When Cows Go Oink, Pigs Go Baaa, and Sheep Go Moo: Development and Regulatory Challenges of Intentional Genomic Alterations in Animals

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ABSTRACT

This Article attempts to clarify the regulatory rationale behind FDA's guidance for industry #187 on genome-edited animals. It also addresses a critical gap in the literature: few scholars have evaluated the risks associated with genome editing in animals from a legal perspective, and none have assessed the question of whether the regulation of intentional genomic alterations in animals is in line with current scientific and technological standards. The Article comes to the conclusion that FDA should continue to use the reasonable set of criteria it has laid down in the guidance for industry #187 and evaluate intentional genomic alterations in animals as a new animal drug. Some policy recommendations are also suggested in this study for further development.

INTRODUCTION

Since the dawn of human civilization, animals have been genetically modified through breeding techniques. Domestic dogs probably represent the longest-running

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genetics experiment, predating even the advent of agriculture. Patterns of genetic differentiation and archeological evidence suggest that the divergence between dogs and wolves occurred 32,000 years ago and that the domestication of dogs may have even occurred 100,000 years ago.[1]

It is only recently, however, that technologies to alter the genomes of various organisms, including animals, have been developed. The synergetic integration of genetic engineering, recombinant DNA technology, and developmental biology has opened the way to a generation of new classes of organisms called transgenic organisms or genetically engineered (GE) organisms.[2] The revolution began in 1972 when Paul Berg and his research team at Stanford University created the first recombinant DNA (rDNA) molecules by combining DNA from two different sources to form a single recombinant molecule.[3] The next landmark came in 1973 when Herbert Boyer and Stanley Cohen created a recombinant DNA molecule by introducing fragments of DNA into a bacterial cell, and then inserting the plasmid vector into bacteria.[4] The team had created the first custom-made organism containing recombined or "recombinant" DNA. The foundations for modern genetic engineering were established. Their studies successfully demonstrated the potential impact of DNA recombinant techniques on agriculture, as well as medicine and pharmacology.[5]

In 1974, the first "transgenic animals" were created.[6] In a promising alternative procedure to tumor transplant models, Rudolf Jaenisch and Beatrice Mintz managed

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[1] Guo-dong Wang, Weiwei Zhai, He-chuan Yang, Ruo-xi Fan, Xue Cao, Li Zhong, Lu Wang, Fei Liu, Hong Wu, Lu-gang Cheng, Andrei D. Pyarkov, Nikolai A. Poyarkov Jr., Shu-sheng Tang, Wen-ming Zhao, Yun Gao, Xue-mei Lv, David M. Irwin, Pater Savolainen, Chung-l Wu & Ya-ping Zhang, *The Genomics of Selection in Dogs and the Parallel Evolution Between Dogs and Humans*, 4 NATURE COMMUN. 1, 1–2, 8 (2013).

[2] Cesare Galli, Andrea Perota, Giovanna Lazzari & Franco Lucchini, *Transgenic Livestock Technologies*, *in* SUSTAINABLE FOOD PRODUCTION 1717, 1724 (Paul Christou et al. eds., 2013). It is important to stress that the abbreviation "GE" is used here only for genetically engineered or genetic engineering and should not be confused with genome editing, the newer and more precise technology. In line with the terminology used in FDA's draft guidance for industry #187 entitled "Regulation of Intentionally Altered Genomic DNA in Animals," we will use the expression "IGA" (intentional genomic alterations) to describe animals with intentional genomic alterations developed through the use of genome editing technologies as well as genetic engineering procedures. *See* U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY #187, GUIDANCE FOR INDUSTRY ON REGULATION OF INTENTIONALLY ALTERED GENOMIC DNA IN ANIMALS 1, 4, 8 (2017), https://www.fda.gov/media/74614/download [hereinafter REGULATION GUIDANCE FOR INDUSTRY #187 (2017)].

[3] David A. Jackson, Robert H. Symons & Paul Berg, *Biochemical Method for Inserting New Genetic Information into DNA of Simian Virus 40: Circular SV40 DNA Molecules Containing Lambda Phage Genes and the Galactose Operon of Escherichia coli*, 69 PROCEEDINGS NAT'L ACAD. SCI. U.S. 2904, 2904 (1972).

[4] Stanley N. Cohen, Annie C. Y. Chang, Herbert W. Boyer & Robert B. Helling, *Construction of Biologically Functional Bacterial Plasmids In Vitro*, 70 PROCEEDINGS NAT'L ACAD. SCI. U.S. 3240, 3240 (1973).

[5] Jiru Xu, Cherie Millar, Anne Loughrey, Colin E. Goldsmith, Wilson A. Coulter, James SG Dooley & John E. Moore, *The Increasing Role of DNA Molecular Technologies in Infection Control-Related Medical Bacteriology: What the Infection Prevention Specialist Needs to Know*, 11 J. INFECTION PREV. 150, 151 (2010), https://journals.sagepub.com/doi/10.1177/1757177410366170?icid=int.sj-full-text.similar-articles.3, [https://perma.cc/9GY9-BLMS].

[6] Rudolf Jaenisch & Beatrice Mintz, *Simian Virus 40 DNA Sequences in DNA of Healthy Adult Mice Derived from Preimplantation Blastocysts Injected with Viral DNA*, 71 PROCEEDINGS NAT'L ACAD. SCI. U.S. 1250, 1250 (1974). It is interesting to note that in a policy statement on therapeutic products derived from transgenic animals, the Food and Drug Administration has defined a transgenic animal as one whose genome has been modified by the transfer of foreign genetic material from another species through human

to stably integrate a purified monkey virus DNA into the blastocyst of a mouse via viral infection of early embryos.[7] Various other species such as rats, cows, pigs, sheep, goats, monkeys, and rabbits soon followed.[8] Fundamental to these techniques was the ability to culture preimplantation embryos of the same age in vitro, allowing a variety of manipulations to be performed.[9] These embryos would then be reintroduced into a recipient uterus.

Since then, new technologies have emerged, and many subsequent studies have developed increasingly accurate techniques for splicing DNA sequences from different genomes and introducing them into various organisms, including animals.[10] Some of these include the use of engineered nucleases technologies, such as HEases (Homing endonucleases),[11] TALENs (transcription activator-like effector nucleases),[12] ZFNs (zinc finger nucleases),[13] and most recently the CRISPR (clustered regulatory interspersed short palindromic repeats)/Cas9 system.[14] The central objective of these nuclease systems is to introduce site-specific genome alterations with high precision, rather than the more random modifications associated with rDNA technology.[15] In the case of HEases, ZFNs, and TALENs, this is achieved by specific intermolecular interactions between nucleotides and protein motifs, while for CRISPR/Cas9, the sequence specificity largely arises from Watson–Crick base pairing between CRISPR RNA (crRNA) and the target DNA site.[16]

The process of producing these site-specific DNA sequence modifications has allowed the genetic manipulation of various organisms on an unprecedented scale,

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intervention. *See* U.S. FOOD & DRUG ADMIN., *Points to Consider in the Manufacture and Testing of Therapeutic Products for Human Use Derived from Transgenic Animals,* DOCKET NO. 95D-0131 (1995), https://www.fda.gov/media/76253/download [https://perma.cc/Z2KH-2J4U].

7 Jaenisch & Mintz, *supra* note 6, at 1251–53.

8 *See, e.g.*, Robert E. Hammer, Vernon G. Pursel, Caird E. Rexroad, Robert J. Wall, Douglas J. Bolt, Karl M. Ebert, Richard D. Palmiter & Ralph L. Brinster, *Production of Transgenic Rabbits, Sheep and Pigs by Microinjection*, 315 NATURE 680, 680–83 (1985); Richard A. Bowen, Michael L. Reed, Angelika Schnieke, George E. Seidel, Jr., Andrew Stacey, W. Kelly Thomas & Osamu Kajikawa, *Transgenic Cattle Resulting from Biopsied Embryos: Expression of C-ski in a Transgenic Calf*, 50 BIOLOGY REPRODUCTION 664, 664 (1994); Gottfried Brem & Mathias Müller, *Large Transgenic Mammals*, *in* ANIMALS WITH NOVEL GENES (Norman Maclean ed., 1994).

9 Ralph L. Brinster & Richard D. Palmiter, *Introduction of Genes into the Germ Line of Animals*, 80 HARVEY LECT. 1, 1 (1984).

10 *See* Mo Li, Keiichiro Suzuki, Na Young Kim, Guang-Hui Liu & Juan Carlos Izpisua Belmonte, *A Cut Above the Rest: Targeted Genome Editing Technologies in Human Pluripotent Stem Cells*, 289 J. BIOLOGICAL CHEMISTRY 4594, 4594 (2014).

11 Frédéric Pâques & Philippe Duchateau, *Meganucleases and DNA Double-Strand Break-Induced Recombination: Perspectives for Gene Therapy*, 7 CURRENT GENE THERAPY 49, 49 (2007).

12 Keith J. Joung & Jeffry D. Sander, *TALENs: A Widely Applicable Technology for Targeted Genome Editing*, 14 NATURE REVS. MOLECULAR CELL BIOLOGY 49, 49 (2013).

13 Fyodor D. Urnov, Edward J. Rebar, Michael C. Holmes, H. Steve Zhang & Philip D. Gregory, *Genome Editing with Engineered Zinc Finger Nucleases*, 11 NATURE REVS. GENETICS 636, 636 (2010).

14 Prashant Mali, Kevin M. Esvelt & George M. Church, *Cas9 as a Versatile Tool for Engineering Biology*, 10 NATURE METHODS 957, 957 (2013).

15 Colin A. Carter & K. Aleks Schaefer, *GM Food Standards and Labeling in the USA*, *in* REFERENCE MODULE IN FOOD SCIENCE 1, 5 (2018).

16 Jinzhi Duan, Guangqing Lu, Zhan Xie, Mingliang Lou, Lei Guo & Yu Zhang, *Genome-Wide Identification of CRISPR/Cas9 Off-Targets in Human Genome*, 24 CELL RES. 1009, 1009 (2014).

leading the regulatory agencies to reassess the safety of intentional genomic alterations in animals.

I. TRACING THE LEGAL EVOLUTION OF THE U.S. REGULATORY FRAMEWORK

Since Cohen and Boyer opened the age of genetic modification in the 1970s describing recombinant-DNA techniques in their seminal publication,[17] scientists have been able to make precisely targeted manipulations of DNA sequences in living organisms. The genetic manipulation of DNA led to the development of new products and opened up the possibility for commercial applications, including transgenic virus-resistant squash and synthetic "human" insulin from *E. coli* bacteria.[18] Along with the scientific impact and commercial innovations, the discovery of rDNA techniques led to global public policy debates about the extent to which genetic manipulation should be allowed to continue.[19] In an effort to raise greater awareness and understanding of these techniques, a variety of scientists, government and regulatory agencies, and the public at large became engaged in a discussion regarding not only the benefits of these technological advances, but also the unforeseen risks.[20]

As a result, an international conference was held at the Asilomar Conference Center in Pacific Grove, California, in February 1975, where participants from research, government, and industry discussed the hazards of rDNA technology to public health and crafted guidelines for research that altered the genomes of living organisms.[21] Although the Asilomar-recommended guidelines did not have legal force, and enforcement relied on scientists' sense of professional obligation, the guidelines were soon followed by a series of political discussions, national debates, and scientific publications about the potential risks of rDNA research.[22] The U.S. National Institutes of Health (NIH) instituted the rDNA Advisory Committee (RAC), now known as the Novel and Exceptional Technology and Research Advisory Committee (NExTRAC), to develop a comprehensive set of rules governing safety issues associated with emerging biotechnologies and enact compulsory provisions regulating rDNA research in federally funded programs.[23] NIH's move was echoed by other federal agencies. In discharging their regulatory functions, the U.S. Food and Drug Administration (FDA),

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[17] Stanley N. Cohen et al., *supra* note 4.

[18] NAT'L ACAD. SCI., ENG'G, & MED., PREPARING FOR FUTURE PRODUCTS OF BIOTECHNOLOGY 15 (2017).

[19] DON LEGGETT & CHARLOTTE SLEIGH, SCIENTIFIC GOVERNANCE IN BRITAIN, 1914–79, 125 (2016).

[20] CHRIS A. WOZNIAK & ALAN MCHUGHEN, REGULATION OF AGRICULTURAL BIOTECHNOLOGY: THE UNITED STATES & CANADA 3–6 (2012).

[21] Gretchen Vogel, *Embryo Engineering Alarm*, 347 SCIENCE 1301, 1301 (2015). The conclusion of this conference was that rDNA research should proceed with "appropriate safeguards." *See* Paul Berg, David Baltimore, Sydney Brenner, Richard O. Roblin & Maxine F. Singer, *Summary Statement of the Asilomar Conference on Recombinant DNA Molecules*, 72 PROCEEDINGS NAT'L ACAD. SCI. U.S. 1981, 1981 (1975).

[22] Stefan Schäfer & Sean Low, *Asilomar Moments: Formative Framings in Recombinant DNA and Solar Climate Engineering Research*, 372 PHIL. TRANSACTIONS, MATHEMATICAL, PHYSICAL, & ENG'G SCI. 1, 2 (2014); *see also* Alan McHughen & Stuart Smyth, *US Regulatory System for Genetically Modified [Genetically Modified Organism (GMO), rDNA or Transgenic] Crop Cultivars*, 6 PLANT BIOTECHNOLOGY 2, 3 (2008).

[23] Recombinant DNA Research Guidelines, 41 Fed. Reg. 27,902, 27,902 (1976).

the U.S. Department of Agriculture (USDA), and the U.S. Environmental Protection Agency (EPA) compelled private entities using rDNA technology to adhere to the NIH guidelines, contributing to establishing a regulatory framework for rDNA research.[24]

Later in the 1980s, amid growing prospects that rDNA technology would generate a slew of new products as a direct consequence of the rapid technological developments, the Office of Science and Technology Policy (OSTP), part of the Executive Office of the President, proposed the "Coordinated Framework for Regulation of Biotechnology" (Coordinated Framework) that would clarify regulatory responsibility to federal agencies using the existing bureaucratic mechanisms.[25] Due to the efforts of the Reagan Administration, this policy document was promulgated and published in June 1986.[26] It outlined and coordinated oversight responsibilities among three different executive branch agencies: FDA, USDA and EPA. In the notice announcing the policy, OSTP stated that the Coordinated Framework was "expected to evolve in accord with the experiences of the industry and the agencies."[27] OSTP also noted that the "[e]xisting statutes provide a basic network of agency jurisdiction over both research and products; this network forms the basis of this coordinated framework and helps assure reasonable safeguards for the public."[28] Most importantly, under the new regulatory framework, rDNA technology was not considered as inherently risky, which meant that products of animal genetic engineering (i.e., food, pharmaceuticals, cosmetics, and other useful products) were not subject to different regulation because they were produced with biotechnology.[29] Regulation was mainly

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[24] John E. Barkstrom, *Recombinant DNA and the Regulation of Biotechnology: Reflections on the Asilomar Conference, Ten Years After*, 19 AKRON L. REV. 81, 87 (1986). Since the primary emphasis of rDNA technology is the development of a product, the final products often fall under the regulatory authority of federal agencies. The Federal Food, Drug, and Cosmetic Act, for instance, prohibits the adulteration "of any food, drug, device, tobacco product, or cosmetic." 21 U.S.C. § 331 (2018). A food is deemed to be adulterated "if it bears or contains any poisonous or deleterious substance which may render it injurious to health." 21 U.S.C. § 342 (2018). Therefore, if there is some factual basis showing that the rDNA produces a "deleterious" substance that may render the food injurious to health or that the rDNA manufacturing process is not in accordance with manufacturing regulations, FDA has the authority to prohibit the entry of such adulterated product into interstate commerce. By the same token, the Toxic Substances Control Act provides that EPA has the authority to question the safety of a particular product or chemical substance if the agency concludes that the "manufacture, processing, distribution in commerce, use, or disposal of a chemical substance or mixture, or that any combination of such activities, presents an unreasonable risk of injury to health or the environment." 15 U.S.C. § 2605(a) (2018). Similarly, under the Federal Insecticide, Fungicide, and Rodenticide Act's provisions, EPA has the authority to refuse registration (a prerequisite to distribution or sale) if there is any unreasonable risk to man or the environment, defined as water, air, land, and all plants and man and other animals living therein. 21 U.S.C. § 331 (2018); *see also The Controversy over the Regulation of Recombinant DNA Research, 1975-1981*, U.S. NAT'L LIBR. OF MED.: PROFILES IN SCIENCE, https://profiles.nlm.nih.gov/spotlight/ff/feature/rdna, [https://perma.cc/LSB7-7KVN]. *See generally* Thomas O. McGarity & Karl O. Bayer, *Federal Regulation of Emerging Genetic Technologies*, 36 VAND. L. REV. 81 (1983).

[25] Proposal for a Coordinated Framework for Regulation of Biotechnology, 49 Fed. Reg. 50,856–50,907 (1984); *see also* NAT'L ACAD. SCI., ENG'G, & MED., *supra* note 18, at 1.

[26] Coordinated Framework for Regulation of Biotechnology, 51 Fed. Reg. 23,301, 23,301 (1986); s*ee also* Adam D. Sheingate, *Promotion Versus Precaution: The Evolution of Biotechnology Policy in the United States*, 36 BRITISH J. POL. SCI. 243, 248 (2006).

[27] JAN-PETER NAP, ATANAS IVANOV ATANASOV & WILLEM J. STIEKEMA, GENOMICS FOR BIOSAFETY IN PLANT BIOTECHNOLOGY 235 (2004).

[28] Proposal for a Coordinated Framework, 49 Fed. Reg. at 23,303.

[29] Sheldon Krimsky, *From Asilomar to Industrial Biotechnology: Risks, Reductionism and Regulation*, 14 SCI. AS CULTURE 309, 314–15 (2005).

focused on the possible negative effects of the products on public health and safety with almost no regard to the processes used to develop them.[30] This meant that products developed through rDNA techniques needed no special or additional regulatory approval.[31] This product-based policy was the result of the concerted efforts of the Reagan administration to support new technologies and to adamantly oppose government regulation.[32]

The OSTP regulatory framework was received with much interest by the scientific community. The U.S. National Academy of Sciences (NAS) produced a 1987 white paper on the introduction of genetically modified organisms into the environment, endorsing the Coordinated Framework's approach. It stated that "the risks associated with the introduction of rDNA-engineered organisms are the same in kind as those associated with the introduction into the environment of unmodified organisms and organisms modified by other genetic techniques."[33]

Under a 1992 policy statement articulating this approach,[34] FDA affirmed that the agency would presume that commercial foods derived from new plant varieties (including plants developed by genetic engineering) were to be classified as generally recognized as safe (GRAS) under the Federal Food, Drug, and Cosmetic Act (FDCA),[35] and therefore the mere presence of rDNA in the food, by itself, would not trigger regulatory action. In the absence of any scientific data showing that GE foods differ significantly from their non-GE counterparts, "there is unlikely to be a safety question sufficient to call into question the presumed GRAS status of such naturally occurring substances and thus warrant formal premarket review and approval by FDA."[36] FDA concluded that there should be a presumption of GRAS status for all foods unless the intended expression product in a food is a "protein, carbohydrate, fat or oil, or other substance that differs significantly in structure, function, or composition from substances found currently in food. Such substances may not be GRAS and may require regulation as a food additive."[37]

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[30] Paul Berg & Maxine F. Singer, *The Recombinant DNA Controversy: Twenty Years Later*, 92 PROCEEDINGS NAT'L ACAD. SCI. U.S. 9011, 9011 (1995). Although the process does not trigger regulation, FDA does take into account the manufacturing process for the products it regulates as it can affect the safety and effectiveness of the product itself. For example, manufacturers must follow Current Good Manufacturing Practice (CGMP) regulations. For IGAs, FDA looks at the process to identify any potential hazards that may have been introduced.

[31] Proposal for a Coordinated Framework, 49 Fed. Reg. at 23,303–04.

[32] *See* Sheingate, *supra* note 26.

[33] NAT'L ACAD. SCI. U.S., *Introduction of Recombinant DNA-Engineered Organisms into the Environment: Key Issues* 1, 6 (1987), https://repository.library.georgetown.edu/handle/10822/540448 [https://perma.cc/FYJ2-TMLK].

[34] Statement of Policy: Foods Derived from New Plant Varieties, 57 Fed. Reg. 22,984 (1992), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/statement-policy-foods-derived-new-plant-varieties [https://perma.cc/6CT4-2GWS].

[35] 21 U.S.C. § 321(s). Generally speaking, food additives are subject to premarket review and approval by FDA. This means that producers have to perform extensive safety testing to demonstrate that food additives are safe under their intended conditions of use. Safety requires proof of a reasonable certainty that no harm will result to consumers. Ingredients that are determined to be GRAS, however, are not subject to the food additive approval process due to a substantial history of safe use. *See* Statement of Policy: Foods Derived from New Plant Varieties, 57 Fed. Reg. at 22,990–91.

[36] *See* Statement of Policy: Foods Derived from New Plant Varieties, 57 Fed. Reg. at 22,990.

[37] *See id.*

II. WHEN ANIMALS BECOME DRUGS: CURRENT REGULATORY ASPECTS OF GENOME-EDITED ANIMALS

As the technology developed and understanding of its risks accumulated, genetic engineering rapidly became a focus for public interest and debate.[38] Studies confirmed that adding foreign genes in order to produce desired traits could affect gene expression and behavior of animals.[39] The potential risks posed by rDNA organisms divided not only the scientific community, but also the general public, and a number of non-profit organizations promoted initiatives to secure compulsory labelling, pre-market safety assessments, and even a moratorium on genetically engineered products.[40]

On the judicial front, questions about genetically engineered food safety and proliferation became more frequent. On May 27, 1998, FDA faced an unprecedented legal challenge over the legitimacy of its regulatory policies. In *Alliance for Bio-Integrity v. Shalala*, a group of citizens concerned about genetically engineered foods containing toxins and violating their religious beliefs filed a lawsuit against the agency challenging its Policy Statement of 1992.[41] The plaintiffs challenged FDA's presumption that GE foods are generally considered safe for human consumption, arguing that the insertion of foreign genes might add new toxins, previously unknown allergens, carcinogens, or degrade nutritional quality.[42] Ultimately, the court upheld FDA's position not to mandate labeling of genetically modified foods solely on differences in the production process.[43] The case, however, increased public awareness of the entry of GE food into the food chain and added to the perception that the government was not regulating these products.[44]

As genetically engineered products started gradually, but steadily, entering the market, FDA began to face unprecedented regulatory challenges. In an effort to

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[38] Emily Marden, *Risk and Regulation: U.S. Regulatory Policy on Genetically Modified Food and Agriculture*, 44 B.C. L. Rev. 733, 736–37 (2003).

[39] For an excellent bibliography of peer reviewed scientific articles pointing out the risks associated with genetic engineering, see Sean A. Weaver & Michael C. Morris, *Risks Associated with Genetic Modification: An Annotated Bibliography of Peer Reviewed Natural Science Publications*, 18 J. AG. & ENV. ETHICS, 157, 170–72 (2005).

[40] Communities such as the City of Cambridge, Massachusetts, appointed a citizen's review board to review the safety of genetic engineering activities and decided to ban recombinant DNA experimentation within their boundaries. *See* Dorothy Nelkin, *Threats and Promises: Negotiating the Control of Research*, 107 DAEDALUS 2, 191 (1978).

[41] Alliance for Bio-Integrity v. Shalala, 116 F. Supp. 2d 166, 170 (D.D.C. 2000). In this case, Alliance for Bio-Integrity filed a complaint asserting, among other grounds, that FDA's 1992 policy on genetically engineered foods was adopted in violation of the Administrative Procedures Act, the National Environmental Policy Act, and the procedures mandated by the FDCA and FDA regulations. *Id.* at 171. More precisely, Alliance for Bio-Integrity challenged FDA's interpretation of the term "material" under 21 U.S.C. § 321(n) of the FDCA, which states that foods shall be deemed misbranded if their labeling "fails to reveal facts . . . material with respect to consequences which may result from the use of the article to which the labeling . . . relates under the conditions of use prescribed in the labeling . . . or under such conditions of use as are customary or usual. *Id.* at 178, 181 (quoting 21 U.S.C. § 321(n)).

[42] *Id.* at 170.

[43] *See id.* at 178 n.8.

[44] *E.g.*, Rebecca Jesada, *Buyer Beware: An Exploration of Health Risks and Legal Policies in Favor of a Labeling Requirement for Genetically Modified Organisms*, 14 J. HEALTH CARE POL'Y S30, S39–41 (2011).

address these challenges, FDA issued guidance for the industry in 2009 explaining its interpretation of the FDCA with respect to intentionally altered genomic DNA of animals.[45]

Before discussing the provisions of the guidance in detail, there are two important aspects that need to be addressed. First, it is important to point out that FDA's authority over the regulation of GE animals comes directly from the FDCA.[46] Such authority to regulate (or not to regulate) GE animals has long been recognized by federal courts. In *International Center for Technology Assessment v. Thompson*, for example, the court held that FDA's decision not to regulate a GE glowing aquarium fish, America's first commercially available GE animal, rests almost exclusively with the agency.[47] This approach has recently been confirmed in a case that specifically challenged FDA's approval of a GE salmon. In the decision, the U.S. District Court for the Northern District of California expressly stated that FDA's "authority to regulate drugs includes the authority to regulate the material used to modify an animal's genetic makeup."[48]

Second, while the FDA guidelines are non-binding recommendations, they often have rule-like effects on regulated entities as they perform an informal policy-making role and provide input into policy-making processes. No entity interested in developing GE animals would therefore depart from FDA guidance documents. In this sense, the 2009 Guidance for Industry #187 entitled "Regulation of Genetically Engineered Animals Containing Heritable rDNA Constructs" establishes a new regulatory pathway for genome-edited animals.[49]

The guidance clarifies that the definition of a drug under the FDCA includes not only substances "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals" but also substances (other than food) "intended to affect the structure or any function of the body of man or other animals."[50] Accordingly, modified rDNA is a drug within the meaning of Section 201(g) of the FDCA as its insertion into the animal's genome is intended to affect the structure or function of the body of the animal.[51]

In the waning days of the Obama Administration, FDA doubled down on this approach and proposed a revised guidance to oversee the use of new genome editing

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[45] U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY #187: REGULATION OF GENETICALLY ENGINEERED ANIMALS CONTAINING HERITABLE RECOMBINANT DNA CONSTRUCTS 1, 5–6 (2009), https://wayback.archive-it.org/7993/20170111005939/http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM113903.pdf [https://perma.cc/77GN-FV3C] [hereinafter GUIDANCE FOR INDUSTRY #187 (2009)].

[46] More precisely, the FDCA states that FDA may issue "guidance documents with public participation and ensure that information identifying the existence of such documents and the documents themselves are made available to the public both in written form and, as feasible, through electronic means." 21 U.S.C. § 371(h)(1)(A). Under the provisions of the FDCA, FDA also has the authority to "set forth initial interpretations of a statute or regulation," subject to the limitation that such documents "shall not create or confer any rights for or on any person." 21 U.S.C. § 371(h)(1)(A), (C).

[47] Int'l Ctr. for Tech. Assessment v. Thompson, 421 F. Supp. 2d 1, 9–11 (D.D.C. 2006).

[48] Inst. for Fisheries Resources v. Hahn, 424 F. Supp. 3d 740, 743 (N.D. Cal. 2019).

[49] *See* GUIDANCE FOR INDUSTRY #187 (2009), *supra* note 45, at 21–26.

[50] *See id.* at 5 (quoting 21 U.S.C. 321 § 201(g)).

[51] *See id.* at 5–7. It must be added that being regulated as a new drug includes FDA control and oversight over the intentionally altered genomic DNA of *all* animals modified by rDNA techniques, including progeny that contain the modification.

techniques.[52] This revised draft version of the guidance has a much broader scope compared to the previous 2009 guidance, as it tackles not only transgenic organisms but all organisms that have DNA inserted through the use of new, groundbreaking technologies such as TALENs, ZFNs, and CRISPR/Cas9.[53] In essence, each specific genomic alteration introduced into animals by genome editing is considered to be a separate new animal drug and subject to FDCA's premarket approval requirements—a process some authors argue "would discourage beneficial uses of genome editing due to the length of the FDA's review."[54] No longer is it the specific insertion of heritable recombinant DNA taken from other organisms that gives rise to the regulatory requirement (i.e., transgenic organisms), but rather *any* intentional genomic alteration introduced by site-directed nucleases into animal genomes. This includes many of the same nucleotide alterations that could have been obtained by conventional breeding methods (i.e., cisgenic organisms).[55]

In line with the provisions of Section 512(a)(1) of the FDCA on premarket approval, developers of animals with intentionally altered genomes are required to file an approval application with FDA and show that their product (the alteration made to the animal's genes) is safe and effective. However, premarket approval may be discretionally denied in circumstances that present low risk, such as in cases where nonfood-producing species that are raised and used in laboratory-controlled conditions contain edited genes.[56]

The regulatory submission process includes seven steps, six of which address identity and safety issues and one which addresses the effectiveness of the product.[57] To comply with the safety requirements, a developer has to describe the animal (step 1), its molecular characterization (step 2), the molecular characterization of its lineage (step 3), the health status of the animal (step 4), the lineage assessment showing that the offspring continue to inherit the altered genomic DNA (step 5), and the food and environmental assessment demonstrating that the animals with intentional genomic alterations are safe to eat and do not cause any significant environmental impacts (step 6).[58]

To prove the effectiveness of a substance intended to modify a particular characteristic of an animal, the developer is required to demonstrate that the animal whose DNA has been intentionally modified has the claimed altered characteristic

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[52] *See* GUIDANCE FOR INDUSTRY #187 (2017), *supra* note 2.

[53] Yvie Yao, *Genome-Edited Animals Are Not Transgenic Animals: Moving Toward Responsible Research and Innovation with New Biotechnologies*, 20 MINN. J. LAW SCI. TECH. 399, 417–18 (2019).

[54] Jonas Monast, *Editing Nature: Reconceptualizing Biotechnology Governance*, 59 B.C. L. REV. 2377, 2401 (2018); *see* also Eric Williams, *CRISPR: Redefining GMOs—One Edit at a Time*, 39 U. ARK. LITTLE ROCK L. REV. 437, 454–56 (2017).

[55] Alison L. Van Eenennaam, *Will—And Should—Gene Edited Animals Be Regulated?*, GENETIC LITERACY PROJECT (2017), https://geneticliteracyproject.org/2017/02/08/will-gene-edited-animals-regulated/ [https://perma.cc/R8LK-ERTV].

[56] Decisions are made on the basis of a case-by-case evaluation by FDA. IGAs with enforcement discretions include IGAs in aquarium fish, intended to cause the fish to fluoresce, and IGAs in miniature swine, intended for use as models of disease. For a detailed list of those IGAs in animals that FDA has determined are low-risk, see *Intentional Genomic Alterations in Animals: Enforcement Discretion*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/animal-veterinary/animals-intentional-genomic-alterations/intentional-genomic-alterations-animals-enforcement-discretion [https://perma.cc/75B6-J5GQ].

[57] *See* GUIDANCE FOR INDUSTRY #187 (2017), *supra* note 2, at 22–27.

[58] WOZNIAK & MCHUGHEN, *supra* note 20, at 310–11.

once the DNA is inserted (step 7).[59] In the case of an animal that grows faster than normal, for example, the developer will have to prove that the growth rate is in line with the expectations claimed in the approval application. Similarly, to prove the effectiveness of a substance intended to express an extractable protein, the developer is required to demonstrate that "the expression product is in fact expressed in the animal"[60] (e.g., that a goat produces an anticlotting protein in its milk).

The guidance for industry #187 constitutes a major shift from a pure product-based system to a more precautionary risk-based approach, which takes into consideration not only the particular composition of the food products derived from genetically engineered animals but also the composition of the genomic alterations to the animals themselves and the specific processes that created those genomic alterations.

III. DETERMINING A NEW FUTURE FOR ANIMAL BIOTECHNOLOGY: TOWARDS STRONGER PRECAUTION?

It may come as no surprise that these new policies have provoked a wide range of reactions in the scientific community.[61] Many argue that FDA's regulation of genome-edited animals is more extensive than necessary as it relates to animals "that could otherwise have been developed through traditional breeding techniques."[62] In January 2019, over 300 scientists—including 260 professors from more than forty academic institutions and a Nobel prize laureate—signed a petition calling for the harmonization of U.S. genome-edited food regulations.[63] They consider that GE food animals produced using modern biotechnologies in the breeding process should not be subject to different or additional premarket requirements if they could be obtained through traditional breeding techniques. FDA, they say, has to date approved only three GE animal-related applications: the GE goat that produces a human biologic in its milk (Atryn; approved 2009),[64] a GE fast growing Atlantic salmon (AquAdvantage Salmon; approved 2015),[65] and a GE chicken that produces a human biologic in its eggs (Kanuma; approved 2015).[66] The petition concludes by demanding "a

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59 *See* GUIDANCE FOR INDUSTRY #187 (2017), *supra* note 2, at 27.

60 *See id.* at 14.

61 Amy Maxmen, *Gene-Edited Animals Face US Regulatory Crackdown*, NATURE (Jan. 19, 2017), http://www.nature.com/news/gene-edited-animals-face-us-regulatory-crack down-1.21331 [https://perma.cc/F9BP-WC8R]; *see also* Williams, *supra* note 54, at 454–55.

62 Alison L. Van Eenennaam, Kevin D. Wells & James D. Murray, *Proposed U.S. Regulation of Gene-Edited Food Animals Is Not Fit for Purpose*, 3 J. SCI. FOOD 1, 4 (2019).

63 *Harmonize US Gene-Edited Food Regulations*, CORNELL ALLI. FOR SCI., https://www.gopetition.com/petitions/harmonize-us-gene-edited-food-regulations.html [https://perma.cc/ED4C-PVKM].

64 FREEDOM OF INFORMATION SUMMARY: ORIGINAL NEW ANIMAL DRUG APPLICATION, NADA 141-294, U.S. FOOD & DRUG ADMIN. (2009), https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/859 [https://perma.cc/VC8V-LL7B].

65 FREEDOM OF INFORMATION SUMMARY: ORIGINAL NEW ANIMAL DRUG APPLICATION, NADA 141-454, U.S. FOOD & DRUG ADMIN. (2015), https://www.fda.gov/media/93801/download_[https://perma.cc/6LCK-PFRG].

66 FREEDOM OF INFORMATION SUMMARY, ORIGINAL NEW ANIMAL DRUG APPLICATION, NADA 141-453, U.S. FOOD & DRUG ADMIN. (2015), https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/2558 [https://perma.cc/3W3U-RUGP]. Since the petition was filed, FDA has approved a fourth GE animal-related application: the GE rabbit that produces a protein necessary for blood coagulation (Sevenfact; approved 2020). *See* U.S. FOOD & DRUG ADMIN., *FDA Approves Additional*

harmonization of the U.S. regulatory approach to genome editing in food species so that both plant and animal breeders have access to genome editing innovations to introduce useful sustainability traits like disease resistance, climate adaptability, and food quality attributes into U.S. agricultural breeding programs."[67]

This approach seems to be too simplified and vaguely grounded as it rests on the overly simplistic assumption that "the effects of genome editing are largely identical to those of the natural processes that continually create variation in the genomes of food animals."[68] To consider intentional genomic DNA alterations the same as the millions of natural genomic mutations that randomly occur in organisms that are generally considered as safe to consume is not scientifically accurate. The process of genetic editing, enabling the deletion or insertion of a particular fragment of a gene, is inherently different from the process of natural genomic alteration that spontaneously occurs in every individual's genome in the absence of exogenous agents. FDA's conservative regulatory approach is directly based on the lack of scientific information supporting the safety of intentional genomic alterations in food animals.[69] This cation seems to be warranted. In a recent study on genetically dehorned calves produced in 2016, FDA researchers found that the DNA of the calves contained unintended genomic alterations.[70]

As the effects of such unanticipated changes are not sufficiently understood, researchers should proceed cautiously. The limited knowledge we have regarding potential unintended consequences of genome editing makes premarket evaluation of the risk rational. The unpredictable risks of genome editing that justify FDA's regulatory approach can be summarized as follows:

A. Structural Alterations in Gene Expression

Genome editing technologies have only been developed in the last decade and their targeting efficiency and accuracy are not yet fully understood. Recent studies point out the paucity of data on the unintended consequences of CRISPR techniques, and researchers have noticed a number of disruptive insertions of different sequences at

Treatment for Adults and Adolescents with Hemophilia A or B and Inhibitors, FDA news release (2020), https://www.fda.gov/news-events/press-announcements/fda-approves-additional-treatment-adults-and-adolescents-hemophilia-or-b-and-inhibitors [https://perma.cc/PX7G-L8MZ].

[67] *Harmonize US Gene-Edited Food Regulations*, *supra* note 63.

[68] Dana Carroll, Alison L. Van Eenennaam, Jeremy F. Taylor, Jon Seger & Daniel F. Voytas, *Regulate Genome-Edited Products, Not Genome Editing Itself*, 34 NAT. BIOTECHNOLOGY 477, 479 (2016).

[69] It must be pointed out that FDA has somehow anticipated these objections in the guidance document of 2017 by deciding not to enforce these provisions for "animals of nonfood-producing species whose genomes have been intentionally altered that are raised and used in contained and controlled conditions such as laboratory animals with intentionally altered genomes used in research institutions." *See supra* notes 59–60 and accompanying text.

[70] Alexis L. Norris, Stella S. Lee, Kevin J. Greenlees, Daniel A. Tadesse, Mayumi F. Miller & Heather A. Lombardi, *Template Plasmid Integration in Germline Genome-Edited Cattle*, 38 NAT. BIOTECHNOLOGY 163, 163–64 (2020).

target sites[71] together with large deletions and complex genomic rearrangements.[72] Unintended on-target mutations may be due to nuclease-induced double stranded breaks (i.e., the technology itself), or they may be caused by an improper repair mechanism of the cell. When these errors occur, they may result in unwanted consequences that have the potential to create new diseases, negative environmental impacts, and unforeseen ecological ramifications. Some of these deletions are large enough to affect the genes located nearby.[73] These studies also observed that DNA breaks introduced by single-guide RNA/Cas9 may induce genomic damage in dividing cells and result in pathogenic consequences.[74]

Gene editing nucleases may also cause genome-wide off-target effects, possibly introducing double-strand breaks at other sites of the genome and leading to small- to large-scale structural alterations in gene expression.[75] These mutations may be associated with harmful biological consequences and unknown long-term effects (e.g., gene-edited pets could have an increased susceptibility to zoonotic pathogens or aggressive traits that pose high risks to humans).[76] To date, the "efficiency," "specificity," and "fidelity" of gene targeting attainable with state-of-the-art nuclease technologies are not sufficiently clear and may depend on multiple factors, including the target cell type, the cell culture, and the chromosome structure.[77]

These issues are mainly assessed under step 6 of the review process, which, as explained above, primarily addresses food safety risks as well as environmental impacts of genome-edited animals.[78] As the Covid-19 outbreak has recently shown, however, conducting animal and environmental investigations to adequately identify zoonotic pathways in the transmission of pathogens between livestock, wildlife, and humans proves to be particularly complex.

B. Germline Alterations

Intentional genomic DNA alterations may not only induce unintended on- and off-target effects leading to visibly/perceptively deleterious phenotypes (e.g., slow growth, instability), but also small-scale mutations resulting in changes in the phenotype that are not apparent in the first-generation offspring of genome-edited

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[71] Ha Youn Shin, Choachen Wang, Hye Kyung Lee, Kyung Hyun Yoo, Xianke Zeng, Tyler Kuhns, Chil Min Yang, Teresa Mohr, Chenhyu Liu & Lothar Hennighausen, *CRISPR/Cas9 Targeting Events Cause Complex Deletions and Insertions at 17 Sites in the Mouse Genome*, 8 NAT. COMMUN. 1, 2–3 (2017).

[72] Michael Kosicki, Kärt Tomberg & Allan Bradley, *Repair of Double-Strand Breaks Induced by CRISPR–Cas9 Leads to Large Deletions and Complex Rearrangements*, 36 NAT. BIOTECHNOLOGY 765, 765–66 (2018).

[73] *Center for Veterinary Medicine Public Webinar: Genome Editing in Animals*, U.S. FOOD & DRUG ADMIN. (Apr. 25, 2019), https://www.fda.gov/animal-veterinary/workshops-conferences-meetings/cvm-public-webinar-genome-editing-animals-04252019-04252019 [https://perma.cc/J6Z4-FPU5] [hereinafter *Center for Veterinary Medicine Public Webinar*].

[74] *See* Kosicki, Tomberg & Bradley, *supra* note 72, at 766.

[75] Xiao-Hui Zhang, Louis Y. Tee, Xiao-Gang Wang, Quan-Shan Huang & Shi-Hua Yang, *Off-Target Effects in CRISPR/Cas9-Mediated Genome Engineering*, 4 MOLECULAR THERAPY: NUCLEIC ACIDS 1, 4 (2015). Some nucleases are currently being designed to result in single strand breaks. While off-target effects can still occur with these nucleases, the hypothesis is that this technology should decrease their occurrence.

[76] NAT'L ACAD. SCI., ENG'G, & MED., *supra* note 18, at 79.

[77] *Center for Veterinary Medicine Public Webinar*, *supra* note 73.

[78] *See supra* text accompanying note 58.

animals (e.g., inactivation of tumor suppressor genes). These unknown long-term effects with germline alterations may not be apparent in early generations. Furthermore, second-site genetic alterations may lead to deleterious changes in the structure and function of particular organisms (i.e., loss-of-function), eventually resulting in their extinction, while other mutations might lead to the development of a new function of the gene product (i.e., gain-of-function).[79] If genetically altered organisms with traits that confer new or enhanced functions are released into the environment without rigorous risk assessments, they may adversely modify the structure of the local ecosystem by replacing native species.[80]

A key worry when using genome editing techniques to engineer improved animal production is the unintended effects associated with on-target and off-target mutations. Although these unintended alterations do not always occur and most of them involve a single nucleotide change (i.e., point mutations), they are cause for greatest concern as the location or dimension of such a mutation does not directly correlate to its impact. Many human and animal diseases, in fact, are monogenic and are often due to a single point mutation in DNA, such as sickle cell anemia, cystic fibrosis, achondroplasia, and Tay-Sachs disease.[81] Moreover, the picture is further complicated by the fact that alterations in the non-coding region may lead to undesired gene expression not only in the proximate location but also in the distal location of the genome.[82] Mutations in these non-coding DNA regions have been proven to play a critical role in cancer development and progression.[83] As discussed above, these issues are evaluated under steps 3 and 5 of the regulatory submission process.[84]

C. Limitations of Sequencing Analysis Technology

From the above considerations, it is clear that human genome editing technologies pose different risks from the naturally occurring genome editing processes. Sequencing analyses used to analyze genes' structures, functions, and evolution are not always able to effectively identify unintended alterations, as there are no standard detection methods available in the field.[85] Conclusions regarding off-target and on-target activity might vary depending on the sequencing analysis and methods used as well as the genomic variations in each individual. This means that insertions, large

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[79] Kasavajhala V. S. K. Prasad, Bao-Hua Song, Carrie Olson-Manning, Jill T. Anderson, Cheng-Ruei Lee, M. Eric Schranz, Aaron J. Windsor, Maria J. Clauss, Antonio J. Manzaneda, Ibtehaj Naqvi, Michael Reichelt, Jonathan Gershenzon, Sanjeewa G. Rupasinghe, Mary A. Schuler & Thomas Mitchell-Olds, *A Gain-of-Function Polymorphism Controlling Complex Traits and Fitness in Nature*, 337 SCIENCE 1081, 1081–84 (2012).

[80] Motoko Araki, Kumie Nojima & Tetsuya Ishii, *Caution Required for Handling Genome Editing Technology*, 32 TRENDS BIOTECHNOLOGY 234, 236 (2014).

[81] ENCYCLOPEDIA OF MEDICAL ANTHROPOLOGY: HEALTH AND ILLNESS IN THE WORLD'S CULTURES 395, 408–09 (Carol R. Ember & Melvin Ember eds., 2004).

[82] A non-coding region of DNA is defined as a component of an organism's DNA that does not code for proteins. *See Center for Veterinary Medicine Public Webinar*, *supra* note 73.

[83] Linda Koch, *Cancer Genomics: Non-Coding Mutations in the Driver Seat*, 15 NATURE REV. GENETICS 574, 574–75 (2014).

[84] *See supra* text accompanying note 58.

[85] Alkan Can, Saba Sajjadian & Evan E. Eichler, *Limitations of Next-Generation Genome Sequence Assembly*, 8(1) NATURE METHODS 61, 61–65 (2011).

scale deletions, lesions, inversions, and chromosomal rearrangements may be possibly missed depending on which sequencing method is applied.

IV. CONCLUDING REMARKS

The democratization and widespread use of genome editing technology in recent years has resulted in an extremely accurate genetic engineering tool, but it has also created a greater need to understand how modifications to a cell's DNA affect the way it functions before such techniques are applied. Due to the lack of scientific evidence regarding potential off-target effects of recent genome editing technology, and the consequent uncertainty over potential risks of creating new biologically hazardous molecules, societies should proceed cautiously in editing DNA. The possibility of unintended biological consequences caused by off-target and on-target modifications affecting other biological pathways led FDA in 2017 to propose a revised policy guidance for producers and developers of animals with intentionally altered genomic DNA. The guidance tackles animals intentionally altered through the use of any genome editing techniques, regardless of the novelty of the modification or the presence of any dangers in the resulting product. Importantly, the revised draft guidance clarifies that FDA is not regulating an animal as a drug. Rather, the agency regulates the intentional alteration of the animal's genome. The rationale for this new regulatory approach lies in an understanding that more caution in research and development is needed when using genome editing technologies to alter animal cells. This ensures a high level of environmental protection through preventative decision-making when risks to human health or the ecosystem have not been determined with sufficient scientific certainty.

V. RECOMMENDATIONS

On the basis of the current state of genome editing, the following recommendations are provided for researchers:

- First, FDA should confirm its draft revision to guidance #187 regarding genome-edited animals. Given the lack of scientific evidence regarding the degree of accuracy, specificity, and side effects of genome editing technology, there is the risk that genetic engineering might be misused in the future to introduce harmful genetic variations into animals intentionally or unintentionally. Thus, safeguarding the public health will require federal regulators, mainly FDA together with USDA and the Centers for Disease Control and Prevention (CDC),[86] to cooperate closely to collect relevant data on antimicrobial resistance, food-borne diseases, and zoonotic diseases caused by new varieties of genome-edited animals. It follows that FDA's role should not be limited to assessing the safety of foods obtained from food-producing animals. FDA's role should be consistent with the need to ensure a more effective human safety assessment of new animal drugs. Therefore, if the adverse effects associated with genetic modification in animals go beyond

[86] CDC is a federal public health agency focusing on infection control. Its mission is, among other things, to promote health and quality of life by preventing and controlling disease. *See* CTRS. FOR DISEASE CONTROL & PREVENTION, https://www.cdc.gov [https://perma.cc/K27N-E62F].

food safety risks, FDA should have the appropriate legal mechanisms to tackle these risks. As the recent Covid-19 outbreak has shown, however, the outcome on public health of emerging zoonotic diseases are extremely difficult to predict in advance. One can see, then, that a critical dimension of consumer protection is to have a solid pre-market approval mechanism for detecting potential harm.[87]

- Second, for greater clarity, FDA should replace the vague term "intentional genomic alterations (IGA)" with "genetically engineered (GE)." In an effort to distinguish rDNA genetic engineering from newer and more precise genome editing technologies such as CRISPR and TALEN, the draft guidance #187 coins the term IGA.[88] Under the guidance, IGA refers to genetic modifications developed through the use of genome editing technologies as well as genetic engineering procedures. We believe that this new terminology creates confusion in the field. Thus, we propose that the meaning of GE should be expanded to include all types of intentional modifications of the characteristics of an organism by manipulating its genetic material, not only rDNA modifications.
- Third, for those genome editing applications which pose *very low risk*, FDA should shift its focus from a process-based to a more risk-based approach. The guidance for industry should clearly indicate those products which, based on scientific evidence, pose very low risks (e.g., biotechnology products which are used in contained and controlled environments). Accordingly, these products should not be subject to the premarket review and approval process. It goes without saying that should the risk factor change due to new scientific findings, FDA would be entitled to revisit its decisions.
- Finally, the burden of proof to demonstrate that a product is unsafe should be placed entirely on FDA in those instances where scientific evidence suggests that genome editing applications present *low risks*. This measure would undoubtedly simplify the regulatory process.

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87 NAT'L ACAD. SCI., ENG'G & MED., *supra* note 18, at 84.

88 *See* REGULATION GUIDANCE FOR INDUSTRY #187 (2017), *supra* note 2, at 4.