *See* 9 C.F.R. §§ 416.2-5.

[45] *See* 9 C.F.R. § 416.16.

[46] *See* 9 C.F.R. § 416.15.

[47] *See* 9 C.F.R. § 417.2(a).

[48] *See* 9 C.F.R. § 417.4(a).

produced and shipped by the official establishment."[49] Since facilities under FSIS oversight will be processing and packaging harvested cell-cultured meat and poultry products, any hazards requiring a HACCP plan will be, at most, no greater than those encountered in a conventional meat processing and packaging facility.[50] Hazards related to slaughter, such as pathogens present on live animals and in slaughter facilities, will not be present on cell-cultured meat and poultry products, which will be sterile when harvested. They are thus likely to have less risk of contamination by pathogens than conventional meat.

FSIS should enforce HACCP requirements through inspections carried out once per day and at least once during every shift that the facilities are open — the same inspection frequency as conventional meat processing facilities. Products that combine cell-cultured meat products with other ingredients should be inspected in the same manner as products that combine conventional meat with other ingredients.[51]

In conclusion, the hazards related to producing meat from cell culture are comparable to certain hazards for conventional meat, and FSIS has already identified well-established controls to effectively mitigate against these hazards.[52]

IV. FSIS Oversight of Labeling for Cell-Cultured Meat and Poultry Products Should Ensure a Fair and Level Playing Field for All Meat and Poultry Producers.

Finally, the Agencies asked how cell-cultured meat and poultry should be labeled. Fundamentally, the same rules should apply to all meat products, regardless of whether they are produced in the conventional manner or through cell culture technology and whether their labels are under FSIS's or FDA's purview.

The companies in this sector are committed to providing clear and truthful labeling that complies with regulatory requirements and addresses consumers' interests. Indeed, producers of

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[49] *See* 9 C.F.R. § 418.3.

[50] Such potential hazards include the presence, contamination, or outgrowth of pathogens and the presence of physical foreign materials. *See* FSIS, Meat and Poultry Hazards and Controls Guide, 32-56 (Mar. 2018), https://bit.ly/2Gfgsec.

[51] As outlined in FSIS's *Food Standards and Labeling Policy Book*, FMIA and PPIA and their implementing regulations "provide for certain exemptions from USDA jurisdiction (and, therefore, inspection), e.g., products prepared for human consumption that contain meat or poultry ingredients in relatively small proportions." FSIS has determined by policy that in the case of livestock ingredients, "relatively small proportions" means "3 percent or less raw meat; less than 2 percent cooked meat or other portions of the carcass; or 30 percent or less fat, tallow or meat extract, alone or in combination" and in the case of poultry: "less than 2 percent cooked poultry meat; less than 10 percent cooked poultry skins, giblets or fat, separately; or less than 10 percent cooked poultry skins, giblets, fat and poultry meat (limited to less than 2 percent) in any combination." Just as with conventional meat, facilities only making products within these percentages – such as soups and frozen pasta dishes – should be inspected by FDA. *See* FSIS, Food Standards and Labeling Policy Book (Aug. 2005), https://bit.ly/2vtncz3; *see also* 9 C.F.R. § 381.15(a) (regarding poultry).

[52] *See supra* note 47.

cell-cultured meat will have an incentive to communicate the nature of the product to consumers for a range of reasons, including growing consumer interest in food production and sustainability as well as explaining differences in price, given that cell-cultured meat products will be introduced at a higher price than conventional meat.[53] Cell-cultured meat companies will have every reason to ensure that their labels and marketing materials provide clear and accurate information to consumers so they know exactly what they are buying when they buy cell-cultured meat.

Cell-cultured meat is expected to be identical to conventionally produced meat in its basic nature, composition, and all other essential characteristics, so producers should be able to use meat-, poultry- and seafood-related terms on their labels. In reviewing labels for cell-cultured meat and poultry products, FSIS should apply the law equally to cell-cultured and conventional meat producers. In addition, to assure consistency across all cell-cultured products under federal labeling laws, FSIS and FDA should take a coordinated approach to labeling.[54]

Once FSIS assumes oversight of post-harvest cell-cultured meat and poultry products, these products should be subject to the same labeling requirements as conventional meat, including any additional labeling requirements that may be developed. Although no new labeling requirements are necessary for these products, any that are implemented — including statements of identity, information about production methods, and species origins of meat — should apply equally to both conventional and cell-cultured meat and poultry products to ensure consistent application of the law, consumer confidence, and to avoid prejudicial requirements that could disadvantage producers.

Cell-cultured meat products should thus be required to use meat nomenclatures such as beef, pork, and chicken like their conventional counterparts, as these products will be designed to meet the product-specific characteristics in terms of composition, species, origin, nutritional profile and other applicable characteristics. This is essential to both consumer safety and transparency. Of course, consumers want to know what they are buying, and if cell-cultured meat products were labeled as something other than meat, this would cause confusion and make it harder for consumers to make informed purchasing decisions.

This is especially critical because meat allergies to virtually every kind of animal tissue (including seafood, poultry, and mammalian tissue) afflict small but significant portions of the population, and failing to require cell-cultured meat products to have accurate meat nomenclature would also unnecessarily put the health — indeed, the lives — of these consumers at risk.[55] Furthermore, under the FMIA and PPIA, all ingredients used to formulate a meat,

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[53] Indeed, because of the benefits conferred by this kind of production process, some consumers will be willing to pay a price premium. See Bruce Friedrich, *Clean Meat Consumer Survey: Public is Hungry for Clean Meat!*, GFI (Aug. 1, 2018), https://bit.ly/2PQsZEe.

[54] The same principle applies to FDA in its enforcement of the FDCA's labeling requirements for products within its purview.

[55] *See, e.g*, Michael F. Sharp & Andreas L. Lopata, *Fish Allergy: In Review*, 46 Clinical Reviews in Allergy & Immunology 258 (2014), https://bit.ly/2rJ8sIg; Michael C. Zacharise, *Severe Allergy to Chicken Meat*, 105 Wis.

poultry, or egg product must be declared in the ingredients statement on product labeling.[56] On a related note, the species origins of cells should be required on labels in the same way that conventional meat products must accurately identify themselves. This is essential for transparency as well as consumer safety. Consumers should be able to identify the kind of meat they are purchasing, which is important both to consumers with meat and poultry and fish allergies, as well as those with religiously prescribed diets that require them to avoid meat from particularly species of animals. A product is misbranded under the FMIA and PPIA when it contains ingredients that are not declared on product labeling, so cell-cultured meat and poultry products would have to disclose that they are meat or poultry to avoid being misbranded.

Finally, under both FSIS and FDA labeling regimes, cell-cultured meat, poultry, and fish products should be held to the same labeling guidelines as their conventional counterparts.[57] However, as noted above, many cell-cultured meat companies do plan to distinguish their products from conventional counterparts with accurate terms like "cell-based" or "cultured," which should be allowed. Additionally, these companies should also be allowed to make additional claims about the reduced environmental impact of these products or their reduced risk of microbial contamination as long as these claims are supported by scientific evidence. FSIS regulations for prior label review require that labels with special statements or claims be submitted to the Labeling and Program Staff for review.[58] Special statements and claims subject to prior approval are "claims, logos, trademarks, and other symbols on labels that are generally not defined in FSIS regulations or the Food Standards and Labeling Policy Book."[59] Examples of logos and symbols relevant to cell-cultured meat and poultry products might include company logos or symbols that indicated the products' origins in cell culture, while special statements and claims might include processing method claims like "cell-based," "cultured," negative claims like "antibiotic-free," health or environmental claims, and claims regarding the treatment of

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Med. J. 50 (2006), https://bit.ly/2LdUIxY; Sheryl van Nunen, *Tick-Induced Allergies: Mammalian Meat Allergy, Tick Anaphylaxis and Their Significance*, 5 Asia Pac. Allergy 3 (2015), https://bit.ly/2rzLeUJ.

[56] *See* 9 C.F.R. §§ 317.2, 381.116, 318.118.

[57] Cell-cultured meat products should be required to use accurate meat nomenclature without also being required to disclose production methods, or if they are, then the same rules should apply to conventional meat products as well. FSIS has not required labeling to disclose production methods as long as the technology does not alter basic nature or essential characteristics of the product or other adversely affect nutritional quality or safety. *See* FSIS & FDA, Food Standards: General Principles and Food Standards Modernization, 70 Fed. Reg. 29,214, 29,222 (May 20, 2005), https://bit.ly/2T27Qt0 (explaining that regulations should not "stifle innovations in food technology" and instead should allow for "technological alternatives and advancements in food processing" that "permit maximum flexibility in the food technology used to prepare standardized foods, so long as that technology does not alter the basic nature or essential characteristics, or adversely affect the nutritional quality, or safety of the food"); FSIS, Meat & Poultry Labeling Terms (last revised Apr. 2011), https://bit.ly/2GwQnHM (explaining that "meat" includes meat products derived from advanced meat/bone separation machinery because such meat products are "comparable in appearance, texture and composition" to "similar meat products derived by hand").

[58] *See* 9 C.F.R. part 412.

[59] FSIS, FSIS Compliance Guideline for Label Approval, 7 (Aug. 2017), https://bit.ly/2GqlBQu.

animals like “slaughter-free.” Any special claims of this kind should be subject to the same evaluative process as claims made by conventional meat products.

V. Conclusion

Secretary Perdue astutely observed to reporters last month, "We don't want this new technology to feel like they've got to go offshore or outside the United States to get a fair regulatory protocol." The United States is currently home to some of the leading cultured meat companies, and the United States can and should play a leading role in bringing cell-cultured meat, poultry, and fish products to the global market in a way that is safe, efficient, and fair. FSIS and FDA's framework for shared oversight of cell-cultured meat and poultry products can facilitate that goal by helping to ensure producers are playing on a level playing field.

Thank you for the opportunity to provide comments on how the Agencies can regulate this industry by using science- and risk-based regulatory approaches under their existing authorities as well as their extensive experience. We appreciate your efforts to guarantee that all producers are playing on a level playing field. We look forward to continued dialogue.

Sincerely,

Carrie Chan
Co-Founder & CEO
Avant Meats

Ido Savir
CEO & Co-founder
SuperMeat

Lou Cooperhouse
President & CEO
BlueNalu, Inc.

Elan Abrell
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Peter Verstrate
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Appendix A

September 25, 2018

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

SUBMITTED ELECTRONICALLY VIA REGULATIONS.GOV

RE: Docket No. FDA-2018-N-2155 for Foods Produced Using Animal Cell Culture Technology; Public Meeting; Request for Comments

Thank you for the opportunity to submit comments on how the Food and Drug Administration (FDA) should evaluate the safety of clean meat (sometimes called cell-based meats or cultured meat).[1] We are grateful to FDA for engaging stakeholders in a robust and open dialogue on these important issues. We appreciate FDA's commitment to enabling innovation and technological advances in the food sector while ensuring the safety of the resulting food products. We also support the agency's commitment to clarify science- and risk-based regulatory policies to advance innovation and increase regulatory predictability.

We have come together to submit these comments to provide FDA with the best information available as the agency considers the appropriate regulation of clean meat and to demonstrate our desire to work with the agency and other stakeholders. Our organizations represent an array of interests united by the desire to see the safe and efficient introduction of clean meat to the U.S. marketplace.

We are heartened that FDA is considering a pathway for clean meat to come to market under the existing regulatory framework. The United States provides robust food regulatory oversight capable of ensuring safe and properly labeled clean meat.

Our comment first addresses the need for clean meat and the reasons that FDA is well situated to ensure its safety and then turns to the specific questions that FDA posed in its request for comments.

[1] Many companies in this space prefer the term "cell-based meats." The Good Food Institute has used the term "clean meat" for two years and continues to use the term for now, but is reevaluating the proper nomenclature for this kind of meat.

I. The Regulatory Path to Market Should Ensure Consumer Safety and Confidence Without Imposing Unnecessary Regulatory Burdens on Producers.

We support FDA's commitment to ensuring food safety while enabling technological advances in the food sector by, among other things, establishing a clear, risk-based, and predictable regulatory system.[2]

There is substantial consumer interest in clean meat[3] for numerous reasons, including lower environmental impacts and increased efficiency, which will enable the production of high-quality protein to feed a growing world population. In particular, clean meat converts inputs into meat much more efficiently than using livestock to convert feed crops into meat and thus requires significantly less land, water, fertilizer, herbicides, and pesticides. Because it does not produce manure, clean meat eliminates this source of air and water pollution (and its attendant harms to the local environment and communities). Clean meat production can be powered through renewable energy sources and is expected to produce lower emissions of greenhouse gasses. Moreover, clean meat requires less land than conventional meat production, and the land that is spared can be dedicated to the production of clean energy, which can power clean meat facilities — which could lead to meat that allows for the production of more energy than is required to produce it. Finally, clean meat will not require prophylactic antibiotics, so it will not drive the evolution of antibiotic-resistant superbugs.[4] Lastly, while clean meat is not substantially different from conventionally-produced meat in its basic nature and composition, it is produced in an aseptic or a sanitary/confined environment, which reduces the risk of microbial contamination.

For these reasons, over the past two years, "clean meat" has been the preferred nomenclature for this method of meat production;[5] however as indicated earlier, cell-based meats is the currently preferred term by many private companies that are operating in this sector. To be clear, we are not suggesting that this nomenclature be used in product labeling, but rather as a shorthand for describing the environmental and other factors that distinguish clean meat from conventional meat production. Individual producers will likely label their products with different terms based upon the composition of the finished product and other relevant product characteristics, working with the appropriate regulatory agency or agencies. This sector is committed to providing clear and truthful labeling that complies with regulatory requirements and addresses consumer interest.

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[2] *See, e.g.*, Transcript of FDA Public Meeting: Foods Produced Using Animal Cell Culture Technology, Docket No. FDA-2018-N-2155 at 14, 24 (July 12, 2018), https://bit.ly/2PI10XO (hereinafter "Transcript of July 12 FDA Meeting").

[3] *See generally* Faunalytics, *Messages to Overcome Naturalness Concerns in Clean Meat Acceptance: Primary Findings* (July 2018), https://bit.ly/2D6MW8Z (Appendix A).

[4] *See* Liz Specht and Christie Lagally, GFI, *Mapping Emerging Industries: Opportunities in Clean Meat* at 2 (June 6, 2017), https://bit.ly/2QCQdPZ (Appendix B).

[5] *See* Bruce Friedrich, GFI, *"Clean Meat" Is Catching On: A Reflection on Nomenclature* (May 24, 2018), https://bit.ly/2NiDBzr (Appendix C).

Producers will have a vested interest in communicating the nature of the product to consumers for a range of reasons, including growing consumer interest in food production and sustainability and explaining differences in price, given that clean meat products likely will be introduced at a higher price than conventional meat. Accordingly, clean meat companies will have every reason to ensure that their marketing materials provide clear and accurate information to consumers so they know exactly what they are buying when they buy clean meat.[6]

In a report published last year, the National Academies of Sciences, Engineering, and Medicine (National Academies) recommended that regulatory agencies develop a single point of entry into the regulatory system to streamline the regulatory approval process for clean meat and other products like it.[7]

FDA is well situated to implement National Academies' recommendation for clean meat products. As FDA explained in its public meeting on July 12, 2018, and in its meeting materials, the agency has the expertise to evaluate the safety of clean meat under its existing authorities. Clean meat facilities resemble food production facilities currently under FDA's oversight and, as the agency has pointed out, it has extensive experience evaluating microbial, algal, and fungal cells generated by large-scale culture that are used as food ingredients or in food production.[8] The agency also manages safety issues associated with animal cell culture manufacturing for therapeutic applications and, therefore, understands issues relating to cell and tissue development.[9]

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[6] Whether clean meat is "meat" comes up in two contexts: whether USDA has regulatory oversight authority based on the agency's regulatory definition of meat and the statutory definition of poultry, and whether clean meat will be able to use meat terms on labels. The disposition of the first issue does not determine the second: that is, clean meat could fall under FDA's purview rather than USDA's and still use meat terminology on the label. Plant-based meats, which are regulated by FDA, already lawfully use meat terms on their labels (with qualifiers or other disclosures).

[7] National Academies of Sciences, Engineering, and Medicine, *Preparing for Future Products of Biotechnology* at 9, 141-144 (2017), https://bit.ly/2MG2Jes (Appendix D).

[8] *See, e.g.*, Transcript of July 12 FDA Meeting at 23 ("For example, FDA has evaluated a variety of foods produced by cell culture, including microbial products such as probiotics, algal products such as spirulina and fungal products or the mycoprotein products as well."); FDA, Notice of Public Meeting; Request for Comments, 83 Fed. Reg. at 28238, 28239 (June 18, 2018) ("FDA will be involved in the regulation of foods generated by animal cell culture technology in light of our broad statutory authority and our extensive expertise and experience in relevant scientific areas. Currently, FDA evaluates microbial, algal, and fungal cells generated by large-scale culture and used as direct food ingredients . . . .").

[9] *See, e.g.*, 83 Fed. Reg. at 28239 (stating that FDA "manages safety issues associated with animal cell culture technology in therapeutic settings"); *see also* Transcript of July 12 FDA Meeting at 21-22.

II. Potential Hazards Associated with Production of Foods Using Animal Cell Culture Technology Are Comparable to Those Associated with Other Forms of Food Production and Processing that FDA Regulates.

In its request for comments, FDA asks what considerations specific to animal cell culture technology would be appropriate to include in evaluating food produced by this method of manufacturing. Fundamentally, our position is that the safety of the final product as consumed — the clean beef, poultry, chicken, seafood, or other meat — is the relevant consideration. As FDA explains in its guidance regarding assessment of the potential effects of changes in food manufacturing, safety evaluations should focus on assessing the identity, intended use, technical effect, and anticipated exposure of a food substance. Further, "[t]he manufacturing process of a food substance is considered for the purposes of safety assessment only insofar as it may affect the properties and safety of the finished product."[10]

Nonetheless, understanding the process by which clean meat is produced and the substances that are expected to be used in the production process should help FDA ensure that the final product is safe. Here, we answer the specific questions that FDA posed in its request for written comments.

- **What kinds of variations in manufacturing methods would be relevant to safety for foods produced by animal cell culture technology?**

The safety of the final product should be assessed in ways that are similar to other foods produced from (non-animal) cell cultures. While there may be variations in production methods or processes that may introduce, for example, different points of potential entry for contaminants, the relevant metric for consumer safety is whether the final product is free from contaminants under applicable standards and the production process otherwise meets good manufacturing practice and other applicable food safety requirements.

In some cases, the types of contaminants that are identified as potential hazards and for which controls are put in place may vary depending on the species or type of cell being cultivated or the conditions of the production environment. The most notable potential variations from a safety perspective involve the types of substances in which the cells will come in contact (see question below). For example, if a company is producing cells that will be used as an ingredient in downstream processes (to make a product like a sausage, for instance), there may not be any scaffolding material involved. Another example is that some production methods may involve microcarriers to which the cells adhere during the proliferation phase, whereas other methods

[10] FDA, Guidance for Industry, *Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances, Including Food Ingredients that are Color Additives* at 13 (June 2014), https://bit.ly/2OxQzWP.

may use cells that naturally grow in suspension. If microcarriers are involved, their safety as an edible component of the final product should be demonstrated, unless they are not present in the final product and this can be sufficiently demonstrated (either because they are degraded during or after harvesting, or because the separation technique to harvest the cells from the microcarriers is sufficiently selective).

- **What kinds of substances would be used in the manufacture of foods produced using animal cell culture technology and what considerations would be appropriate in evaluating the safety of these uses?**

Clean meat production will require up to three main material inputs: the cells, the cell culture medium, and the scaffold. Because the cells are derived directly from species and breeds that are routinely farmed for meat, they will physiologically mimic cells within animal muscle tissue. Thus, the final products should not have a substantially different safety or nutritional profile than conventional meat from the same species.[11] A cell culture medium will be required for all clean meat production, as it supplies nutrients to the animal cells to enable the cells to reproduce and create the biomass that will eventually be consumed. Scaffolds, which provide a support structure to help the cells create a desirable, meat-like texture, will be used by some companies for certain types of products, but are not as a rule required in clean meat production.[12]

The cell culture medium used by producers to date contains ingredients that are frequently used in food and for which food-grade suppliers are available. These ingredients include salts, sugars, and amino acids. These materials are already widely used in the food industry, and their safety is well understood and documented.[13]

The medium may also contain recombinant proteins and/or small molecules present at low concentrations. The recombinant proteins would be produced through methods currently used to make enzymes and other food processing aids routinely used in the food industry. In addition, the same host strains that are widely used to make such food enzymes likely will be used to manufacture recombinant proteins for use in the production of clean meat. While these proteins or molecules could be present in the final product at very low levels, FDA could require that any trace levels are not biologically active or are below a certain threshold that would ensure safety. As such, the methods for evaluating the safety of recombinant proteins should be the same as

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[11] Although not required for clean meat production, some companies may opt for genetic engineering, including recombinant engineering, of cell lines used in clean meat production or acquire cell lines derived from genetically engineered animals.

[12] *See* Elizabeth Specht et al., *Opportunities for Applying Biomedical Production and Manufacturing Methods to the Development of the Clean Meat Industry*, 132 Biochem. Eng. J. 161-168 (Apr. 15, 2018), https://bit.ly/2NkHC6s (Appendix E).

[13] *See generally* 21 C.F.R. parts 182, 184.

those used to evaluate recombinant proteins used in other food products, such as chymosin for cheese or pectinase for fruit juice clarification.[14]

Scaffolds for clean meat will be comprised of edible materials that may or may not biodegrade — and thus may or may not be present at detectable levels in the final product — during the manufacture of clean meat. These may include polysaccharides like alginate (derived from seaweed),[15] cellulose derived from plants,[16] or textured proteins derived from plant protein isolates, among other materials. These materials are already widely used in the food industry, and their safety is well documented.

- **Are the potential hazards associated with production of foods using animal cell culture technology different from those associated with traditional food production/processing? Is there a need for unique control measures to address potential hazards associated with production of foods using animal cell culture technology?**

FDA is well positioned to require that adequate preventative controls are in place to mitigate potential hazards and thereby ensure that clean meat is safe. As discussed during the FDA public meeting, the hazards and controls related to clean meat production are not substantially different from other foods developed using cell culture technology. These hazards and controls are well established and understood. Moreover, FDA has extensive experience evaluating products produced using cell culture technology, as well as inspecting the facilities in which these products are manufactured.

The primary hazards could include the introduction of contaminants at various stages in the production process, similar to other cell culture and fermentation technologies, and the introduction of unintended substances through food packaging, which is a common hazard in food production generally. Contamination should be monitored for each batch to ensure that adventitious agents are not present in the final product at harmful levels, as with any food product. Closed-containment bioprocess designs developed elsewhere in biopharma and other industrial biotechnology applications (including those for producing food processing aids like

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[14] *See, e.g.*, 21 C.F.R. § 184.1685 (FDA's regulation listing chymosin as generally recognized as safe); FDA, Substances Added to Food (formerly EAFUS), Pectinase from *Bacillus Subtilis*, https://bit.ly/2NXh5fa (last accessed Sept. 20, 2018); FDA, Substances Added to Food (formerly EAFUS), Pectinase from *Aspergillus Niger*, https://bit.ly/2MPuP6X (last accessed Sept. 20, 2018); *see also, e.g.*, FDA, Response Letter GRAS Notice No. GRN 000089 (Apr. 3, 2002), https://bit.ly/2xAF7T1.

[15] *See, e.g.*, 21 C.F.R. §§ 184.1187, 184.1724 (FDA's regulations listing calcium alginate and sodium alginate as generally recognized as safe).

[16] *See, e.g.*, 21 C.F.R. §§ 182.1480, 182.1745 (FDA's regulations listing methylcellulose and sodium carboxymethylcellulose as generally recognized as safe).

recombinant enzymes), in conjunction with stringent operational protocols, could be used to minimize the risk of contamination.

The animal cells will not be viable when they are sold in supermarkets or restaurants because animal cells have a very short period of viability when removed from culture. Therefore, there is no need to evaluate proliferation capacity or other living traits of the cells at the time of harvest or at point of purchase by a consumer. This is no different from meat derived from animal slaughter, where the animal cells themselves are non-viable at the point of consumption even if consumed raw.[17]

Finally, the materials that come into contact with the cells during cultivation should be evaluated for suitability for food, just like any other processing aid or packaging material used in the food industry. For example, it is possible that the early stages of the seed train will be cultivated in single-use polymer bags. These materials should be evaluated for leaching in the same way that food packaging is evaluated, with consideration given to the duration and conditions (such as temperature and pH) of contact with the material.

Conclusion

Cell culture technology will enable the production of high-quality protein foods without posing risks that cannot be managed effectively by responsible producers. FDA can regulate this industry by using science- and risk-based regulatory approaches under its existing authorities as well as its extensive experience to help ensure the safe production of clean meat.

This industry is committed to cooperation and transparency. We are excited about the opportunity to produce safe, efficient, and delicious foods for American consumers, and we look forward to continued collaboration with FDA as we prepare to bring our foods to market.

Thank you for the opportunity to submit these comments. We look forward to continued dialogue.

Sincerely,

Lou Cooperhouse, President & CEO, BlueNalu, Inc.
Peter Verstrate, CEO, Mosa Meat
Darren Henry Ph.D., Founder, Seafuture
Ido Savir, Co-Founder & CEO, SuperMeat
Jessica Almy, Director of Policy, The Good Food Institute
Liz Specht, Ph.D., Senior Scientist, The Good Food Institute

[17] The danger associated with raw conventional meat consumption is due to the presence of live bacterial contaminants, not from the animal cells themselves; clean meat will be devoid of these bacterial contaminants.

Appendix B

Messages to Overcome Naturalness Concerns in Clean Meat Acceptance: Primary Findings

July 2018

Authors: Jo Anderson & Chris Bryant

Research team: Jo Anderson (Faunalytics), Chris Bryant (University of Bath), Kathryn Asher (Animal Charity Evaluators; formerly Faunalytics), Che Green (Faunalytics), Kris Gasteratos (Cellular Agriculture Society), Bruce Friedrich (The Good Food Institute), Jeff Rotman (Deakin University), Jamie Macfarlane (The Good Food Institute).

Funding: We gratefully acknowledge Animal Charity Evaluators and the Animal Advocacy Research Fund for their assistance in funding this project.

Introduction

Studies of clean meat (also called cultured meat, in vitro meat, etc.) to date have found that consumers' willingness to eat it is uncertain (Pew Research, 2014; Slade, 2018; Surveygoo, 2018; The Grocer, 2017; Wilks & Phillips, 2017; YouGov, 2013).

One of consumers' primary concerns about clean meat is its alleged unnaturalness. This is a theme that has been seen in many qualitative studies (Laestadius, 2015; Verbeke, Marcu, et al., 2015) and cited as one of the most common reasons for rejecting clean meat in surveys (The Grocer, 2017). Indeed, Siegrist and Sütterlin (2017) have demonstrated that the perceived unnaturalness of clean meat explains a great deal of consumers' safety concerns. Further, Siegrist, Sütterlin, and Hartmann (2018) show that this perception evokes disgust and likely causes rejection of clean meat in practice.

Similar consumer concerns likely contributed to policies restricting the cultivation of genetically modified (GM) foods in Western Europe (Schurman, 2004). Thus, identifying effective strategies for addressing the appeal to nature may be crucial to the success of clean meat.

Contents

The goal of this study was to find ways of describing clean meat that could address naturalness concerns and increase acceptance of this new product. Participants read one of three messages intended to address those concerns or a control message similar to those currently in use. They then answered questions about their acceptance of clean meat: willingness to try it, beliefs about it, emotional reaction to it, willingness to pay for it, and more.

We looked at whether different messages produced more or less acceptance of clean meat, and at overall rates of acceptance in the study relative to previous studies. Successful aspects of these messages can be used by advocates, lobbyists, and others to promote clean meat. The ultimate goal is to reduce reliance on animal farming by encouraging as many people as possible to switch to clean meat once it becomes available.

Key Findings

This report describes all analyses in detail in the Results section. Below we offer the most noteworthy findings.

1. **Telling potential consumers about the unnatural side of conventionally-produced meat was effective:** Potential consumers who read about the unnatural conditions in which farmed animals are raised were convinced that conventional meat is unnatural.

2. **Describing conventionally-produced meat as unnatural produced the most acceptance of clean meat:** Potential consumers who read this message were willing to pay more for clean meat than those who didn't. People who read this message also tended to be the most positive about clean meat in a variety of other ways: in their attitudes, feelings, and beliefs.

3. **Trying to directly reduce naturalness concerns was ineffective:** The other two messages tested in this study—which described the natural side of clean meat and attacked the idea that naturalness is important, respectively—were not convincing to participants. Given that these messages were developed by subject matter experts with multiple rounds of feedback, these arguments may be difficult or impossible to use effectively.

4. **This study's messages produced more acceptance of clean meat than has been observed in many previous studies:** All participants read a short introductory description of clean meat, then saw one of four experimental messages. Both the description and the messages described clean meat in positive terms, indicating its aesthetic and nutritional parallels with conventional meat and its benefits for the environment, health, and animals. They also, of course, used the term "clean meat" rather than an alternative. All of these features produced rates of willingness to eat clean meat that were higher than those observed in most previous research.

Specifically, in this study, **66.4%** of people were willing to try clean meat, **45.9%** were willing to buy clean meat regularly, and **52.8%** were willing to eat clean meat as a replacement for conventional meat. In contrast, a similar study conducted by Wilks and Phillips (2017) that examined base rates of acceptance without positive messaging found a similar rate of willingness to try clean meat (65.3%), but substantially lower rates of willingness to eat it regularly (32.6%) and willingness to replace conventional meat (31.5%). Other recent studies that did not employ positive messaging have found lower rates of willingness to eat clean meat as well (e.g., Pew Research, 2014; Surveygoo, 2018). Despite differences in methodology across these studies, this provides some evidence that positive, educational messaging like ours may be effective in raising consumers' confidence in clean meat.

Further research will be needed to determine which aspects of this messaging are effective, as this study did not directly compare them. This type of research would be similar to studies conducted by Verbeke, Sans and Van Loo (2015) and Bekker, Fischer, Tobi and Van Trijp (2017) in Belgium and the Netherlands, respectively. In those studies, reading positive information about clean meat made participants more willing to try it and improved their attitudes toward it.

Methodology

Terminology

Throughout the present study, we used the term 'clean meat,' though it is also sometimes called 'cultured meat' or 'in vitro meat.' We made this decision because several studies have shown that consumer acceptance is likely to be highest when using this name (Animal Charity Evaluators, 2017; The Good Food Institute, 2017) and subsequently, many organizations manufacturing clean meat will likely use this term. Therefore, a study using this nomenclature is likely to have the highest external validity.

At the same time, this choice of terminology represents a more conservative approach: To the extent that the name 'clean meat' reduces feelings of disgust compared to other names associated with the product, its effectiveness may overlap with the experimental conditions, which are also intended to reduce disgust. Thus, using this name reduced the chance of detecting a difference in acceptance between the control and experimental conditions.

Sample & Procedure

Data were collected in January/February 2018. A census-balanced, representative sample of U.S. adults was recruited through the research firm Ipsos. Each person received Ipsos credit worth approximately $2 for their participation. The final sample of 1,185[1] people exceeded the 1,100 that our power analysis deemed necessary (details

Table 1. Demographic Characteristics of Sample

Full sample (*n*)	**1,185**
Female (%)	52.9
Age (Average)	47.3
Race/Ethnicity (%)	
White, non-Hispanic	64.8
Hispanic or Latino/Latina	13.8
Black or African American	12.2
Other races/More than one race	9.2
Region (%)	
Northeast	19.8
Midwest	20.6
South	37.3
West	22.3
Education (%)	
Less than high school graduate	1.6
High school graduate	35.7
Some college, no degree	27.3
Associate degree	5.6
Bachelor's degree	16.7
Master's degree	9.1
Professional or doctorate degree	4.0
Income (%)	
Less than $20,000	11.9
$20,000 to $39,999	19.7
$40,000 to $59,999	17.6
$60,000 to $79,999	14.9
$80,000 to $99,999	8.6
$100,000 or more	27.3
Diet* (%)	
Omnivore	91.8
Red meat avoider	3.5
Pescetarian	2.5
Vegetarian	1.4
Vegan	0.8

* Categories were extrapolated from a basic consumption question: "Which of the following do you eat at least occasionally?"

[1] A surprisingly high proportion of survey respondents were automatically ejected from the study for failing one of two basic attention checks: Of 1,648 people who started the survey, 463 (28%) were removed. Although this ensures that those who completed the study were paying attention, it may introduce a degree of selection bias and could be indicative of low panel quality.

are available in the research design document).

Demographic characteristics of the sample are shown in Table 1.

We used an experimental survey design to compare the efficacy of four different messages addressing the naturalness concern. The design and experimental procedure for this study were pre-registered with the Open Science Framework.

The study procedure was as follows: Participants were block randomized to one of four conditions based on gender and diet (two characteristics found to predict acceptance of clean meat in previous studies).[2] All participants answered questions about their familiarity with clean meat and read a brief passage describing it, to ensure that everyone's familiarity was equivalent before they received the experimental message.

The descriptive passage said: "Clean meat (also called cultured meat or in-vitro meat) is real meat which is grown from animal cells without the need to raise animals. It should not be confused with meat substitutes such as soy, since it is real animal meat: it has the same taste, texture, and the same or better nutritional content as conventionally-produced meat."[3]

The questions about participants' familiarity with clean meat are shown in Table 2. One preceded the descriptive passage, and one followed it, as indicated.

Table 2. Self-Rated Familiarity with Clean Meat

Question	Responses	Percentage (%)
Have you heard the term "clean meat" before? (It has sometimes been referred to as "cultured meat" or "in-vitro meat" as well)? *[asked before descriptive passage was provided]*	Yes No Unsure	25.1 59.7 15.3
Prior to this study, to what extent were you familiar with clean meat (including under another name, such as cultured meat or in-vitro meat)? *[asked after descriptive passage was provided]*	Not at all familiar A little bit familiar Moderately familiar Familiar Very familiar	64.1 21.3 7.8 4.4 2.5

Participants then read one of four experimental messages. Each one began with the same introductory paragraph, followed by one of the four messages about naturalness: an argument that clean meat is natural, an argument that conventionally-produced meat is unnatural so clean meat is preferable, an argument challenging the appeal to nature, or a control message about the

[2] No significant differences between experimental groups emerged on relevant demographic factors including age, gender, race, state, education, income, and familiarity with clean meat. This demonstrates that random assignment was successful.

[3] It is worth noting that the provision about taste, texture, and nutritional value has not been included in most previous research. It was included in this study to accurately reflect the conditions under which clean meat will come to market.

benefits of clean meat for health, the environment, and animals. The messages are shown in Table A-1 in Appendix A.

Following the experimental message, participants answered questions to examine whether the messages had the intended effect (called "manipulation checks"). They then responded to questions about their behavioral intentions, attitudes, beliefs, affective (emotional) reactions, and willingness to pay (WTP) for clean meat (chicken nuggets, beef burgers, and fish sticks). These measures are summarized in Tables A-2 and A-3 in Appendix A. For the full survey in context, with details of randomization, see the research design document.

Results

Details of the statistical analyses are provided in Appendix B. For the full set of pairwise comparisons for self-report variables, see Appendix C.

This section of the report shows the average response to each message for each outcome variable. **When the average for one of the experimental messages was significantly different from in the control condition, it is presented in bold.**

Did Participants Believe the Experimental Messages?

Analyses of the manipulation checks revealed that the experimental messages produced mixed results, as described below. Table 6 shows the average response to each message.

Table 6. Manipulation Check Averages

	Clean meat is natural	Conventional meat is unnatural	Challenging appeal to nature	Control
Perceived unnaturalness of clean meat	3.0	2.9	3.0	3.0
Perceived unnaturalness of conventional meat	2.6	**2.8**	2.5	2.5
Perceived importance of naturalness	3.9	3.8	3.7	3.8

Response options ranged from 1 (*strongly disagree*) to 5 (*strongly agree*). Bold = significantly different from control.

Perceived unnaturalness of clean meat

If the messaging was persuasive, participants in the 'clean meat is natural' condition would have been less likely to perceive clean meat as unnatural than in the control condition, but there was no significant difference, as shown in Table 6. This finding strongly suggests that our attempt to convince participants of the naturalness of clean meat was unsuccessful.

Given that no significant condition differences emerged, we considered the top-line results, which indicated that concerns about the naturalness of clean meat were held by only a minority of participants. Across all conditions, **34.1%** agreed or strongly agreed with the statement that "clean meat is unnatural," while **34.2%** disagreed or strongly disagreed, and **31.6%** neither agreed nor disagreed.

Perceived unnaturalness of conventional meat

As shown in Table 6, the manipulation check supported the success of the persuasive messaging arguing that conventional meat is unnatural: Participants in that condition were significantly more likely to perceive conventional meat as unnatural than in the control condition.

Considering the results across all participants and conditions, **20.0%** agreed or strongly agreed with the statement that "conventionally-produced meat is unnatural," while **48.9%** disagreed or strongly disagreed, and **31.1%** neither agreed nor disagreed. However, it is important to note the significant variation by condition, as shown in Table 6.

Perceived importance of meat naturalness

If the messaging was persuasive, participants in the 'challenging the appeal to nature' condition would have been less likely to perceive naturalness as important than in the control condition, but the difference between these two means was not significant, as shown in Table 6. This finding suggests that our attempt to convince participants that naturalness in meat is unimportant was relatively unsuccessful.

Considering the results across all participants and conditions, **65.8%** agreed or strongly agreed with the statement that "it is important for meat to be natural," while only **8.6%** disagreed or strongly disagreed, and **25.7%** neither agreed nor disagreed. However, there was again significant variation by condition that must be noted, as can be seen in Appendix C. Differences between the control and experimental conditions were not significant so they are not described here.

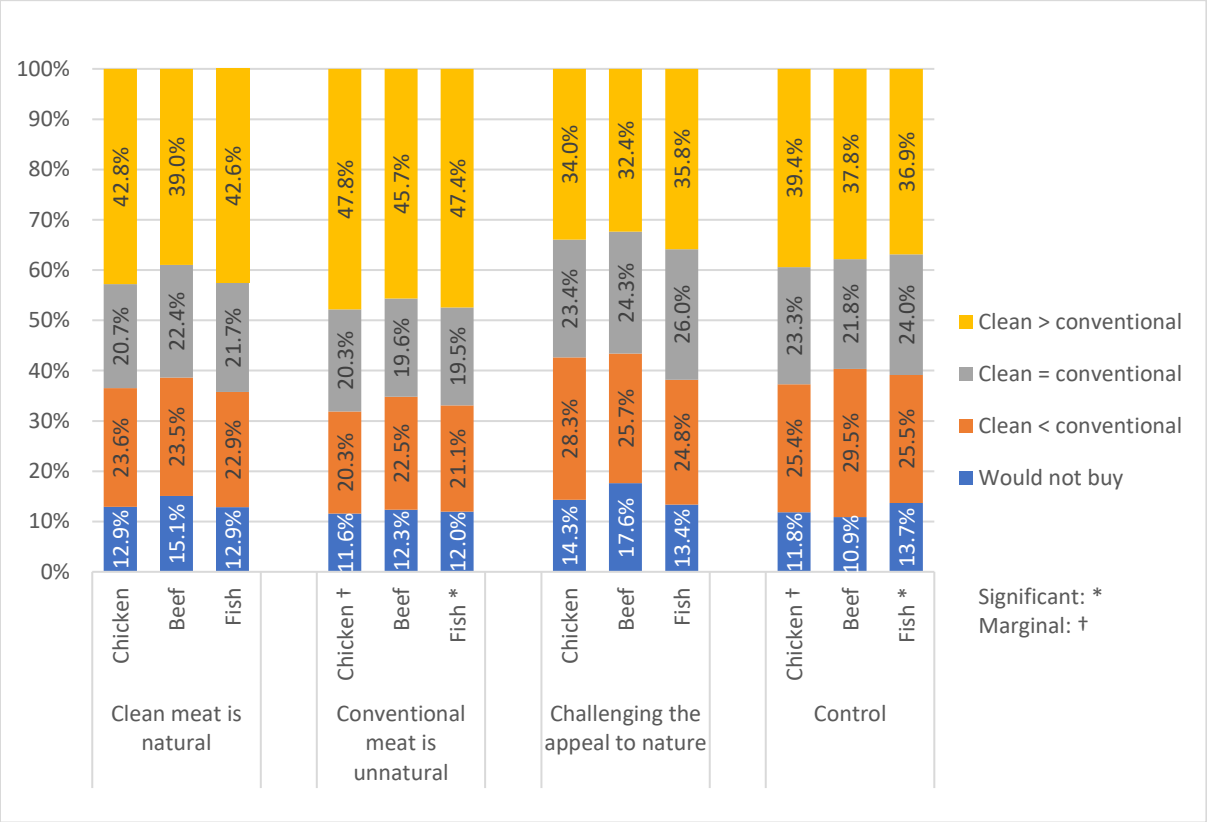
Willingness to Pay (WTP) for Clean Meat

Figure 1 shows participants' WTP for clean meat. It shows the results separately for each of the four messages tested and three hypothetical clean meat products. As the graph indicates, all three products showed similar results. Although we analyzed them separately, that overall pattern should be considered. Using the significance conventions laid out in Appendix B, several findings are worth noting.

First, relative to the control condition, people in the 'conventional meat is unnatural' condition were willing to pay significantly more for fish (p = .03; indicated with *) and marginally more for chicken

(p = .08; indicated with †). The findings for beef, while non-significant (p = .13), were in the same direction.[4,5]

Figure 1: Willingness to pay for clean meat relative to conventional meat



We know that advocates and manufacturers of clean meat would like a better idea of the actual amounts people will be willing to pay. Because of this keen interest and the lack of available data, we will provide rough estimates in a follow-up blog post. Although we hope this analysis will be useful, it is also quite speculative, with several important limitations to bear in mind.

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[4] Of less relevance to advocates, people in the 'conventional meat is unnatural' condition were willing to pay significantly more than in the 'challenging the appeal' condition for chicken (p = .002) and beef (p = .002), and marginally more for fish (p = .03; marginal at the Bonferroni-corrected post-hoc alpha level of .0167).

[5] To ensure that these results are not reliant on the particular analysis we chose, we also conducted non-parametric tests comparing the median WTP for each product in the experimental conditions against the control condition. The analyses comparing conventional meat is unnatural to control were marginally significant for chicken, beef, and fish (ps < .06), which supports the results of our main WTP analysis. Neither of the other two experimental conditions differed, significantly or marginally, from the control condition.

Behavioral Intentions

The average self-reported willingness to try clean meat and other behavioral intentions items mirrored the pattern of the WTP findings above, but none of the differences were significant. The average responses for each message are shown in Table 7. For full details, see Appendix C.

Table 7. Average Behavioral Intentions

	Clean meat is natural	Conventional meat is unnatural	Challenging appeal to nature	Control
Willingness to try clean meat	3.8	4.0	3.8	3.9
Willingness to buy clean meat regularly	3.5	3.6	3.4	3.5
Willingness to eat clean meat as a replacement for conventional meat	3.5	3.7	3.5	3.6
Willingness to eat clean meat compared to plant-based substitutes (current consumers, *n* = 381)	3.7	3.8	3.5	3.7
Willingness to eat clean meat compared to plant-based substitutes (non-consumers, *n* = 804)	3.8	3.9	3.8	3.8

Response options ranged from 1 (*definitely no*) to 5 (*definitely yes*).

Table 8 shows a breakdown of the responses for each of the behavioral intentions items. Overall rates of acceptance were fairly high.

Table 8. Behavioral Intentions Responses

Question | Sample		Responses	Percentage (%)
Would you be willing to try clean meat?		Definitely yes	33.8
		Probably yes	32.6
		I am unsure	21.6
		Probably no	6.1
		Definitely no	6.0
Would you be willing to buy clean meat regularly?		Definitely yes	17.5
		Probably yes	28.4
		I am unsure	37.7
		Probably no	8.9
		Definitely no	7.5
Would you be willing to eat clean meat as a replacement for conventionally-produced meat?[1]		Definitely yes	17.8
		Probably yes	35.0
		I am unsure	30.4
		Probably no	9.4
		Definitely no	7.5
How willing would you be to eat clean meat compared to plant-based substitutes (e.g., soy)?	Current eaters of plant-based substitutes (*n* = 381)	Much more	24.4
		Somewhat more	32.3
		Neither more nor less	28.9
		Somewhat less	8.4
		Much less	6.0
How willing would you be to eat clean meat compared to plant-based substitutes (e.g., soy)?	Current non-eaters of plant-based substitutes (*n* = 804)	Much more	28.2
		Somewhat more	34.5
		Neither more nor less	27.1
		Somewhat less	4.4
		Much less	5.8

[1]For this question, participants were also given the option of selecting 'Not applicable (I do not eat conventionally-produced meat).' It was selected by 19 participants.

Specifically, in this study, 66.4% of people were (probably or definitely) willing to try clean meat, 45.9% were willing to buy clean meat regularly, and 52.8% were willing to eat clean meat as a replacement for conventional meat. In contrast, a study conducted by Wilks and Phillips (2017) that examined base rates of acceptance without positive messaging found a similar rate of willingness to try in-vitro meat[6] (65.3%), but substantially lower rates of willingness to eat it regularly (32.6%) and willingness to replace conventional meat (31.5%).

Other studies that did not use positive messaging have also found low rates of willingness to eat clean meat. A few years ago, Pew Research (2014) estimated that 20% of U.S. adults would eat "meat that was grown in a lab" and YouGov (2013) found that 19% of UK adults would eat "artificial meat" (their terminology). More recently, the Grocer (2017) estimated that 16% of adults in the UK would buy clean meat (reported in Bryant & Barnett, 2018), and Surveygoo (2018) reported that 40% of U.S. adults and 18% of UK adults would be willing to eat clean meat.

[6] The term they used in the study.

Beliefs about Clean Meat

None of the experimental messages produced significantly more positive beliefs than the control message, although the 'conventional meat is unnatural' message performed better than the 'challenging the appeal to nature' message in several cases, as shown in Appendix C.

The only significant difference from the control message was on the belief that clean meat would be environmentally friendly: Participants who read the 'challenging the appeal to nature' message were significantly *less* likely to believe this.

The average responses for each message are shown in Table 9.

Table 9. Average Beliefs about Clean Meat

	Clean meat is natural	Conventional meat is unnatural	Challenging appeal to nature	Control
Clean meat is likely to be healthy	3.6	3.8	3.5	3.7
Clean meat is likely to be safe for human consumption	3.7	3.8	3.6	3.7
Clean meat is more environmentally-friendly than conventionally-produced meat	4.0	4.1	**3.9**	4.1
Clean meat is likely to look, taste, smell, and feel the same as conventionally-produced meat	3.6	3.7	3.5	3.6
Clean meat will have benefits for society	3.8	3.8	3.7	3.9

Response options ranged from 1 (*strongly disagree*) to 5 (*strongly agree*). Bold = significantly different from control.

Table 10 shows a breakdown of the responses for each of the beliefs statements. Overall, beliefs about clean meat were generally positive. It is also worth noting the relatively high rates of "neither agree nor disagree" responses. This suggests that a substantial proportion of the population has largely unformed opinions about clean meat and may be persuadable with education.

Table 10. Behavioral Intentions Responses

	Responses	Percentage (%)
Clean meat is likely to be healthy	Strongly disagree	3.5
	Disagree	5.9
	Neither agree nor disagree	34.1
	Agree	39.2
	Strongly agree	17.3
Clean meat is likely to be safe for human consumption	Strongly disagree	3.7
	Disagree	5.1
	Neither agree nor disagree	30.4
	Agree	41.2
	Strongly agree	19.7
Clean meat is more environmentally-friendly than conventionally-produced meat	Strongly disagree	2.6
	Disagree	3.0
	Neither agree nor disagree	21.9
	Agree	40.8
	Strongly agree	31.7
Clean meat is likely to look, taste, smell, and feel the same as conventionally-produced meat	Strongly disagree	3.5
	Disagree	10.3
	Neither agree nor disagree	30.0
	Agree	41.5
	Strongly agree	14.8
Clean meat will have benefits for society	Strongly disagree	3.5
	Disagree	5.6
	Neither agree nor disagree	26.2
	Agree	41.2
	Strongly agree	23.5

Attitude

None of the experimental messages produced significantly more positive attitudes than the control message, although again, the ‘conventional meat is unnatural’ message performed better than the ‘challenging the appeal to nature’ message (see Appendix C).

The ‘challenging the appeal to nature’ message produced significantly worse attitudes than the control message. This finding recommends not using this type of argument.

The average responses for each message are shown in Table 11.

Table 11. Average Attitudes toward Clean Meat

	Clean meat is natural	Conventional meat is unnatural	Challenging appeal to nature	Control
Attitude toward clean meat	4.8	5.1	**4.7**	5.0

Response options ranged from 1 (*extremely bad/unpleasant*) to 7 (*extremely good/pleasant*). Bold = significantly different from control.

Table 12 shows a breakdown of the responses for each of the two attitude items. Overall, attitudes toward clean meat were generally positive.

Table 12. Attitude Responses

	Responses	Percentage (%)
For me to eat clean meat would be…	Extremely bad	3.4
	Bad	2.3
	Somewhat bad	3.8
	Neither good nor bad	26.8
	Somewhat good	18.1
	Good	28.8
	Extremely good	17.0
For me to eat clean meat would be…	Extremely unpleasant	4.6
	Unpleasant	4.0
	Somewhat unpleasant	7.3
	Neither unpleasant nor pleasant	36.1
	Somewhat pleasant	17.3
	Pleasant	20.9
	Extremely pleasant	9.7

Affect

'Affect' refers to an in-the-moment emotional state. No significant differences in the affect composite (i.e., the average of the six affect items) emerged between conditions.

The average responses for each message are shown in Table 13.

Table 13. Average Affective Reaction to Clean Meat

	Clean meat is natural	Conventional meat is unnatural	Challenging appeal to nature	Control
Positive affect	3.4	3.6	3.4	3.5

The affect composite included three positively-worded items and three negatively-worded items. The items were coded so that higher scores represent more positive affect. Response options ranged from 1 (*not at all*) to 5 (*extremely*).

Table 14 shows a breakdown of the responses for each of the affect items. Overall, people felt fairly neutral about clean meat, showing no strong positive or negative bias.

One particular affect item—disgusted—is worth additional consideration, given its connection to the alleged unnaturalness of clean meat (Siegrist et al., 2018). Just 5.2% of participants said they felt extremely disgusted about the idea of eating clean meat, whereas 57.6% said they felt not at all disgusted. Disgust was low overall (M = 1.8) and did not differ significantly by condition.[7]

[7] All post hoc corrected *p*s > .22.

Table 14. Affect Items

Measure	Responses	Percentage (%)
Disgusted*	Extremely	5.2
	Quite a bit	5.1
	Moderately	10.1
	A little	21.9
	Not at all	57.6
Excited	Extremely	12.0
	Quite a bit	15.9
	Moderately	21.2
	A little	21.4
	Not at all	29.6
Anxious*	Extremely	5.2
	Quite a bit	12.3
	Moderately	19.1
	A little	30.4
	Not at all	33.0
Comfortable	Extremely	12.5
	Quite a bit	17.5
	Moderately	27.3
	A little	22.1
	Not at all	20.7
Ethical	Extremely	17.0
	Quite a bit	22.4
	Moderately	26.6
	A little	16.9
	Not at all	17.0
Immoral*	Extremely	4.0
	Quite a bit	4.7
	Moderately	9.9
	A little	16.2
	Not at all	65.2

*This item was reverse-scored for creating the affect composite.

Overall Pattern of Results: Supplementary Analysis

We created a composite variable representing overall clean meat acceptance for a supplementary analysis.[8] The goal of this analysis was to aid interpretation by providing an overall picture of the pattern of results for the self-report measures (essentially averaging all the results).

[8] Compositing is supported by a very high reliability score, $\alpha = .95$, and most correlations between predictors being 0.5 or greater (Song, Lin, Ward, & Fine, 2013). This composite was created by averaging standardized versions of all self-report outcome variables in the study: the attitude composite, the affect composite, the five cognitive beliefs items, and the four behavioral intentions items. The predictor variables used in this analysis were also standardized.

When all self-report measures are considered together, only one difference between averages was significant: Participants in the 'conventional meat is unnatural' condition were more accepting of clean meat than those in the 'challenging the appeal' condition (p = .008).[9] Thus, it is clear that of these two messages, arguing for the unnaturalness of conventional meat is the better choice.

Conclusions

This study's messages produced more acceptance of clean meat than has been observed in many previous studies. Specifically, in this study, **66.4%** of people were willing to try clean meat, **45.9%** were willing to buy clean meat regularly, and **52.8%** were willing to eat clean meat as a replacement for conventional meat.

In contrast, a similar study conducted by Wilks and Phillips (2017) that examined base rates of acceptance without positive messaging found a similar rate of willingness to try clean meat (65.3%), but substantially lower rates of willingness to eat it regularly (32.6%) and willingness to replace conventional meat (31.5%). Other recent studies that did not employ positive messaging have found lower rates of willingness to eat clean meat as well (e.g., Pew Research, 2014; Surveygoo, 2018). Despite differences in methodology across these studies, this provides some evidence that positive, educational messaging like ours may be effective in raising consumers' confidence in clean meat.

Further research will be needed to determine which aspects of this messaging are effective, as this study did not directly compare them. This type of research would be similar to studies conducted by Verbeke, Sans and Van Loo (2015) and Bekker, Fischer, Tobi and Van Trijp (2017) in Belgium and the Netherlands, respectively. In those studies, reading positive information about clean meat made participants more willing to try it and improved their attitudes toward it.

Experimental Messages

Although the experimental messages were developed with several rounds of consultation from researchers and industry insiders and were pretested for how well they conveyed the intended meaning, our checks suggested that only one of the three was truly successful in convincing readers of that message. Participants accepted the argument that conventionally-produced meat is unnatural, but not that clean meat is natural nor that naturalness should not matter.

Most notably, the 'conventional meat is unnatural' message performed best when participants were asked how much they were willing to pay for clean meat. When they read about the unnaturalness of conventional meat, participants were willing to pay more for clean meat than for conventional meat.

On the self-report measures, the argument that conventional meat is unnatural did not significantly out-perform a control message, although it produced the most positive results of the four conditions on almost all outcomes (see Table 6). The only significant difference was between the

[9] Pairwise differences between means were examined using Tukey's HSD. All other *p*s > .12.

'conventional meat is unnatural' and 'challenging the appeal to nature' conditions—the latter performing the worst.

In sum, the argument that conventional meat is unnatural influenced participants' willingness to pay for clean meat more than it did their stated intentions, beliefs, and feelings about it. The reason for this is logical: As the manipulation check showed, this argument influenced perceptions of conventional meat but not clean meat. The study's self-report measures did not assess the appeal of conventional meat directly or indirectly, but the WTP measure did, by pitting the two products against each other. However, to the extent that the WTP measure is more similar to real consumer behavior than self-reported scale ratings, this is a tentatively positive result for advocates. This is explored further below.

Implications

In a real-world context, consumers will not answer questions about their willingness to eat clean meat, they will be faced with a choice between it and the more familiar, conventionally-produced meat. These results suggest that, in that choice context, focusing on the unnatural aspects of conventional meat may be the most effective way of increasing interest in clean meat. In short, it appears to make consumers more aware of the positive contrast between them.

That being said, such an approach would represent a fairly aggressive stance towards conventional meat producers, which may not be an optimal strategy for advancing clean meat. Several conventional meat producers are already backing clean meat technology, so encouraging others to do so as well may be a better strategy than fighting them with legal challenges or marketing. This question warrants further consideration.

Given the care that was taken in developing the experimental messages, and the lack of other effects, we believe it is reasonable to interpret these results as an indication that arguing for clean meat's naturalness or the unimportance of naturalness are difficult strategies to use effectively.

Limitations

As with all research, this study was subject to several limitations. First, because only U.S. adults were studied, the findings may not be generalizable to other cultures or countries.

In addition, the proportion of would-be participants who were removed for failing attention checks was higher than we would like. Although their removal ensures data quality, it may introduce some selection bias. More generally, it may be indicative of low panel quality.

It is also worth noting several limitations of the WTP measure in particular. First, it is important to bear in mind that this measure directly followed positive messaging about clean meat, potentially producing higher values than would be observed in reality. In addition, because this measure is hypothetical, it is susceptible to the commonly-observed *hypothetical bias*, in which consumers tend to overestimate how much they are willing to pay for a product (e.g., Loomis, 2011). It is for this reason that we have provided only broad WTP categories above and focused on the comparison between conditions.

Participants' self-report responses may also be subject to bias. First, forecasting error is probable: Predicting one's own future attitudes and behaviors towards a product which is not yet available

is difficult (Bryant & Barnett, 2018). Unfortunately, there is little that can be done to avoid it, as clean meat is not yet available. Hypothetical and predictive questions are the only option, though we took care to frame them as realistically as possible.

Finally, participants may have been subject to social desirability bias—answering as they believe others would want them to—for questions about a product with such profound ethical and environmental implications (Grimm, 2010). That said, because even participants who read our control message were exposed to arguments about these implications, we believe that the potential impact of this bias is minimal.

Future Directions

We suggest that future research carefully consider whether trying to directly overcome perceptions of unnaturalness is the most effective option before pursuing it further—a few of this study's effects suggest there may even be potential for it to backfire. These results suggest that a focus on the unnaturalness of conventionally-produced meat is more likely to be effective, but as noted above, this is not without risk of alienating potential allies.

In addition, the effectiveness of the 'conventional meat is unnatural' message in this study was limited, with mixed results across different outcome measures. We recommend that, if this is to be considered as a strategy for advancing clean meat, further testing of similar and stronger messages should be carried out.

The overall high rates of clean meat acceptance observed in this study suggest another potential strategy: that providing potential consumers with positive educational messaging about the benefits and characteristics of clean meat may be a good way to reduce the emphasis on naturalness before it becomes the focus of the conversation. This study does not provide strong evidence about this possibility because we did not include a no-message control group, opting instead for current messaging. Previous research that has directly examined the impact of positive messaging has found that it can be effective (Verbeke et al., 2015; Bekker et al., 2017).

We recommend that future research do more to examine which aspects of educational messages are most effective in increasing acceptance rates: for instance, information about the taste, texture, and nutritional profile, or the health, environmental, or animal welfare benefits. This study included all of these to apparent good effect, but further experimental research will be needed to narrow down the key ingredients so that they can be emphasized.

References

Animal Charity Evaluators. (2017). *"Clean" Meat or "Cultured" Meat: A Randomized Trial Evaluating the Impact on Self-Reported Purchasing Preferences.* Retrieved 13 June, 2017, from https://animalcharityevaluators.org/blog/clean-meat-or-cultured-meat-a-randomized-trial-evaluating-the-impact-on-self-reported-purchasing-preferences/

Bekker, G. A., Fischer, A. R. H., Tobi, H., & van Trijp, H. C. M. (2017). Explicit and implicit attitude toward an emerging food technology: The case of cultured meat. *Appetite, 108*, 245–254. https://doi.org/10.1016/j.appet.2016.10.002

Bryant, C. J., & Barnett, J. C. (2018). Consumer acceptance of cultured meat: A systematic review. *Meat Science, 143*, 8-17. doi: https://doi.org/10.1016/j.meatsci.2018.04.008

Grimm, P. (2010). Social desirability bias. *Wiley International Encyclopedia of Marketing.* doi: 10.1002/9781444316568.wiem02057

Laestadius, L. (2015). Public Perceptions of the Ethics of In-vitro Meat: Determining an Appropriate Course of Action. *Journal of Agricultural & Environmental Ethics, 28*, 991-1009. doi: 10.1007/s10806-015-9573-8

Loomis, J. (2011). What's to know about hypothetical bias in stated preference valuation studies? *Journal of Economic Surveys, 25*, 363–370. https://doi.org/10.1111/j.1467-6419.2010.00675.x

Pew Research (2014). *U.S. views of technology and the future: Science in the next 50 years.*

Schurman, R. (2004). Fighting "Frankenfoods": Industry opportunity structures and the efficacy of the anti-biotech movement in Western Europe. *Social Problems, 51*, 243-268.

Siegrist, M., & Sütterlin, B. (2017). Importance of perceived naturalness for acceptance of food additives and cultured meat. *Appetite, 113*, 320-326. doi: 10.1016/j.appet.2017.03.019

Siegrist, M., Sütterlin, B., & Hartmann, C. (2018). Perceived naturalness and evoked disgust influence acceptance of cultured meat. *Meat Science, 139*, 213-219.

Slade, P. (2018). If you build it, will they eat it? Consumer preferences for plant-based and cultured meat burgers. *Appetite, 125*, 428-437.

Song, M., Lin, F., Ward, S. E., & Fine, J. P. (2013). Composite variables: When and how. *Nursing Research*, *62*, 45–49. https://doi.org/10.1097/NNR.0b013e3182741948

Surveygoo. (2018). *Nearly one in three consumers willing to eat lab-grown meat, according to new research.* Retrieved March 1, 2018, from https://www.datasmoothie.com/@surveygoo/nearly-one-in-three-consumers-willing-to-eat-lab-g/

The Good Food Institute. (2017). *Clean meat: The naming of tissue-engineered meat*. Retrieved 13 June, 2017, from http://mfait.gfi.org/the-naming-of-clean-meat

The Grocer. (2017). Meat the future... and how to market it. Retrieved February 21, 2017, from http://www.thegrocer.co.uk/buying-and-supplying/categories/meat/meat-the-future-and-how-to-market-it/546754.article

Verbeke, W., Marcu, A., Rutsaert, P., Gaspar, R., Seibt, B., Fletcher, D., & Barnett, J. (2015). 'Would you eat cultured meat?': Consumers' reactions and attitude formation in Belgium, Portugal and the United Kingdom. *Meat Science, 102*, 49-58. doi: 10.1016/j.meatsci.2014.11.013

Verbeke, W., Sans, P., & Van Loo, E. J. (2015). Challenges and prospects for consumer acceptance of cultured meat. *Journal of Integrative Agriculture, 14*, 285-294. doi: 10.1016/S2095-3119(14)60884-4

Wilks, M., & Phillips, C. J. (2017). Attitudes to in vitro meat: A survey of potential consumers in the United States. *PloS One, 12*.

YouGov (2013). *No British demand for fake meat.* Retrieved August 13, 2017, from https://yougov.co.uk/news/2013/08/05/no-demand-fake-meat/

Appendix A: Messages and Measures

Table A-1. Experimental Messages[10]

Section/Condition	Message
Introductory passage (shown to all participants)	Clean meat is real meat, grown from animal cells without the need to raise and slaughter farm animals. It has significant benefits for the environment, animals, and human health. Products include chicken (as shown), beef, and more!
Clean meat is natural	Clean meat products are made using a natural process very similar to the way yogurt and beer are fermented. This is a method which has been used in food manufacturing for thousands of years. The development of clean meat resembles how muscles naturally grow within an animal very closely. In fact, this process of cell growth is present in all natural life. Clean meat has many benefits for human health, animals, and the environment. But best of all, it's all-natural!
Conventional meat is unnatural	Production of conventional meat today is far from natural. Animals are fed antibiotics and hormones so that they grow much faster and larger than they would in nature. Unsanitary farming conditions increase the risk of contamination from feces, as well as viruses and bacteria. The meat also contains additives, artificial coloring, and preservatives, and is often treated with radiation. Clean meat avoids all of those issues. It has many benefits for human health, animals, and the environment. But best of all, it's just meat!
Challenging the appeal to nature	You might think that clean meat is unnatural, but naturalness does not necessarily mean goodness. Indeed, most modern food (including rice, tomatoes, milk, and – yes – meat) has been manipulated by people to make it suit our needs, and it is tastier and more nutritious as a result. On the other hand, some plants (like many types of poisonous mushroom) are completely natural but can easily kill you. Clean meat has many benefits for human health, animals, and the environment. It's a perfect example of humans improving on nature!
Control	There are many reasons to eat clean meat: It requires much less water to produce and will cause far less climate change than conventionally-produced meat; it doesn't require animals to suffer or die; it can feed far more people from the same amount of land; and it has the same or better nutritional content as conventionally-produced meat. In sum, clean meat has many benefits for human health, animals, and the environment. But best of all, it's delicious real meat!

[10] In order to hold constant features of the messages other than the content, these messages were kept as similar as possible in length and reading level. They were also informally pretested on a small convenience sample to confirm that they related narrowly to the intended message.

Table A-2. Scale Measures

Manipulation Checks	Response Options
1. Clean meat is unnatural.	Strongly disagree (1) to Strongly agree (5)
2. Conventionally-produced meat is unnatural.	
3. It is important for meat to be natural.	
Behavioral Intentions	**Response Options**
1. Would you be willing to try clean meat?	Definitely no (1) to Definitely yes (5)
2. Would you be willing to buy clean meat regularly?	
3. Would you be willing to eat clean meat as a replacement for conventionally-produced meat?[1]	
4. How willing would you be to eat clean meat compared to plant-based substitutes (e.g., soy)?	Much less (1) to Much more (5)
Attitudes	**Response Options**
1. For me to eat clean meat would be…[2]	Extremely good (1) to Extremely bad (7)
2. For me to eat clean meat would be…	Extremely unpleasant (1) to Extremely pleasant (7)
Cognitive Beliefs	**Response Options**
1. To what extent do you think that eating clean meat is likely to be healthy?	Strongly disagree (1) to Strongly agree (5)
2. To what extent do you think that clean meat is likely to be safe for human consumption?	
3. To what extent do you think that clean meat is more environmentally friendly than conventionally-produced meat?	
4. To what extent do you think that clean meat is likely to look, taste, smell, and feel the same as conventionally-produced meat?	
5. To what extent do you think that clean meat will have benefits for society?	

Table A-2, Continued

Affect ("Indicate the extent to which each of the following describes your feelings about eating clean meat")	**Response Options**
1. Disgusted[2]	Not at all (1) to Extremely (5)
2. Excited	
3. Anxious[2]	
4. Comfortable	
5. Ethical	
6. Immoral[2]	

[1]For this question, participants were also given the option of selecting 'Not applicable (I do not eat conventionally-produced meat).'
[2]Denotes item was reverse scored.

Table A-3. WTP Measure

Page 1 (Introduction)

Imagine that it is a few years in the future. Clean meat has been tested and approved for sale in the US. You are at your usual supermarket buying groceries. You will now be presented with several product choices. Please be as honest and accurate as possible in your responses.

Page 2 (WTP for Chicken)

You are looking at frozen ***chicken nuggets***, and there are two options: conventionally-produced meat or clean meat.

conventionally-produced chicken nuggets	***Clean chicken nuggets***
25 oz. box	25 oz. box
Approx. 8 servings	Approx. 8 servings
$6.99	***???***

The conventionally-produced chicken nuggets cost ***$6.99***, as shown above. What is the most you would be willing to pay for the clean chicken nuggets? Please enter it in the box below.

☐

OR

If you would not buy the clean chicken nuggets at any price, please select this statement (click on it to highlight) instead of entering a value above.

Page 3 (presented if box is checked instead of entering a value)

You have indicated that you would not buy the clean chicken nuggets at any price. Would you buy the conventionally-produced chicken nuggets for $6.99 instead?

☐ Yes

☐ No

Note. There were three measures of WTP for clean versus conventional meat. This table shows the WTP for chicken nuggets. The other two measures described beef burgers (with a value of $9.99 for the conventional meat) and fish sticks (with a value of $5.99 for the conventional meat).

Appendix B: Analysis Details

Statistical analyses were performed using IBM SPSS Statistics, Version 22.

Per the pre-registered analysis plan, multivariate outliers were detected and reeled in to avoid extreme values exerting undue influence on subsequent analyses using methods discussed by Judd, McClelland, and Ryan (2017). This resulted in outlier values in outcome variables being adjusted to the nearest acceptable value for between 41 and 106 records per variable. The pattern of results did not differ substantially if outliers were left unadjusted.

For the main analyses, ANOVAs were used to compare measures of behavioral intentions, cognitive beliefs, attitudes, and affective responses between experimental conditions.

For willingness to try clean meat, which was considered a primary analysis in the pre-registration, planned pairwise comparisons were conducted between the control condition and each experimental condition. The other three pairwise analyses for willingness to try clean meat were Bonferroni-corrected.

All pairwise comparisons for the other Likert-type measures, which were considered secondary analyses, were corrected for post hoc analysis using Tukey's HSD, which is designed for making all possible comparisons.

Finally, ordinal regression was used to compare WTP for clean meat between experimental conditions. This was also considered a primary analysis, so as with willingness to try clean meat, planned pairwise comparisons were conducted between the control condition and each experimental condition. The other three pairwise analyses for WTP were Bonferroni-corrected.

Appendix C: Pairwise Comparisons

Table C-1, on the next page, shows the results of all pairwise comparisons for the self-report measures.

Statistically significant differences between pairs of means are indicated using subscript letters. Means that differ significantly have different subscripts, whereas means that do not differ share a subscript. For example, in the ‘perceived importance of naturalness’ row, those in the ‘clean meat is natural’ condition showed significantly higher agreement than those in the ‘challenging appeal to nature’ condition (as indicated by subscripts a and b, which these two conditions do not share). However, those in the ‘conventional meat is unnatural’ condition and the control condition were not significantly different from the other conditions (as indicated by subscripts a and b, which are shared with all other conditions). As shown, most outcome variables did not differ significantly between conditions, though there were some significant differences in attitude and cognitive beliefs.

Table C-1. Outcome Variables in Each Experimental Condition and Overall

		Condition Means			
Measure	**Overall mean**	**Clean meat is natural**	**Conventional meat is unnatural**	**Challenging appeal to nature**	**Control**
Manipulation checks (5-point scale)					
Perceived unnaturalness of clean meat	2.98	3.01_{a}	2.91_{a}	3.03_{a}	2.99_{a}
Perceived unnaturalness of conventional meat	2.58	2.55_{a}	2.82_{b}	2.48_{a}	2.48_{a}
Perceived importance of naturalness	3.80	3.94_{a}	3.82_{ab}	3.69_{b}	3.77_{ab}
Behavioral intentions (5-point scale)					
Willingness to try clean meat	3.88	3.81_{a}	3.98_{a}	3.81_{a}	3.91_{a}
Willingness to buy clean meat regularly	3.47	3.45_{a}	3.57_{a}	3.38_{a}	3.49_{a}
Willingness to eat clean meat as a replacement for conventional meat	3.54	3.48_{a}	3.65_{a}	3.45_{a}	3.57_{a}
Willingness to eat clean meat compared to plant-based substitutes (current consumers, *n* = 381)	3.67	3.66_{a}	3.77_{a}	3.48_{a}	3.74_{a}
Willingness to eat clean meat compared to plant-based substitutes (non-consumers, *n* = 804)	3.81	3.76_{a}	3.91_{a}	3.77_{a}	3.79_{a}
Cognitive beliefs (5-point scale)					
Perceived healthiness of clean meat	3.64	3.61_{ab}	3.78_{a}	3.53_{b}	3.65_{ab}
Perceived safety of clean meat	3.71	3.68_{ab}	3.83_{a}	3.63_{b}	3.73_{ab}
Perceived environmental friendliness of clean meat	4.03	4.04_{ab}	4.09_{a}	3.87_{b}	4.10_{a}
Perceived similarity in taste of clean meat to conventional meat	3.57	3.58_{ab}	3.65_{a}	3.46_{b}	3.60_{ab}
Perceived benefits to society of clean meat	3.79	3.75_{a}	3.82_{a}	3.71_{a}	3.87_{a}
Attitude & Affect					
(Positive) attitude (7-point scale)	4.88	4.78_{ab}	5.07_{c}	4.70_{a}	4.98_{bc}
(Positive) affect (5-point scale)	3.47	3.41_{a}	3.55_{a}	3.42_{a}	3.49_{a}

Appendix C

Preparing for Future Products of Biotechnology

Committee on Future Biotechnology Products and Opportunities to Enhance Capabilities of the Biotechnology Regulatory System

Board on Life Sciences

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Contents

Select Acronyms and Abbreviations

AHPA	Animal Health Protection Act
APHIS	Animal and Plant Health Inspection Service
ARS	Agricultural Research Service
BRAG	Biotechnology Risk Assessment Grants
Bt	*Bacillus thuringiensis*
BWG	Biotechnology Working Group
CAD	Computer-Aided Design
Cas9	CRISPR-Associated Protein 9
CDC	Centers for Disease Control and Prevention
CPSC	Consumer Product Safety Commission
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeat
CSIRO	Commonwealth Scientific and Industrial Research Organisation
DARPA	Defense Advanced Research Projects Agency
DBTL	Design-Build-Test-Learn
DIYbio	Do-It-Yourself Biology
DNA	Deoxyribonucleic Acid
DOE	U.S. Department of Energy
dsDNA	Double-Stranded DNA
DSHEA	Dietary Supplement Health and Education Act
ELSI	Ethical, Legal, and Social Implications
EOP	Executive Office of the President
EPA	U.S. Environmental Protection Agency
ESA	Endangered Species Act
EUP	Experimental Use Permit

FACA	Federal Advisory Committee Act
FBI	Federal Bureau of Investigation
FDA	U.S. Food and Drug Administration
FDCA	Food, Drug, and Cosmetic Act
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FONSI	Finding of No Significant Impact
FTE	Full-Time Employee
FWS	U.S. Fish and Wildlife Service
GE	Genetically Engineered
GRAS	Generally Recognized as Safe
GRO	Genomically Recoded Organism
IARPA	Intelligence Advanced Research Projects Agency
IDE	Investigational Device Exemption
iGEM	International Genetically Engineered Machine
INAD	Investigational New Animal Drug
IND	Investigational New Drug
MAGE	Multiplex Automated Genome Engineering
MCAN	Microbial Commercial Activity Notice
NEPA	National Environmental Policy Act
NGO	Nongovernmental Organization
NIH	National Institutes of Health
NIST	National Institute of Standards and Technology
NMFS	National Marine Fisheries Service
NOI	Notice of Intent
NSF	National Science Foundation
ORD	Office of Research and Development
OSHA	Occupational Safety and Health Administration
PIP	Plant-Incorporated Protectant
PPA	Plant Protection Act
PPDC	Pesticide Program Dialogue Committee
rDNA	Recombinant DNA
RFI	Request for Information
RNA	Ribonucleic Acid
RNAi	RNA Interference
SAP	Scientific Advisory Panel
ssDNA	Single-Stranded DNA
TALEN	Transcription Activator-Like Effector Nuclease
TSCA	Toxic Substances Control Act

USDA	U.S. Department of Agriculture
USGS	U.S. Geological Survey
ZFN	Zinc Finger Nuclease

Summary

In July 2015, the Office of Science and Technology Policy in the Executive Office of the President initiated an effort to modernize the U.S. regulatory system for biotechnology products consisting of three primary activities:

1. Development of an update to the Coordinated Framework for Regulation of Biotechnology (referred to hereafter as the Coordinated Framework) to clarify the roles and responsibilities of the agencies that regulate the products of biotechnology;
2. Formulation of a long-term strategy to ensure that the federal regulatory system is equipped to efficiently assess the risks, if any, associated with future products of biotechnology while supporting innovation, protecting health and the environment, promoting public confidence in the regulatory process, increasing transparency and predictability, and reducing unnecessary costs and burdens; and
3. Commission of an external, independent analysis of the future landscape of biotechnology products with a primary focus on potential new risks and risk-assessment frameworks.

With regard to the third item, the U.S. Environmental Protection Agency (EPA), the U.S. Food and Drug Administration (FDA), and the U.S. Department of Agriculture (USDA) were charged to

> Commission an external, independent analysis of the future landscape of biotechnology products that will identify (1) potential new risks and frameworks for risk assessment and (2) areas in which the risks or lack of risks relating to the products of biotechnology are well understood. The intent of this review is to help inform future policy making. It is also anticipated that due to the rapid pace of change in this arena, an external analysis would be completed at least every 5 years.[1]

[1]Executive Office of the President. 2015. Memorandum for Heads of Food and Drug Administration, Environmental Protection Agency and Department of Agriculture. July 2. Available at https://obamawhitehouse.archives.gov/sites/default/files/microsites/ostp/modernizing_the_reg_system_for_biotech_products_memo_final.pdf. Accessed January 31, 2017.

BOX S-1
Statement of Task

An ad hoc committee of the National Academies of Sciences, Engineering, and Medicine will produce a report designed to answer the questions "What will the likely future products of biotechnology be over the next 5–10 years? What scientific capabilities, tools, and/or expertise may be needed by the regulatory agencies to ensure they make efficient and sound evaluations of the likely future products of biotechnology?"

The committee will

- Describe the major advances and the potential new types of biotechnology products likely to emerge over the next 5–10 years.
- Describe the existing risk-analysis system for biotechnology products including, but perhaps not limited to, risk analyses developed and used by EPA, USDA, and FDA, and describe each agency's authorities as they pertain to the products of biotechnology.
- Determine whether potential future products could pose different types of risks relative to existing products and organisms. Where appropriate, identify areas in which the risks or lack of risks relating to the products of biotechnology are well understood.
- Indicate what scientific capabilities, tools, and expertise may be useful to the regulatory agencies to support oversight of potential future products of biotechnology.

Human drugs and medical devices will not be included in the purview of the study per a sponsor's request.

To accomplish this directive, the three regulatory agencies asked the National Academies of Sciences, Engineering, and Medicine to convene a committee of experts to conduct the study "Future Biotechnology Products and Opportunities to Enhance Capabilities of the Biotechnology Regulatory System." Committee members were selected because of the relevance of their experience and knowledge to the study's specific statement of task (Box S-1), and their appointments were approved by the President of the National Academy of Sciences in early 2016.

THE COMMITTEE'S PROCESS

To address its statement of task, the Committee on Future Biotechnology Products and Opportunities to Enhance Capabilities of the Biotechnology Regulatory System spent several months gathering information from a number of sources. It heard from 74 speakers over the course of three in-person meetings and eight webinars and received responses to a request for information from a dozen federal agencies. It also solicited statements from members of the public at its in-person meetings and accepted written comments through the duration of the study. The committee also made use of several recent National Academies studies related to future products of biotechnology, particularly *Industrialization of Biology: A Roadmap to Accelerate the Advanced Manufacturing of Chemicals*,[2] *Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values*,[3] and *Genetically Engineered Crops: Experiences and*

[2]NRC (National Research Council). 2015. Industrialization of Biology: A Roadmap to Accelerate the Advanced Manufacturing of Chemicals. Washington, DC: The National Academies Press.

[3]NASEM (National Academies of Sciences, Engineering, and Medicine). 2016. Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values. Washington, DC: The National Academies Press.

Prospects.[4] The committee reviewed these reports and reflected on their recommendations related to the Coordinated Framework, with the aim of understanding how those prior recommendations fit with the broader view of biotechnology products in this report and the opportunities to enhance the capabilities of the biotechnology regulatory system. For its purposes, the committee defined *biotechnology products* as products developed through genetic engineering or genome engineering (including products where the engineered DNA molecule is itself the "product," as in an engineered molecule used as a DNA information-storage medium) or the targeted or in vitro manipulation of genetic information of organisms, including plants, animals, and microbes. The term also covers some products produced by such plants, animals, microbes, and cell-free systems or products derived from all of the above.

FUTURE BIOTECHNOLOGY PRODUCTS

The committee was charged to describe biotechnology products likely to emerge in the next 5–10 years. The committee scanned the horizon for new products by inviting product developers to speak at the various meetings; reviewing submitted public comments; reading scientific literature, popular press reports, and patents; consulting previous reports by the National Academies; searching publicly available projects developed by international Genetically Engineered Machine teams;[5] and checking information available on regulatory agencies' websites and crowdfunding websites. It also made use of the Synthetic Biology Database[6] curated by the Woodrow Wilson Center. Based on this exercise, the committee anticipates that the scope, scale (number of products and variants thereof), and complexity of future biotechnology products may be substantially different from products developed as of 2016.

The committee grouped future products into three major classes: open-release products, contained products, and platforms. Table S-1 summarizes types of open-release products that the committee saw on the horizon, that is, plants, animals, microbes, and synthetic organisms that have been engineered for deliberate release in an open environment. The ability to sustain existence in the environment with little or no human intervention is a key change between existing products of biotechnology and some of the future ones anticipated in this class. Furthermore, the types of environments in which a product may persist are likely to become more diverse. Plants and insects may be designed to continue in low-management systems such as forests, pastures, and cityscapes; microbes may be developed to persist in those environments as well as in mines, waterways, and animal guts. The committee thought that future open-release products would be developed for familiar uses, such as agricultural crops, but would also likely be developed for uses such as cleaning up contaminated sites with engineered microbes, replacing animal-derived meat with meat cultured from animal cells, and controlling invasive species through gene drives.[7]

On the basis of its information-gathering efforts, the committee concluded that future biotechnology products that are produced in contained environments are more likely to be microbial based or synthetically based rather than based on an animal or plant host (Table S-2). Organisms of many genera are used in fermenters to produce commodity chemicals, fuels, specialty chemicals

[4]NASEM. 2016. Genetically Engineered Crops: Experiences and Prospects. Washington, DC: The National Academies Press.

[5]See team list for iGEM championship. Available at http://igem.org/Team_List?year=2016&name=Championship&division=igem. Accessed February 12, 2017.

[6]Synthetic Biology Products and Applications Inventory. Available at http://www.synbioproject.org/cpi. Accessed October 11, 2016.

[7]A *gene drive* is a system of biased inheritance in which the ability of a genetic element to pass from a parent to its offspring through sexual reproduction is enhanced. Thus, the result of a gene drive is the preferential increase of a specific *genotype*, the genetic makeup of an organism that determines a specific *phenotype* (trait), from one generation to the next, and potentially throughout the population.

TABLE S-1 Market Status of Products Designed for Open Release in the Environment[a]

	Product Description	On Market[b]	Under Development[c]	Early-Stage Concept
Plants and Plant Products	*Bt* crops with recombinant DNA[d] (rDNA)	✓		
	Herbicide-resistant crops with rDNA	✓	✓	
	Disease-resistant crops with rDNA	✓	✓	
	RNAi[e] modified crops	✓	✓✓✓	✓✓✓
	Fragrant moss		✓	
	Do-it-yourself glowing plants		✓	
	Genome-edited[f] crops		✓✓✓	✓✓✓
	Crops with CRISPR[g] knockouts		✓✓✓	✓✓✓
	Grasses for phytoremediation		✓	
	Plants as sentinels		✓	
	Crops with increased photosynthesis efficiency		✓	
	Ever-blooming plants			✓
	Nitrogen-fixing nonleguminous plants			✓
	Bioluminescent trees			✓
	Plants with gene drives for conservation purposes			✓
	Plants with gene drives for agricultural purposes			✓
Animals and Animal Products	Fluorescent zebra fish	✓		
	Sterile insects		✓	
	Genome-edited animals (e.g., polled cattle)		✓	✓
	Reduced-allergen goat's milk		✓	
	Landmine-detecting mice		✓	
	Animals revived from near extinction or extinction			✓
	Animals with gene drives for control of invasive mammals			✓
	Animals with gene drives for control of insect pests			✓
Microbes and Microbial Products	Biosensors/bioreporters		✓	
	Bioremediation		✓	
	Engineered algal strains		✓✓✓	
	Nitrogen-fixing symbionts		✓	
	Probiotics			✓
	Genomically engineered microbial communities			✓✓✓
	Biomining/bioleaching			✓✓✓
Synthetic Organisms/ Nucleic Acids	Cell-free products		✓	
	DNA barcodes to track products	✓	✓	
	RNA-based spray for insect-pest control		✓	
	Genomically recoded organisms			✓
	Biological/mechanical hybrid biosensors		✓	✓

✓✓✓ = an area the committee has identified as having high growth potential.

[a]The table reflects the market status of products at the time the committee was writing the report.

[b]"On Market" is equivalent to "in use"; thus, products that have received regulatory approval but are not in use were not considered by the committee to be "On Market."

[c]"Under development" spans products from the prototype stage to field trials.

[d]*Recombinant DNA* is a novel DNA sequence created by joining DNA molecules that are not found together in nature.

[e]*RNAi* or *RNA interference* is a natural mechanism found in nearly all organisms in which the levels of transcripts are reduced or suppressed and can be exploited with biotechnology to modify an organism.

[f]*Genome editing* is a specific modification of the DNA of an organism to create mutations or introduce new alleles or new genes.

[g]*CRISPR* or *clustered regularly interspaced short palindromic repeat* is a naturally occurring mechanism of immunity to viruses found in bacteria that involves identification and degradation of foreign DNA. This natural mechanism has been manipulated by researchers to develop genome-editing techniques.

TABLE S-2 Market Status of Contained Products[a]

	Product Description	On Market[b]	Under Development[c]	Early-Stage Concept
Animals/Plants and Animal/Plant Products	Transgenic laboratory animals (mini-swine, mice, rats, dogs)	✓	✓✓✓	
	Genetically engineered salmon grown in land-based facilities	✓		
	Animal cell culture–derived products (e.g., cowless leather and cowless meat)		✓✓✓	✓✓✓
	Polymers produced by plants for industrial use		✓	
	Greenhouse crops with CRISPR knockouts		✓	
Microbes and Microbial Products	Industrial enzymes	✓	✓	✓
	Biobased chemicals to replace fossil fuel feedstocks	✓	✓	✓
	Bioluminescent microbes for home and landscape uses		✓	✓
	Yeast-derived molecules to create products (e.g., vanillin, stevia, saffron, egg whites, milk protein, gelatin)	✓	✓✓✓	✓✓✓
	Synthetic silk		✓	
	Bacterium-derived antimicrobials		✓	
	Genomically engineered bacterial strains for fermentation-based products		✓✓✓	
	Gas-phase microbial systems		✓	
	Algae-derived products (e.g., substitute for shark fins and shrimp, biofuels, ethylene)		✓✓✓	✓✓✓
	Probiotics			✓
	Leaching/metal recycling organisms			✓
Synthetic Organisms/ Nucleic Acids	Organ-on-a-chip		✓	
	V. natriegens platform	✓	✓	
	Genomically recoded organisms		✓✓✓	✓✓✓
	Cell-free expression systems		✓✓✓	✓✓✓
	Biological–mechanical hybrid biosensor		✓	✓
	Implantable biosensors		✓	✓

✓✓✓ = an area the committee has identified as having high growth potential.

[a]The table reflects the market status of products at the time the committee was writing the report.

[b]"On Market" is equivalent to "in use"; thus, products that have received regulatory approval but are not in use were not considered by the committee to be "On Market."

[c]"Under development" spans products from the prototype stage to field trials.

or intermediates, enzymes, polymers, food additives, and flavors. When considering the laboratory as a contained environment, many examples of transgenic animals from vendors are widely used today for research and development. Because performing biotechnology in contained environments allows higher control over the choice of host organism, systems with advanced molecular toolboxes are already in high use.

Biotechnology platforms are tools that are used in the creation of other biotechnology products. They include products that are traditionally characterized as "wet lab," such as DNA/RNA, enzymes, vectors, cloning kits, cells, library prep kits, and sequencing prep kits, and products that are "dry lab," such as vector drawing software, computer-aided design software, primer calculation software, and informatics tools. These two categories continue to meld as newer approaches are published or commercialized.

There are a variety of technical, economic, and social trends that are driving and that will con-

tinue to drive the types of biotechnology products developed in the next decade. Technical and economic trends in the biological sciences and biological engineering are accelerating the rate at which new product ideas are formulated and the number of actors who are involved in product development. With regard to social trends, it was evident to the committee through its information-gathering activities and the mechanisms for public comment that there are many competing interests, risks, and benefits regarding future biotechnology products; it was also clear that the United States and international regulatory systems will need to achieve a balance among these competing aspects when considering how to manage the development and use of new biotechnology products. Many sectors of society have concerns over the safety and ethics of various biotechnologies, whereas others see prospects for biotechnology to address challenging social and environmental issues. Biotechnology products that are on the horizon are likely to generate substantial public debate. For example, gene-drive technology, for which there have already been numerous studies and reports regarding its use, is a technological advance that will increase the amount of public debate and for which society will have to take a balanced approach among the interested and affected parties, developers, and scientists.

THE BIOTECHNOLOGY REGULATORY PROCESS AND THE COORDINATED FRAMEWORK

The committee was asked to describe the existing risk-analysis system for biotechnology products and to describe each agency's authorities as they pertain to the products of biotechnology. In order to carry out these portions of its statement of task, the committee reviewed the regulatory authorities that apply to biotechnology products.

The committee found that the Coordinated Framework appears to have considerable flexibility in statutory authority to cover a wide range of biotechnology products. In some cases, however, the jurisdictions of EPA, FDA, and USDA are defined in ways that may leave gaps or redundancies in regulatory oversight. Even when jurisdiction exists, the available legal authorities may not be ideally tailored to new and emerging biotechnology products. Furthermore, agencies other than EPA, FDA, and USDA will likely have responsibilities to regulate some future biotechnology products, and their roles are not well specified in the Coordinated Framework.

Despite the flexibility of the Coordinated Framework to cover a wide range of biotechnology products, the committee also found that the existing biotechnology regulatory system is complex and could be considered to appear fragmented, resulting in a system that is difficult for product developers—including individuals, nontraditional organizations, and small enterprises—as well as consumers, product users, and interested members of the public to navigate. This complexity can cause uncertainty and a lack of predictability for developers of future biotechnology products and creates the potential for loss of public confidence in oversight of future biotechnology products.

The increased rate of new product ideas means that the types and number of biotechnology products in the next 5–10 years may be significantly larger than the current rate of product introduction. EPA, FDA, USDA, and other relevant agencies will need to be prepared for this potential increase, including finding effective means of evaluation that maintains public safety, protects the environment, and satisfies the statutory requirements appropriate for each agency. The increased number of actors who are involved in product development means that the regulatory agencies will need to be prepared to provide information regarding the regulatory process to groups that may have little familiarity with the Coordinated Framework. This group of actors may include small- and medium-sized enterprises, do-it-yourself (DIY) bioengineers, or developers supported by crowdfunded activities with direct-to-consumer distribution models and the potential for domestic manufacturing.

UNDERSTANDING RISKS RELATED TO FUTURE BIOTECHNOLOGY PRODUCTS

The committee was asked to determine whether future products could pose different types of risks relative to existing products and organisms. In all the types of products summarized above, advances in biotechnology are leading to products that involve the transformation of less familiar host organisms, have multiple engineered pathways, are comprised of DNA from multiple organisms, or are made from entirely synthetic DNA. Such products may have few or no comparators[8] to existing nonbiotechnology products, which function as the baseline of comparison in current regulatory risk assessments of biotechnology products. Figure S-1 summarizes the progression in terms of complexity and novelty that the committee thought was likely in future biotechnology products over the next 5–10 years. Products that fit in column A are those similar to existing biotechnology products evaluated under the existing Coordinated Framework and for which current methods of risk assessment can be applied. Examples include new genetically engineered crops and fermentation-based production of small molecules, enzymes, or other biochemicals. Products described by column B are those that represent an expansion of the familiar set of organismal hosts and genetic pathways, for which there are few comparators but nonetheless well-established approaches to assessing risk. Examples include animal cell culture–derived products (such as cowless meat or leather) and plants for bioremediation, decoration, or other environmental or consumer use. Products in column C are those that are currently at the forefront of research activities, where the use of rapid design-build-test-learn cycles allows much more complex designs of genetic pathways in a wider variety of host organisms, but which also represent more sophisticated uses of products, such as open release into the environment of organisms intended to modify populations of natural organisms. Examples include genetically engineered mosquitoes for fighting malaria or the Zika virus, genomically engineered microorganisms, and implantable biosensors. Such products are on the horizon, but at the time the committee was writing its report, most had not yet entered the biotechnology regulatory system. The few that had entered the system had few or no nonbiotechnology products to which they could be compared, and, as they were first-of-their-kind products, no previous biotechnology product had established a path to follow through the regulatory system. Finally, products in column D represent those in which multiple organisms may be used in complex microbial communities, such as microbiome engineering and synthetic consortia for bioremediation or biomining applications. These products also have no comparators (or the relevance of potential comparators is ambiguous) and no established regulatory path.

For future biotechnology products in all degrees of complexity and novelty, the committee considered the risk-assessment endpoints related to human health or environmental outcomes, such as illness, injury, death, or loss of ecosystem function. It concluded that the endpoints are not new compared with those that have been identified for existing biotechnology products, but the intermediate steps along the paths to those endpoints have the potential to be more complex, more ambiguous, and less well characterized. In addition, the committee found that the scope, scale, complexity, and tempo of biotechnology products that are likely to enter the regulatory system in the next 5–10 years have the potential to critically stress the regulatory agencies, both in terms of capacity and expertise. Furthermore, many early-stage developers of biotechnology products or biological technology that may lead to products do not currently consider regulatory perspectives or future requirements during technology (and sometimes product) development, which has the potential to complicate the evaluation of risks associated with the release of future biotechnology products. It will clearly be important for EPA, FDA, USDA, and other agencies relevant to the future regulation of biotechnology products to maintain an assessment of the scope of these products and be prepared to evaluate them as they are submitted for regulatory assessment.

[8]The term *comparator* refers to a known nonbiotechnology organism that is similar to the engineered organism except for the engineered trait.

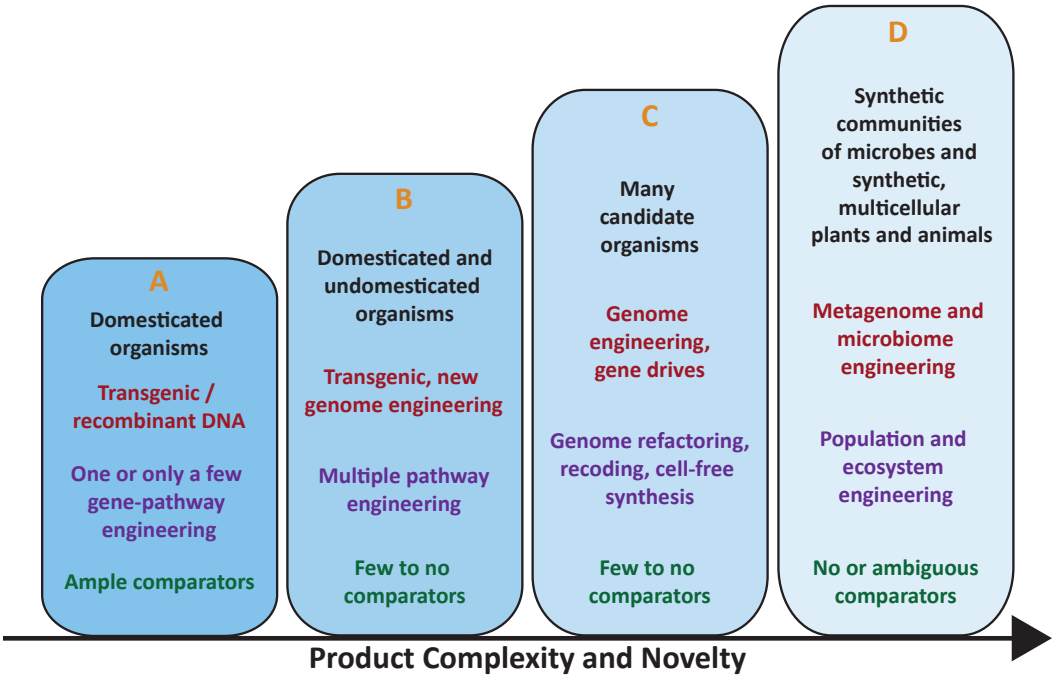

FIGURE S-1 Characteristics of future biotechnology products, organized by similar levels of complexity in terms of types and number of organisms, genes and traits, and comparators involved.
NOTE: Products of biotechnology can be conceptualized as fitting into the depicted columns with the indicated characteristics, moving toward column D as a product increases in complexity and likelihood of providing new challenges for risk assessment.

OPPORTUNITIES FOR ENHANCEMENT OF THE BIOTECHNOLOGY REGULATORY SYSTEM

A major task of the committee was to indicate what scientific capabilities, tools, and expertise may be useful to the regulatory agencies to support oversight of future products of biotechnology. The committee requested information from federal agencies regarding current investments in regulatory science.[9]

At a high level, the committee found that there are existing frameworks, tools, and processes for risk analyses and public engagement that can be used to address the many issues that are likely to arise in future biotechnology products in a way that balances competing issues and concerns. However, given the profusion of biotechnology products that are on the horizon, there is a risk that the capacity of the regulatory agencies may not be able to efficiently provide the quantity and quality of risk assessments that will be needed. An important approach for dealing with an increase in the products of biotechnology will be the increased use of stratified approaches to regulation, where new and potentially more complex risk-analysis methods will need to be developed for some

[9]As discussed in Chapter 4, on the basis of definitions provided by FDA and the Society for Risk Analysis, the committee understood regulatory science to involve developing and implementing risk-analysis methods and maximizing the utility of risk analyses to inform regulatory decisions for biotechnology products, consistent with human health and environmental risk–benefit standards provided in relevant statutes.

products, while established risk-analysis methods can be applied or modified to address products that are *familiar* or that require *less complex* risk analysis. With this approach, new risk-analysis methods are focused on products with *less familiar* characteristics and/or *more complex* risk pathways. Multiple criteria are usually embedded within risk analyses to ascertain if an estimated level of risk is consistent with the risk-management goals established during the problem-formulation phase of a risk assessment. In some cases, additional risk analyses may be needed to refine risk estimates, to evaluate risk-mitigation measures, or both. In order to implement the appropriate rigor of risk analyses for new biotechnology products, it will be necessary to establish scientifically rigorous criteria based on factors affecting the perception of risk, the degree of uncertainty, and the magnitude of risk and nature of potential risks.

To help articulate what capabilities, tools, and expertise might be useful to meet these objectives, the committee created a conceptual map for decision making aimed to assess and manage product risk, streamline regulation requirements, and increase transparency, as shown in Figure S-2.

As envisioned by the committee, a single point of entry (illustrated in Figure S-2) could be used by a product developer to evaluate whether the intended use of the product is regulated under

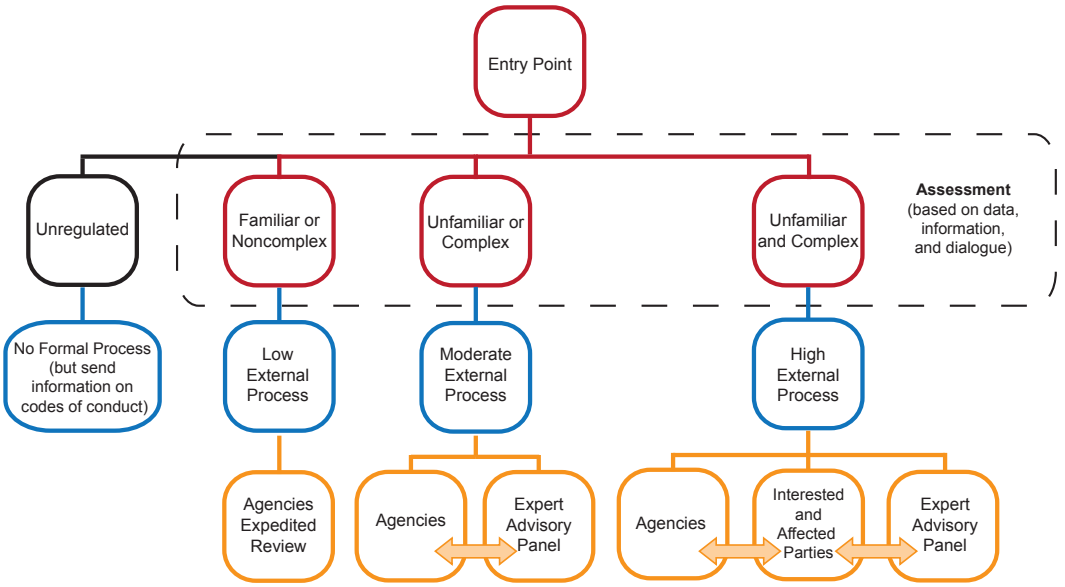

FIGURE S-2 Providing access to the U.S. regulatory system through a single point of entry.
NOTES: Potential product developers and interested parties would begin by going to an entry point and providing characteristics of the intended product and its use pattern. If the product does not fall under a federal statute, the developer would be notified that the product is not federally regulated. If the product is regulated, the appropriate agency or agencies would be identified for the developer. An evaluation of the product's familiarity to regulatory agencies and its complexity in terms of risk analyses as compared to existing biotechnology products would be ascertained (red bins). Depending on the product's familiarity and the complexity of its risk analysis, a different set of risk-analysis processes would be employed (blue boxes). For products that are *familiar* to the regulatory agencies and are *not complex*, a more expedited process could be used under the assumption that relevant risk-analysis processes are well established. For products that are *less familiar*, *more complex*, or *less familiar and more complex*, increasingly unique risk-analysis processes (that incorporate additional external input) may need to be established.

a given statute and provide a determination of whether the product is *familiar and not complex*, is *unfamiliar or complex*, or is *unfamiliar and complex* compared to existing biotechnology products. Once a determination has been made, the appropriate processes within the relevant agency (or agencies) would be used to provide the necessary risk analysis to support a regulatory decision. For products that are *familiar and noncomplex*, an expedited process might be used (for example, a notification process). For products that are determined to be *unfamiliar or complex* or *unfamiliar and complex*, new human health and ecological risk-analysis methods might be needed to inform a regulatory decision. A desirable feature of an integrated, stratified approach to regulatory oversight is that over time product types originally placed in the *unfamiliar or complex* bin or the *unfamiliar and complex* bin would "move" to a bin of less complexity or more familiarity based on experience gained in evaluating additional products in a category.

SUMMARY CONCLUSIONS

On the basis of its assessment of the trends in biotechnology, the likely products of biotechnology in the next 5–10 years, and the current authorities and capabilities of the regulatory agencies, the committee identified a set of broad themes regarding future opportunities for enhancement of the U.S. biotechnology regulatory system.

The bioeconomy is growing rapidly and the U.S. regulatory system needs to provide a balanced approach for consideration of the many competing interests in the face of this expansion. The competing interests and concerns articulated by the Executive Office of the President include supporting innovation, protecting human health, preserving biodiversity, reducing negative environment effects, promoting public confidence in the regulatory process, increasing transparency and predictability in the regulatory process, reducing unnecessary costs and burdens, making use of new tools from a broad range of disciplines, and interacting with the global economy. The pipeline of biotechnology products likely to emerge over the next decade probably will result in disruptive innovations and significant societal impacts; a carefully balanced, coordinated approach toward future biotechnology products that incorporates input from stakeholders—including interested and affected parties, relevant federal agencies, and nontraditional product developers—will be required.

The profusion of biotechnology products over the next 5–10 years has the potential to overwhelm the U.S. regulatory system, which may be exacerbated by a disconnect between research in regulatory science and expected uses of future biotechnology products. The number and complexity of products, new pathways to risk-assessment endpoints, large range of types of products (for example, those for open release in the environment or marketed as direct-to-consumer), new actors (including DIY bioengineers, small- and medium-sized enterprises, and crowdfunders), and complex alignment of potential future products with agency authorities are likely to change rapidly as biotechnology advances. A disconnect between research in regulatory science and its use in biotechnology research and product development creates a situation in which new products may be conceived and designed without sufficient consideration of regulatory requirements, which can lead to surprises and delays late in the development cycle. The update to the Coordinated Framework[10] and the *National Strategy for Modernizing the Regulatory System for Biotechnology Products*,[11] recently released by the Executive Office of the President, provide

[10]Executive Office of the President. 2017. Modernizing the Regulatory System for Biotechnology Products: An Update to the Coordinated Framework for the Regulation of Biotechnology. Available at https://obamawhitehouse.archives.gov/sites/default/files/microsites/ostp/2017_coordinated_framework_update.pdf. Accessed January 30, 2017.

[11]*National Strategy for Modernizing the Regulatory System for Biotechnology Products* is available at https://obamawhitehouse.archives.gov/sites/default/files/microsites/ostp/biotech_national_strategy_final.pdf. Accessed January 31, 2017.

an excellent starting point for addressing the products that will appear in the next 5–10 years. But additional investments are needed to be prepared for the subsequent generation of products that are on the horizon and to ensure that there is a consistent, efficient, and effective decision-making framework that continues to balance innovation and safety.

Regulators will face difficult challenges as they grapple with a broad array of new types of biotechnology products—for example, cosmetics, toys, pets, and office supplies—that go beyond contained industrial uses and traditional environmental release (for example, *Bt* or herbicide-resistant crops). The diversity of biotechnology products anticipated over the next decade confronts consumer- and occupational-safety regulators with two related challenges:

1. To find jurisdiction under existing statutes to regulate all the products that may pose risks to consumers and
2. To utilize the best available risk-analysis tools consistent with agency authorities to provide nuanced oversight that protects consumers while fostering beneficial innovation.

Existing statutes offer promising pathways to meet these challenges, although there may be cases when a novel product falls outside the jurisdiction of EPA, FDA, or USDA and is either in a jurisdictional gap (where no regulator has authority to address potential safety concerns) or under the jurisdiction of another agency, such as the Consumer Product Safety Commission, that has fewer statutory authorities and capabilities to conduct rigorous and timely risk analysis. For this reason, EPA, FDA, and USDA may at times need to make use of the flexibility available under their statutes to minimize gaps in jurisdiction and to position novel products under the statutory framework most suited to each product's characteristics and level of risk.

The safe use of new biotechnology products requires rigorous, predictable, and transparent risk-analysis processes whose comprehensiveness, depth, and throughput mirror the scope, scale, complexity, and tempo of future biotechnology applications. Regulatory oversight that is unnecessarily complex runs the risk of driving an "imitate not innovate" mentality and may not scale to match the pace of biotechnology innovation. Building on the approach outlined in the *National Strategy*, the committee believes that the advancement of existing risk-analysis methodologies within an easily accessible, participatory governance framework can establish an oversight process that matches the scope, scale, complexity, and tempo of future technological developments and increases public confidence in the safety of products entering the marketplace.

In addition to the conclusions and recommendations from this report, **EPA, FDA, USDA, and other agencies involved in regulation of future biotechnology products would benefit from adopting recommendations made by previous National Academies' committees related to future products of biotechnology, which are consistent with the findings and recommendations in this report.** Given the assessments of some future biotechnology products and the role of the regulatory system, many of the recommendations of previous National Academies' committees are directly relevant and should be considered when taking actions to enhance the capabilities of the U.S. biotechnology regulatory system.

SUMMARY RECOMMENDATIONS

On the basis of its conclusions, the committee developed a number of detailed recommendations regarding actions that can be taken to enhance the capabilities of the biotechnology regulatory system in order to be prepared for anticipated future products of biotechnology.

Recommendation 1: EPA, FDA, USDA, and other agencies involved in regulation of future biotechnology products should increase scientific capabilities, tools, expertise, and horizon scanning in key areas of expected growth of biotechnology, including natural, regulatory, and social sciences.

The information gathered by the committee indicates a substantial new set of technologies that are being brought to bear in future products and the agencies should continue to maintain their scientific capabilities across a broad range of disciplines. Example priority areas, discussed in more detail in the body of the report, including areas such as comparators, off-target gene effects, and phenotypic characterization; genetic fitness, genetic stability, and horizontal gene transfer; impacts on nontarget organisms; control of organismal traits; modeling (including risk-analysis approaches under uncertainty) and life-cycle analyses; monitoring and surveillance; and economic and social costs and benefits.

- Recommendation 1-1: Regulatory agencies should build and maintain the capacity to rapidly triage products entering the regulatory system that resemble existing products with a history of characterization and use, thus reducing the time and effort required for regulatory decision making, and they should be prepared to focus questions on identifying new pathways to risk-assessment endpoints associated with products that are unfamiliar and that require more complex risk assessments.
- Recommendation 1-2: In order to inform the regulatory process, federal agencies should build capacity to scan the horizon continuously for new products and processes that could present novel risk pathways, develop new approaches to assess and address more complex risk pathways, and implement mechanisms for keeping regulators aware of the emerging technologies they have to deal with.
- Recommendation 1-3: EPA, FDA, USDA, and other relevant federal agencies should work together to (a) pilot new approaches for problem formulation and uncertainty characterization in ecological risk assessments, with peer review and public participation, on open-release products expected during the next 5 years; (b) formulate risk–benefit assessment approaches for future products, with particular emphasis on future biotechnology products with unfamiliar functions and open-release biotechnology products; and (c) pool skills and expertise across the government as needed on first-of-a-kind risk–benefit cases.
- Recommendation 1-4: EPA, FDA, USDA, and other relevant federal agencies should create a precompetitive or preregulatory review "data commons" that provides data, scientific evidence, and scientific and market experience for product developers.
- Recommendation 1-5: Consistent with the goals and guidance stated by the Office of Science and Technology Policy in the Executive Office of the President in its July 2015 memo, the Biotechnology Working Group should implement a more permanent, coordinated mechanism to measure progress against and periodically review federal agencies' scientific capabilities, tools, expertise, and horizon scanning as they apply to the profusion of future biotechnology products.

Recommendation 2: EPA, FDA, and USDA should increase their use of pilot projects to advance understanding and use of ecological risk assessments and benefit analyses for future biotechnology products that are unfamiliar and complex and to prototype new approaches for iterative risk analyses that incorporate external peer review and public participation.

The rate of technology development in the biological sciences and engineering will create a situation in which many new types of products will be developed in the next 5–10 years. In order to handle the scope and complexity of future biotechnology applications, the regulatory agencies should make use of pilot products to identify ways to improve the comprehensiveness, effectiveness, and throughput of the regulatory process.

- Recommendation 2-1: Regulatory agencies should create pilot projects for more iterative processes for risk assessments that span development cycles for future biotechnology products as they move from laboratory scale to field or prototype scale to full-scale operation.
- Recommendation 2-2: Government agencies should pilot advances in ecological risk assessments and benefit analyses for open-release products expected in the next 5–10 years, with external, independent peer review and public participation.
- Recommendation 2-3: Government agencies should initiate pilot projects to develop probabilistic estimates of risks for current products as a means to compare the likelihood of adverse effects of future biotechnology products to existing biotechnology and nonbiotechnology alternatives.
- Recommendation 2-4: Regulatory agencies should make use of pilot projects to explore new methods of outreach to the public and developer community as a means of horizon scanning, assessing need areas for capability growth, and improving understanding of the regulatory process.
- Recommendation 2-5: EPA, FDA, and USDA should engage with federal and state consumer- and occupational-safety regulators that may confront new biotechnology products in the next 5–10 years and make use of pilot projects, interagency collaborations, shared data resources, and scientific tools to pilot new approaches for risk assessment that ensure consumer and occupational safety of new biotechnology products, particularly those that may involve novel financing mechanisms, means of production, or distribution pathways.

Recommendation 3: The National Science Foundation, the U.S. Department of Defense, the U.S. Department of Energy, the National Institute of Standards and Technology, and other agencies that fund biotechnology research with the potential to lead to new biotechnology products should increase their investments in regulatory science and link research and education activities to regulatory-science activities.

Increased investments in regulatory science will be needed to align desired science advancements with existing and anticipated regulatory requirements. It will be valuable for developers of biotechnology to incorporate regulatory perspectives earlier in the product and technology development process, and the research funding agencies can help enhance the regulatory system by increasing the awareness of regulatory science at an early stage.

- Recommendation 3-1: The federal government should develop and implement a long-term strategy for risk analysis of future biotechnology products, focused on identifying and prioritizing key risks for unfamiliar and more complex biotechnology products, and work to establish appropriate federal funding levels for sustained, multiyear research to develop the necessary advances in regulatory science.
- Recommendation 3-2: Federal agencies that fund early-stage biotechnology-related research and regulatory agencies should provide support to academic, industry, and government researchers to close gaps and provide linkages to market-path requirements for regulatory success.

- Recommendation 3-3: Government agencies that fund biotechnology development, working together with regulatory agencies and each other, should also invest in new methods of understanding the ethical, legal, and social implications associated with future biotechnology products.
- Recommendation 3-4: Government agencies with an educational mission, including those that support scientific training, should identify and fund activities that increase awareness and knowledge of the regulatory system in courses and educational materials for students whose research will lead to advances in biotechnology products.

5

Opportunities to Enhance the Capabilities of the Biotechnology Regulatory System

The profusion of products and the growing number of actors in the biotechnology space described in Chapter 2 present many challenges to the U.S. biotechnology regulatory system. The present chapter outlines a framework for risk analysis targeted at the types and scale of products anticipated and describes what tools, expertise, and scientific capabilities are required within and beyond the regulatory agencies in order to support oversight of future biotechnology products. The focus is not just on the regulatory process, but the broader context of presubmission and post-market activities that are an important part of the overall regulatory framework and that can provide a balanced approach to capabilities required for regulation of future biotechnology products.

As technologies and basic knowledge advance, a regulatory system should be able to adapt to new risks of future biotechnology products and also to adjust to well-established categories of products as their level and types of risk become better understood. As discussed in Chapters 2, 3, and 4, the scope, scale, complexity, and tempo of future products is expected to increase rapidly, and this increase has the potential to overwhelm the existing regulatory system. In addition, the new types of actors and new types of business models that will be involved in the development of technology and products means that the regulatory system will likely need to provide information to a broader group of stakeholders with diverse backgrounds and expertise. Finally, the possibility that some future products of biotechnology will be controversial may require substantial conversation and public debate throughout the phases of the regulatory process. A regulatory system with a greater emphasis on stratified approaches that prioritize the regulatory agencies' familiarity with a product, the complexity of the risk assessment for the product, and the anticipated risk associated with the product (that is, proportionate oversight) could contribute to meeting the increased demands on the system.

The 2016 *National Strategy for Modernizing the Regulatory System for Biotechnology Products* issued by the Executive Office of the President recognizes the increased complexity of future biotechnology products and provides a strategic plan for ensuring that federal agencies can efficiently assess any risks associated with such products (EOP, 2016). It also describes several approaches to increasing public participation in the process and incorporating science-driven decision making

BOX 5-1
Governance, Oversight, and Regulation

The terms governance, oversight, and regulation are used in regulatory science to capture different aspects of risk management (Figure 5-1). Following Kuzma (2006), *governance* can be broadly defined as a complex set of values, norms, processes, and institutions through which society manages technology development and deployment and resolves conflict formally or informally. Governance includes *oversight*, which is defined more narrowly as watchful and responsible care or regulatory supervision. *Regulation* is a subcategory of oversight and governance and represents an authoritative rule dealing with details or procedure or a rule or order issued by an executive authority or regulatory agency of a government and having the force of law. Therefore, regulation can be an important element of governance but can also be excluded from a governance system. Oversight can include codes of conduct, voluntary data-sharing programs, and public–private partnerships for certification standards as well as regulations. Risk analysis for future products of biotechnology can occur within a formal statute-based regulatory system or outside of one. Governance can include risk analyses from standard-setting international bodies, academics, nongovernmental organizations, think-tanks, and companies, whether or not those products are submitted for formal regulatory oversight. Oversight programs like voluntary standard setting, sharing of data, and risk-mitigation activities can occur outside of legal authorities.

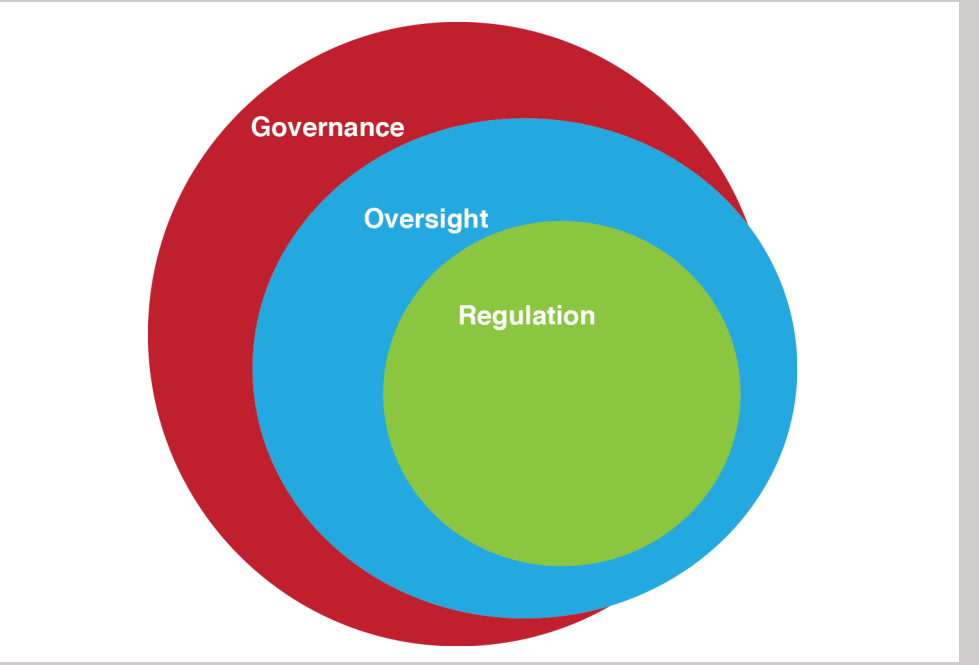

FIGURE 5-1 Relationships of governance, oversight, and regulation.
SOURCE: Illustration by J. Kuzma.

(EOP, 2016). This chapter describes some of the properties that will be important for risk analysis of the next generation of products, with the intent of providing insight that can be used by the agencies in evaluating the capabilities required to perform appropriate oversight (Box 5-1).

CONSISTENT, EFFICIENT, AND EFFECTIVE DECISION MAKING FOR FUTURE PRODUCTS OF BIOTECHNOLOGY

A key property of the U.S. biotechnology regulatory system, well articulated in the update to the Coordinated Framework, is that it effectively protects human health and the environment through a safety-evaluation process that can be understood by members of the public (EOP, 2017). As described in Chapter 3, the structure of the Coordinated Framework presents considerable flexibility for regulating future products of biotechnology but requires the agencies to appropriately apply their statutory authority. Multiple agencies may have jurisdiction over a given product, while other products may not be explicitly covered by any statute or federal agency. Either situation could lead to uncertainty in regulatory jurisdiction. The regulatory route may also be unclear at the time future products are developed. This uncertainty in regulatory jurisdiction "can make it difficult for the public to understand how the safety of biotechnology products is evaluated and create challenges for small and mid-sized businesses navigating the regulatory process" (EOP, 2017:1). As articulated in both the update to the Coordinated Framework and the *National Strategy*, the desired state is one in which there is a consistent, efficient, and effective decision-making framework that continues to protect human health and the environment. This section provides some properties of the risk-analysis system that will be important for meeting these goals for products anticipated in the next 5–10 years.

Preparing for Increased Scope, Scale, and Complexity of Biotechnology Products

A key theme throughout this report is the increase in scope, scale, and complexity that will accompany future biotechnology products. Scope is the new types of biotechnology products that have not yet been seen by regulators. Scale refers to the number of products as well as the number of variants of products that may interact with the regulatory system. Complexity refers to the number of traits that may be involved in a single product and the interactions between the various elements in a product. Increased scope and complexity are key components of future products that may have fewer or no comparators to nonbiotechnology products or no similar existing biotechnology products and thus little or no familiarity within the regulatory system.

Though the scale of products is likely to increase, some of this volume will be comprised of new products with a composition similar to existing biotechnology products with a history of characterization and safe use. Such products should be familiar to regulatory agencies and should have low complexity because the risk analyses for such products are well understood. The introduction of an already approved *Bt* protein into a new crop variety is an example. Another example of a product for which an *a priori* argument for familiarity and low complexity might be made is an organism that contains only a loss-of-function mutation in a gene or genes because such mutations arise spontaneously in nature. Provided the loss-of-function mutation does not create a new reading frame that encodes a novel protein, an organism with such a mutation is likely to be not complex in terms of risk analysis. A benefit of products that are *familiar and not complex* is the savings to regulators in terms of time and effort spent on designing and implementing risk analyses. These savings in time and resources can then be applied to devising and implementing risk analyses for products that are less familiar, more complex, or less familiar and more complex. It will be important in implementing the update to the Coordinated Framework (EOP, 2017) to make use of scientific tools to evaluate when new products can be categorized as *familiar and not complex* by comparison with the existing base of scientific knowledge and to apply appropriate oversight to those products (including no regulatory oversight, if appropriate) based on scientifically sound risk analyses.

Other new products—such as organisms with entirely new pathways assembled from many genes derived from multiple unrelated sources, perhaps including synthetic genes, and engineered

microbial communities planned for open-environmental release in which some community members contain engineered pathways—will pose challenges for the regulatory system because the regulatory agencies have not seen these types of products before and because the products do not have nonbiotechnology products to which they can be easily compared. Such products would be *unfamiliar* and have *high complexity* for the regulatory agencies.

Examples of products that pose new regulatory challenges are organisms engineered to contain gene drives, which are designed to introduce a trait that spreads throughout the species population. A trait could be designed to modify a species, such as one that reduces the species' ability to transmit a disease, or to eliminate a species, which may be the case when trying to exterminate a particular disease vector from a geographical region. In the case of gene drives in insects, the same public health benefit of disease elimination could be attempted by releasing sterile males of the species (Krafsur, 1998; Benedict and Robinson, 2003), but the use of a gene drive may be more effective in reducing the population size of the target species. However, gene drives may pose new complexity for risk assessments if the speed with which the target-species population is depressed exceeds current ecological and evolutionary rates. Additional risk-assessment endpoints and pathways to those endpoints may also need to be addressed. Examples of pathways to risk-assessment endpoints could include the probability that off-target gene effects could result in an unanticipated phenotype, the probability that the gene drive could mutate and result in an unanticipated phenotype, or the changes that the system (or its mutations) could cause in a community food web. Although these examples do not represent new risk-assessment endpoints, they may require more sophisticated risk analyses, with consideration of increasingly complex interactions. As noted in Recommendation 6-3 of the National Academies report on gene drives (NASEM, 2016a:128): "To facilitate appropriate interpretation of the outcomes of an ecological risk assessment, researchers and risk assessors should collaborate early and often to design studies that will provide the information needed to evaluate risks of gene drives and reduce uncertainty to the extent possible."

Another example of a new type of product is one that would enable the "deextinction" of a species. At the time the committee was writing its report, there were projects under way to "deextinct" the passenger pigeon and the woolly mammoth (or arguably a relative), among other animals (Biello, 2014; Callaway, 2015; Shapiro, 2015). If release to a natural ecosystem is a goal of such a project, a meaningful risk assessment should include wildlife ecologists and local experts from the area of release, including those with knowledge about migratory routes, to assist in assessing effects on the existing function and structure in the community.

An important approach for dealing with an increase in the products of biotechnology will be the increased use of stratified approaches to regulation, where new and potentially more complex risk-analysis methods will need to be developed for some products, while established risk-analysis methods can be applied or modified to address products that are familiar or that require less complex risk analysis. With this approach, new risk-analysis methods are focused on products with less familiar characteristics, more complex risk pathways, or both. Multiple criteria are usually embedded within risk analyses to ascertain if an estimated level of risk is consistent with the risk-management goals established during the problem-formulation phase of a risk assessment. In some cases, additional risk analyses may be needed to refine risk estimates, to evaluate risk-mitigation measures, or both. Criteria that could be applied to biotechnology products have also been used for risk analysis of other emerging technologies that integrate health, environmental, and life-cycle effects and occupational and socioeconomic risks, and these criteria can be weighted and rated by experts or stakeholders (Linkov et al., 2007; Tsang et al., 2014). In order to implement the appropriate rigor of risk analyses for new biotechnology products, it will be necessary to establish scientifically rigorous criteria based on factors affecting the perception of risk, the degree of uncertainty, and the magnitude of risk and nature of potential risks.

Enhancing the Responsiveness of the Regulatory System

At the time the committee was writing its report, there was no regulation, law, or statute to mandate a central review of biotechnology products or to develop an oversight system that is coordinated among agencies, minimizes gaps and redundancies in product review, provides more certainty for product developers as to the regulatory path, and embraces the principles of anticipation, participation, responsiveness, and transparency. The update to the Coordinated Framework (EOP, 2017) and the *National Strategy* (EOP, 2016) recognize the need for addressing these issues and provide a set of first steps for doing so. In this section, the committee provides some insights on how these topics might be addressed for the types of products that are anticipated in the next 5–10 years.

As described in Chapter 3, the statutory authorities that apply to some of the future products of biotechnology can be confusing and better coordination among the agencies would be beneficial so that risk analyses cover the impacts of biotechnology products more comprehensively in some cases or avoid duplication of data submissions in others. For example, as of 2016, genetically engineered insects were regulated by the U.S. Food and Drug Administration (FDA) under the Federal Food, Drug, and Cosmetic Act (FDCA) and environmental assessments were performed under the National Environmental Protection Act (NEPA).[1] Crops with resistance to targeted insects through the insertion of genetic material from *Bacillus thuringiensis* were reviewed by the U.S. Department of Agriculture (USDA; under the Plant Protection Act to evaluate if the crop could be a pest) and the U.S. Environmental Protection Agency (EPA; under the Federal Insecticide, Fungicide, and Rodenticide Act [FIFRA]) to determine if the *Bt* toxin, the insecticide produced by the plant, would cause unreasonable adverse effects to humans and the environment); product developers of these crops also consulted with FDA (under the FDCA) before commercial release to ensure the food products derived from the engineered plant were substantially equivalent to corn products already in the marketplace. These examples underscore that developers of future products of biotechnology would benefit substantially from access to timely, consistent, and unambiguous feedback from the federal regulatory system as to whether or not a product is regulated and, if so, which agency or agencies would be response for regulatory oversight.

One possible approach would be to consider the development of a single "point of entry" as a mechanism for initiating the cross-agency cooperation that is articulated in the update to the Coordinated Framework and in the *National Strategy*. Box 5-2 provides an example of what such a mechanism could look like that would operate with the agencies' existing statutory authorities. A collection of integrated resources could be maintained that provide a means for developers to initially determine if their product falls under regulation and, if so, an initial "read" on the regulatory pathway likely to be required for a future regulatory decision. A single point of entry could also provide an accessible public face for the regulatory system where interested parties can explore and understand the nature of the regulatory process. In addition, such a point of entry could be used to enable the federal agencies to decide early in the product-development cycle which authorities are relevant in cases where there have not been precedents. Throughout the process, developers would also have access to ombudsmen within each agency for additional assistance and feedback, including an opportunity to meet with the lead agency prior to a decision on a proposed oversight approach.

The concept of a single point of entry is already available for some distinct parts of the regulatory system; for example, crop developers can submit a letter to the "Am I Regulated" site[2] of

[1] In January 2017, FDA issued a draft guidance on mosquito-related products to clarify that its definition of nonfood regulated articles no longer included those "intended to function as pesticides by preventing, destroying, repelling, or mitigating mosquitoes for population control purposes. FDA believes that this interpretation is consistent with congressional intent and provides a rational approach for dividing responsibilities between FDA and EPA in regulating mosquito-related products" (FDA, 2017:6575).

[2] Am I Regulated Under 7 CFR part 340? Available at https://www.aphis.usda.gov/aphis/ourfocus/biotechnology/am-i-regulated. Accessed January 15, 2017.

BOX 5-2
Use of a Single Point of Entry for Application of Risk Analysis to Future Products of Biotechnology

Figure 5-2 describes a possible structure for providing a stratified approach to regulatory assessment of future products of biotechnology and explains how this structure could be used in a larger risk-assessment framework as an illustration of how a variety of science-based mechanisms might be useful in considering future products of biotechnology.

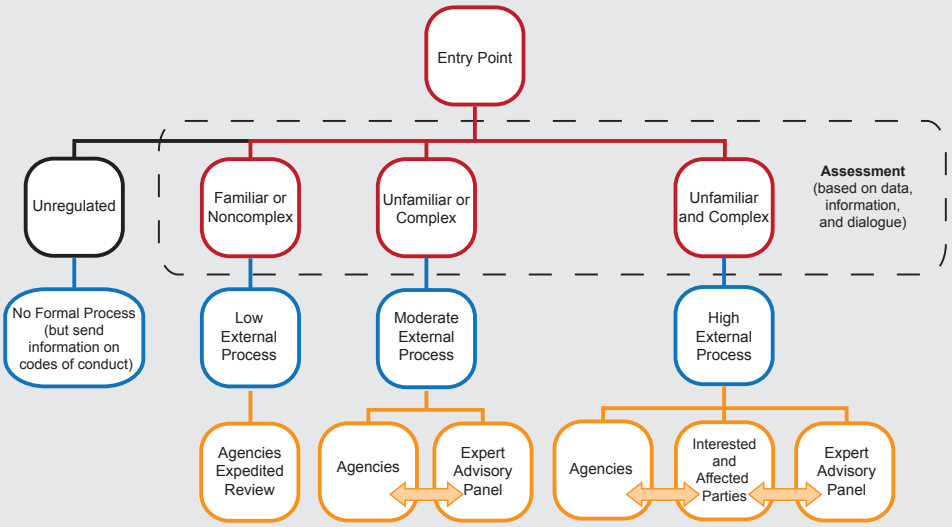

FIGURE 5-2 Providing access to the U.S. regulatory system through a single point of entry.
NOTES: Potential product developers and interested parties would begin by going to an entry point and providing characteristics of the intended product and its use pattern. If the product does not fall under a federal statute, the developer would be notified the product is not federally regulated. If the product is regulated, the appropriate agency or agencies would be identified for the developer. An evaluation of the product's familiarity to regulatory agencies and its complexity in terms of risk analyses as compared to existing biotechnology products would be ascertained (red bins). Depending on the product's familiarity and the complexity of its risk analysis, a different set of risk-analysis processes would be employed (blue boxes). For products that are *familiar* to the regulatory agencies and are *not complex*, a more expedited process could be used, under the assumption that relevant risk-analysis processes are well established. For products that are *less familiar*, *more complex*, or *less familiar and more complex*, increasingly unique risk-analysis processes (that incorporate additional external input) may need to be established.

Starting at the top of the diagram, a first query from a product developer might be to evaluate whether the intended use of the product is regulated under a given statute. Developers and their advisors (for example, legal counsel and risk-analyses consultants) can independently decide if their products are or are not regulated, but the single point of entry provides a voluntary opportunity to get input from the regulatory agencies. If the product is not regulated (the "unregulated" bin), the resources available through the point of entry could also provide information about voluntary stewardship programs if available.[a] If the intended product is regulated, the developer would be informed as to which regulatory agency or agencies have oversight. A determination would also be made as to whether the product is *familiar and not complex*, is *unfamiliar or complex*, or is *unfamiliar and complex* compared to existing biotechnology products. Products would be assumed to have increasing levels of uncertainty in risk estimates depending on the level of familiarity and the degree of complexity, but the product's actual probability of causing adverse effects, once determined, may or may not be of concern, based on the statutory requirements relevant for the product's use pattern. For products that are *unfamiliar and complex*, this process could involve external input from stakeholders and experts.

Once a determination has been made, the appropriate processes within the relevant agency (or agencies) would be used to provide the necessary risk analysis to support a regulatory decision. Products that fall in the bin of *familiar and noncomplex* could be regulated by notification (for example, some FDA and USDA actions) or a rapid, streamlined approval (for example, EPA's 90-day decision time frame for new biotechnology organisms under the Toxic Substances Control Act and its streamlined risk analyses for substantially similar pesticide products under the Federal Insecticide, Fungicide, and Rodenticide Act). Products for open release into minimally managed or unmanaged environments might be covered under a programmatic NEPA finding of no significant impact or environmental assessment, an Endangered Species Act no-effects determination or consultation, or both, as appropriate. Products that are determined to be *unfamiliar or complex* or *unfamiliar and complex* would likely require modification of or establishment of risk-analysis methods because there would be little or no existing regulatory decisions from which existing risk analyses could be directly applied. The level of effort needed to develop risk analyses would increase moving from the *unfamiliar or complex* bin to the *unfamiliar and complex* bin. There could also be additional risk-assessment tiers for some products within the bins depending on the pattern of the criteria mentioned in the text. The amount and nature of external input (see NRC, 1996, 2008, 2009) would depend on a product's level of familiarity and the degree of complexity. Assessments would also be expected for new use-pattern requests of existing products; however, depending on the similarity to an existing approved use, the level of effort for all parties could be reduced.

Following a decision, intensity of post-market surveillance or monitoring (if on a case-by-case basis it is determined to be necessary to address a risk-assessment uncertainty or assess effectiveness of a risk-mitigation measure) would be scaled with the outcome of the risk-based regulatory decision. Monitoring would likely be more intensive for open-release products associated with the *unfamiliar and complex* bin. Depending on the type of product, some may be required to undergo statutorily mandated reevaluation in specified time frames or as needed based on results of monitoring information.

A desirable feature of an integrated, stratified approach to regulatory oversight is that over time product types originally placed in the *unfamiliar or complex* bin or the *unfamiliar and complex* bin would "move" to a bin of less complexity or more familiarity based on experience gained in evaluating additional products in a category. This paradigm does not imply that products that are *familiar and not complex* necessarily have a low probability of causing adverse effects nor does it imply a product with less familiarity or more complexity necessarily has a high probability of causing adverse effects. Rather, for products that are *familiar and not complex*, the developer's and agency's risk assessors and managers and interested and affected parties can draw upon existing information and risk analyses for similar products, which should facilitate the efficiency of the regulatory decision even if a complex risk analysis is required. For products that are *unfamiliar or complex* or *unfamiliar and complex*, the risk-analysis processes may need to be developed based on limited information and experience and may perhaps require a *de novo* approach. These risk-analysis approaches would likely benefit from external scientific peer review and input from interested and affected parties. Regardless of the initial determination, risk-analysis approaches for products may become more or less complicated over time as new information from monitoring or additional laboratory and field studies becomes available. Proposed decisions to move product types between bins could include public comment and could be informed by external peer review, using best available science, and external party engagement as appropriate.

The outcome of external peer reviews of products evaluated through this process could also help inform the agencies' research agenda to support risk-assessment and risk-management decision making. In this regard the process is envisioned to reflect a design-build-test-learn paradigm in the development and application of risk-based decision making. In addition, developers for products in the *unfamiliar or complex* bin or the *unfamiliar and complex* bin could be encouraged to engage with the appropriate authorities early and while the product is still in the research and development pipeline to help guide dialogue on information needs for the assessment and streamline or target information needs for risk assessments.

While this approach does not eliminate the time and resource investments for a developer pursuing a first-of-a-kind product, data compensation measures in existing statutes, reduced registration fees for small business, and assistance grants from the small business administration, for example, could reduce the financial burden for smaller companies.

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[a]For products that do not fall under a regulatory authority, industry or nongovernmental organization consortia could develop stewardship programs or third-party certification procedures that, as appropriate, mimic principles in the proposed framework.

USDA's Animal and Plant Health Inspection Service (APHIS) to find out if the agency considers their crop a regulated article. This process lets the crop developers know earlier if their crop is regulated or not, and it lets USDA know earlier what kind of crops are being developed. The concept is also a stated intent of the *National Strategy*. Descriptions were given in the *National Strategy* for multiple online resources maintained by each of EPA, FDA, and USDA, though these were not yet integrated at the time the committee's report was written and hence product developers and other interested parties had to navigate multiple sites that reflect the complexity of the regulatory system and the agencies' jurisdictions. There are examples from the European Union that collect together various product types into a single point of entry and provide a means for public consultation in the context of allergenicity assessment.[3] A similar system for the U.S. regulatory system could provide a more easily navigated system for identifying the regulatory routes for a given product class.

It was not within the committee's statement of task to delineate how a single point of entry could be crafted and implemented. As mentioned, such a mechanism could operate within the agencies' statutory authorities and could range in concept from greater cooperation among the agencies in terms of sharing resources to more consistent and rigorous interagency working group collaboration. Alternatively, it could be operated by an existing coordinating unit within the executive branch or by a new agency created to be the "front door" for all biotechnology products, although the latter option would require new legislation from Congress. However it might be constructed, a key element of an effective single point of entry will be the establishment of criteria that provide guidance on the regulatory route that will be required. This guidance would not necessarily be exclusively consultative or structured through case-by-case deliberations. There are good examples of published guidance used within federal agencies that provide interested parties with relevant information, such as the content of agency website information regarding navigation through the system, and methodological guidance, such as EPA Guidelines for Ecological Risk Assessment (EPA, 1998) and FDA Guidance for Industry.[4] There are clear needs for this information to be improved and continually updated, and this would be an important facet of the point-of-entry implementation. Internationally, regulatory guidance is more commonly available than in the United States; examples are the European Food Safety Authority guidance developed in response to European Union directives (EFSA, 2010, 2011a,b,c). Experience elsewhere with the use of such guidance could be considered when designing a single point of entry to be used within the Coordinated Framework.

As described in Box 5-2, the criteria for which bin a product would fall into would be based on familiarity with existing, regulated products (there should be greater certainty as to how to undertake a risk assessment with a familiar product as compared to an unfamiliar product). Additional product attributes such as the degree of confinement and/or containment (greater confinement/containment should reduce the likelihood of environmental exposure), whether it is living or nonliving (a living product may increase uncertainty and unpredictability of the assessment), and reversible or nonreversible product deployment (a nonreversible deployment may increase the complexity of risk-management measures to mitigate adverse effects) need to be considered in determining the appropriate bin for a new product (see Figure 5-2). The greater the amount and specificity of information a developer can provide for a product (including a proposed risk-analysis approach) through the single entry point, the more efficiently the agencies should be able to determine the product's level of familiarity and the degree of complexity. The development and use of the multidimensional decision criteria for bin placement could be informed by external, independent peer review and input from interested and affected parties. Developers might be able to self-score their product as to the appropriate bin, but the ultimate determination would be an inherently govern-

[3]Register of Questions. Available at http://registerofquestions.efsa.europa.eu/roqFrontend. Accessed January 15, 2017.

[4]Guidance for Industry, Biotechnology Guidances. Available at http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm123631.htm. Accessed January 9, 2017.

mental decision by the appropriate regulatory authorities. The developer would be notified of the determination and provided a pointer to more information about the appropriate agency and point of contact. Consistent with the guidelines developed by the International Risk Governance Council (Renn, 2005; IRGC, 2015) and the 1996 National Research Council report *Understanding Risk* (NRC, 1996), the level of participation of outside experts, stakeholders, and interested and affected parties and the level of effort for both developer and the regulatory agencies would increase from the bin for *familiar and not complex* products through to the bin for *unfamiliar and complex* products. The model used by the International Risk Governance Council for managing different types of risk problems is illustrative of the degree of agency and stakeholder involvement that may be necessary depending on a product's familiarity and complexity (Table 5-1). Thus, as complexity increases, so does a need for engaging external experts, industry stakeholders, and interested and affected parties in the dialogue.

The method and amount of public engagement for future biotechnology products would also vary according to familiarity and complexity. Products that are *unfamiliar and complex* could require external peer review and input from interested and affected parties. The peer review and input from parties would be facilitated by one or more of the appropriate/relevant agencies—broad agency engagement is desirable if additional, future product types are envisioned to have different regulated uses. Peer review or public engagement could be designed to protect confidential business information as needed. External peer review or external party input could be used for problem formulation and then for the subsequent draft risk assessment. Iterative risk-assessment and risk-management decision making may be appropriate based on the nature and extent of the estimated risk and associated uncertainties. Peer review and engagement by external parties on potential future products could also be initiated by the regulatory agencies based on horizon scanning. Undertaking such proactive, pilot projects will increase preparedness.

A product developer would not have to use the voluntary point of entry and could independently determine whether or not their product is regulated. If it determines the product is regulated, the developer could independently ascertain the statute(s) and agency (or agencies) appropriate for the situation and directly submit the product for review; if an incorrect determination was made, the developer could subsequently work with the regulatory agencies to route the submission to the appropriate agency. A developer could use in-house expertise, private-sector consultative legal and regulatory-science expertise, or both to provide general and product-specific guidance. At the time the committee was writing its report, this practice was common within the business community for

TABLE 5-1 Escalating Levels of Expert and Stakeholder Involvement and Effort in the Management of Different Types of Risk Problems

Risk Problem	Simple	Complexity	Uncertainty	Ambiguity
Actors	Regulatory Agency Staff	Regulatory Agency Staff External Experts	Regulatory Agency Staff External Experts Industry Stakeholders Affected Parties	Regulatory Agency Staff External Experts Industry Stakeholders Interested and Affected Parties
Remedy	Statistical Risk Analysis	Probabilistic Risk Modeling	Risk Balancing with Probabilistic Risk Modeling	Risk Tradeoff Analysis and Deliberation with Risk Balancing and Probabilistic Risk Modeling

SOURCE: Adapted from Renn (2005).

dealing with regulatory issues under the Coordinated Framework. The committee recognized from the presentations it heard from startup companies and small firms and from its deliberations that this approach is currently used, especially with those businesses with some degree of in-house experience and resources, but it is not easily or routinely used by a host of smaller enterprises entering into the biotechnology product space. Therefore, a formal structure governed through collaboration among the regulatory agencies, such as that described in Box 5-2, is an important consideration for future products of biotechnology.

Risk Analysis and Public Participation

In updating the Coordinated Framework and presenting the *National Strategy*, the federal agencies have taken into account the nature of biotechnology products that were visible in 2016. In looking at the products of biotechnology that are likely to emerge in the next 5–10 years, Chapter 2 describes some of the features of future products that will challenge the system and Chapter 4 articulates some of the challenges in applying the Coordinated Framework. In moving from products that are in columns B and C to those in column D of Figure 2-6, it will be important for agencies to be prepared for products that involve substantial internal complexity, complex interactions with the environment, relatively few or no comparators to nonbiotechnology products for use in risk analysis, and have little similarity with existing biotechnology products. In this section, the committee articulates some of the features of these types of products and provides possible perspectives on how risk analysis could be performed.

Natural-science evidence, social and economic evidence, and values all influence risk analyses for future biotechnology products (NRC, 1996; Thompson, 2007; Kuzma and Besley, 2008; IRGC, 2015). Given the diversity, pervasiveness, and power of new biotechnology methods and products, public concerns that have followed and are likely to continue to follow biotechnology products into the market, and increasing complexities and uncertainties associated with anticipating the human health and environmental effects of unfamiliar and unconfined releases of biotechnology products or living genetically engineered organisms, it will become increasingly important to develop oversight systems that are adaptive, iterative (learning from past experiences or new data and information, or new concerns that emerge), and engage a wider range of expertise (Wilsdon and Willis, 2004; Stirling, 2007; Meghani and Kuzma, 2011; Ramachandran et al., 2011; Marchant and Wallach, 2015).

The social-science literature suggests several middle-ground approaches to framing future conversations that could increase public confidence in the oversight of products of biotechnology. Paradigms of responsible innovation (Stilgoe et al., 2013), critical realism (Freudenburg, 1996), strong objectivity (Harding, 1996), and analytical–deliberative risk analysis (NRC, 1996) all recognize that what is available in the empirical world is useful but also that human interpretation brings meaning to that evidence and is just as crucial. These frameworks address concerns of multiple stakeholders and disciplines, consider what evidence or risk-mitigation strategies could help address those concerns, anticipate which of biotechnology products or processes should receive greater regulatory scrutiny and which should receive less, and prepare for future concerns and products by beginning the deliberations and identifying regulatory-science needs further upstream in product development (Barben et al., 2007; Kuzma et al., 2008; Guston, 2014). Life-cycle analysis of energy, water, and chemical inputs and outputs, risk–benefit analyses, the risk of doing nothing compared to alternatives, and cultural considerations (especially to disenfranchised groups) could also be part of the oversight. These approaches will be especially important for open-release, unfamiliar applications of biotechnology such as deextinction and gene drives and for other future biotechnology products that have complex interactions and risk pathways. These approaches may also be important to provide an opportunity for future governance that is science informed, public guided, and value attentive.

A common recommendation from prior National Academies reports is the need to increase public participation in the regulatory process (see, for example, NRC, 2008). As indicated already above, it is likely that future products of biotechnology could be controversial due to their complex interactions with the environment and society, and the committee anticipates that additional concern from the public will be a common feature of many future biotechnology products. Increasing public participation in the regulatory process raises the possibility of increases in agencies' costs and inefficiencies in the overall decision-making process. Other parties may be concerned that such an approach could be fraught with complications in ensuring a balanced representation of viewpoints.

Oversight of complex and interdependent activities by their very nature requires input from multiple developers and interested and affected parties to develop and revise approaches over time. Formulating an agency approach for such complex scenarios "in secret" (bureaucratic closure) or behind closed doors with a select group of developers or interested parties (private bureaucratic learning) increases the risk of failure due to retribution from excluded participants or lack of agency capacity or statutory jurisdiction to address all the tasks needed for implementation (Moffitt, 2014). To explore these concerns, the committee considered ways additional external participation may be incorporated in those future biotechnology products that are *unfamiliar and complex*. The proposed uses of public participation and external peer review are generally consistent with a paradigm articulated by Moffitt (2014; see Figure 5-3). This paradigm acknowledges two dimensions in an agency's regulatory decision making: (a) implementation independence to implementation interdependence and (b) lack of or incomplete information and understanding to full information and understanding.

In cases where a regulatory agency has high interdependence (for example, it is supporting a future voluntary, self-regulation system where the agency depends on technology developers for oversight implementation or its decision must be integrated with input from another agency) but has a high level of information, the agency could distribute information to developers that the agency depends on as well as to the public to transparently share current information strengths and limitations to develop the oversight approach ("participatory bureaucracy"). A participatory bureaucracy can increase the chance of success by exposing any information gaps and including the values of the developers and interested and affected parties in a voluntary program. When an agency has high interdependence and a low level of information, employing participatory bureaucracy can create new information by engaging input from experts, developers, and interested and affected parties. In cases where an agency has high interdependence, a lack of knowledge, and employs a closed process for making a decision, it increases the likelihood of "eroding bureaucratic administration when it prevents bureaucrats from acquiring needed expertise, from considering helpful alternatives or from learning from experience and mistakes" (Moffitt, 2014:47). Furthermore, a bureaucratic closed or private learning approach to developing and implementing an oversight approach could increase the likelihood of challenges (legal or otherwise) due to the opaque nature of decision making and the exclusion of informed input from groups (developers and interested and affected parties alike) outside the bureaucracy or outside the limited set of groups that were invited by an agency for consultation. This perspective is consistent with the findings of numerous science and technology policy scholars who have looked at biotechnology and concluded the same (Harding, 1996; Bozeman and Saretwitz, 2005; Thompson, 2007; Meghani and Kuzma, 2011; Kuzma, 2013).

One possible approach for including external input is through the use of advisory boards implemented through the Federal Advisory Committee Act (FACA) to assess strengths and limitations of alternative risk-analysis approaches by engaging developers and interested and affected parties and gaining external scientific peer review. The employment of a FACA process does not come time or cost free, and the costs of implementing such an approach could outweigh the benefits of gaining input and advice and sharing information (Balla and Wright, 2003; Box 5-3). There are also criticisms of the use of FACA groups that include allegations of privileging specific interest groups,

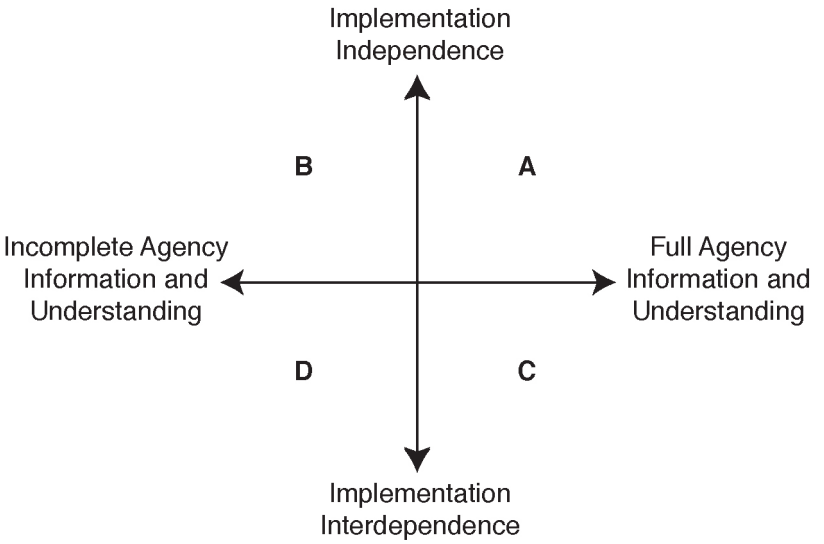

FIGURE 5-3 Participation in American bureaucracy by task-specific information and implementation conditions.
NOTES: In cases where an agency has regulatory independence and full knowledge to undertake its regulatory tasks, it could opt to make decisions "in house" and not share knowledge or decision-making logic publicly in a meaningful way (quadrant A, "bureaucratic closure"). If the agency has high independence and incomplete knowledge, it could gather information from outsiders "behind closed doors" (quadrant B, "private bureaucratic learning"). In situations where the agency has high interdependence, it could opt to share information, realizing the need to protect confidential business information, and create a process to take in and address additional information (quadrant C, "participatory bureaucratic oversight"). In cases where an agency has high interdependence but limited knowledge on an issue, it could publicly acknowledge its lack of information and initiate a public learning process to inform the future decision (quadrant D, "participatory bureaucratic learning").
SOURCE: Adapted from Moffitt (2014).

limiting use of agency expertise, promoting secrecy rather than transparency, or driving acceptance of an agency's position rather than receiving advice and input on an agency's options (Moffitt, 2014). These concerns need to be addressed in an advisory process, and the committee suggests the agencies consider the program-management and conduct-of-practices principles provided in the 2008 National Research Council report *Public Participation in Environmental Assessment and Decision Making*, which include

1. Clarity of purpose and diagnosis of context,
2. Commitment to use the process to inform their actions,
3. Adequate funding and staff,
4. Appropriate timing in relation to decisions,
5. Focus on implementation,
6. Monitoring of the process and adjusting tools and techniques as needed,
7. Inclusiveness of participation,
8. Collaborative problem formulation and process design,
9. Transparency of the process, and
10. Good-faith communication.

BOX 5-3
Studies Evaluating the Costs and Benefits of Using Federal Advisory Committees

There appear to be a small number of published studies that quantitatively compared the costs or time in making regulatory decisions with and without receiving input and advice from a federal advisory committee authorized under the Federal Advisory Committee Act (FACA). Studies that have been undertaken are limited to the FDA FACA committees that provide advice and input on new drug applications and premarket device applications (Lavertu and Weimer, 2010; Moffitt, 2014). These committees are comprised of individuals with expertise regarding the drug or device application at hand and include scientific and medical experts as well as representatives of relevant industry, consumer, or patient groups. The committees are typically used when the means to address the uncertainty in the costs and benefits of the decision exceed FDA's technical capabilities or capacity (low knowledge) and/or when the decision has numerous interdependent tasks (i.e., implementation tasks that may be required of the drug manufacturer, physicians, etc.), which if not addressed effectively increase the likelihood of implementation failure.

Moffitt (2014) reported that when taking into account drug risks, those drugs that received an advisory review were significantly less likely to have black box warnings[a] required on their labels due to post-market adverse effects and less likely to be withdrawn from the market. Although the costs of using an advisory committee were not compared to the costs of developing and issuing a black box label or implementing and enforcing a market withdrawal, it seems reasonable to assume such costs to FDA and the risks to users of the products would be higher than a scenario where the likelihood of future adverse effects were identified prior to market approval.

Lavertu and Weimer (2010) analyzed advisory committee reviews of new drugs and devices over the period 1997–2006. These authors reported that the time taken to approve a drug was not significantly longer when input from the FACA committee was requested; however, decisions for medical devices did take longer when referred to the advisory committee. For new drugs, it took FDA an average of 526 days to make an approval without advice from the committee and an average of 525 days when the committee was convened. Of note, in those instances when the advisory committee reached consensus on an approval decision, the time for an FDA decision was 456 days on average, which includes the time to manage the advisory committee process. These findings indicate that consistent external advice and input can significantly reduce decision time, but even in those cases where committee advice does not resolve the uncertainties identified by FDA, presumably the input further enhances the agency's decision documentation but not at the expense of increasing the overall time to a decision. A comparison of the time taken to make a rejection decision with and without advisory committee advice was not possible since the number of rejection decisions and the time taken for those decisions when the advisory committee was not convened are not readily available.

While there are no published analyses of the costs and benefits of EPA's use of its Scientific Advisory Panel (FIFRA required a FACA committee to provide external, scientific peer review to EPA on pesticide risk-assessment issues), decision review times are estimated to be 6 months longer with a science advisory panel (SAP) review of a plant-incorporated protectant risk assessment and registration service fees (which cover, in part, EPA's costs for reviewing pesticide applications) are approximately $60,000 higher.[b] EPA indicates that its use of the SAP is for when scientific data for a decision are complex. EPA further notes that it

> often seeks technical advice from the Scientific Advisory Panel on risks that pesticides pose to wildlife, farm workers, pesticide applicators, nontarget species, as well as insect resistance, *and novel scientific issues surrounding new technologies* (emphasis added). The scientists of the SAP neither make nor recommend policy decisions. They provide advice on the science used to make these decisions. Their advice is invaluable to the EPA as it strives to protect humans and the environment from risks posed by pesticides. Due to the time it takes to schedule and prepare for meetings with the SAP, additional time and costs are needed.[c]

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[a]Black box warnings appear on prescription drug labels to call attention to serious or life-threatening risks. See FDA (2012).

[b]PRIA Fee Category Table – Biopesticides Division – PIP. Available at https://www.epa.gov/pria-fees/pria-fee-category-table-biopesticides-division-pip. Accessed September 14, 2016.

[c]Ibid.

Ginsberg (2015) also noted that an effective FACA process entails securing clear agency commitment; finding a balance between responsiveness to the agency and independence; leveraging resources through collaboration with similar FACA groups; and evaluating a FACA group's usefulness to identify future directions or improvements.

The committee also reviewed the potential role stakeholder rulemaking and private standard setting could play in enhancing efficiency in the proposed decision-making framework. The committee concluded in some circumstances these approaches may be preferable to a FACA process or a process in which the agency independently establishes and implements a regulatory process or requirement (see Box 5-4).

TECHNICAL TOOLBOX AND CAPABILITIES FOR RISK ASSESSMENT AND REGULATORY SCIENCE

The committee synthesized information received during public meetings, webinars, and the results of National Academies reports (NRC, 2013; NASEM, 2016a,b), symposia (Drinkwater et al., 2014; Roberts et al., 2015), and relevant publications to identify gaps in risk-analyses tools and possible approaches that could be advanced to close these gaps. Addressing these gaps through a design-build-test-learn paradigm can help support development of a responsive research agenda and staffing plans for enhancing existing capacity, capability, and expertise needed for efficient and sound evaluations of future products of biotechnology. Separately, the tools and technologies used by product developers could be enhanced to ensure a higher probability of success in navigating the regulatory system. Finally, the committee identified specific needs in the area of regulatory science. The committee recognizes that the tools and techniques described here require a depth of data and analysis that may be inconsistent with the degree of risk that can be anticipated for many future products of biotechnology. Their blanket application would be inconsistent with tiered risk-assessment strategies and with the capacity available in the public and private sectors. The intent of the committee is to highlight the emergence of these approaches and their application for clarification of regulatory understanding of future products, especially when qualitative or deterministic risk analyses are uncertain as to whether they are incorporating well-characterized, worst-case assumptions to support the safety standard associated with risk-management decision criteria (see Box 4-2).

Implementation of Probabilistic Risk Analyses Associated with Future Products of Biotechnology

As discussed in Chapter 4, probabilistic risk analysis has not been widely used in the regulation of biotechnology products. However, the use of quantitative risk assessment is well established in many fields and is applied to questions of ecological, food-safety, biosecurity, and biological risk. The most common application of quantitative risk assessment for biotechnology products is for the purposes of insect-resistance management of *Bt* crops (Storer, 2003), but there are also examples of quantitative nontarget-species ecological risk assessment (Sears et al., 2001), dietary exposure assessment (Exponent, 2005), and endangered-species risk assessment (Peterson et al., 2006) that have been used for regulatory decision making. The Coordinated Framework would benefit from fuller implementations of probabilistic methodologies when appropriate in light of challenges to the regulatory system that are expected to occur. This section proposes the need for more probabilistic risk assessments than were conducted when the committee was writing its report. In addition, this section discusses the need to conduct risk analyses that are proportional to the quantitative risks assessed to prevent the problem of "second-order risk" (that is, the risk of missing a significant risk versus the risk of overanalyzing a negligible risk).

BOX 5-4
Stakeholder Rulemaking: A Potential Process for Public Participation

A potential alternative or complement to using a Federal Advisory Committee Act (FACA) process or public rulemaking could be stakeholder rulemaking. As summarized by Weimer (2006) and Weimer and Wilk (2016), Congress must authorize an agency to employ stakeholder rulemaking, including use of agency funds for implementing and supporting the process to ensure continuity. Congressional authorization creates a nongovernmental organization (NGO) that is charged to develop and adopt rules for a specific function or activity. Typically, the NGO has an executive board and supporting committees that include experts in the relevant fields as well as interested and affected parties. Meetings of the NGO's committees are open to the public. The NGO has an established charter to formulate rules under a specified voting procedure. A rule developed by the NGO based on majority vote can be implemented immediately because the necessary actions required by the rule are carried out by the members of the NGO. A stakeholder rule does not impose legally binding rules. However, if members of an NGO reach a consensus on a private rule, an agency could proceed with formal rulemaking. Current examples of stakeholder rulemaking include those made by the Internet Corporation for Assigned Names and Numbers, the Organ Procurement and Transplantation Network, and eight regional fish councils that have sole jurisdiction in devising fishery regulations.

A potential strength of stakeholder rulemaking is technical efficiency. Stakeholder rulemaking is likely to be technically efficient when the major stakeholders in an NGO have a stake in the outcome and the required expertise can be employed more rapidly than possible by the agency alone or through public rulemaking or a FACA process. It is important to note that while stakeholder rulemaking can be more technically efficient, the outcome of the rule may or may not be desirable to all interested and affected parties (Weimer, 2006).

A less expansive form of stakeholder rulemaking is private standard setting (Weimer, 2006). Organizations such as UL (previously known as Underwriters Laboratories), the American Society for Testing and Materials, and the American National Standards Institute maintain a wide range of standards. Industry committees that coordinate generally recognized as safe (GRAS) analyses and propose determinations for food flavoring[a] and cosmetic ingredients[b] have been in place for decades. Private standards are not legally binding and do not involve an explicit delegation of rulemaking authority, but they can be adopted by regulatory agencies and be required in private contracts. The standards can support market claims for products, thereby providing a competitive advantage, which in turn can drive compliance.

In the context of the committee's illustrative decision-making framework for the Coordinated Framework, a stakeholder rulemaking process may have merit for classes of products that may not clearly fall under a specific statute (for example, products that are not plant pests) or for products that may potentially fall under multiple statutes. Stakeholder rulemaking could also be employed to more efficiently develop and modify decision making for classes of products within the *familiar and noncomplex* bin, to optimize notification procedures and establish protocols for data sharing among developers. Private standard setting could be employed for future consumer products and food additives, to establish testing methods for data needed to support risk assessments, and for establishing information knowledge bases and metadata requirements to support developers and agency risk assessors.

[a]See, for example, Flavor & Extract Manufacturers Association, About the FEMA GRAS™ Program. Available at http://www.femaflavor.org/gras. Accessed January 9, 2017.

[b]See, for example, Cosmetic Ingredient Review. Available at http://www.cir-safety.org. Accessed January 9, 2017.

Biotechnology products are diverse and therefore may vary in their associated risks. That is, some biotechnology products could be used with a lower probability of risks (for example, crops genetically engineered with insect resistance or bacteria within bioreactors that are similar to engineered products already in commerce with a familiar risk profile) while other biotechnology products may have uncertain risks at greater spatial and temporal scales to consider (for example, organisms with gene drives or genetically altered bacteria released into an open environment). For

better understood products, available information from analogous systems or organisms or analyses of the published literature (for example, meta-analyses or pathway analyses) may suffice to assess associated risks. In contrast, unfamiliar products for which there is not a sufficient baseline of information may require more sophisticated quantitative analyses to estimate their associated risks. In cases of high uncertainty, data may need to be generated to be able to estimate risk with acceptable confidence.

Probabilistic approaches are summarized by recent National Academies reports and the scientific literature (for example, Suter, 2007; Warren-Hicks and Hart, 2010; NRC, 2013; NASEM, 2016a). A National Research Council report (NRC, 2013) described three principle steps in preparing a probabilistic risk assessment, which the present committee concludes are also applicable for assessing risks of biotechnology products:

- Describe uncertainty for variables with distributions (realizing all variables in a model need not require the same degree of data intensity).
- Propagate uncertainty through distributions of exposure and effects variables.
- Integrate exposure and effect estimates to calculate risk probabilities.

Example calculation methods include Monte Carlo analyses, Bayesian methods (some of which also use Monte Carlo simulations), and uncertainty bounding analyses (Warren-Hicks and Hart, 2010; NRC, 2013; NASEM, 2016a). At the time the committee was writing its report, probabilistic approaches were rarely implemented in ecological risk assessments for chemical pesticides (NRC, 2013). On the basis of the committee's limited survey of existing risk assessments, environmental assessments, and environmental impact statements for biotechnology products, probabilistic analyses have seldom been undertaken. The committee believes that the risk analyses customarily conducted in environmental assessments and environmental impact statements required by NEPA may be inadequate to characterize the risks of certain future products of biotechnology. The committee found no statutory restriction that precludes the regulatory agencies from conducting quantitative risk assessments.

The further need for quantitative approaches for human health and environmental safety involves questions of multiple exposures, complex mixtures, and vulnerable populations, which represent broad stakeholder concerns often considered to be inadequately captured in risk analyses. A recognized need in quantitative risk assessment is improved cumulative risk assessments combining risks of aggregate exposure to mixtures that include all routes, pathways, and sources (NRC, 2009). Revision and extension of existing approaches to cumulative risk assessment will be needed to fully analyze future products of biotechnology.

Even under conditions of unfamiliarity and complexity, probabilistic risk assessments can be used to identify where information is missing. Several researchers from the Commonwealth Scientific and Industrial Research Organisation in Australia have used a combination of stakeholder, expert, and public input; Bayesian elicitation; and fault-tree analysis to develop and quantify (with uncertainty) risks from genetically engineered fish (Hayes et al., 2014) and genetically engineered insect pests (Murphy et al., 2010; Murray et al., 2016). These serve as models for both probabilistic risk analysis and public engagement in an analytical–deliberative process (NRC, 1996).

The quantitative risk analyses discussed above support the means to refine risk analyses by incorporating new data through iterative assessments and enable risk assessors, risk managers, and stakeholders to refine risk-management options as needed to meet the regulatory standard for a safety finding (NRC, 2013). An established probabilistic risk-assessment framework for a given product for a suite of use-pattern scenarios (such as those proposed in Chapter 4) also can facilitate timely updates to risk estimates based on new information and help form hypotheses for causes of unexpected risks that may emerge.

The regulatory agencies vary in the degree in which risk-assessment tiers can be implemented in concert with risk-management needs. For example, EPA's pesticide risk-analysis approach uses risk-assessment tiers with increasing resolution based on the results of lower-tier risk assessments, the endpoints of concern, and the nature of requested use patterns. In addition, EPA can implement a higher-tier risk assessment to refine an existing assessment, based on adverse-effect information submitted through Section 6(a)2 of FIFRA (40 C.F.R. Part 159)[5] and Section 8(e) of the Toxic Substances Control Act (TSCA).[6] In addition, FIFRA requires EPA to reevaluate registered pesticides at least once every 15 years to ensure the existing risk analysis and regulatory decision are current with the state of the science and policy (40 C.F.R. Part 155).[7] It is more difficult for USDA–APHIS to implement iterative risk analyses because the agency as of 2016 did not have authority to reassess products once they were deregulated (McHughen and Smyth, 2008).

Ecological Risk Assessment Within the Context of Future Biotechnology Products

Ecological risk assessment for future biotechnology products and their release scenarios will necessitate more emphasis on measurement and modeling of effects to populations and communities within landscapes than has been necessary with biotechnology products regulated in the 1990s and 2000s. Further challenges arise regarding the biological responses that are used to determine effects to entities of concern for ecological risk assessment (Forbes et al., 2001). The relationship between lethal and sublethal effects to individuals and the survival and reproduction of populations is a continuing uncertainty in the ecological risk-assessment process (NRC, 2013). Typical laboratory toxicity tests focus mostly on individuals through measurements of lethality, growth rate, or both and occasionally have been extended to measures more directly representative of populations (reproductive success). Field-scale studies may more fully encompass populations and communities through consideration of abundance for greater numbers of taxa (Naranjo et al., 2005). An emphasis in ecological risk assessment on individuals in and near production fields is logical and has been successful in understanding single-stressor effects within fields of genetically engineered crops as of 2016.

The environments in which some future biotechnology products will be deployed, however, will represent a dynamic temporal–spatial mosaic where multiple novel stressors with sometimes overlapping effects are being introduced at large geographic scales such as a watershed or geopolitical region and where there may be incomplete quantitative description of effects on populations. Simple approaches for lower-tier screening that may consider effects that may scale in the environment include simple functional ecology models based on life statistics for trophic–functional types to determine the magnitude of effect necessary to become evident in the ecosystem (Raybould et al., 2011) or considerations of aggregate sensitivity to species occurring within the environment (Wolt and Peterson, 2010; Wolt, 2011). These approaches, however, still place boundaries on the system to encompass limited spatial and temporal scales, thus leaving unanswered changes occurring in the contiguous landscape over time. Future products of biotechnology designed for open release in minimally managed or unmanaged environments will introduce an increasing diversity of potential environmental stressors that will necessitate improved ecological risk assessment to forecast potential effects with a view toward understanding and managing ecological services at the landscape level. The limitations of species-specific modeling and measurement in landscapes

[5]Incident Reporting by Pesticide Manufacturers/Registrants. Available at https://www.epa.gov/pesticide-incidents/incident-reporting-pesticide-manufacturers-registrants. Accessed September 14, 2016.

[6]Reporting a TSCA Chemical Substance Risk Notice. Available at https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/reporting-tsca-chemical-substantial-risk-notice. Accessed September 14, 2016.

[7]Registration Review Process. Available at https://www.epa.gov/pesticide-reevaluation/registration-review-process. Accessed September 14, 2016.

argue for a more generalized approach focusing on functional groups and their distribution and density among elements within the landscape (Caron-Lormier et al., 2009, 2011) for certain products intended for open release in low-management environments.

To explore how ecological risk assessment might be applied, government agencies could pilot advances in ecological risk assessments and benefit analyses for open-release products expected over the next 5–10 years. Aspects to be explored could include external, independent peer review, public participation, and whether agencies' staff will need new skills on quantitative risk-assessment practices. Risk assessors have used stakeholder and public-informed processes for broader ecological risk analyses of genetically engineered crops and fish to incorporate on-the-ground knowledge and values associated with multiple ecological and societal risk-assessment endpoints, especially in stages of problem formulation and risk-management options (Nelson et al., 2004; Kapuscinski et al., 2007). Multicriteria approaches to choose ecological indicators for risks to biodiversity and fault-tree analysis have also been applied to genetically engineered plants (Andow et al., 2013). These examples point to integration of multiple risk-assessment endpoints, modeling approaches, and societal values in the risk-assessment process. The agencies would benefit from a review of over two decades of literature on iterative and engaged methods of risk analysis for transgenic organisms.

Public–private investments in new environmental risk–benefit analytical approaches, including the identification of information needs; the development of assay methods and laboratory and field-study designs and monitoring protocols; and models (conceptual through computational) to inform risk assessments across appropriate biological, spatial, and temporal scales can also be used to address potential ecological outcomes associated with future open-release biotechnology products.

Enhancing the Capabilities, Expertise, and Tools of Regulatory Agencies

In the previous sections of this report, needed risk-analysis knowledge and technological capabilities were noted. Chapter 2 describes types of future biotechnology products, many of which will not have obvious comparators to nonbiotechnology products and in turn may require a new generation of risk-analysis approaches. Some of the use patterns for future products also highlight the need for developing spatially and temporally explicit risk-assessment capabilities. In addition, Chapter 2 points to the potential increase in the sheer number of products that may need to be assessed in the future, which highlights the need for an effective, high-throughput risk-analysis system. In Chapter 4, the need for probabilistic assessments to better interpret comparative risk assessments and management options was introduced. The above section "Consistent, Efficient, Effective Decision-Making Processes for Future Products of Biotechnology" also raises the need for assessing similarities and differences among biotechnology products and anticipates a stratified assessment process that in some cases will be highly reliant on access to existing risk-analysis data or data summaries for biotechnology products already in the market. To this end, a suite of publicly available physical and computational models and methodologies that can be accessed for risk assessments with different degrees of complexity would be helpful. Examples of sampling designs and indicators to support post-market surveillance and monitoring programs would also be beneficial.

To organize the discussion on risk-analysis tools needed for products expected in the next 5–10 years, the committee adapted categories of future research needs prepared through workshop deliberations addressing the need for a research agenda exploring the ecological implications of synthetic biology (Drinkwater et al., 2014) and a workshop and Delphi study on synthetic-biology governance (Roberts et al., 2015). The research areas identified to address gaps in risk analyses include many of those the committee sought information for in its request for information (RFI) to federal agencies (see Chapter 4 and Appendix C): comparators, off-target gene effects, and phenotypic characterizations; gene fitness, genetic stability, and horizontal gene transfer; control

of organismal traits; monitoring and surveillance; modeling and life-cycle analyses; and economic and social costs and benefits. The responses to the RFI indicate that some work is being done in these areas, but the committee thinks it is likely insufficient for the number and kinds of biotechnology products the agencies can expect to see. The committee also identified molecular characterization and standardization of risk-analysis methods and data management as areas in need of research.

Comparators, Off-Target Gene Effects, and Phenotypic Characterization

As discussed earlier in this chapter, there is a need to advance quantitative comparisons that can facilitate assessment of future biotechnology products. A key characteristic of the risk-assessment process in use at the time the committee was writing its report was comparability between biotechnology products and their nonbiotechnology counterparts. However, as noted in Chapter 4, the use of nonbiotechnology comparators is becoming more challenging. Transformations can be made in host organisms that are not well characterized, and there may not be baseline data on the nontransformed counterpart host. Furthermore, some new biotechnology products may contain only synthetic DNA, which would have no nonbiotechnology counterpart. Therefore, the idea of "comparator" may need to expand to include similar existing biotechnology products with which regulatory agencies already have experience.

Methods to quantitatively compare products will be needed for determining which bin is appropriate for a new product; selecting data from other product data sets for screening-level risk assessments or problem formulation; selecting data to use in effects or exposure analysis steps in a risk assessment; and selecting data to generate a risk characterization of a new product and/or place a characterization of a new product in context with an existing, similar product. Elements of a risk assessment are typically considered against baseline nonbiotechnology comparators to address whether, other than the intended change of the modification, the observed attributes of the transformed organism represent a substantive change relative to the comparators. The degree of uncertainty in making comparisons will need to be quantified given that different risk-assessment steps or scenarios can tolerate different levels of uncertainty at key decision points; that is, findings in risk assessments are worded in language specific to the statute under which they are being evaluated, but in every instance represent an "as safe as" determination.

Research approaches need to address questions raised by risk assessors and managers concerning comparisons that are context specific and reflect the need to assess similarity across levels of biological organization and spatial and temporal scales. Issues and questions raised in risk analyses can inform development of a research agenda. For example, products may be comparable at one level of biological organization, but not at other levels (for example, target genes and off-target genes and their expression, to protein structure and function, to biochemical function, tissue/organ function, organismal, population, and community effects). There may be variability in comparability for the same biotechnology product under different environmental conditions. Products may be comparable in terms of affecting a common physiological function, but the mechanisms by which they initiate the physiological responses could be very different. Some products may be comparable in terms of the genes being manipulated, but the commercial application of the products and their use patterns may be different. Depending on the risk-analysis question, the products may be considered comparable (that is, two open-release products initiate perturbations in the same invasive weed organism in a similar manner, but with some differences in off-target gene effects), but in the context of their environmental-effects analysis and their impact on nontarget organisms they may or may not be comparable: If one product has been deployed in Gulf Coast estuaries, how comparable will its effects be to the other product's effects if it is intended for open release in estuaries along the U.S. mid-Atlantic coast?

Research in this area will also need to support computational approaches for estimating missing data from data available for existing, comparable products and identifying gaps in specific information that may require targeted testing. A systematic approach, taking advantage of horizon scanning, to establish the biological knowledge bases needed to inform computational similarity analyses systems and develop decision-support systems to facilitate analyses will also be needed.

In addition to comparators, research on phenotypic characterization is also needed to advance understanding of trait function and potential ecological consequences over the short and long term as well as understanding on how environmental context can affect phenotypic expression.

Gene Fitness, Genetic Stability, and Horizontal Gene Transfer

Engineered organisms that reproduce can suffer mutations that affect the physiology of the organism, leading to the potential for "instability" in the genome (engineered genetic constructs mutating in ways that could cause loss of function). In addition, many organisms can incorporate DNA from their environment, leading to the possibility of horizontal gene transfer.[8] Techniques to measure these properties, including how these properties may vary with different environmental interactions, are needed. This research area includes evaluation and advancement of environmental models to assess properties; engineering for unanticipated interactions; developing standardized metrics and quantitative thresholds; and the interplay of fitness and stability, especially if an organism loses its containment mechanism.

Future approaches for risk assessment can be more streamlined, less costly, more comprehensive, and unbiased by utilizing state-of-the-art assay tools—for example, automated high-throughput biochemical assays, next-generation DNA sequencing, and advanced mass spectrometry technologies—integrated with high-capacity data storage and analytics. Rather than obtaining a targeted snapshot of single-few genomic loci via Southern blot, polymerase chain reaction, or Sanger sequencing to characterize a genetic modification, risk assessment at the molecular level should leverage recent advances in next-generation DNA sequencing and associated whole-genome sequence information to obtain an unbiased assessment of both the targeted and off-target genetic modifications in the species, whether altered by biotechnology or not (Pauwels et al., 2015). Similarly, untargeted mass spectrometry for metabolomics and proteomics is one approach for enhanced safety assessment of biotechnology products because it provides an unbiased assessment into potential pleiotropic effects derived from a modified organism (Ryals, 2016).

Control of Organismal Traits (Containment and Confinement)

Given that open-release products are deployed in dynamic environments, quantitative assessments of the safety, security, and stability of biotechnology-derived organisms should be tailored for the proper context. Metrics to test for biotechnology-derived organisms in open environments should measure

- Intrinsic biocontainment (i.e., escape frequencies into the natural environment),
- Genetic isolation (i.e., flow of horizontal gene transfer),
- Watermarking (i.e., unique sequence identifiers in the genomes of biotechnology-derived organisms), and
- Functional impact on the environment, including on nontarget organisms.

[8]Horizontal gene transfer is common in nonbiotechnology organisms.

Possible areas of research include biocontainment schemes that can be adaptive to different intended applications, environmental settings, or both; establishing redundant, stacked containment approaches; and assessing the reliability of engineered reversibility.

Monitoring and Surveillance

Following completion of a premarket risk assessment, with a decision to allow the use of the products under specified conditions, there may be a need for monitoring or surveillance to evaluate specific assumptions in risk assessments, to address uncertainties in the evaluation of a risk hypothesis in an assessment, to assess the effectiveness of any required risk-mitigation measures, or all the above. In instances where products enter the marketplace through a notice to the appropriate regulatory agency, post-market monitoring or surveillance may be used to determine if future risk analyses and potential risk mitigation may be needed following use of the products (for example, cosmetics). To ensure data obtained from monitoring or surveillance address risk-management needs, designs and indicators need to be developed to directly address specific areas of uncertainties and risk hypotheses.

Examples of questions that may need to be answered through monitoring and surveillance for different types of products include the following:

1. What is the current baseline of allergic responses to certain classes of cosmetics and the contribution of specific products? Has the introduction of a new class of living cosmetics increased or decreased the rate of allergic responses?
2. Has the removal of contaminants by a consortium of microbes at a site met the remediation goals, has the consortium been confined or contained as planned, and is the habitat responding as predicted?
3. Has the introduction of a gene drive to suppress a pest population achieved the suppression as predicted, and has the ecosystem responded as predicted with the removal/suppression of the target pest? If not, why not? Has the gene drive appeared somewhere it was not supposed to (that is, in a nontarget organism)? Has the gene drive mutated?
4. Are the discharges of living engineered microorganisms into publicly owned treatment works or receiving waterbodies altering existing microbial communities in an unanticipated manner?

The sampling designs for monitoring and surveillance—for example, stratified, probability-based survey designs or fixed-site sampling programs at the national, regional, state, or watershed scale—will need to be established to address specific questions that arise for specific products or types of products. Frequency of sampling also needs to be established for addressing specific questions. Perhaps some questions concerning future biotechnology products could be integrated within existing monitoring programs (with inclusion of new indicators), while other questions may require unique monitoring programs, sampling designs, and diagnostic indicators. Although open-release products will offer little opportunity for environmental recall should unanticipated ecological effects be observed, the committee observed that environmental release in managed versus unmanaged or low-management conditions presents differences in complexity that will influence monitoring designs and potential variations in risk management.

Research to support monitoring and surveillance will be needed to assess movement and effects of specific product applications and may also be needed to provide a broad-based assessment of environmental conditions. Indicators will be needed to assess status and trends at the molecular level (for example, metagenomics) and to track changes in structural or functional attributes of ecosystems. Monitoring designs and protocols will likely be established and directed for specific

issues, but research is needed to ascertain the extent to which data sets derived with different survey features and indicators can be integrated to maximize the use of available resources.

Modeling and Life-Cycle Analyses

Both physical and computational models will be needed to help inform uncertainties in risk assessments. Physical models, such as mesocosms or controlled field studies, can provide information in specific places and time periods. For example, mesocosm experiments with GE versus wild-type Japanese medaka (*Oryzias latipes*) were used to assess gene flow over time in the life cycle of the fish (Pennington et al., 2010), indicating that such studies are possible and exist in the academic literature but are not routinely used in USDA or FDA assessments with live organisms. Computational models can be used to support the development of conceptual models within the problem-formulation phase of a risk assessment and to predict ecological and evolutionary responses in other places and time frames (that is, over decades rather than several years) that cannot be evaluated with a physical model. In some cases, the findings of a computational model may be needed prior to undertaking outdoor studies to help ascertain if there is an acceptable level of risk to undertake a study. Results from a computational model can provide insights for designing experiments with physical models. Optimally, collection of data through the use of physical models and computational models develops iteratively, each informing the other (NRC, 2007). Furthermore, a 2007 National Research Council report (2007:102–103) recommended

> Using adaptive strategies to coordinate data collection and modeling should be a priority of decision makers and those responsible for regulatory model development and application. The interdependence of measurements and modeling needs to be fully considered as early as the conceptual model development phase. Developing adaptive strategies will benefit from the contributions of modelers, measurement experts, decision makers, and resource managers.

Research is needed to advance physical (for example, microcosms, mesocosms, and controlled field studies) and computational models to improve understanding of the ecological implications of genome engineering and to reduce uncertainties in predicting future ecoevolutionary dynamics over time frames of years to decades, which will support life-cycle analyses. Identifying gaps in current physical and computational models is needed to prioritize desired, future capabilities.

Physical Models. Microcosms, mesocosms, and controlled field studies are approaches to generate data that can reduce uncertainty in assessing potential effects across levels of biological organization, space, and time (Drinkwater et al., 2014). The 2016 National Academies report on gene drives articulated a phased testing approach for gene drives that includes research preparation, laboratory research, field research, staged environmental release, and post-release surveillance to gather information to support risk assessments and risk-mitigation measures to reduce potential nontarget effects (NASEM, 2016a). That report also provided examples of field and environmental field research for biocontrol and existing engineered organisms. External peer reviews of effects of herbicides in aquatic ecosystems (EPA, 2012b) and effects of insecticides on honey bees (EPA, 2012a) also provide insights on the design and execution of mesocosm and field studies that are intended to support ecological risk assessments. Clarity in ecosystem definition and model system design (for example, its size and composition), type of risk-assessment endpoints and responses measured (including recovery of community structure and function), and approaches to interpret and extrapolate data are important features of successful studies.

Although the need for undertaking field studies to evaluate future biotechnology products is recognized, EPA in 1992 determined that field studies or mesocosm experiments for pesticide registrations would no longer be required due to uncertainty in data interpretation and a conclusion

that the information gained from such studies did not alter risk-assessment conclusions based on data derived from laboratory studies (EPA, 2004). The agency can, however, conditionally require mesocosm and field studies for chemical pesticides[9] and plant-incorporated protectants (Rose, 2007) on a case-by-case basis. USDA–APHIS uses a similar rationale for tiered testing regimes extending from the laboratory to the field. The current, limited experience in using results from physical models to inform ecological risk assessments indicates proactive research is needed on the development of study designs and risk-analysis methods for future open-release biotechnology products. Pilot efforts could be undertaken to develop and evaluate new approaches for using physical models to assess population, community, and ecosystem effects. Advances should be linked to the design-build-test-learn cycle and the scaled release of biotechnology products (from laboratory scale to small field trials, larger field trials, and eventually full-scale deployment). Consistent with this perspective, the 2016 National Academies report on gene drives (NASEM, 2016a) noted that support mechanisms for risk assessment, public engagement, and governance will be needed throughout a phased testing scheme.

Computational Models. Some future biotechnology products could be assessed with a high degree of specificity concerning spatial and temporal dimensions (for example, bacteria within bioreactors) while assessments for other biotechnology products have a more complex dimensionality to consider (for example, open-release organisms with gene drives and genetically altered bacteria consortia for open release). For new products, probabilistic risk assessments that can use information and methods available for analogous systems and organisms may be completed with a lower level of effort as compared to assessments involving unfamiliar products or products with more complex spatial and temporal use patterns. As the complexity of an assessment increases (dimensionality and number and nature of the risk-assessment endpoints), computational models to support more sophisticated quantitative analyses to estimate ecological risks and evolutionary responses will likely be required because existing assessments that provide baseline information or methods will be limited. Modeling will also support life-cycle analyses for existing and future products and can be used to help inform the socioeconomic tradeoffs associated with oversight decisions. These modeling efforts will entail integration with existing approaches to assess water and fossil-fuel utilization and other ecological goods and services.

The risk estimates and descriptions in human health and ecological risk assessments for existing biotechnology products are typically qualitative in nature; however, certain portions of an assessment may be quantitative, such as for estimates of human dietary exposure assessment or determining nontarget species sensitivity. The current assessments may provide a limited discussion of the uncertainties associated with risk estimates with the overall risk-assessment conclusion based on the perspective that assumptions used in a risk assessment will provide an adequate margin of safety. The influence these assumptions have on a quantitative estimate of risks needs clarification.

In the development cycle of future models to estimate risks of biotechnology products, the committee supports the 2007 National Research Council report (NRC, 2007:161) recommendation that model *evaluation*, rather than *validation*, be employed:

> Model evaluation is the process of deciding whether and when a model is suitable for its intended purpose. This process is not a strict verification procedure but is one that builds confidence in model applications and increases the understanding of model strengths and limitations. Model evaluation is a multifaceted activity involving peer review, corroboration of results with data and other information, quality assurance and quality control checks, uncertainty and sensitivity analyses, and other activities.

[9]See 40 C.F.R. Part 158.

Economic and Social Costs and Benefits

As discussed in Chapter 2, biotechnology products can have economic and social benefits, but they also frequently involve economic and social risks and tradeoffs. How important concerns about future biotechnology products are in comparison to the benefits provided depends on the social and cultural position of different communities, interpretation of evidence, context, and an individual's and social group's perception of risk and technologies. Research that teases out the social and economic tradeoffs involved in developing (or not developing) a biotechnology product is important for responsible decision making about technological development. However, the committee understands that social and economic research is not within the remit of every regulatory agency. Analyses that go beyond the direct health and environmental effects of biotechnology may be conducted by product developers, academe, and think-tanks. These analyses can be helpful to regulatory agencies when communicating about the possible risks and benefits involved in biotechnology products and in increasing public understanding about the science of risk assessment and the limitations of regulatory risk assessments. More research on how to consider the multiple socioeconomic, cultural, and indirect health effects of biotechnology products is needed, as these studies are not typically funded by current government programs (see Chapter 4).

Molecular Characterization as a Preliminary Assessment Tool

Molecular characterization of biotechnology products can provide important precursor information that can guide the direction and extent of human health and ecological risk assessments necessary for regulatory decisions (Corrigan-Curay et al., 2015). For instance, for the case of genome-edited plants, the use of whole-genome sequencing and/or evaluated bioinformatics models can establish the frequency of off-target mutations within the genome resulting from CRISPR-Cas9 genome editing and therefore addresses the probability for indirect downstream effects from the genome-edited product (Wolt et al., 2016). Establishing that off-target gene mutation frequencies are at or below natural mutation frequencies also indicates that nontransformed plant varieties may be appropriate comparators for genome-edited varieties. Similarly, molecular characterization can determine if CRISPR-Cas9 reagents are removed in breeding selection by establishing that transgenic elements are absent, and this can provide assurance that a gene drive has not been accidentally released as an unintended residual effect of genome engineering (Akbari et al., 2015).

More generally, advanced molecular approaches provide a possible avenue to address potential ecological risks through proper design and interdiction or elimination of poor design in biotechnology products. Such molecular characterization is critical for early screening to triage (potential) products into bins based on familiarity and/or complexity and therefore appropriately direct regulatory-science resources; this is particularly valuable as the pace of product innovation increases and stresses the regulatory system.

Standardization of Methods and Data

New approaches to conduct risk assessment will leverage state-of-the-art tools and capabilities from high-throughput and automated experimentation in genomics, metabolomics, and proteomics to site-specific and potentially national-scale monitoring programs. While cognizant of the need to establish the performance of new assay methods, the committee encourages a process for evaluating assays by determining if they are fit for their intended purpose and avoid costly and timely assay validation processes. In this regard, the committee encourages implementing an approach to establish assay performance criteria, as was being developed to evaluate bench-level and high-

throughput in vitro assays for chemical risk assessments (OECD, 2014). The use of private standard setting could provide the means to increase the efficiency of establishing performance-based assays.

Comprehensive assessment of future biotechnology products will likely generate large data sets of unprecedented size and complexity that will require state-of-the-art data storage and analytics. There will be a need to enhance existing data storage and information-technology analytical capabilities to rapidly accommodate and analyze the large data sets generated from -omics approaches to assessment. There will also be a need to establish standards under which some data sets can be made publicly available, while protecting confidential information as appropriate under federal statutes. A 2009 National Research Council report concluded with respect to advanced risk-assessment methods that "there is a need for simplified risk-assessment tools (such as databases, software packages, and other modeling resources) that would allow screening-level risk assessments and could allow communities and stakeholders to conduct assessments and thus increase stakeholder participation" (NRC, 2009:10).

In response to regulatory concerns regarding the validation and integrity of proprietary data sources used for industry data analysis and risk assessment, some shared, transparent, and publicly available resources already have been developed. Three examples are

- Allergen Online, a peer-reviewed allergen list and sequence-searchable database intended for the identification of proteins that may present a potential risk of allergenic cross-reactivity curated by the University of Nebraska.[10]
- The International Life Sciences Institute crop composition database, which summarizes ranges in nutrient, toxicant, and antinutrient content of crops for use in substantial-equivalence comparisons.[11]
- The CRISPR Genome Analysis Tool curated by Iowa State University and used for design and analysis of guide RNA for minimization of off-target genome edits.[12]

Given the large amounts of data that will be generated to support modeling and monitoring efforts, some degree of standardized methodologies and information systems will be required. Issues that will require attention include standardizing notation; standardizing testing procedures and assessment paradigms; characterizing the potential impacts of similar testing protocols on risk assessments; and approaches for collecting and integrating data from existing and future risk assessments and environmental impact statements, without compromising product developers' data compensation rights when specified under a relevant statute. Another possible approach that would be enabled by common standards for data would be the creation of scientifically based, evidence-oriented "dossier" approaches for the submission of one, common scientific information and test data kit that can be used by all agencies for different purposes with different risk standards. To improve the consistency and predictability of risk assessment for future products of biotechnology, common standards for the information that is provided for different product classes as part of the assessment process could be used.

Enhancing the Capabilities and Tools of Product Developers to Enable Future Biotechnology Products to Traverse the Regulatory Path

In addition to needs in regulatory science for the regulatory agencies, there are also risk-analysis considerations and data generation that developers might employ in their design work

[10]AllergenOnline. Available at http://www.allergenonline.org. Accessed January 15, 2017.

[11]The International Life Sciences Institute Crop Composition Database, Version 6. Available at https://www.cropcomposition.org/query/index.html. Accessed January 15, 2017.

[12]CRISPR Genome Analysis Tool. Available at http://cbc.gdcb.iastate.edu/cgat. Accessed January 15, 2017.

to optimize efficient risk analyses when a product is submitted for regulatory review. This section discusses the apparent discontinuity between basic bioscience activities and the regulatory process for biotechnology products. It then explores the development of tools that bridge the gap between fundamental biotechnology design-build-test-learn activities and the action of performing a regulatory assessment on a specific product submission. In considering options to employ approaches described below, beginning with simpler products (such as those intended to be contained and that have only one or a few deleted genes) would support developing design-build-test-learn cycles that eventually could be scaled to the potential open release into the environment of more complicated biotechnology products.

The tools used for regulatory assessments are aligned to guidance or statutes that are often not transparent to early-stage researchers or product developers. As the scale and complexity of the development process increases, failure to incorporate elements into early-stage product candidates leads to rework, delays, or abandonment of the product candidate in the regulatory process. Alternatively, being aware of criteria considered key to assessments of safe use might allow the developer to incorporate these early in a way that facilitates safety by design. Tools that bridge early research demands with anticipation of downstream regulatory requirements can increase the efficiency, predictability, and outcomes of regulatory assessments. Several examples of horizon scanning and anticipatory governance (Guston, 2014) for synthetic-biology products already exist; for example, a policy Delphi study focused on four cases of synthetic biology to outline research needs and governance issues for each using surveys, interviews, and a workshop. At the workshop, the most important research needs and governance opportunities and challenges were assessed for biomining, deextinction, Cyberplasm, and nitrogen-fixing microbes in the presence of a group of multidisciplinary scholars and practitioners coming from nongovernmental organizations, industry, academe, and government (Roberts et al., 2015). Another example of multiparty input in horizon scanning of potential future products which considered future regulatory needs was the Woodrow Wilson Center report *Creating a Research Agenda for the Ecological Implications of Synthetic Biology*, which identified several priority research areas (Drinkwater et al., 2014). Such workshops could serve as a model for identifying the risk-assessment tools needed in early-stage research to anticipate the downstream regulatory requirements of future biotechnology products.

A key aspect in considering these tools versus those discussed in the section "Enhancing the Capabilities, Expertise, and Tools of Regulatory Agencies" are that these are intended to be anticipatory to risk assessment. They are also tied to the technical drivers (see Chapter 2) that are enabling creation of future products. The tools here are envisioned to bridge conceptual gaps that could arise when products that fall within columns C and D of Figure 2-6 are actually placed into a regulatory framework that is underpinned by practices which might not be scalable.

The first category of tools would facilitate adoption and assessment of future products destined for open release into the environment. The key gap is biology knowledge on open-release use-pattern scenarios. The tools needed would establish systematic frameworks to enable evaluation of design or deployment concepts that have been recommended for genetic biocontainment. Such examples include modern kill-switch implementation and nutritional or genetic orthogonality. These design components need to be validated in a product-dependent framework at the point of entry to the regulatory system, but more generally they need validation as types of technologies in increasingly relevant systems. These systems might include at-scale fermentation or simulated environmental releases, up to assessment in actual limited environmental release.

Likewise, creation of proven models for microbial gene flow relevant to biotechnology products in environmental scenarios is a general need that anticipates future microbial products intended for environmental release. Establishing risk-assessment frameworks and metrics involves integrating current concepts of microbial ecology and would result in qualitative or quantitative scenarios that are important to new types of products. As a given product approaches the regulatory framework, these

models will provide insight to help ascertain the degree of oversight proportional to the risks posed by the specific product.

The tools of computational biology need to be focused on resolving questions and establishing evaluation frameworks directly relevant to increasing the probability of success in the regulatory framework. Currently such tools are heavily deployed on enabling early-stage discovery or development. The adaptation of these tools to the task of predictive modeling on environmental open-release scenarios would benefit later-stage risk assessment but can inform release scenario design, and possibly point to new opportunities to design, monitor, or enhance features of future products destined for deliberate release. The development of better in silico modeling systems for outcomes relevant to health, environment, and safety questions is important as the scale or complexity of systems advances. Access to such evaluated tools would enable developers to make better design decisions earlier in development and could also be designed to be responsive to advances in knowledge within the system's technical domain, such as environment or health. This could enable the developer to prescreen or iterate designs to optimize desired outcomes, which is consistent with previous calls to design safety into biotechnology products as a first priority (Kapuscinski et al., 2003).

One example that illustrates a near-term opportunity is in computational assessment of allergen potential of a gene or gene product. Some current risk-assessment frameworks require detection and assessment of "stop to stop" codon hypothetical reading frames in all six frames (Young et al., 2012), some with no minimum length (EFSA, 2011b). Any hypothetical reading frame thus detected is taken through the computational analysis for allergenicity (Schein et al., 2007; Goodman et al., 2016). The increased use of computer-aided design systems for rapid design and assembly iteration represents an opportunity to incorporate a computational assessment early in the development process to minimize or eliminate the number of these hypothetical open reading frames during initial construct design in anticipation of a future regulatory assessment process (Galdzicki et al., 2014; Christen et al., 2015; Nielsen et al., 2016). Furthermore, by incorporating such a search and creating open-source tools to eliminate undesirable features in fundamental DNA design–build software, it may enable diffusion of this aspect of safety into the community of developers regardless of their size or knowledge of the downstream regulatory assessment framework (though with the caveat that if the downstream framework is based on faulty scientific assumptions or extra factors of conservatism, designers may limit their choices for product development by accepting rather than challenging the science). Likewise, in scenarios where a community of researchers has found value in creating libraries of standardized parts or standardized parts sequences, frameworks that allow routine screening of these resources, which are themselves a product of biotechnology, increase their utility in development work and enable safety by design at the earliest stages of a project.

A particular detail with regard to the intersection of gene sequence composition and regulatory assessment could impact the deployment of safeguarding concepts such as watermarking or DNA barcodes (Gibson et al., 2010; Liss et al., 2012; Iftikhar et al., 2015). As just mentioned, sequences subject to a regulatory review process are analyzed for many features, and the use of watermarking technology could introduce features that negatively affect the regulator's analysis of the introduced genetic elements. Therefore, automated DNA design systems that could ensure optimum balance between the objective of sequence tagging and minimizing sequences of concern would be beneficial. Ease of access to such design tools which also incorporate sequence analysis schemes important to regulatory assessment could also facilitate the incorporation of such safeguarding elements by developers.

Another example of an anticipatory computational tool would be implementation of a computational framework by which novel chassis would receive a systematic taxonomic classification. The Coordinated Framework invokes genus-level classification of the host and donor in many regulatory submission documents. To the extent that such foundational information is considered essential for proper risk framing in the future, one can anticipate that developers of future products

of biotechnology, which rely on novel or orthogonal chassis, will need a scientifically sound route for establishing taxonomy.

Lastly, future products of biotechnology, particularly those in columns C and D of Figure 2-6, could require development of frameworks for rationalizing use of -omics data in anticipation of their increasing use in making risk-analysis decisions. In particular, developing nonarbitrary decision frameworks for choice of comparators will have an important impact on future risk analysis as the regulatory system is faced with increasing types of hosts and increasingly novel, engineered hosts; this will be a large undertaking and is best achieved through development of risk-analysis guidance that utilizes far-reaching engagement from an array of experts with public input. Analytical and information-technology resources that support appropriate experimental designs for using -omics data in comparative work should be enabled, including development of guidance on what is important to measure by when within a development pathway—that is, what information from the suite of -omics tools would be helpful in a consultation phase prior to submission and what information will likely be required during the submission would need to be clarified.

SUMMARY AND CONCLUSIONS

As technologies and basic knowledge advance, the regulatory system needs to be able to adapt to new risks of future biotechnology products and also to adjust to well-established categories of products as their level and types of risk become better understood. A regulatory system with a greater emphasis on stratified approaches that prioritize the regulatory agencies' familiarity with a product, the complexity of the risk assessment for the product, and the anticipated risk associated with the product (that is, proportionate oversight) could contribute to meeting the increased demands on the system.

Conclusion 5-1: It would be beneficial to develop clear points of entry for biotechnology stakeholders that provide guidance, support, and direction to future product developers on the appropriate regulatory path for products of biotechnology on the basis of organism, product attributes, and release environment.

Given the diverse set of new actors who are likely to develop new products of biotechnology, it is important that there be a consistent approach to regulatory oversight that supports a product-based, science-driven risk assessment of consumer safety and environmental protection. Clear points of entry for biotechnology stakeholders might include a federally operated Web portal, interagency coordinating office, or targeted outreach efforts (for instance, to small business using the Small Business Administration networks). Stakeholders of interest include large industry, small- and medium-sized enterprises, the do-it-yourself biology community, direct-to-consumer entrepreneurs, nongovernmental organizations with interests in one or more classes of biotechnology products, and the public at large.

The development, use, and regular updating of guidance documents have proven effective and useful by EPA, FDA, and USDA in providing predictable pathways to market and increasing regulatory input quality. Future guidance documents will need to provide clear indications of the criteria that will be used to perform risk assessments and what processes and timelines will apply. Several such efforts were already under way at the time the committee was writing its report and were described in the update to the Coordinated Framework. Documents that bridge the different agencies and provide a more concise and unified description of the regulatory routes would be particularly helpful.

Conclusion 5-2: To be prepared for the anticipated profusion of future biotechnology products, the regulatory system should use scalable and proportional methods of risk assessment, capable of handling significant increases in the rate of biotechnology product innovation, the number of biotechnology products, the complexity of interactions, and the diversity of actors (who may have varying experience with the regulatory process).

On the basis of the information gathered as part of this study, the committee concluded that there is a strong possibility that the number of products per year that require federal oversight will increase and the complexity of future assessments for these products—and the associated level of effort required on the part of appropriate regulatory authorities—will also increase. Some future products of biotechnology will be familiar and fit into product categories for which there is already substantial experience and risk-analysis approaches are well defined and well understood. An approach that focuses the most attention and resources on developing risk-analysis methods for products that are unfamiliar and more complex in terms of risk analyses should be used.

Conclusion 5-3: Participatory governance processes are available for unfamiliar and more complex products of biotechnology, especially open-release products, to enhance input from experts, developers, and interested and affected parties early in the decision-making process.

Future biotechnology products and their use patterns will be increasingly dissimilar to existing biotechnology products and relatively well-understood applications; this is especially true for open-release products that may interact with the natural environment in increasingly complex ways. Participatory governance can help inform the development and implementation of an efficient process for identifying regulatory routes. To this end, approaches to efficiently address product-deployment cycles can engage diverse stakeholders and social and natural scientists with diverse expertise to establish a rigorous system based on research in social and natural sciences and practical policy experiences. Risk analyses for unfamiliar and more complex products will benefit from participatory governance by gaining a more complete appreciation of societal values to inform definition of risk-assessment endpoints in problem formulation, consideration of uncertainties in risk characterization, and formulation of risk-management options. Participation or peer review by independent experts will enable the strongest possible scientific judgments in performing risk analyses.

This conclusion is supported by a recommendation in the National Academies report on gene drives (NASEM, 2016a:10), which stated:

> Governing authorities, including research institutions, funders, and regulators, should develop and maintain clear policies and mechanisms for how public engagement will factor into research, ecological risk assessments, and public policy decisions about gene drives. Defined mechanisms and avenues for such engagement should be built into the risk assessment and decision-making processes from the beginning.

Conclusion 5-4: Ecological risk assessment provides a methodology for more quantitative risk assessments for future biotechnology products and their release scenarios but will require more emphasis on measurement and modeling of effects on populations, communities, and ecosystems.

Comprehensive, efficient, and unbiased risk analysis requires regulatory expertise commensurate with the scale and complexity of future biotechnology products. Tools that can bridge early research demands with anticipation of downstream regulatory requirements can increase the efficiency and predictability of outcomes in regulatory assessments.

Future products of biotechnology provide many opportunities for improving risk analyses. Deficiencies in risk analyses include inadequate use of planning and problem-formulation steps in risk assessments and a resulting lack of clarity in the factors considered in selecting risk-assessment endpoints and in establishing conceptual models (that is, the rationale for determining what needs to be protected from potential harm by biotechnology products; what is the object of the protection; and what is the assumed path to harm). Increasing the quantitative nature of risk analyses required by the Coordinated Framework can, along with methods to elicit probabilities and uncertainties in the absence of empirical data (for example, Bayesian methods or fault-tree assessments), contribute to utilizing proportional efforts in risk analyses.

Conclusion 5-5: There are many opportunities for enhancing the capabilities, expertise, and tools available to regulatory agencies in areas that are likely to see increased emphasis and complexity in future products of biotechnology.

Given the nature of future biotechnology products, there are a diversity of knowledge and technological gaps in current risk-analysis approaches that if addressed on a case-by-case basis could overwhelm the capacity and capability of regulatory agencies to make efficient and sound evaluations. Risk analysis must be capable of adapting and responding to the rapid pace of technology and information. The regulatory agencies may wish to consider establishing a common risk-assessment infrastructure focused on the assessment of products designed for open release into the environment. There are unique research and risk-analysis needs for future biotechnology products, but some of the needs are similar, if not identical, to needs also faced for assessing the probability of adverse effects from other nonbiotechnology stressors. Resources in national and international programs managing these efforts could be leveraged. In addition, opportunities to establish public–private partnerships to address research needs should be explored in an open, transparent process.

Future biotechnology products will be more complex in terms of their internal and external interactions, and it is critical that the agencies involved in regulation of biotechnology develop and maintain scientific capabilities, tools, and expertise in relevant areas. Furthermore, it will be essential that the agencies stay appraised of technology trends so that they can engage in meaningful discussions with technology and product developers early in the product-development cycle, where there is often the best opportunity to affect future technologies. Determination of the key areas of scientific capability will need to adapt to the emerging technologies that underlie future products of biotechnology. On the basis of the current level of federal investments (see Chapter 4), some of the key areas of regulatory-science research for the products of biotechnology likely in the next 5–10 years include comparators, off-target gene effects, and phenotypic characterization; gene fitness, genetic stability, and horizontal gene transfer; impacts on nontarget organisms; control of organismal traits; modeling (including risk-analysis approaches under uncertainty) and life-cycle analyses; monitoring and surveillance; and economic and social costs and benefits.

Conclusion 5-6: There are many opportunities for enhancing the capabilities and tools of technology and product developers to enable future products to traverse the regulatory path.

There are substantial opportunities for the use of improved methods for scientific evaluation, risk assessment, and community engagement related to future products of biotechnology that can be applied by technology and product developers. In order to ensure that the regulatory framework is able to make use of the best available tools in performing its oversight and regulation responsibilities, it will be important to invest in those tools and make them available to regulators and product developers. Areas for consideration include stochastic methods, advances in uncertainty analysis,

better ways to integrate and interpret both qualitative and quantitative data, and communication strategies.

REFERENCES

Akbari, B.O.S., H.J. Bellen, E. Bier, S.L. Bullock, A. Burt, G.M. Church, K.R. Cook, P. Duchek, O.R. Edwards, K.M. Esvelt, V.M. Gantz, K.G. Golic, S.J. Gratz, M.M. Harrison, K.R. Hayes, A.A. James, T.C. Kaufman, J. Knoblich, H.S. Malik, K.A. Matthews, K.M. O'Connor-Giles, A.L. Parks, N. Perrimon, F. Port, S. Russell, R. Ueda, and J. Wildonger. 2015. Safeguarding gene drive experiments in the laboratory. Science 349(6251):927–929.

Andow, D., G.L. Lövei, S. Arpaia, L. Wilson, E.M. Fontes, A. Hilbeck, A. Lang, N. Van Tuat, C. Pires, E. Sujii, C. Zwahlen, A.N. Birch, D.M. Capalbo, K. Prescott, C. Omoto, and A.R. Zeilinger. 2013. An ecologically-based method for selecting ecological indicators for assessing risks to biological diversity from genetically-engineered plants. Journal of Biosafety 22(3):141–156.

Balla, S.J., and J.R. Wright. 2003. Consensual rule making and the time it takes to develop rules. Pp. 187–206 in Politics, Policy, and Organizations: Frontiers in the Scientific Study of Bureaucracy, G.A. Krause and K.J. Meier, eds. Ann Arbor: University of Michigan Press.

Barben, D., E. Fisher, C. Selin, and D.H. Guston. 2007. Anticipatory governance of nanotechnology: Foresight, engagement, and integration. Pp. 979–1000 in The Handbook of Science and Technology Studies, 3rd Ed., E. Hackett, O. Amsterdamska, M.E. Lynch, and J. Wajcman, eds. Cambridge, MA: MIT Press. Available at https://www.hks.harvard.edu/sdn/articles/files/Barben-STS_Handbook-Anticipatory_Governance_Nanotechnology-08.pdf. Accessed October 28, 2016.

Benedict, M.Q., and A.S. Robinson. 2003. The first releases of transgenic mosquitoes: An argument for the sterile insect technique. Trends in Parasitology 19(8):349–355.

Biello, D. August 29, 2014. Ancient DNA could return passenger pigeons to the sky. Scientific American. Available at https://www.scientificamerican.com/article/ancient-dna-could-return-passenger-pigeons-to-the-sky. Accessed January 8, 2017.

Bozeman, B., and D. Sarewitz. 2005. Public values and public failure in US science policy. Science and Public Policy 32(2):119–136.

Callaway, E. 2015. Mammoth genomes hold recipe for Arctic elephants. Nature 521(7550):18–19.

Caron-Lormier, G., D.A. Bohan, C. Hawes, A. Raybould, A.J. Haughton, and R.W. Humphry. 2009. How might we model an ecosystem? Ecological Modelling 220(17):1935–1949.

Caron-Lormier, G., D.A. Bohan, R. Dye, C. Hawes, R.W. Humphry, and A. Raybould. 2011. Modelling one ecosystem: The example of agro-ecosystems. Ecological Modelling 222(5):1163–1173.

Christen, M., S. Deutsch, and B. Christen. 2015. Genome calligrapher: A Web tool for refactoring bacterial genome sequences for de novo DNA synthesis. ACS Synthetic Biology 4(8):927–934.

Corrigan-Curay, J., M. O'Reilly, D.B. Kohn, P.M. Cannon, G. Bao, F.D. Bushman, D. Carroll, T. Cathomen, J.K. Joung, D. Roth, M. Sadelain, A.M. Scharenberg, C. von Kalle, F. Zhang, R. Jambou, E. Rosenthal, M. Hassani, A. Singh, and M.H. Porteus. 2015. Genome editing technologies: Defining a path to clinic. Molecular Therapy 23(5):796–806.

Drinkwater, K., T. Kuiken, S. Lightfoot, J. McNamara, and K. Oye. 2014. Creating a Research Agenda for the Ecological Implications of Synthetic Biology. MIT Center for International Studies, Cambridge, MA, and Woodrow Wilson International Center for Scholars, Washington, DC. Available at https://www.wilsoncenter.org/sites/default/files/SYNBIO_create%20an%20agenda_v4.pdf. Accessed August 10, 2016.

EFSA (European Food Safety Authority). 2010. Guidance on the environmental risk assessment of genetically modified plants. EFSA Journal 8(5):1879–1989.

EFSA. 2011a. Guidance on conducting repeated-dose 90-day oral toxicity study in rodents on whole food/feed. EFSA Journal 9(12):2438.

EFSA. 2011b. Guidance on risk assessment of food and feed from genetically modified plants. EFSA Journal 9(5):2150.

EFSA. 2011c. Guidance on the post-market environmental monitoring (PMEM) of genetically modified plants. EFSA Journal 9(8):2316.

EOP (Executive Office of the President). 2016. National Strategy for Modernizing the Regulatory System for Biotechnology Products. Available at https://obamawhitehouse.archives.gov/sites/default/files/microsites/ostp/biotech_national_strategy_final.pdf. Accessed January 31, 2017.

EOP. 2017. Modernizing the Regulatory System for Biotechnology Products: An Update to the Coordinated Framework for the Regulation of Biotechnology. Available at https://obamawhitehouse.archives.gov/sites/default/files/microsites/ostp/2017_coordinated_framework_update.pdf. Accessed January 30, 2017.

EPA (U.S. Environmental Protection Agency). 1998. Guidelines for Ecological Risk Assessment. Federal Register 63:26846–26924.

EPA. 2004. Overview of the Ecological Risk Assessment Process in the Office of Pesticide Programs, U.S. Environmental Protection Agency. Endangered and Threatened Species Effects Determinations. Available at https://www.epa.gov/sites/production/files/2014-11/documents/ecorisk-overview.pdf. Accessed September 14, 2016.

EPA. 2012a. SAP Minutes No. 2012-06: A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding Pollinator Risk Assessment Framework. Available at https://www.regulations.gov/document?D=EPA-HQ-OPP-2012-0543-0047. Accessed September 14, 2016.

EPA. 2012b. SAP Minutes No. 2012-05: A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding: Problem Formulation for the Reassessment of Ecological Risks from the Use of Atrazine. Available at https://www.epa.gov/sites/production/files/2015-06/documents/061212minutes.pdf. Accessed September 14, 2016.

Exponent. 2005. DEEM-FCID TM Distributional Acute Dietary Exposure Analysis Program, Version 2.03. Exponent, Washington, DC.

FDA (U.S. Food and Drug Administration). 2012. A Guide to Drug Safety Terms at FDA. FDA Consumer Health Information. November. Available at http://www.fda.gov/downloads/ForConsumers/ConsumerUpdates/UCM107976.pdf. Accessed January 9, 2017.

FDA. 2017. Regulation of Mosquito-Related Products; Draft Guidance for Industry; Availability. Federal Register 82:6574–6575.

Forbes, V.E., P. Calow, and R.M. Sibly. 2001. Are current species extrapolation models a good basis for ecological risk assessment? Environmental Toxicology and Chemistry 20(2):442–447.

Freudenburg, W.R. 1996. Strange chemistry: Environmental risk conflicts in a world of science, values, and blind spots. Pp. 11–36 in Handbook for Environmental Risk Decision Making: Values, Perceptions, and Ethics, C.R. Cothern, ed. Boca Raton, FL: Lewis Publishers.

Galdzicki, M., K.P. Clancy, E. Oberortner, M. Pocock, J.Y. Quinn, C.A. Rodriguez, N. Roehner, M.L. Wilson, L. Adam, J.C. Anderson, B.A. Bartley, J. Beal, D. Chandran, J. Chen, D. Densmore, D. Endy, R. Grünberg, J. Hallinan, N.J. Hillson, J.D. Johnson, A. Kuchinsky, M. Lux, G. Misirli, J. Peccoud, H.A. Plahar, E. Sirin, G-B. Stan, A. Villalobos, A. Wipat, J.H. Gennari, C.J. Myers, and H.M. Sauro. 2014. The Synthetic Biology Open Language (SBOL) provides a community standard for communicating designs in synthetic biology. Nature Biotechnology 32(6):545–550.

Gibson, D.G., J.I. Glass, C. Lartigue, V.N. Noskov, R.-Y. Chuang, M.A. Algire, G.A. Benders, M.G. Montague, L. Ma, M.M. Moodie, C. Merryman, S. Vashee, R. Krishnakumar, N. Assad-Garcia, C. Andrews-Pfannkoch, E.A. Denisova, L. Young, Z.-Q. Qi, T.H. Segall-Shapiro, C.H. Calvey, P.P. Parmar, C.A. Hutchison, H.O. Smith, and J.C. Venter. 2010. Creation of a bacterial cell controlled by a chemically synthesized genome. Science 329(5987):52–56.

Ginsberg, W. 2015. Creating a Federal Advisory Committee in the Executive Branch. Washington, DC: Congressional Research Service.

Goodman, R.E., M. Ebisawa, F. Ferreira, H.A. Sampson, R. van Ree, S. Vieths, J.L. Baumert, B. Bohle, S. Lalithambika, J. Wise, and S.L. Taylor. 2016. AllergenOnline: A peer-reviewed, curated allergen database to assess novel food proteins for potential cross-reactivity. Molecular Nutrition and Food Research 60:1183–1198.

Guston, D.H. 2014. Understanding anticipatory governance. Social Studies of Science 44(2):218–242.

Harding, S. 1996. Rethinking standpoint epistemology: What is "strong objectivity"? Pp. 235–248 in Feminism and Science, E.F. Keller and H. Longino, eds. Oxford: Oxford University Press.

Hayes, K.R., B. Leung, R. Thresher, J.M. Dambacher, and G.R. Hosack. 2014. Meeting the challenge of quantitative risk assessment for genetic control techniques: A framework and some methods applied to the common Carp (*Cyprinus carpio*) in Australia. Biological Invasions 16(6):1273–1288.

Iftikhar, S., S. Khan, Z. Anwar, and M. Kamran. 2015. GenInfoGuard—a robust and distortion-free watermarking technique for genetic data. PLOS ONE 10(2):e0117717.

IRGC (International Risk Governance Council). 2015. Guidelines for Emerging Risk Governance. Lausanne, Switzerland: IRGC. Available at https://www.irgc.org/wp-content/uploads/2015/03/IRGC-Emerging-Risk-WEB-31Mar.pdf. Accessed October 17, 2016.

Kapuscinski, A.R., R.M. Goodman, S.D. Hann, L.R. Jacobs, E.E. Pullins, C.S. Johnson, J.D. Kinsey, R.L. Krall, A.G. La Viña, M.G. Mellon, and V.W. Ruttan. 2003. Making "safety first" a reality for biotechnology products. Nature Biotechnology 21:599–601.

Kapuscinski, A.R., S. Li, K.R. Hayes, and G. Dana, eds. 2007. Environmental Risk Assessment of Genetically Modified Organisms, Vol. 3. Methodologies for Transgenic Fish. Cambridge, MA: CABI. Available at https://gmoera.umn.edu/sites/gmoera.umn.edu/files/environmental_risk_assessment_volume_3.pdf. Accessed October 28, 2016.

Krafsur, E.S. 1998. Sterile insect technique for suppressing and eradicating insect populations: 55 years and counting. Journal of Agricultural Entomology 15(4):303–317.

Kuzma, J. 2006. Nanotechnology oversight and regulation—just do it. Environmental Law Reporter 36:10913–10923.

Kuzma, J. 2013. Properly paced or problematic? Examing governance of GMOs. Pp. 176–197 in Innovative Governance Models for Emerging Technologies, G. Marchant, K. Abbott, and B. Allenby, eds. Cheltenham, UK: Edward Elgar.

Kuzma, J., and J.C. Besley. 2008. Ethics of risk analysis and regulatory review: From bio- to nanotechnology. Nanoethics 2(2):149–162.

Kuzma, J., J. Romanchek, and A. Kokotovich. 2008. Upstream oversight assessment for agrifood nanotechnology: A case studies approach. Risk Analysis 28(4):1081–1098.

Lavertu, S., and D.L. Weimer. 2010. Federal advisory committees, policy expertise, and the approval of drugs and medical devices at the FDA. Journal of Public Administration Research and Theory 21:211–237.

Linkov, I., F.K. Satterstrom, J. Steevens, E. Ferguson, and R.C. Pleus. 2007. Multi-criteria decision analysis and environmental risk assessment for nanomaterials. Journal of Nanoparticle Research 9(4):543–554.

Liss, M., D. Daubert, K. Brunner, K. Kliche, U. Hammes, A. Leiherer, and R. Wagner. 2012. Embedding permanent watermarks in synthetic genes. PLOS ONE 7(8):e42465.

Marchant, G.E., and W. Wallach. 2015. Coordinating technology governance. Issues in Science and Technology 31(4):43–50.

McHughen, A., and S. Smyth. 2008. U.S. regulatory system for genetically modified [genetically modified organism (GMO), rDNA or transgenic] crop cultivars. Plant Biotechnology Journal 6(1):2–12.

Meghani, Z., and J. Kuzma. 2011. The "revolving door" between regulatory agencies and industry: A problem that requires reconceptualizing objectivity. Journal of Agricultural and Environmental Ethics 24(6):575–599.

Moffitt, S.L. 2014. Making Policy Public: Participatory Bureaucracy in American Democracy. New York: Cambridge University Press.

Murphy, B., C. Jansen, J. Murray, and P. De Barro. 2010. Risk Analysis on the Australian Release of *Aedes aegypti* (L.) (Diptera: Culicidae) Containing *Wolbachia*. Indooroopilly, Australia: CSIRO.

Murray, J.V., C.C. Jansen, and P. De Barro. 2016. Risk associated with the release of *Wolbachia*-infected *Aedes aegypti* mosquitoes into the environment in an effort to control dengue. Frontiers in Public Health 4:43.

Naranjo, S.E., G. Head, and G.P. Dively. 2005. Field studies assessing arthropod nontarget effects in *Bt* transgenic crops: Introduction. Environmental Entomology 34(5):1178–1180.

NASEM (National Academies of Sciences, Engineering, and Medicine). 2016a. Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values. Washington, DC: The National Academies Press.

NASEM. 2016b. Genetically Engineered Crops: Experiences and Prospects. Washington, DC: The National Academies Press.

Nelson, K.C., G. Kibata, L. Muhammad, J. Okuro, F. Muyekho, M. Odindo, A. Ely, and J. Waquil. 2004. Problem formulation and options assessment (PFOA) for genetically modified organisms: The Kenya case study. Pp. 57–82 in Environmental Risk Assessment of Genetically Modified Organisms, Vol. 1. A Case Study of Bt Maize in Kenya, A. Hilbeck and D.A. Andow, eds. Cambridge, MA: CABI.

Nielson, A.A., B.S. Der, J. Shin, P. Vaidyanathan, V. Paralanov, E.A. Strychalski, D. Ross, D. Densmore, and C.A. Voight. 2016. Genetic circuit design automation. Science 352(6281):aac7341.

NRC (National Research Council). 1996. Understanding Risk: Informing Decisions in a Democratic Society. Washington, DC: National Academy Press.

NRC. 2007. Models in Environmental Regulatory Decision Making. Washington, DC: The National Academies Press.

NRC. 2008. Public Participation in Environmental Assessment and Decision Making. Washington, DC: The National Academies Press.

NRC. 2009. Science and Decisions: Advancing Risk Assessment. Washington, DC: The National Academies Press.

NRC. 2013. Assessing Risks to Endangered and Threatened Species from Pesticides. Washington, DC: The National Academies Press.

OECD (Organisation for Economic Co-operation and Development). 2014. Guidance Document for Describing Non-Guideline In Vitro Test Methods. Series on Testing and Assessment No. 211. Paris: OECD.

Pauwels, K., S.C. De Keersmaecker, A. De Schrijver, P. du Jardin, N.H. Roosens, and P. Herman. 2015. Next-generation sequencing as a tool for the molecular characterisation and risk assessment of genetically modified plants: Added value or not? Trends in Food Science & Technology 45(2):319–326.

Pennington, K.M., A.R. Kapuscinski, M.S. Morton, A.M. Cooper, and L.M. Miller. 2010. Full life-cycle assessment of gene flow consistent with fitness differences in transgenic and wild-type Japanese medaka fish (*Oryzias latipes*). Environmental Biosafety Research 9(1):41–57.

Peterson, R.K., S.J. Meyer, A.T. Wolf, J.D. Wolt, and P.M. Davis. 2006. Genetically engineered plants, endangered species, and risk: A temporal and spatial exposure assessment for Karner blue butterfly larvae and Bt maize pollen. Risk Analysis 26(3):845–858.

Ramachandran, G., S. Wolf, J. Paradise, J. Kuzma, R. Hall, E. Kokkoli, and L. Fatehi. 2011. Recommendations for oversight of nanobiotechnology: Dynamic oversight for complex and convergent technology. Journal of Nanoparticle Research 13(4):1345–1371.

Raybould, A., G. Caron-Lormier, and D.A. Bohan. 2011. Derivation and interpretation of hazard quotients to assess ecological risks from the cultivation of insect-resistant transgenic crops. Journal of Agricultural and Food Chemistry 59(11):5877–5885.

Renn, O. 2005. Risk Governance: Towards and Integrative Approach. Geneva: IRGC.

Roberts, J.P., S. Stauffer, C. Cummings, and J. Kuzma. 2015. Synthetic Biology Governance: Delphi Study Workshop Report. GES Center Report No. 2015.2. Available at https://research.ncsu.edu/ges/files/2014/04/Sloan-Workshop-Report-final-ss-081315-1.pdf. Accessed October 17, 2016.

Rose, R.I., ed. 2007. White Paper on Tier-Based Testing for the Effects of Proteinaceous Insecticidal Plant-Incorporated Protectants on Non-Target Arthropods for Regulatory Risk Assessments. Environmental Protection Agency and U.S. Department of Agriculture–Animal and Plant Health Inspection Service. Available at https://www.epa.gov/sites/production/files/2015-09/documents/tier-based-testing.pdf. Accessed January 15, 2017.

Ryals, J. 2016. Metabolomics as a High Resolution Phenotyping Tool. Webinar presentation to the National Academies of Sciences, Engineering, and Medicine Committee on Future Biotechnology Products and Opportunities to Enhance Capabilities of the Biotechnology Regulatory System, July 29.

Schein, C.H., O. Ivanciuc, and W. Braun. 2007. Bioinformatics approaches to classifying allergens and predicting cross-reactivity. Immunology and Allergy Clinics of North America 27:1–27.

Sears, M.K., R.L. Hellmich, D.E. Stanley-Horn, K.S. Oberhauser, J.M. Pleasants, H.R. Mattila, B.D. Siegfried, and G.P. Dively. 2001. Impact of Bt corn pollen on monarch butterfly populations: A risk assessment. Proceedings of the National Academy of Sciences of the United States of America 98(21):11937–11942.

Shapiro, B. 2015. How to Clone a Mammoth: The Science of De-Extinction. Princeton, NJ: Princeton University Press.

Stilgoe, J., R. Owen, and P. Macnaghten. 2013. Developing a framework for responsible innovation. Research Policy 42(9):1568–1580.

Stirling, A. 2007. Risk, precaution and science: Towards a more constructive policy debate. EMBO Reports 8(4):309–315.

Storer, N.P. 2003. A spatially explicit model simulating western corn rootworm (Coleoptera: Chrysomelidae) adaptation to insect-resistant maize. Journal of Economic Entomology 96(5):1530–1547.

Suter, G.W., II. 2007. Ecological Risk Assessment, 2nd Ed. Boca Raton, FL: CRC Press.

Thompson, P.B. 2007. Food Biotechnology in Ethical Perspective, 2nd Ed. The International Library of Environmental, Agricultural and Food Ethics Vol. 10. Dordrecht, Netherlands: Springer.

Tsang, M.P., M.E. Bates, M. Madison, and I. Linkov. 2014. Benefits and risks of emerging technologies: Integrating life cycle assessment and decision analysis to assess lumber treatment alternatives. Environmental Science & Technology 48(19):11543–11550.

Warren-Hicks, W.J., and A. Hart. 2010. Application of Uncertainty Analysis to Ecological Risks of Pesticides. Boca Raton, FL: CRC Press.

Weimer, D.L. 2006. The puzzle of private rulemaking: Expertise, flexibility, and blame avoidance in U.S. regulation. Public Administration Review 66(4):569–582.

Weimer, D.L., and L. Wilk. 2016. Allocation of indivisible life-saving goods with both intrinsic and relational quality: The new deceased-donor kidney allocation system. Administration and Society 1–30.

Wilsdon, J., and R. Willis. 2004. See-Through Science: Why Public Engagement Needs to Move Upstream. London: Demos.

Wolt, J.D. 2011. A mixture toxicity approach for environmental risk assessment of multiple insect resistance genes. Environmental Toxicology and Chemistry 30(3):763–772.

Wolt, J.D., and R.K.D. Peterson. 2010. Prospective formulation of environmental risk assessments: Probabilistic screening for Cry1A(b) maize risk to aquatic insects. Ecotoxicology and Environmental Safety 73:1182–1188.

Wolt, J.D., K. Wang, D. Sashital, and C.J. Lawrence-Dill. 2016. Achieving plant CRISPR targeting that limits off-target effects. The Plant Genome 9(3).

Young, G.J., S. Zhang, H.P. Mirsky, R.F. Cressman, B. Cong, G.S. Ladics, and C.X. Zhong. 2012. Assessment of possible allergenicity of hypothetical ORFs in common food crops using current bioinformatics guidelines and its implications for the safety assessment of GM crops. Food and Chemical Toxicology 50:3741–3751.

Appendix D

THE GOOD FOOD INSTITUTE

October 22, 2018

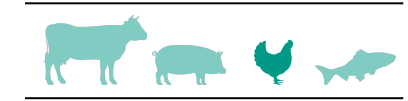
The current state of the cell-based meat industry

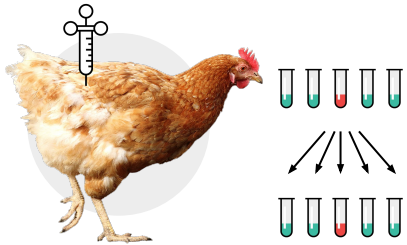
David Welch, Ph.D.
Director of Science and Technology, The Good Food Institute

Cell-Based Meat Production at Scale

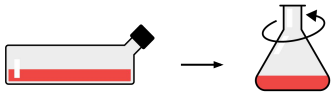
SAMPLE

A small sample of cells is obtained from an animal.



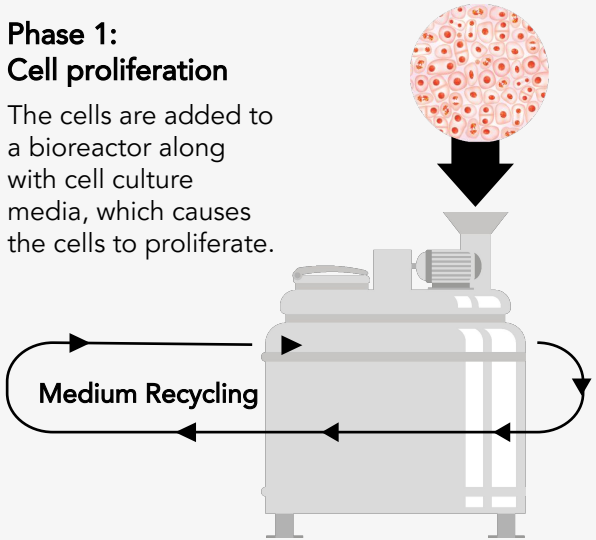


CELL STARTER CULTURE



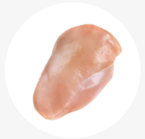
Phase 1:
Cell proliferation

The cells are added to a bioreactor along with cell culture media, which causes the cells to proliferate.

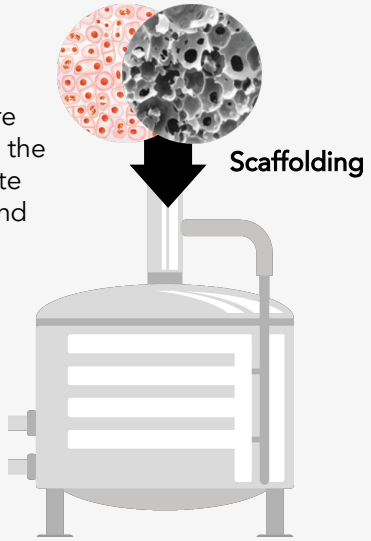


Phase 2:
Tissue Perfusion

A change in culture conditions pushes the cells to differentiate into muscle, fat, and connective tissue.



Final Product



CELLS AT MATURATION

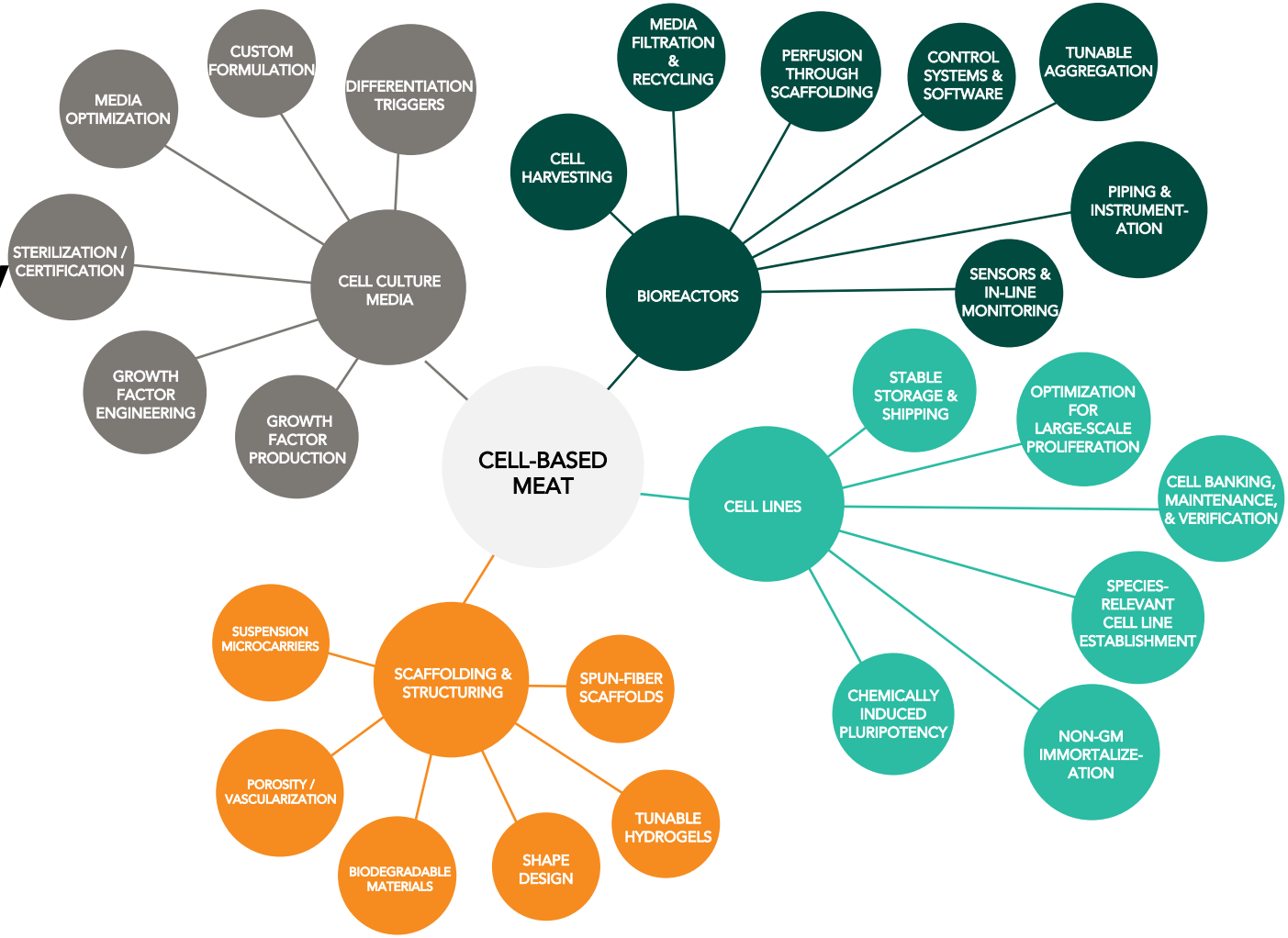
Primarily muscle, fat, and connective tissue.

Fat Cell

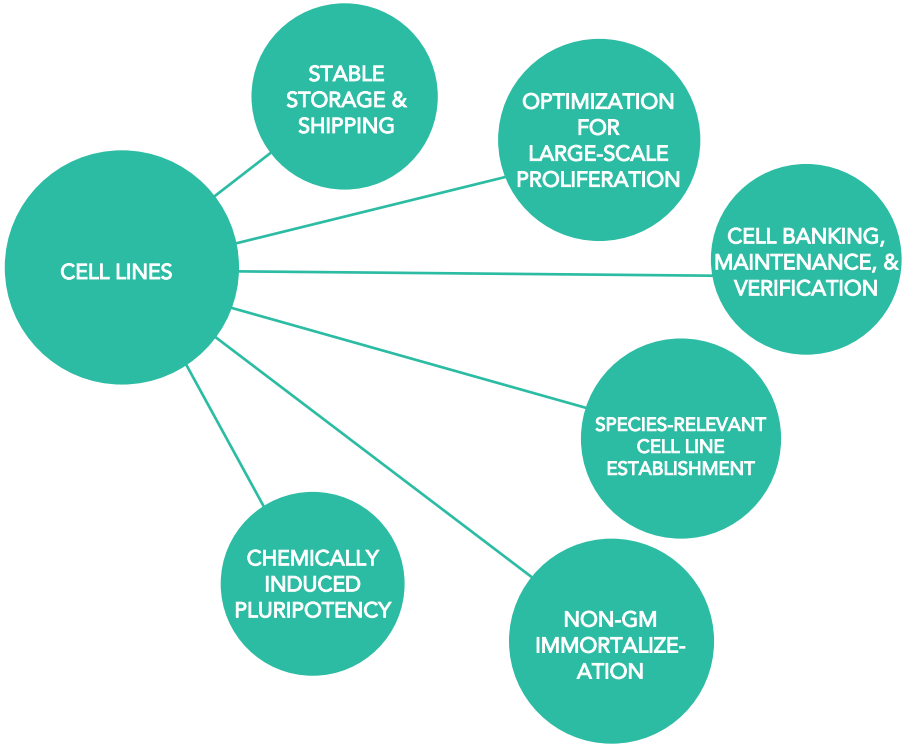
Muscle Cell

Fibroblast Cell

Cell-Based Meat Technology Mind Map



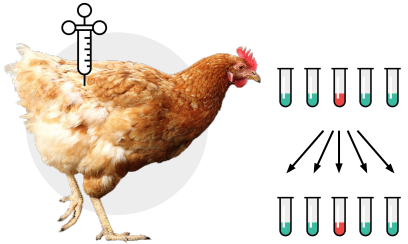
Cell Line Development



Cells can be **pluripotent, multipotent,** or **specialized** (such as adult stem cells).

Proliferative capacity: the ability to continuously multiply.

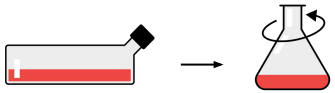
Stability: exhibiting predictable behavior generation after generation.

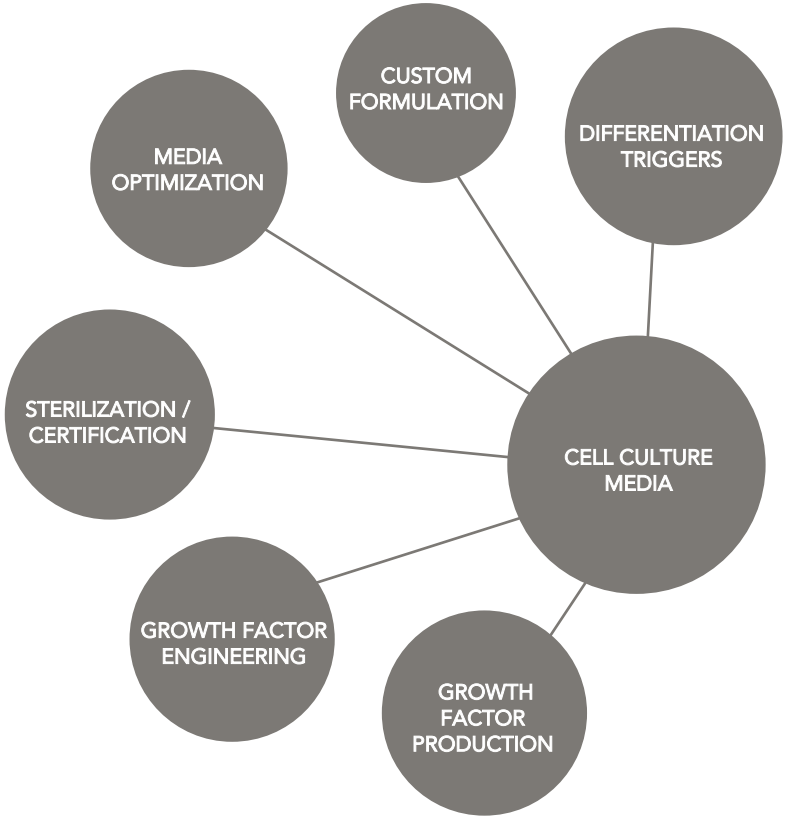


Cell Culture Medium

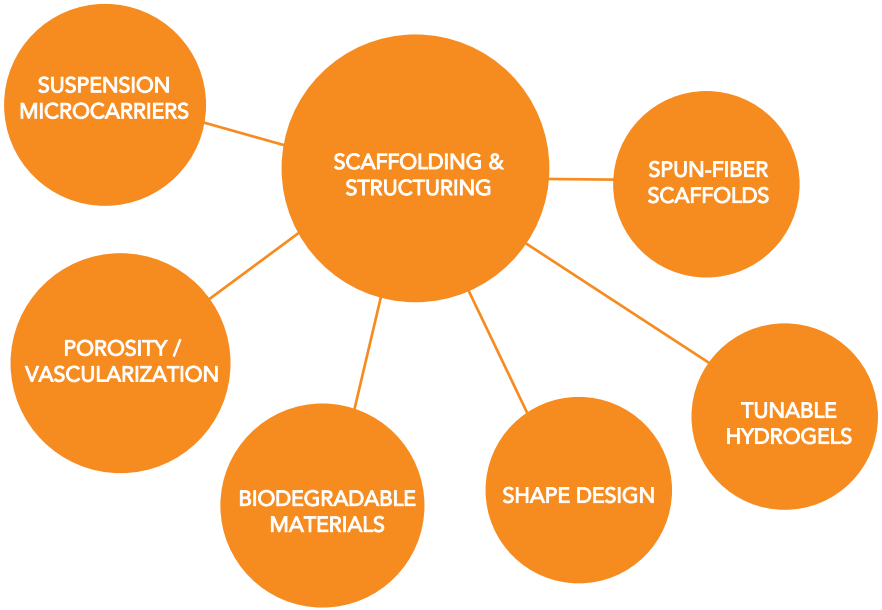
Basal medium: the basic nutrients that cells need to grow (salts, sugars, amino acids, etc.)

Growth factors: signaling proteins that can control animal cell behavior (growth, differentiation, attachment to scaffold, etc.)



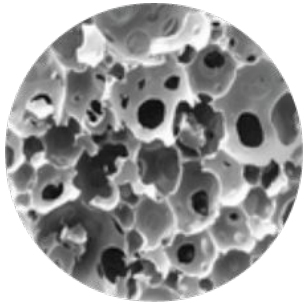


Scaffolding

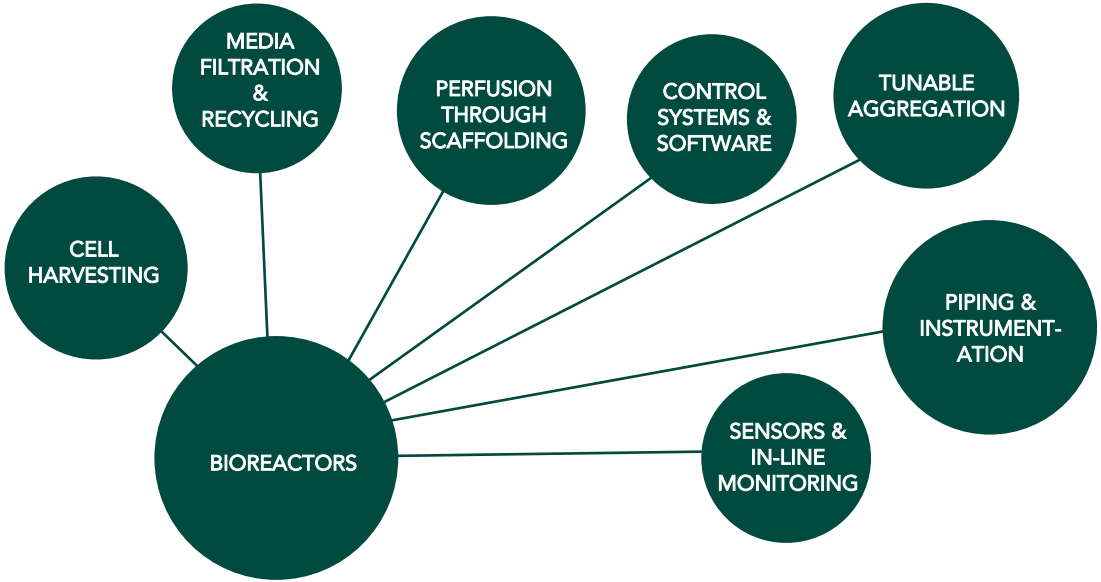


Scaffolds can be **biodegradable** or integrated into the final product.

Scaffolds for cell-based meat are expected to be comprised of edible materials.

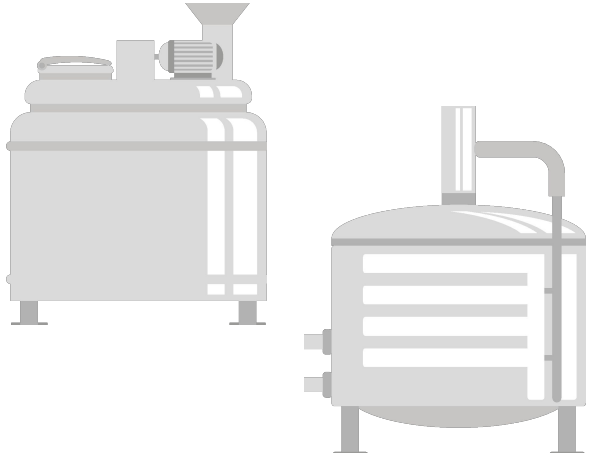


Bioreactors



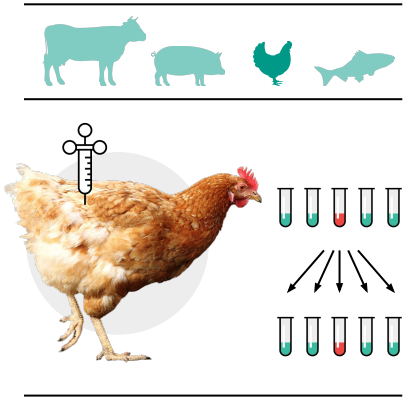
Stirred-tank bioreactors are widely used in large-scale **suspension** animal cell culture.

Tissue perfusion bioreactors will require additional engineering for scale-up.



Potential risks from source materials: animal cell lines

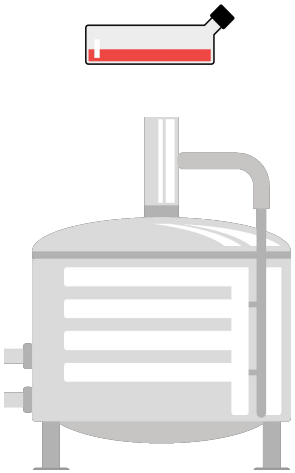
CELL LINES



- We expect **cell lines** to be similar to those used in applications with FDA oversight.
- **Existing FDA guidance documents** provide guidelines and well established tests for adventitious agent detection.
- Examples of relevant FDA guidance documents:
  - Guidance for Industry: Cell-Based Products for Animal Use
  - Guidance: Content & Format CMC for Vaccine & Related Product
  - Guidance: Points to Consider in the Characterization of Cell Lines Used to Produce Biologicals

Production of substances during the culture process

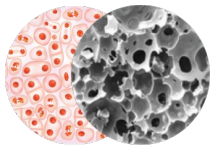
CELL CULTURE MEDIUM

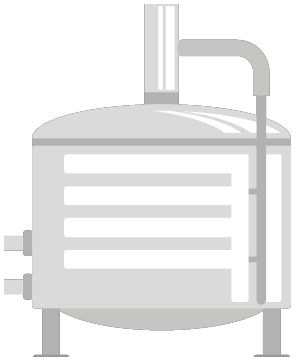


- We expect the **cell culture medium** to contain ingredients that are widely used in the **food industry**, and their safety is well understood and documented.
- The medium may also contain **recombinant proteins and/or small molecules** present at low concentrations. We expect these to be produced through methods currently used to make **enzymes and other food processing aids routinely used in the food industry.**
- **FDA Guidance on Enzyme Preparations** and numerous **GRAS submissions** involving enzyme preparations used in food products (e.g., GRN 22, GRN 24, GRN 43) provide well established relevant methods and tests for the assessment of cell culture media.

Production of substances during the culture process

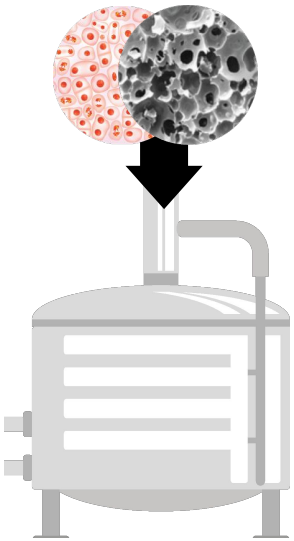
SCAFFOLDS





- **Scaffolds** for cell-based meat will be comprised of **edible materials**, such as alginate or cellulose, that may or may not biodegrade.
- As with cell culture media, scaffolds may also contain recombinant proteins and/or small molecules present at low concentrations.
- These materials are already widely used in the **food industry**, and tests for assessing their safety are well established.
- The **Guidance on Enzyme Preparations** and numerous **GRAS submissions** involving enzyme preparations used in food products provide well established relevant methods and tests for the assessment of scaffolds.

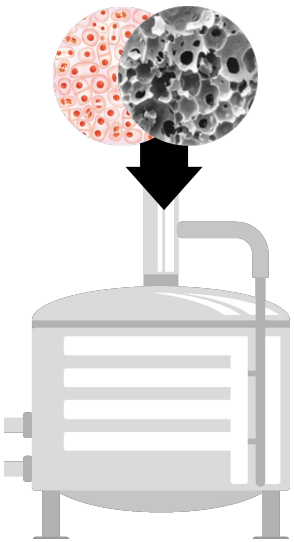
Properties of cultured cells: potential harmful substances



Final Product

- The **cell culture process** and conditions in the **bioreactor** could cause cells to create substances at levels different from those in an intact animal. Examples include:
  - Growth factors and other molecules produced by intra- and inter-cellular signaling
  - Production of unintended or abnormal levels of metabolites
  - Genetic and epigenetic drift that could alter protein expression levels
  - Endogenous retroviruses or other species-specific viruses
- **Well established and documented controls and assays**, including PCR and ChIP assays, exist to **detect abnormal levels** of such substances.

Properties of cultured cells: nutrition



Final Product

- Because the **cells used in cell-based meat** will be derived directly from species and breeds that are routinely farmed for meat, we expect that they will **physiologically mimic** cells within animal muscle tissue.
- **Guidelines** and **established tests** to compare the **nutritional and compositional qualities** of cell-based meat to that of conventional meat are available (e.g., Animal Cloning Risk Assessment, GRAS submissions, such as GRN 000168 and GRN 000313, involving meat and poultry-based ingredients used in meat and poultry products).

Conclusions and Recommendations

- We expect **cell culture technology** to enable the production of **high-quality protein foods** without posing risks that cannot be **managed effectively** through the use of well understood and established controls by responsible producers.
- The **core technology** for cell-based meat production is well understood.
- **Cellular events** unique to cell-based meat can be characterized and assessed with **existing, well established tests**.
- **Documented guidelines and tests** exist that can be applied to cell-based meat to **identify and characterize potential hazards and assess risks.**
- FDA can regulate this industry by using **science- and risk-based regulatory approaches** under its existing authorities as well as its extensive experience to help ensure the safe production of cell-based meat.

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