June 19, 2017

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Submitted Electronically via Federal eRulemaking Portal
(http://www.regulations.gov)

Re: Docket Number: FDA-2008-D-0394: Regulation of Intentionally Altered Genomic DNA in Animals; Draft Guidance for Industry; Notice of Availability[1]

Dear Dr. Lux:

The Biotechnology Innovation Organization (BIO) appreciates this opportunity to provide comments to the Food and Drug Administration (FDA) on its request for comments on the draft guidance for industry (GFI) #187, entitled *Regulation of Intentionally Altered Genomic DNA in Animals*[2]. This draft guidance would revise GFI #187 entitled "Regulation of Genetically Engineered Animals Containing Heritable Recombinant DNA Constructs" (current GFI #187)[3]. As described in the Federal Register, "this draft revision of current GFI #187 expands the scope of guidance to include animals intentionally altered through the use of genome editing techniques." The draft revised GFI#187 would apply to 'those animals whose genomes have been intentionally altered using modern molecular techniques[4] '"

BIO is the world's largest biotechnology trade association, representing small and large companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of healthcare, agricultural, industrial and environmental biotechnology products. BIO represents its members in a number of matters related to the

[1] FR 82: No.12 January 19, 2017 6561 – 6564 at https://www.gpo.gov/fdsys/pkg/FR-2017-01-19/pdf/2017-00839.pdf
[2] Draft GFI #187
https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM113903.pdf
[3] GFI #187 Regulation of Genetically Engineered Animals Containing Heritable rDNA constructs.
https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052463.pdf (document now archived on FDA website)
[4] FR 82: No.12 January 19, 2017 page 6562.

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uses of biology-based technologies in agriculture, animal health and human health, and in particular, has a strong interest in the sound regulatory oversight of animal biology products.

Over time, animal researchers and breeders have developed a continuum of genetic modification techniques that have improved and broadened their capacity to make use of the two mechanisms that nature uses to generate variation in a population. Those are (1) changing the makeup of an organism's existing genes, and (2) combining existing genes in different combinations. This genetic modification continuum is characterized by an increased understanding of life at the cellular and molecular levels. As a result of that deeper understanding, the genetic modification methods used by breeders have become much more precise over time. That precision, informed by science, reaches a new high point with genome editing tools and techniques.

In assessing the regulatory pathway for animal products developed using these innovative tools and techniques, BIO asks that FDA adhere to fundamental principles set forth originally by the White House Office of Science and Technology Policy in the 1986 Coordinated Framework[5] and 1992 Scope Policy[6] and on which the U.S. Government in general, and FDA in particular, have repeatedly relied: (1) the risk of a product is based on the nature of the product and not the process used to produce it; and (2) the degree of regulation should be proportionate to the degree of risk. These same principles were reviewed and reaffirmed by the regulatory agencies in the 2016-17 update of the Coordinated Framework. Therefore, additional regulatory principles set forth in the 1986 Coordinated Framework and 1992 Scope Policy should continue to provide the conceptual grounding and framework that FDA uses in the future for pre-market oversight of biology-based products and are fundamental to all of BIO's answers to the questions posed by FDA in its request for comment. They are as follows:

- The purpose of government regulation of biology-based products, as with any safety regulation, is to limit any unreasonable risks to the public and the environment.
- A determination to exercise oversight within the scope of discretion afforded by statute should be based on evidence that the risk presented by introduction of an organism in a particular environment used for a particular type of application is unreasonable.
- It is the characteristics of the organism, the environment and the application of the organism that determine risk or lack thereof of the organism, not the technique used

[5] Executive Office of the President. Office of Science and Technology Policy. Coordinated Framework for Regulation of Biotechnology, 51 FR 23302, June 26, 1986. http://www.aphis.usda.gov/brs/fedregister/coordinated_framework.pdf

[6] OSTP. 1992. 57 FR 6753, February 27, 1992. Exercise of Federal Oversight within Scope of Statutory Authority: Planned Introductions of Biotechnology Products into the Environment. https://www.whitehouse.gov/sites/default/files/microsites/ostp/57_fed_reg_6753__1992.pdf

to produce the organism. Indeed the new technologies of molecular modification may increase the potential for safe planned introductions because they employ techniques that are more precise and more efficient than traditional cross-breeding.
- Organisms with new phenotypic trait(s) conferring no greater risks to the target environment than the parental organisms should be subject to a level of oversight no greater than that associated with the unmodified organism.
- If oversight is skewed only at one type of technology the burden will be skewed against that technology and will hinder its development

In its request for comments, FDA has expressed an intention to subject animals intentionally altered through the use of genome editing techniques to premarket review under the Federal Food, Drug, and Cosmetic Act's new animal drug provisions. This position, which is necessarily based on the idea that all genetic modifications created by humans in purpose-bred animals are "intended to affect the structure or any function" of the animal, is in significant tension with risk-based, product-based regulation, given that FDA has never exercised its oversight for animals genetically modified using the techniques employed before the development of recombinant DNA (rDNA) technology. The only differences between genome editing on one hand, and conventional cross breeding, or rDNA technology on the other, is specificity.

And because the U.S. government, in general, and FDA, in particular, have repeatedly said that the process of modification is independent of the safety of the organism, the justification for expanding the scope to include "those animals whose genomes have been intentionally altered using modern molecular techniques" is unclear, as is the agency's focus on whether changes were made with "intention," which is irrelevant to risk or safety.

In addition, FDA's approach as set forth in the proposed revision to GFI #187 is directly contrary to the regulatory approach to advanced breeding methods proposed by other Coordinated Framework agencies with oversight of agricultural products and to the approaches being considered by the United States' trading partners. Speaking with a single, unified regulatory voice with respect to the regulation of products of these new tools and techniques will help to ensure that the United States remains a leader in agricultural innovation.

Accordingly, BIO supports the position that, where it can be shown that a new trait has been provided to animals using genome editing tools that are essentially a more precise method of animal breeding, the resulting animals should not be treated differently for purposes of pre-market review than those animals modified through more traditional breeding methods that have a history of safe use. Because the proposed revision to GFI #187 runs directly contrary to this position, BIO respectfully asks that the proposal be withdrawn by the Agency.

BIO appreciates the opportunity to respond to the specific questions posed by FDA, and we look forward to continuing to work with FDA in the future to ensure that the Agency's approach to genome editing is rational, science-based and risk proportionate and promotes American innovation.

Sincerely,

Dana O'Brien
Executive Vice President

cc. Laura Epstein, FDA-CVM

INTRODUCTION

This is a critical time in the development of the newest biology-based technologies: an array of genome editing techniques that target sites in an organism's genetic material with remarkable precision and lead to highly specific changes to its genome. In choosing if and how they will regulate categories of products derived from genome editing technologies, governments around the world are determining whether these technologies will be readily available to public sector researchers and small companies or will be research and product development tools that only large companies can afford to use.

The U.S. Government, in general, and FDA, in particular, have repeatedly stated that:

- The risk of a biotechnology product is based on the nature of the product and not the process used to produce it;
- The degree of regulation should be proportionate to the degree of risk.

We urge FDA to adhere to those principles, set forth originally by the White House Office of Science and Technology Policy in the 1986 Coordinated Framework[7] and 1992 Scope policy[8]. The strength and validity of the U.S government's statements merit review, because they are rational, science-based and risk proportionate. In 2016-17, the U.S. government reviewed and reaffirmed the Coordinated Framework and 1992 Scope policy statement[9]. Therefore, BIO assumes these documents provide the conceptual framework and principles the agencies will use in the future to regulate biotechnology products.

Because the U.S. government has repeatedly stated that the risk of the product is based on the nature of the product and not the process, our comments provide information about historical context and scientific basis for understanding risk. The information provide below about genetic modification that occurs naturally, without human intervention, or that is intentionally caused by humans in certain animals provides a useful baseline for reference. That context is critical for accurately assessing the risks of products of genome editing, since the method of genetic modification is not the most important determinant of risk.

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[7] Executive Office of the President. Office of Science and Technology Policy. Coordinated Framework for Regulation of Biotechnology, 51 FR 23302, June 26, 1986. http://www.aphis.usda.gov/brs/fedregister/coordinated_framework.pdf

[8] OSTP. 1992. 57 FR 6753, February 27, 1992. Exercise of Federal Oversight within Scope of Statutory Authority: Planned Introductions of Biotechnology Products into the Environment. https://www.whitehouse.gov/sites/default/files/microsites/ostp/57_fed_reg_6753__1992.pdf

[9] The U.S. Government reaffirmed the scope guiding principles most recently in its 2017 update to the Coordinated Framework https://www.epa.gov/sites/production/files/2017-01/documents/2017_coordinated_framework_update.pdf and 2016 National Strategy https://www.epa.gov/sites/production/files/2016-12/documents/biotech_national_strategy_final.pdf

BACKGROUND

HISTORY OF INTENTIONAL GENETIC ALTERATION

Genome editing technologies represent the next step in a continuum of genetic modification methods that began with the simple act of domestication. Thousands of years ago, humans began herding sheep and goats, keeping cattle and swine, and taming dogs and cats. Raising animals for a specific purpose relaxed the forces of natural selection acting on the protected species, and artificial selection, imposed by their protectors, took its place. Analogous to natural selection, artificial selection preserves only some of the genetic variants derived from spontaneous mutation and nature's random mating processes, and discards others before they reproduce. As a result, genes for traits that best meet human needs - more milk, better wool, docile nature - are retained; other genes disappear from the domesticated population and the genetic makeup of that population becomes differentiated from their wild ancestors.

When scientists uncovered the basics of animal reproduction in the late 1700's, humans began controlling which animals mated rather than simply selecting from an array of randomly generated genetic combinations. Combining the process of controlled breeding with artificial selection (selective breeding) increased the prevalence of preferred characteristics in the breeding populations of purpose-bred animals much more rapidly.

The rediscovery of Mendel's work at the beginning of the 20th century gave breeders insight into the hereditary mechanisms they wanted to direct down certain pathways. Using their greater knowledge of heredity, reproductive physiology and embryology, animal scientists developed a host of assisted reproductive technologies (ART) during the 20th century, which have been used primarily to improve animal agriculture[10]. The ever-expanding array of science-based techniques - artificial insemination, frozen semen, estrus synchrony, superovulation, *in vitro* fertilization, embryo transfer, embryo splitting – allows animal breeders to spread superior genetics through a breed much quicker, much farther, and with lower rates of disease transmission. As a result, milk production per cow increased almost three fold from 1940 – 1995, primarily due to repeated use of frozen semen from select bulls. Similar gains occurred in poultry production during the same time frame in large part due to genetic improvement through breeding: on average, a broiler reached market weight in half the time on 50% less feed. Egg production per hen grew from 134 to over 250 annually; by 2000 the average had grown to 300 eggs/hen.

[10] When using the term *animal agriculture,* we are referring to livestock, poultry and aquaculture in total. *Livestock* includes cattle, sheep, horses, goats, and other domestic animals ordinarily raised or used on the farm. Domesticated fowl are considered poultry and not livestock. Aquaculture, also known as fish or shellfish farming, refers to the breeding, rearing, and harvesting of animals in all types of water environments including ponds, rivers, lakes, and the ocean.

While those gains are impressive, animal breeders were limited in what they could achieve; they could only combine existing genes via sexual reproduction. Spontaneous mutations were the sole source of new genetic variants, or alleles, that could be used to improve a breed. In the early 1900's, using fruit flies, scientists discovered that radiation could be used to induce heritable genetic changes. However, unlike crop improvement, the discovery of induced mutagenesis did not directly affect animal agriculture.

It was not until new scientific discoveries in the 1960's related to genetic engineering, or recombinant DNA (rDNA) technology, that livestock, poultry and fish breeders were able to produce genome maps which made genome wide selection and marker assisted selection possible in animal agriculture. Also, a spontaneous, beneficial mutation that occurs in other species can be used to improve any breed with rDNA technology.

The evolution of genetic modification techniques has reached a pinnacle of precision with genome editing techniques. By using the tools of genome editing animal scientists are able to improve on all of the earlier genetic modification techniques. The extraordinary specificity associated with genome editing is made possible not only by the new molecular tools, but also as a result of the wealth of information provided by the many animal genome sequencing projects that have been carried out by scientists around the world over the past two decades. It is because of the information provided by those projects that breeders are able to target a precise site in the genome.

It is important to note that all of the forms of genetic modification utilized by animal breeders and researchers occur in nature[11], and the molecular tools that allow for precise changes are molecules that naturally-occurring organisms use every day.

In summary, animal researchers and breeders have developed a continuum of genetic modification techniques that have improved and broadened their capacity to make use of the two mechanisms that nature uses to generate variation in a population:

1. changing the makeup of an organism's genetic material, and
2. combining genes that occur in a population in different combinations.

The genetic modification continuum is characterized by an increased understanding of life at the cellular and molecular levels. As a result of that deeper understanding, the genetic modification methods used by breeders have become much more precise over time. That precision, informed by science, reaches a new high point with genome editing tools and techniques.

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[11] Arber, W. 2007. Genetic variation and molecular evolution. In Genomics and Genetics volume 1, pp. 385-406. R.E. Myers, editor. Wiley.
Arber, W. 2010. Genetic engineering compared to natural genetic variations. New Biotechnology. 27: 517-521

OVERARCHING REGULATORY PRINCIPLES

In the 1980-90's, a number of countries recognized that a proliferation of regulations was creating significant obstacles to economic growth and innovation without providing the countervailing benefit of enhanced protection of the environment or human health. In response, each country began a systematic review of its regulatory structures and processes. These self-evaluations led to a number of generally agreed to principles of good regulation that countries increasingly use in guiding their revisions to and development of regulations[12]. The U.S. government articulated these principles in a 1992 Executive Order[13]; each subsequent Administration, including the current one, has reaffirmed them[14]. The principles, as articulated by the Organization of Economic Cooperation and Development (OECD) in 1995, are provided in Appendix A. We highlight key principles below:

- Regulate only when there is a significant problem that needs to be solved and government regulation is the best mechanism for solving it.
- If the government decides regulation is warranted, it should first articulate the problem it is trying to solve to ensure the regulations it develops will solve the problem in a cost-effective manner and without impeding innovation unnecessarily
- The benefits of regulation should justify the costs, and the degree of regulation should be commensurate with the risk
- Base decisions on the best scientific and technical information concerning the need for and consequences of the intended regulation.
- Avoid development of regulations that are inconsistent, incompatible or duplicative.
- Select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety) and other advantages.
- Review regulations on a regular basis to ensure they still serve regulatory objectives in the least burdensome way.

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[12] OECD. 1995. Recommendation of the Council on Improving the Quality of Government Regulation. http://acts.oecd.org/Public/Info.aspx?lang=en&infoRef=C(95)21/FINAL; OECD.1997. The OECD Report on Regulatory Reform: Synthesis. http://www.oecd.org/gov/regulatory-policy/2391768.pdf; APEC-OECD. 2005. Integrated Checklist on Regulatory Reform http://www.oecd.org/regreform/34989455.pdf OECD. 2005. Guiding Principles for Regulatory Quality and Performance. http://www.oecd.org/fr/reformereg/34976533.pdf; Middle East and North Africa-OECD.2009. Regional Charter for Regulatory Quality. http://www.oecd.org/mena/governance/45187832.pdf; OECD. 2012. Recommendation of the Council on Regulatory Policy and Governance http://www.oecd.org/regreform/regulatory-policy/49990817.pdf

[13] EO 12866 (Sept 1993) 3 CFR 638 *Regulatory Planning and Review*. http://www.archives.gov/federal-register/executive-orders/pdf/12866.pdf

[14] EO 13422 (January 2007) 72 CFR 2763. https://www.gpo.gov/fdsys/pkg/FR-2007-01-23/pdf/07-293.pdf; EO 13563 (January 18, 2011) Improving Regulation and Regulatory Review http://www.whitehouse.gov/the-press-office/2011/01/18/executive-order-13563-improving-regulation-and-regulatory-review; EO 13610 (May 10, 2012) Identifying and Reducing Regulatory Burdens http://www.whitehouse.gov/the-press-office/2012/05/10/executive-order-identifying-and-reducing-regulatory-burdens; https://www.whitehouse.gov/the-press-office/2017/02/24/presidential-executive-order-enforcing-regulatory-reform-agenda; https://www.whitehouse.gov/the-press-office/2017/05/08/memorandum-regulatory-reform-officers-and-regulatory-policy-officers

REGULATORY PRINCIPLES AND THE COORDINATED FRAMEWORK

The Coordinated Framework for the Regulation of Biotechnology (Coordinated Framework)[15], as articulated initially in 1986, clarified in 1992[16], and confirmed most recently in 2016-17 by FDA and the other regulatory agencies with oversight of agricultural products[17], is consistent with the general principles of good regulation described above.

Adhering to the first principle of appropriate regulation – regulate only when there is a problem that needs to be solved - the Coordinated Framework, a policy issued by the White House Office of Science and Technology Policy (OSTP), said that the federal regulatory agencies would focus on only those products that presented a potential risk, when compared to similar products that have a history of safe use and consumption.

The regulatory principle of consistency underpins the fundamental structure of the Coordinated Framework. Because the potential uses and potential risks posed by products developed through modern biotechnology are the same, in kind, as existing products with similar traits that are developed with other methodologies, the Coordinated Framework relies on existing laws that were passed to regulate similar products in order to protect the public and the environment[18]. Thus, products with similar traits pose similar risks, and the Coordinated Framework paves the way for similar products to be regulated in similar ways.

Importantly, OSTP's Coordinated Framework recognized that while the statutory bases for regulation among the involved agencies may differ, common principles should govern decisions on how to exercise discretionary oversight over biotechnology products. The White House, through the OSTP, articulated those agreed to principles, which were proposed by an interagency working group, in its 1992 policy, which is discussed below.

The Coordinated Framework also recognized that, as more is learned, regulations should evolve and be refined. As biotechnology moved from contained laboratory research to the development and testing of potential products, the developers of the Coordinated

[15] OSTP. 1986. Coordinated Framework for Regulation of Biotechnology. 51 Fed. Reg. 23302, 23304

[16] OSTP. 1992. 57 FR 6753, February 27, 1992. Exercise of Federal Oversight within Scope of Statutory Authority: Planned Introductions of Biotechnology Products into the Environment. https://www.whitehouse.gov/sites/default/files/microsites/ostp/57_fed_reg_6753__1992.pdf

[17] The U.S. Government reaffirmed the scope guiding principles most recently in its 2017 update to the Coordinated Framework https://www.epa.gov/sites/production/files/2017-01/documents/2017_coordinated_framework_update.pdf and 2016 National Strategy https://www.epa.gov/sites/production/files/2016-12/documents/biotech_national_strategy_final.pdf

[18] This approach was consistent with the findings of the OECD's Ad Hoc Group of Experts, which was convened in July 1983. They produced the report Recombinant DNA Safety Considerations. https://www.oecd.org/sti/biotech/40986855.pdf The report recommends the following, which was adopted by the OECD Council: "There is no scientific basis for specific legislation for the implementation of rDNA techniques and applications. Member countries should examine their existing oversight and review mechanisms to ensure that adequate review and control may be applied while avoiding any undue burdens that may hamper technological developments in this field."

Framework encouraged federal agencies to follow the pattern established by the National Institutes of Health (NIH) for biotechnology products. The NIH had successfully applied this regulatory principle in its oversight of genetic engineering laboratory research in the years that preceded the Coordinated Framework as scientists verified that the initial guidelines had been overly restrictive.[19]

Finally, with respect to the regulatory principles above, the 1986 Coordinated Framework sets forth regulatory approaches that are science-based and risk-proportionate. Findings from laboratory work using rDNA techniques, which had allowed NIH to relax its guidelines, were reaffirmed by the U.S. National Academies in two reports. Their findings provided sound scientific footing for the U.S. approach to regulating biotechnology products. Key findings of the 1987 National Academy of Sciences report[20] include the following:

- There is no evidence that unique hazards exist in the use of rDNA organisms or in the transfer of genes between unrelated organisms.

- The risks associated with rDNA organisms are the same in kind as those associated with unmodified organisms or organisms modified by other genetic techniques

These findings were completely consistent with the international scientific community's views, as expressed in the OECD report, *Recombinant DNA Safety Considerations*[21] and in a number of statements released by interdisciplinary groups of scientists, brought together to specifically address questions related to the risks of rDNA organisms[22]. The findings were later confirmed in the 1989 report by the National Research Council (NRC)[23], which focused on the essential role that familiarity plays in the assessing risks of organisms with a history of safe use that were genetically modified by other methods.

In the intervening 30 years since the Coordinated Framework was established, significant experience and familiarity with new biotechnology products has accrued. Simultaneously, our understanding of molecular biology has grown by leaps and bounds. Nothing has occurred and nothing has been discovered that provides evidence to challenge the validity of the viewpoints

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[19] Proposed Revised Guidelines for Research Involving Recombinant DNA Molecules FR 42:49596-49609 Sept 27, 1977; Proposed Revised Guidelines for Research Involving Recombinant DNA Molecules FR: 43:332042-33178. July 28 1978; Guidelines for Research Involving Recombinant DNA Molecules FR 43:60080-60131 December 22, 1978; Guidelines for Research Involving Recombinant DNA Molecules FR 45:6724-6749. January 29, 1980; Guidelines for Research Involving Recombinant DNA Molecules FR 45:77384-77409. November 28, 1980; Guidelines for Research Involving Recombinant DNA Molecules FR 47:17166-17198 April 21, 1982

[20] National Academy of Sciences. 1987. Introduction of DNA-Engineered Organisms into the Environment: Key Issues

[21] OECD. 1985. Recombinant DNA Safety Considerations. https://www.oecd.org/sti/biotech/40986855.pdf

[22] International Council of Scientific Unions. 1987. Scientific Committee on Genetic Experimentation. Joint Statement. Bellagio, Italy. Fiskel and Covello (editors). 1988. Safety Assurance for Environmental Introductions of Genetically Engineered Organisms: Workshop Summary. NATO ASI Series. Springer-Verlag.

[23] The National Research Council is the body that carries out the studies of the National Academies, which include the National Academy of Sciences, National Academy of Engineering and Institute of Medicine.

expressed by the scientific community in the 1980's. In no fewer than 10 reports, including one in 2016, the NAS and NRC have restated, unequivocally, the principles described above. So, too, has the European Commission (EC) verified the safety of genetically engineered organisms predicted by the NAS and NRC decades earlier. In a 2010 report[24] that summarized over 25 years of EC-funded research specifically focused on identifying the risks of rDNA techniques and rDNA organisms, the EC makes the following statements:

> "According to the results of these projects, there is, as of today, no scientific evidence associating GMOs with higher risks for the environment or for food and feed safety than conventional plants and organisms."

THE 1992 OSTP POLICY - EXERCISE OF OVERSIGHT WITHIN SCOPE OF STATUTORY AUTHORITY

While the 1986 Coordinated Framework assigns regulatory responsibilities for specific biotechnology products to various agencies that have appropriate authorities, the 1992 OSTP Policy, *Exercise of Federal Oversight within the Scope of Statutory Authority*[25] (the Scope Policy) requires the agencies to show discretion in using those authorities for regulating biotechnology products. In keeping with the regulatory principles articulated above, the Scope Policy sets forth a risk-based approach that outlines how agencies should exercise their oversight authority within the scope of discretion afforded by statutes:

> "Statutory provisions necessarily define the boundaries of the scope of discretion afforded to executive branch agencies to exercise oversight. Within the scope of authority provided by statute, federal agencies shall exercise oversight of planned introductions of biotechnology products into the environment only upon evidence that the risk posed by the introduction is unreasonable[26]."

Not only is it risk-based, but the Scope Policy is also scientifically sound. In keeping with the scientific principles articulated by NAS, NRC, and international scientific organizations, it instructs agencies to focus on the characteristics of the product and the environment into which it is introduced, not the process by which the product is created:

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[24] Kessler, C. and I. Economidis (editors) 2001. EC-sponsored research on safety of genetically modified organisms: a review of results; Economidis,I., Danuta Cichoka and Jen Hogel (editors) 2010. A decade of EU-funded GMO research (2001-2010) https://ec.europa.eu/research/biosociety/pdf/a_decade_of_eu-funded_gmo_research.pdf

[25] OSTP. 1992. 57 FR 6753, February 27, 1992. Exercise of Federal Oversight within Scope of Statutory Authority: Planned Introductions of Biotechnology Products into the Environment. https://www.whitehouse.gov/sites/default/files/microsites/ostp/57_fed_reg_6753__1992.pdf

[26] Ibid., page 6756

"Exercise of oversight in the scope of discretion afforded by the statute should be based on the risk posed by the introduction, not the process by which it was produced."

The Scope Policy repeatedly emphasizes the regulatory principle that the benefits of regulation should justify the costs, and the degree of regulation should be commensurate with the risk:

"In order to ensure that limited federal oversight resources are applied where they will accomplish the greatest net beneficial protection of public health and the environment, oversight will be exercised only where the risk is unreasonable, that is when the value of the reduction in risk obtained by additional oversight is greater than the cost thereby imposed [27]."

"The extent and type of oversight will thus be commensurate with the gravity and type of risk being address, the costs of alternative oversight options, and the effect of additional oversight on existing incentives[28]."

RESPONSES TO QUESTIONS POSED BY FDA

In responding to the questions posed by FDA, BIO notes the following key points.

Diversity of Genome Editing Applications

Genome editing may be used to provide different traits and new applications in a wide array of animals. The diversity of animals that may have edited genomes:

- ranges from invertebrates, such as insects and nematodes, to primates
- includes animals that will be used in basic biomedical research, for companionship or will become part of the food supply
- could include insects, such as silkworms, or honeybees
- includes animals that are wild and free living, or animals that are domesticated and live in confined settings such as laboratories or agricultural production facilities, or animals that are wild, but are also confined.

Unless stated otherwise, please assume our answers focus on agricultural species of vertebrates that live in various levels of confinement, depending on the application and animal.

[27] Ibid, page 6758
[28] Ibid page 6568

Regulatory Principles

BIO relies heavily on the positions espoused in the 1986 Coordinated Framework[29] and 1992 Scope Policy[30] to guide our responses to the questions posed by FDA in its Notice of Availability of proposed revisions to GFI #187. As we stated in the Introduction to our comments, the U.S. government reviewed and reaffirmed the Coordinated Framework and 1992 Scope Policy statement in 2016-17. BIO, therefore, assumes that the fundamental regulatory principles set forth in these documents will continue to provide the conceptual grounding and framework that FDA uses in the future for oversight of biology-based products. Therefore, certain concepts and principles, all of which are found in the 1992 Scope Policy, are fundamental to all of BIO's answers to the questions posed. They are as follows:

- The purpose of government regulation of biology-based products, as with any safety regulation, is to limit any unreasonable risks to the public and the environment.
- A determination to exercise oversight within the scope of discretion afforded by statute should be based on evidence that the risk presented by introduction of an organism in a particular environment used for a particular type of application is unreasonable.
- It is the characteristics of the organism, the environment and the application of the organism that determine risk or lack thereof of the organism, not the technique used to produce the organism. Indeed the new technologies of molecular modification may increase the potential for safe planned introductions because they employ techniques that are more precise and more efficient than traditional cross-breeding.
- Organisms with new phenotypic trait(s) conferring no greater risks to the target environment than the parental organisms should be subject to a level of oversight no greater than that associated with the unmodified organism.
- If oversight is skewed only at one type of technology the burden will be skewed against that technology and will hinder its development

The Intention Factor

FDA's policy for regulating genetically modified animals focuses on intention. If however, and solely for purposes of discussion, genetic modifications in an animal species were found to present risks that were significant enough to use resources on mandatory review and approval, and if those very same types of genetic changes are occurring much more often in nature in the same animal species, should the government attend to these risks? What is the

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[29] Executive Office of the President. Office of Science and Technology Policy. Coordinated Framework for Regulation of Biotechnology, 51 FR 23302, June 26, 1986. http://www.aphis.usda.gov/brs/fedregister/coordinated_framework.pdf

[30] OSTP. 1992. 57 FR 6753, February 27, 1992. Exercise of Federal Oversight within Scope of Statutory Authority: Planned Introductions of Biotechnology Products into the Environment. https://www.whitehouse.gov/sites/default/files/microsites/ostp/57_fed_reg_6753__1992.pdf

relevance of intention or lack of intention if the risks occurring in nature have already been determined not to warrant regulation?

Oversight Discretion

The definition of a drug in section 201(g) of the Federal Food Drug and Cosmetic Act (FD&C Act (21 U.S.C. 321 et seq.) includes "articles intended for use in the diagnosis, cure, mitigation, treatment or prevention of diseases in man or other animals"; and "articles (other than food) intended to affect the structure or any function of the body of man or other animals." The definition of "new animal drug" in section 201(v) of the FD&C Act includes any drug intended for use in animals that is not generally recognized as safe and effective for use under the conditions prescribed, recommended, or suggested in the drug's labeling, or that is so recognized but has not been used to a material extent or for a material time.

If it is FDA's position that all genetic modifications created by humans in purpose-bred animals are "intended to affect the structure or any function" of the animal, then it must be noted that FDA has never exercised premarket oversight for animals genetically modified using the techniques employed before the development of rDNA technology. This no doubt is due, at least in part, to this principles articulated in the Scope Policy and by OECD.

As to genome editing, the main difference between:

1. targeted mutagenesis through genome editing and induced or spontaneous mutations is specificity;
2. genome editing that introduces genetic material from within the species' gene pool and conventional cross breeding is specificity;
3. genome editing that introduces genetic material from outside of the animal's gene pool and rDNA technology is specificity.

Consequently, in light of the science and FDA's previous statements, quoted above, BIO believes that FDA must articulate the problem it is trying to solve when it states "this draft revision of current GFI #187 expands the scope of guidance to include animals intentionally altered through the use of genome editing techniques."

Because the U.S. government, in general, and FDA, in particular, have repeatedly said that the process of modification is independent of the safety of the organism, the justification for expanding the scope to include "those animals whose genomes have been intentionally altered using modern molecular techniques[31]" is unclear.

[31] FR 82: No.12 January 19, 2017 page 6562.

FDA's Approach

FDA precedes four of the questions on which it seeks comments (2a – 2d) with this statement:

> " The set of questions for which FDA seeks public input relates to whether there is any existing empirical evidence demonstrating that certain types of genome editing may pose minimal risk."

This can be read to suggest a precautionary approach which assumes that:

- Genome editing will lead to products that have safety concerns or, at best, non-minimal risks.
- However, there may be some exceptions that might merit exclusions.

With respect to any concerns that FDA may have regarding potential risks posed by genome editing, it would be helpful for stakeholders if the agency were to articulate those concerns. BIO has not been able to identify the scientific rationale for this approach. Genome editing techniques can be used to create products that are similar or identical to products created with traditional breeding and mutagenesis – genetic medication techniques that FDA excludes from premarket oversight in the proposed revisions to GFI#187 - that would have similar risks, due to the intended change. However, due to the precision of genome editing, the unintended effects are likely to be significantly less.

BIO includes an extensive list of references on the dynamic nature of genomes in nature (see Appendix B) largely in response to this assumption underlying four of FDA's questions. Scientific understanding of the molecular basis, impacts and prevalence of genetic variation has grown exponentially in the past 20 years. High throughput genomic analysis, in conjunction with gene expression profiling, has provided scientists with an unprecedented opportunity to:

- assess the frequency and magnitude of naturally occurring genetic changes that resemble those that scientists induce using the many genetic modification techniques available to them, and

- determine the phenotypic effects of those changes at every level of biological organization from the gene to the whole organism.

To implement a science-based, risk-proportionate pre-market regulatory approach to genome editing, FDA and other regulatory bodies should consider viewing the concept of risk through the lens provided by nature. Clearly a genetic modification event does not, in and of itself, equate to risk. The risks of any conceivable genetic change created with the genetic modification techniques that scientists use intentionally are dwarfed by the

magnitude, frequency and remarkable creativity of nature's mechanisms for creating genetic variation.

BIO supports the position that new traits provided to animals using genome editing tools that are essentially a more precise way of cross-breeding or inducing mutations should not be treated differently from a regulatory perspective than those organisms modified through these more traditional genetic modification methods.

Question 2a: Are there categories of animals whose genomes have been intentionally altered for which specific empirical evidence indicates that there are no significant target animal, user safety, food safety, or environmental risks? If so, what is that evidence?

If the change made through genome editing techniques could be achieved by cross breeding, induced mutagenesis or it occurs in nature, and FDA sees no need to require pre-market review of those end products to ensure the lack of risks to the target animal, user, food safety and the environment, it is difficult to understand why FDA needs additional empirical evidence to justify NOT subjecting a genome edited product with similar traits, that will be used in similar ways, in similar environments. The method that is used to produce the same endpoint as an "article" that is not regulated as a new animal drug is irrelevant to risk.

Assuming FDA intends to continue regulating animals that contain a heritable genetic construct, then when genome editing tools are used to insert foreign genetic material, those products would be captured by the definition in the existing version of GFI #187. However, in those cases where the inserted construct contains genetic material that could have been added through traditional breeding or created through standard mutagenesis techniques, but was simply added with a different, more precise tool, those products should be excluded from the definition in the previous version of GFI #187. This would be consistent with the stated policy of the FDA and OSTP that similar products should be regulated in similar ways and the nature of the product determines the risk, not the process used in creating the product.

Rather than working from the *a priori* assumption that all genome edited products pose non-minimal risks and should be subject to a mandatory pre-market review and approval process until empirical evidence proves otherwise, FDA should focus solely on products that are more likely to pose risks.

Question 2b. Are there categories of animals whose genomes have been intentionally altered for which empirical evidence exists to demonstrate that genome editing is durable on a genotypic and phenotypic level and would

continue to be durable over the lifetime of a particular product? If so, what is that evidence?

Researchers have provided evidence that the various genome editing tools have led to comparable levels of hereditary durability in various species. Those peer-reviewed papers are listed in Appendix C.

Perhaps more importantly, durability of inheritance over generations is a product quality trait that is absolutely essential to breeders and product developers. If the genetic modification is not durable, irrespective of how it was created, the product will not be commercially viable.

Question 2c. Is there empirical evidence to demonstrate that there are degrees of introduced changes (e.g., insertions or deletions of any size or single nucleotide substitutions) that are likely to pose less risk than other changes? If so, what is that evidence?

The degree of genetic change that occurs in genome editing can be orders of magnitude less than what occurs in cross breeding, induced mutagenesis or in nature. Because FDA has said it intends to exclude products of traditional breeding and mutagenesis from pre-market review, then BIO believes FDA needs to provide science-based justification for requiring pre-market review and approval for genome edited products that have similar traits to those that could be created through traditional breeding and mutagenesis.

Question 2d. Is there empirical evidence that indicates that the degree of taxonomic relationship between the introduced gene and the recipient animal influences the health of that recipient animal or the extent to which the trait is expressed? If so, what is that evidence?

This questions was asked and answered repeatedly in the 1970's-80's by NIH researchers, the NAS, NRC, ICSU, OECD, WHO and other scientific organizations. The degree of taxonomic relationship between the introduced gene and recipient animal has no bearing on risk[32].

[32] NIH. July 7, 1976. Recombinant DNA Research: Guidelines. 41. Fed.Reg. 27911-27943. Proposed Revised Guidelines for Research Involving Recombinant DNA Molecules FR 42:49596-49609 Sept 27, 1977; Proposed Revised Guidelines for Research Involving Recombinant DNA Molecules FR: 43:332042-33178. July 28 1978; Guidelines for Research Involving Recombinant DNA Molecules FR 43:60080-60131 December 22, 1978; Guidelines for Research Involving Recombinant DNA Molecules FR 45:6724-6749. January 29, 1980; Guidelines for Research Involving Recombinant DNA Molecules FR 45:77384-77409. November 28, 1980; Guidelines for Research Involving Recombinant DNA Molecules FR 47:17166-17198 April 21, 1982; National Academy of Sciences. 1987. Introduction of DNA-Engineered Organisms into the Environment: Key Issues; OECD. 1985. Recombinant DNA Safety Considerations.

Since the 1970's-80's, there is no new evidence that would justify changing this widely accepted viewpoint. Instead, the view that taxonomic distance is irrelevant to risk has been reaffirmed in no fewer than 10 NAS reports, including one published in 2016. In addition, over 240 scientific societies around the world have confirmed the position that risk is related to attributes of the product and is unrelated to the genetic modification method or degree of taxonomic difference[33].

Question: We seek the public's input on how to refer to these animals. In the past, FDA has used the term "genetically engineered" to refer to animals containing recombinant DNA constructs intended to alter the structure or function of the body of the animal. For this draft revised guidance, we have used the phrase "animals whose genomes have been altered intentionally." Other terms that could be used include "genome edited animals," "intentionally altered animals," or expanding the term "genetically engineered" to include the deliberate modification of the characteristics of an organism by manipulating its genetic material. The public is encouraged to suggest other phrases that are accurate and inclusive.

BIO appreciates the question, however, our answer depends on the reason underlying FDA's need to ask the question. That said, the goal in choosing a term should always be clear communication with the target audience.

FDA has a responsibility to be as clear as possible about the scope of its regulatory oversight when communicating with

- the regulated community so that a developer will know the regulatory status of a product it is considering developing, and
- other regulatory bodies, both in the U.S. and internationally, so that they can understand FDA's approach and compare it to their regulatory approaches.

In those situations, BIO encourages FDA to be as precise as is necessary to meet the needs of those groups. The term you use should allow the regulated community, regulators and others to define, quite specifically, the category of genetically modified

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https://www.oecd.org/sti/biotech/40986855.pdf; International Council of Scientific Unions. 1987. Scientific Committee on Genetic Experimentation. Joint Statement. Bellagio, Italy. Fiskel and Covello (editors). 1988. Safety Assurance for Environmental Introductions of Genetically Engineered Organisms: Workshop Summary. NATO ASI Series. Springer-Verlag. Tiedje, J.M. et.al. 1989 The planned introductions of genetically engineered organisms: Ecological considerations and recommendations. Ecology. 70:298-315

[33] http://www.siquierotransgenicos.cl/2015/06/13/more-than-240-organizations-and-scientific -institutions-support-the-safety-of-gm-crops

products within the continuum of genetically modified products that are subject to the requirements in GFI #187.

With respect to the "the public", we suggest that FDA use a term that will help to inform the public about the

- continuum of genetic modification techniques
- ways in which these techniques are the same as and/or different from other genetic modification techniques.

Through our experiences we have learned that much of the public's apprehension about genetically engineered plants and animals is due solely to the public's mistaken belief that genetic modification is brand new and is the exclusive province of scientists in lab coats. Once people understand that all living organisms, including plants and animals used for food, have been genetically modified, the lens through which they view products of genetic engineering changes. By understanding that all living organisms have been genetically modified, the public is able to ask much better questions about:

- how genetic engineering and genome editing differ from earlier techniques and from each other, as appropriate, and
- whether the new techniques introduce new risks or new issues.

Finally the term FDA uses should make it clear that these are tools that can be used to achieve various goals. The first step in using the tools wisely is determining the goals the tools should serve.

Appendix A. OECD Principles for Better Regulation

1. There is a problem that needs to be addressed.
The problem to be solved should be precisely stated, giving clear evidence of its nature and magnitude, and explaining why it has arisen.

2. Government action is justified.
Intervention should be based on clear evidence that government action is justified, given the nature of the problem, the likely benefits and costs of action, and alternative mechanisms for addressing the problem.

3. Regulation is the best form of government action for addressing the problem.
Regulators should carry out, early in the regulatory process, an informed comparison of a variety of regulatory and non-regulatory policy instruments, considering relevant issues such as costs, benefits, distributional effects, and administrative requirements.

4. There is a legal basis for regulation
Regulatory processes should be structured so that all regulatory decisions rigorously respect the "rule of law", i.e., responsibility should be explicit for ensuring that all regulations are authorised by higher level regulations/laws, are consistent with treaty obligations, and comply with legal principles such as certainty and proportionality.

5. Decide on the appropriate level (or levels) of government for this action
Regulators should choose the most appropriate level of government to take action, or, if multiple levels are involved, should design effective systems of coordination between levels of government.

6. The benefits of regulation justify the costs
Regulators should estimate the total expected costs and benefits of each regulatory proposal and of feasible alternatives, and should make the estimates available in accessible format to decision-makers. The costs of government action should be justified by its benefits before action is taken.

7. The distribution of effects across society is transparent
To the extent that distributive and equity values are affected by government intervention, regulators should make the distribution of regulatory costs and benefits across social groups clear to all.

8. The regulation is clear, consistent, comprehensible, and accessible to users
Regulators should determine if rules will be understood by likely users, and to that end should take steps to ensure that the text and structure of rules are as clear as possible.

9. All interested parties should have the opportunity to present their views
Regulations should be developed in an open and transparent fashion, with appropriate procedures for effective and timely input from interested parties, such as affected businesses and trade unions, other interest groups, or other levels of government.

10. Compliance must be achievable
Regulators should assess the incentives and institutions through which the regulation will take effect and design responsive implementation strategies that make the best use of them.

Appendix B. References on dynamic nature of eukaryotic genomes

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