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Date: **February 7, 2012**

**Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740-3835**

DEAR SIRs:

The undersigned signatories, Food & Water Watch,¹ Consumers Union,² and the Center for Food Safety³ (“Petitioners”), submit this petition pursuant to the Food, Drug and Cosmetics

¹ Food & Water Watch is a national non-profit consumer organization that advocates to ensure that food, water and fish is safe, accessible and sustainably produced.

² Consumer Reports is the world’s largest independent product-testing organization. Using its more than 50 labs, auto test center, and survey research center, the nonprofit rates thousands of products and services annually. Founded in 1936, Consumer Reports has over 8 million subscribers to its magazine, website, and other publications. Its advocacy division, Consumers Union, works for health reform, food and product safety, financial reform, and other consumer issues in Washington, D.C., the states, and in the marketplace.

Act § 409(b)(1), 21 U.S.C. § 348(b)(1) (2006) (the “Act”), and the Food and Drug Administration’s (the “Agency”) regulations, 21 C.F.R. §§ 10.20 and 171.1 (2011), with respect to ABT Technologies’ (“ABT”) genetically engineered (“GE” or “transgenic” or “genetically modified”) AquAdvantage salmon.⁴ Attached hereto, in triplicate, and constituting a part of the petition is all information required to be submitted under 21 C.F.R. § 171.1(A)-(H) (2011).

³ The Center for Food Safety is a national, non-profit, membership organization dedicated to protecting human health and the environment by curbing the use of harmful food production technologies and by promoting organic and other forms of sustainable agriculture. CFS has over 200,000 members across the country and has worked on issues pertaining to genetically engineered fish since 2001.

⁴ More technically speaking: a triploid female Atlantic salmon bearing a single copy of the stably integrated α -form of opAFP-GHc2 at the α -locus in the EO-1 α line.

Petition To Deem ABT Technologies' Genetically Engineered AquAdvantage Salmon An Unsafe Food Additive

I. Executive Summary

The undersigned signatories, Food & Water Watch,⁵ Consumers Union,⁶ and the Center for Food Safety⁷ (“Petitioners”), submit the attached document, which, along with the attached FDA Form 3503 and attachments, constitutes a food additive petition and all required supplemental information with respect to ABT Technologies’ (“ABT”) genetically engineered (“GE” or “transgenic” or “genetically modified”) AquAdvantage salmon,⁸ pursuant to the Food, Drug and Cosmetics Act § 409(b)(1), 21 U.S.C. § 348(b)(1) (2006) (the “Act”), and the Food and Drug Administration’s (the “Agency”) regulations, 21 C.F.R. §§ 10.20 and 171.1 (2011).

This petition respectfully requests that the Office of Food Additive Safety (“OFAS”) take all of the following actions:

- Review ABT’s application for AquAdvantage salmon under the Act’s food additive provisions. Atlantic salmon is a substance traditionally regarded as safe. ABT’s GE process significantly alters the salmon’s composition, however, in a way that is reasonably expected to alter its nutritive value or concentration of constituents, and the new substance raises safety concerns. Under the Agency’s regulations and guidelines, such a substance must be treated as a food additive and the Agency must make a closer inquiry into the safety of its consumption, including, but not limited to, subjecting it to extensive pre-market testing.

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⁷ The Center for Food Safety is a national, non-profit, membership organization dedicated to protecting human health and the environment by curbing the use of harmful food production technologies and by promoting organic and other forms of sustainable agriculture. CFS has over 200,000 members across the country and has worked on issues pertaining to genetically engineered fish since 2001.

⁸ More technically, ABT’s seeks approval for a triploid female Atlantic salmon bearing a single copy of the stably integrated α -form of opAFP-GHc2 at the α -locus in the EO-1 α line.

- Review the gene expression product (the “GEP”) of the recombinant DNA (“rDNA”) construct of the AquAdvantage salmon, among other components, as food additives under the Food, Drug and Cosmetics Act § 201(s), 21 U.S.C. § 321 (2006).
- Render the GEP of the AquAdvantage salmon an added substance under the Act’s adulteration provisions.
- Make a finding that neither the AquAdvantage salmon, nor the GEP used to create it, is generally recognized as safe (“GRAS”) for human consumption. Food additives are presumed to be unsafe, and the processor carries the burden to prove that a food additive is GRAS. The data supplied by ABT to the Agency’s Center for Veterinary Medicine (“CVM”), which are the only known data on the transgenic salmon, are incomplete and biased and cannot be relied upon to show that AquAdvantage salmon is safe to consume.

If the Agency were to permit the first GE animal to enter the food supply without review as a food additive as sought in this petition, neither AquAdvantage salmon nor its component GEP will have been subjected to the appropriate safety assessments, rendering such a decision contrary to the law and otherwise arbitrary and capricious.

II. **Background** (corresponding to FDA Form 3503 Parts I, II, and III)

The AquAdvantage salmon that is the subject of this petition would be the first GE animal meant for human consumption. The company ABT genetically engineers the salmon by inserting an rDNA construct into diploid Atlantic salmon. Additional steps in the process result in triploid salmon that are all females and that contain three sets of chromosomes.⁹ The rDNA construct inserted into the salmon is made up of two components: a Chinook salmon growth-hormone gene and a gene sequence from an ocean pout intended to promote the regulation of the growth hormone. Synthetic linkers are also added to help assemble the two inserts. Both the ocean pout protein and the synthetic linkers act as the backbone of the rDNA construct.¹⁰ The

⁹ Rearranging the chromosomes is supposed to ensure that the female salmon are infertile.

¹⁰ Food and Drug Administration Center for Veterinary Medicine. Veterinary Medicine Advisory Committee. *Briefing Packet: AquAdvantage Salmon*, 10-11, (September 20, 2010 (pre-released September 3, 2010)) (hereinafter, “Briefing Packet”) (Attached as Exhibit A).

Chinook salmon growth hormone is the primary GEP of the rDNA construct, which actively causes AquAdvantage salmon to undergo an increase in growth rate that causes it to reach market size in half the time.¹¹

ABT has now submitted its new animal drug application (“NADA”) to CVM for review, and, as part of this process, the Agency is to take into consideration the evaluation of the Veterinary Medicine Advisory Committee (“VMAC”). To make its evaluation, VMAC reviewed the Agency’s briefing packet and ABT’s research, contained in the Environmental Assessment.¹² Utilizing VMAC’s recommendations, CVM will make its decision on whether or not to approve ABT’s AquAdvantage salmon.

The primary responsibility of CVM is to evaluate the safety of new animal drugs and animal feed. To do so, CVM is essentially applying a “substantial equivalence” test, which is a basic comparison of characteristics and composition between the GE animal and its non-GE counterpart.¹³ Substances that are subject to a food additive review, on the other hand, must undergo comprehensive toxicological studies from producers wanting to market their product to ensure that foods entering the market are safe to consume and are properly labeled.

Because AquAdvantage salmon genetic construct is the first GE animal genetic construct meant for human consumption, any unintended consequences of the genetic modification will be directly passed from animals to humans. And while some of the unintended byproducts are better understood, such as elevated levels of the potentially harmful IGF-1 hormone or increased allergenicity, many are unknown.

¹¹ ABT Technologies, <http://www.aquabounty.com/products/aquadvantage-295.aspx> (last visited September 8, 2011) (Attached as Exhibit B).

¹² Briefing Packet at 17 (Attached as Exhibit A).

¹³ See e.g., *id.* at 5 (“The food and feed safety step of the hierarchical review process addresses the issue of whether food or feed from the GE animal poses any risk to humans or animals consuming edible products from GE animals compared with the appropriate non-transgenic comparators.”) (emphasis added).

As discussed in detail in this petition, not only is it critical that AquAdvantage salmon be subject to OFAS's more in-depth studies in order to fully understand the consequences of ingesting the GE animal and to determine whether it is truly safe for human consumption, the Agency's regulations, guidelines, and organic statute require it.

III. **PETITION** (corresponding to FDA Form 3503 Parts IV.A, V, and VI)

A. In accordance with Agency regulations, OFAS must review AquAdvantage salmon as a food additive.

As outlined in this section, under the Agency's regulations, OFAS must review AquAdvantage salmon and all of its components as food additives and subject them to closer inquiry, such as extensive pre-market testing. The Agency's general classification of rDNA constructs as new animal drugs does not displace or override the Agency's regulations and guidelines, and nothing precludes the Agency from also regulating GE salmon and its components as food additives. A contrary determination would be arbitrary and capricious and in contravention of these regulations and guidelines.¹⁴

According to the Agency's regulations, "[a]ny substance of natural biological origin that has been widely consumed for its nutrient properties in the United States prior to January 1, 1958, without known detrimental effect, for which no health hazard is known, that has had significant alteration of composition by breeding^[15] or selection^[16] after January 1, 1958, where the change may be reasonably expected to alter the nutritive value or the concentration of

¹⁴ See *Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto. Ins.*, 463 U.S. 29, 43 (1983). See also 21 C.F.R. § 10.115(d)(3) (2011) ("... FDA employees may depart from guidance documents only with appropriate justification and supervisory concurrence.") (Attached as Exhibit C).

¹⁵ "Breeding" means "[t]o raise animals or plants, often to produce new or improved types." The American Heritage Science Dictionary, 2002, Houghton Mifflin.

¹⁶ "Selection" means "a natural or artificial process that results or tends to result in the survival and propagation of some individuals or organisms but not of others with the result that the inherited traits of the survivors are perpetuated. Merriam-Webster's Medical Dictionary, 2007, Merriam-Webster, Inc.

constituents” will be “reviewed as and affirmed as GRAS or determined to be a food additive....”¹⁷ Food substances that are not GRAS will be categorized as food additives, and the Agency will issue a notice in the Federal Register providing for the use of the additive in food or require the discontinuation of the additive.¹⁸

In the case of the present petition, Atlantic salmon and all of its components (which obviously have been widely consumed for their nutrient and generally non-adverse properties before January 1, 1958 and to the present) have undergone significant alteration due to breeding or selection through genetic engineering to create the AquAdvantage salmon, and this change is reasonably expected to alter the nutritive value or the concentration of the Atlantic salmon’s constituents, as detailed below. Therefore, the Agency is obligated to review the substance to determine whether it is GRAS or an unsafe food additive. Since the Agency cannot find AquAdvantage salmon to be GRAS, as also demonstrated below, the Agency must find AquAdvantage to be an unsafe food additive.¹⁹

This aligns with the agency’s current guidelines. From its first guidance issued on the subject of bioengineered foods in 1992, the Agency has said that genetically engineered foods would fall under its food additive provisions. The Guidance to Industry for Foods Derived from New Plant Varieties (“1992 Guidance”), which the VMAC’s briefing packet cites for support,²⁰ reiterates the above-cited regulations and says that foods or substances of natural biological

¹⁷ 21 C.F.R. § 170.30(f)(2) (2011) (Attached as Exhibit D).

¹⁸ Id. § 170.38(b)(1)-(2), (c) (2011) (Attached as Exhibit E).

¹⁹ 21 C.F.R. § 170.38(c)(1)-(4) (2011) (Attached as Exhibit E).

²⁰ Briefing Packet at 10-11 (Attached as Exhibit A).

origin that have historically been regarded as safe, but that have been significantly altered by modification, “fall within the scope of the FDA’s food additive authority.”²¹

The Agency’s 1993 Toxicological Principles for the Safety Assessment of Food Ingredients Redbook II (the “Redbook”), which expanded on the 1992 Guidance, concurred,²² saying that while “substances that have a safe history of use in food and substances that are substantially similar to such substances generally would not require extensive pre-market safety testing[,]... [s]ubstances that raise safety concerns would be subjected to closer inquiry.”²³ Thus, this guidance from the Agency indicates that it is proper to use conventional testing techniques, including pre-market review, when evaluating genetically engineered foods.²⁴

AquAdvantage salmon is indeed a substance that raises safety concerns. For example, as discussed below, AquAdvantage salmon exhibits potentially dangerous levels of the growth hormone IGF-1 and also could have elevated allergen potency. Indeed, a failure of OFAS to review AquAdvantage salmon under the food additive provisions given the IGF-1 levels in salmon would be an arbitrary and capricious disregard of these guidelines.²⁵

²¹ Food and Drug Administration. Guidance to Industry for Foods Derived from New Plant Varieties, 57 Fed. Reg. 22984, 17 (May 29, 1992) *available at* <http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/Biotechnology/ucm096095.htm> (last visited April 13, 2011) (hereinafter “1992 Guideline”) (Attached as Exhibit F). Notwithstanding the guidance’s name suggesting it applies only to plants, the Agency’s cited regulations do not make such a distinction. 21 C.F.R. § 170.30(f)(2) (2011) (Attached as Exhibit D).

²² It is unclear why such a determination would not apply to all bioengineered foods regardless of whether they are from plant or animal origin, given that the Redbook 2000 considered and incorporated information related to the emerging issues presented in the “Redbook II” into Redbook 2000, and the latter makes no such distinction between foods derived from new plant varieties and foods derived from animals through biotechnology.

²³ Food and Drug Administration, Toxicological Principles for the Safety Assessment of Food Ingredients Redbook 1993, Chapter VII. C. Safety of Foods and Food Additives Developed by Biotechnology (July, 2000 updated July, 2007) (hereinafter “Redbook”) (Attached as Exhibit G).

²⁴ Conventional testing includes, but is not limited to, pathological studies, *see id.* at 40, genetic toxicity tests, *see id.* at 55, and bacterial reverse genetic mutation tests. *See id.* at 59.

²⁵ *Cf. International Ladies’ Garment Workers’ Union v. Donovan*, 722 F.2d 795 (D.C. Cir. 1983) (finding that the Secretary of Labor acted arbitrarily and capriciously for rescinding a long-standing regulation without considering alternatives to its decision or providing an explanation as to its rescission).

Moreover, because AquAdvantage salmon is a whole food that requires comprehensive analysis to determine its safety, only a review of AquAdvantage Salmon as a food additive would bring it into compliance with the Codex Alimentarius Commission Guidelines (“Codex Guidelines”). The Agency said it would adhere to these guidelines,²⁶ but it is not doing so. As mentioned above, CVM is essentially reviewing the NADA using a substantial equivalence test. Under the Codex Guidelines, however, the safety assessment method recommended for whole foods is a much stricter multidisciplinary approach.²⁷ Since whole foods are “a complex mixture of compounds, often characterized by a wide variation in composition and nutritional value[,]”²⁸ the Codex Guidelines warn that whole foods that have undergone genetic modification require a “more focused approach” when assessing their safety.²⁹ Furthermore, the Codex Guidelines state multiple times that, in certain circumstances, such as where the data are insufficient³⁰ or genetic modification changes the characteristic of a food,³¹ additional data or information may be necessary, and “...the use of appropriate conventional toxicology or other studies on the new substance may be necessary.”³²

Indeed, a majority of countries require mid- and long-term toxicity tests for whole foods that have undergone genetic modification, asserting that a substantial equivalence test is not a viable measure to determine safety when such foods have been modified for their metabolism, as

²⁶ Food and Drug Administration, 187 Guidance for Industry Regulation of Genetically Engineered Animals Containing Heritable Recombinant DNA Constructs, 23 (January 15, 2009) (hereinafter “187 Guidance”) (“[t]he information needed to establish food safety for food from GE animals under an NADA is consistent with that described in the Codex Guidelines.”) (Attached as Exhibit H).

²⁷ Codex Alimentarius Commission: *Foods derived from modern biotechnology*, 2009 at 60, available at <ftp://ftp.fao.org/docrep/fao/011/a1554e/a1554e00.pdf>. (hereinafter “Codex Guidelines”) (Attached as Exhibit I).

²⁸ *Id.* at 59.

²⁹ *Id.* at 60.

³⁰ *Id.* at 62.

³¹ *Id.* at 70.

³² *Id.* at 67.

AquAdvantage has, because the altered characteristics are so unpredictable.³³ If the Agency regulates AquAdvantage salmon solely using the approach it is following for reevaluating it as a new animal drug, instead of as a whole food, it will be contrary to the Codex Guidelines' more rigorous safety assessment approach.³⁴

While the Agency's most recent guidance on bioengineered foods, 187 Guidance for Industry Regulation of Genetically Engineered Animals Containing Heritable Recombinant DNA Constructs ("187 Guidance"), indicates that the Agency intends to treat rDNA constructs used to create GE animals as new animal drugs, nothing in the guidance indicates that it is intended to displace older guidance nor retract existing regulations. Indeed, the 187 Guidance expressly says that past laws and guidelines apply to the regulation of GE animals.³⁵ Therefore, even if the Agency's preferred approach is to evaluate part of the GE animal as a new animal drug, it must also adhere to its existing regulations and treat the substance as a food additive when breeding or selection through genetic engineering reasonably expects to alter the substance's nutritive value or the concentration of constituents.

There is no valid reason that OFAS would be precluded from regulating AquAdvantage as a food additive simply because the Agency is also potentially regulating its rDNA construct as a new animal drug. Should the Agency, as it has in the past, merely justify such a decision by referencing 21 U.S.C. § 321(s)(5) (2006),³⁶ which says that "[t]he term 'food additive' . . . does

³³ Oliver Le Curieux-Belfond et al., *Factors to consider before production and commercialization of aquatic genetically modified organisms: the case of transgenic salmon*, 12 *Envtl. Sci. & Pol'y*, 170, 175-176 (2009), available at http://www.gmo-free-regions.org/fileadmin/files/gmo-free-regions/Food_and_Democracy/B2_LeCurieux_Vandelac_Caron_Seralini.pdf (last visited April 5, 2011) (hereinafter "Le Curieux-Belfond study") (Attached as Exhibit J).

³⁴ Codex Guidelines at 57 (Attached as Exhibit I).

³⁵ 187 Guidance at 4 (Attached as Exhibit H).

³⁶ See e.g., Center for Food Safety, 01P-0230, 2001 (Dep't. of Health and Human Services. Jan 15, 2009) (Attached as Exhibit K).

not include...a new animal drug,”³⁷ it would be to blatantly misconstrue the language and history of the statute. There is no indication that Congress intended this provision to mean that simply because part of a food’s production process involves a new animal drug, the Agency cannot review other parts involving food additives.

Indeed, such an interpretation would be contrary to the Agency’s past treatment of substances as both new animal drugs and food additives depending on how the substances are used. Many of these interpretations have been upheld by the courts. See U.S. v. Naremco Inc., 553 F.2d 1138, 1143 (8th Cir. 1977) (holding that gentian violet is considered an animal drug when ingested for short periods of time and a food additive when consumed on a daily basis). See also U.S. v. 45/194 Kg. Drums of Pure Vegetable Oil, 961 F.2d 808, 810 (9th Cir. 1992) (finding that the defendant failed to file a food additive petition before exporting the oil to the United States when the FDA’s Important Alert 66-04 provided that “[evening primrose] oil may be sold as a food or drug if: (1) when sold as a drug, it is considered a new drug...or (2) when sold as a food, it is considered a food additive, and prior to marketing a food additive petition is submitted to FDA ...”).

Moreover, the Agency’s own regulations provide this flexibility in other contexts. For example, 21 C.F.R. § 558.15(a) (2011) provides that “[t]he Commissioner of Food and Drugs will propose to revoke currently approved subtherapeutic...uses in animal feed of antibiotic and sulfonamide drugs whether granted by approval of new animal drug applications, master files *and/or antibiotic or food additive regulations...[,]*” (emphasis added), indicating that the Agency believes it has the authority to regulate antibiotic and sulfonamide drugs as new animal drugs as well as food additives and that these categories are not mutually exclusive.

³⁷ Attached as Exhibit L.

Therefore, the Agency cannot simply point to the general statutory provisions and say it is precluded from regulating AquAdvantage salmon and its components as a food additive simply because it treats the products' rDNA construct as new animal drug. And a failure to provide a reasonable explanation as to why AquAdvantage salmon and its components are not a food additive, when its regulations make plain that they are covered by the Act's food additive provisions, would be arbitrary and capricious and clearly outside of the Agency's discretion.³⁸

- B. The AquAdvantage's GEP³⁹ falls under the statutory definition of a food additive because it is a substance that results in its becoming a component that affects the characteristics of food.

According to the Food, Drug and Cosmetics Act, a food additive is:

any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food; and including any source of radiation intended for any such use), if such substance is not generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures...to be safe under the conditions of its intended use.

21 U.S.C. § 321(s) (2006).⁴⁰ Therefore, in order to fall under the definition of a food additive, 1) a substance must result in its becoming a component, and 2) the substance must affect the characteristics of a food.

All food additives are presumed to be unsafe,⁴¹ and "[t]he processor bears the burden of showing that the substance is GRAS."⁴² If a food additive is deemed unsafe by scientific experts, then the Agency considers it adulterated under 21 U.S.C. § 342(a)(1) (2006) and the

³⁸ See Motor Vehicle Mfrs. Ass'n., 463 U.S. 29.

³⁹ Under 21 C.F.R. § 170.30(f)(2) (2011) (Attached as Exhibit E), the entire AquAdvantage salmon and all of its components should be reviewed as food additives, as discussed above. The remainder of this petition focuses on one particular component, the GEP, and petitions OFAS to deem it an unsafe food additive.

⁴⁰ Attached as Exhibit L.

⁴¹ 21 U.S.C. § 348(a) (2006) (Attached as Exhibit M).

⁴² U.S. v. Two Plastic Drums, 984 F.2d 814, 816 (7th Cir. 1993).

food is barred from entering the market.

1. *The Gene Expression Product (GEP) is a substance that results in its becoming a component of the AquAdvantage Salmon because it has been directly and intentionally inserted into it.*

To satisfy the first part of the two-part test for food additive regulation, the substance must result, either directly or indirectly, in becoming a component. Here, the Chinook salmon growth hormone is the primary GEP, or biochemical material resulting from expression of the rDNA construct. Its direct effects include the alteration of hormone levels, including those of IGF-1 and allergenicity in the product.⁴³ As discussed in this section, the GEP is a component of AquAdvantage salmon because ABT inserted the rDNA construct into AquAdvantage salmon to produce the GEP to intentionally cause AquAdvantage salmon to grow faster.

A substance that “directly...results in its becoming a component” of a food is one that is “intended for use in or on food...[,]”⁴⁴ whereas a substance that “indirectly results in its becoming a component” is one that “shall not be intended to accomplish any physical or technical effect in the food itself...”⁴⁵ Substances that directly or indirectly become components of food fall under the food additive provisions of the Act.

ABT has inserted the rDNA construct into AquAdvantage salmon and bred the salmon to select for its precise positioning in the salmon’s genome so that it would express the Chinook salmon growth hormone. It cannot be argued that ABT did not intend for the GEP to become a component or affect the characteristics of AquAdvantage salmon, because, if not for the GEP becoming a component of AquAdvantage salmon, the intended characteristics of the salmon, namely the increased maturity rate, would not occur. Therefore, since the insertion of the GEP

⁴³ It may also be why the AquAdvantage salmon has a lower ratio of Omega 6 to Omega 3 fats. Briefing Packet at 95, tbl. 28 (Attached as Exhibit A).

⁴⁴ 21 C.F.R. § 172.5(a)(2) (2011) (Attached as Exhibit C).

⁴⁵ 21 C.F.R. § 174.5(a)(1) (2011) (Attached as Exhibit N).

was intentional, the GEP is necessarily a substance that is a direct result of it becoming a component of AquAdvantage salmon.

Furthermore, the Agency itself has said that the GE animal *contains* the rDNA construct.⁴⁶ Thus, it must follow that the GEP of the rDNA construct is also contained in the AquAdvantage salmon, and the GEP is a component of AquAdvantage salmon.

2. *The GEP affects the characteristics of AquAdvantage salmon because it alters non-GE salmon's nutritional content and increases the levels of IGF-1 and potential allergens.*

To satisfy the second part of the two-part test for a food additive regulation, a substance that becomes a component of food must affect the characteristics of the food regardless of whether it was added during processing. See *U.S. v. Ewig Bros. Co.*, 502 F.2d 722 (7th Cir. 1974) (finding that DDT was an additive in smoked chub even though it was also a component of the raw product). Effects need not be material⁴⁷ to cause a change in the food's characteristics, nor alter the food's organoleptic properties,⁴⁸ because the food additive provisions do not speak to "material" facts like the food labeling provisions do. So long as the food is altered in some way that changes its natural characteristics, the second part of the two-

⁴⁶ 187 Guidance at 19 (Attached as Exhibit H).

⁴⁷ Under the food labeling provisions, a label is misleading if it reveals facts "material in light of such representations or material with respect to consequences..." 21 U.S.C. § 321(n) (2006) (Attached as Exhibit L). The Agency can require labeling for a product when, without such labeling, there would be an omission of "material" facts to the consumer about consequences from the product's use. If a consumer can be led to assume that a food has the same functional or organoleptic properties as another food, but in reality it does not, then the Agency will render the food mislabeled.

⁴⁸ The Agency defines material changes as those that alter the food's composition, nutritional, or organoleptic properties. *Background Document: Public Hearing on the Labeling of Food Made from the AquAdvantage Salmon*, 1 (August, 2010). Available at http://www.fda.gov/Food/LabelingNutrition/FoodLabelingGuidanceRegulatoryInformation/Topic-SpecificLabelingInformation/ucm222608.htm#_ftnref22 (last visited April 4, 2011) (Attached as Exhibit O). Organoleptic properties are "those that stimulate the sensory organs, such as texture or aroma." Food and Drug Administration. *Id.* at 1, n.1

part test for the food additive regulation is satisfied.⁴⁹

The GEP affects the characteristics of Atlantic salmon in several ways, including affecting the salmon's nutritional content. An initial examination of IGF-1 in GE salmon showed increased levels. A second evaluation, which only examined diploid salmon, still showed higher mean levels although their significance was diminished by small sample sizes and the inclusion of an additional salmon with non-detectable levels.⁵⁰ Similar trends, and similar data problems, were found in Vitamin B6.⁵¹ Omega-3 to omega-6 ratio levels were also decreased in GE salmon.⁵² Moreover, the AquAdvantage salmon showed statistically significant differences in composition, including protein values (albumin, globulin, total protein, albumin:globulin ratio), calcium, cholesterol, phosphorous, total bilirubin, aspartate aminotransferase and glucose.⁵³ And, according to the Agency, "lipid and energy were significantly lower in the genetically engineered salmon pre-smolts relative to comparators, while moisture content was significantly higher."⁵⁴ Indeed, the GE salmon expressed double-digit differences in 22 of the 60 analytes examined by ABT, notably including a 57.8 percent greater total fat content.⁵⁵ In an additional three analytes, all fatty acids, the GE salmon expressed triple-digit increases.⁵⁶ Compared to the farm control, the GE salmon expressed double-digit differences in 19 analytes, and in one measure, free fatty acids, the GE salmon's levels were 125.0 percent greater.⁵⁷

⁴⁹ Nothing in the statute indicates that Congress intended for the food additive provisions of the Act to be read conterminously as its labeling provisions. Indeed, the language of both statutes is completely different.

⁵⁰ Briefing Packet at 68-69 (Attached as Exhibit A)

⁵¹ *Id.* at 90, tbl. 26 (Attached as Exhibit A).

⁵² *Id.* at 95, tbl. 28.

⁵³ *Id.* at 35.

⁵⁴ *Id.* at 44.

⁵⁵ *Id.* at 80-86, tbls. 21-25.

⁵⁶ *Id.*

⁵⁷ *Id.*

Furthermore, the GEP substantially affects the salmon's physical characteristics by artificially increasing the rate at which it matures. Indeed, the GEP is *intended to affect* the characteristics of AquAdvantage salmon by artificially increasing the rate at which non-GE salmon grows to maturity. The Agency says, “[t]he rDNA construct in a GE animal...is intended to affect the structure or function of the body of the GE animal....”⁵⁸ Also, “the site at which an rDNA construct is located can affect...the health of the animal....”⁵⁹ Additionally, the Agency reports that GE animals undergo a “transformative event” due to the insertion of the rDNA construct.⁶⁰ Since the GEP is the sole active component of the rDNA construct causing or contributing to such changes, the GEP is affecting the structure or function of AquAdvantage salmon.

Therefore, the GEP must be regulated as a food additive because it directly results in its becoming a component of AquAdvantage salmon and affects the nutritional and physical characteristics of AquAdvantage salmon.

3. *AquAdvantage salmon is an adulterated food under § 402(a) of the Act because it contains an added substance that is poisonous or deleterious and that may render AquAdvantage salmon injurious to health.*

In addition to the Agency finding the GEP to be a food additive, the Agency must find the GEP to be an added substance under the Act's adulteration provisions because it is a poisonous or deleterious substance that is artificially inserted into Atlantic salmon, possibly rendering the salmon injurious to health. Both Congress and the courts have spoken on this issue, and it is clear that the GEP falls within the adulteration provisions of the Act.

The Act states that “[a] food shall be deemed to be adulterated (a)(1) if it bears or

⁵⁸ 187 Guidance at 5 (attached as Exhibit H).

⁵⁹ Id.

⁶⁰ Id.

contains any poisonous or deleterious substance which may render it injurious to health; but in case the substance is not an added substance such food shall not be considered adulterated....” 21 U.S.C. § 342(a)(1) (2006).⁶¹ Substances that have been artificially inserted into food will be deemed added substances. See U.S. v. Coca Cola, 241 U.S. 265, 284 (1915) (stating that “Congress, we think, referred to ingredients artificially introduced; these are described as ‘added.’”) See also U.S. v. Anderson Seafoods Inc., 622 F.2d 157 (5th Cir. 1980) (holding that, mercury, found naturally in swordfish, was deemed an added substance when the result of human intervention. “[A]dded’ is attributable to acts of man whereas ‘not-added’ arises out of nature.” (citing to the H.R. Rep. No. 59-2118, at 6, 7, 11 (1906)). Similarly, the Agency “regards any substance that is not an inherent constituent of food or whose level in food has been increased by human intervention to be “added” within the meaning of section 402(a)(1) of the act.”⁶² See Nat’l Nutritional Foods Ass’n v. Kennedy, 572 F.2d 377, 392 (2d Cir. 1978) (ruling that vitamins and minerals, substances generally considered foods, can be found to be food additives).

If the added substance “may render” a food injurious to health, then it is deemed adulterated under the Act.⁶³ Cf. U.S. v. Ewig Bros. Co., 502 F.2d 715 (7th Cir. 1974) (finding that the Agency has the authority to render DDT an added substance in smoked chub despite the fact that it was safe to consume at low levels). The Agency must find that the GEP is an added substance because it is a hormone removed from Chinook salmon meant to increase the speed at which Atlantic salmon grows to maturity. It is artificially added to Atlantic salmon, likely increasing the level of IGF-1, possibly rendering AquAdvantage salmon injurious to health. While IGF-1 is a naturally occurring protein produced by many animals, including salmon, and

⁶¹ Attached as Exhibit P.

⁶² 1992 Guidance at 14 (Attached as Exhibit F) (citing to U.S. v. Anderson Seafoods, Inc., 622 F.2d 157 (5th Cir. 1980).

⁶³ Id. (citing to Anderson Seafoods, Inc., 622 F.2d 157).

produced by the human liver in response to an increase in human growth hormone, when it is present in the body at elevated levels, IGF-1 is a known cancer promoter, linked to breast, colorectal, prostate, and lung cancer, as described in more detail below.

In no way is the GEP an inherent constituent of AquaAdvantage salmon, because the GEP injected into Atlantic salmon is removed from Chinook salmon, which is an entirely different genus of salmon that could not naturally breed with the Atlantic salmon. Likewise, the elevated levels of the growth hormone, which are intended to artificially increase AquaAdvantage salmon's growth rate, may be unnaturally high. It is clear that Atlantic salmon would not contain genes from Chinook salmon and exhibit these abnormal characteristics if not for human intervention, and it would be clearly arbitrary and capricious for the Agency to find the GEP not to be an added substance that may render the food injurious to human health.

- C. The GEP of AquaAdvantage salmon cannot be GRAS because the scientific community disputes the safety of gene manipulation in animals and because ABT's studies show that the GEP in AquaAdvantage salmon causes potentially dangerous effects.

In order for a food additive to qualify as GRAS, there must be "a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use." 21 C.F.R. § 170.3(i) (2011).⁶⁴ Furthermore, an *expert consensus* must find the additive safe.⁶⁵ A "genuine dispute among qualified experts" is sufficient to preclude a finding that the substance is generally regarded as safe.⁶⁶ The processor bears the burden to show that the additive is GRAS,⁶⁷ and food additives are "presumed to be unsafe unless the Secretary of Health

⁶⁴ Attached as Exhibit Q.

⁶⁵ Weinberger v. Hynson, Westcott & Dunning, Inc., 412 U.S. 609, 632 (1973).

⁶⁶ U.S. v. An Article of Food, 752 F.2d 11, 15 n.6 (1st Cir. 1985).

⁶⁷ See U.S. v. Two Plastic Drums, 984 F.2d 814, 816 (7th Cir. 1993) ("The FDA can prevent the sale of products containing a food additive unless and until the processor shows that the substance, when added to food, is generally recognized as safe.") U.S. v. 29 Cartons of An Article of Food, 987 F.2d 33, 35 (1st Cir. 1993) (quoting S. Rep. No. 2422, 85th Cong., 2d Sess. (1958)). If the product containing a food additive is not GRAS and the Secretary of Health and Human Services does not issue a regulation prescribing the conditions of a food additive's safe use, then,

and Human Services has promulgated a regulation ‘prescribing the conditions under which such additive may be safely used’ or providing for ‘investigational use by qualified experts.’”⁶⁸

Generally speaking, there is no expert consensus on the safety of GE animals because the results of genetic manipulation are so unpredictable. “Scientists do not have the capacity to control nor really understand the genome of living organisms. In particular, the risks of transgenesis arise from the lack of control over the number of sequences and sites of insertion, the rate of expression of the transgene, the complexity of interactions between the gene networks, the multiplicity of gene functions, epigenetics and the interactions with environment.”⁶⁹ The rearranging of genetic material is a natural result of evolution, but it is also a random process.⁷⁰

The experts who designed the Codex Guidelines agree. “Unintended effects can result from the random insertion of DNA sequences into the animal genome, which may cause disruption or silencing of existing genes, activation of silent genes, or modifications in the expression of existing genes.”⁷¹ For example, in one independent study on GE fish, only 2 to 3 percent of Coho salmon showed gene expressions of the genetically engineered Chinook growth hormone gene, but, after mating with non-GE salmon, the progeny inexplicably exhibited 75 percent of the same gene expression.⁷² In another independent study, genetic modification of a

under 21 U.S.C. §342(a)(1), the food additive will be deemed adulterated, and, under §§ 334(a)(1) and 334(d), adulterated foods are subject to seizure, condemnation, and destruction of sale. 21 U.S.C. §§ 334(a)(1), 334(d) (2006) (Attached as Exhibit R).

⁶⁸ See *U.S. v. 45/194 Kg. Drums of Pure Vegetable Oil*, 961 F.2d 808, 812 (9th Cir. 1992) (citing *U.S. v. An Article of Food*, 678 F.2d 735, 737 (7th Cir. 1982) (quoting 21 U.S.C. § 348(a) and (i)), *cert. denied*, 506 U.S. 940 (1990). See also 21 C.F.R. § 170.38(c)(1)-(4) (“Substances not GRAS are food additives and the Commissioner of the Agency will either provide for the use of the additive or require its discontinuation.”) (Attached at Exhibit D).

⁶⁹ Le Cruieux-Belfond study at 174 (Attached as Exhibit J).

⁷⁰ *Id.* at 175.

⁷¹ Codex Guidelines at 61 (Attached as Exhibit I).

⁷² Le Cruieux-Belfond study at 174 (Attached as Exhibit J) (citing Robert H. Devlin et al., *Transmission and phenotypic effects of an antifreeze/GH gene construct in coho salmon (Oncorhynchus kisutch)* 137 *Aquaculture* 161-169 (1995)).

loach (a type of fish) egg involving growth hormones enhanced the growth rate of 7.5 percent of GE loach by up to a factor of 35, but when the study was repeated in the exact same manner, there was considerable variability in growth rate as well as other unexpected results.⁷³

Moreover, at a September 2010 meeting, VMAC members described the approach employed by the Agency in its risk assessment as lacking in rigor and poorly designed,⁷⁴ marveled at the underpowered (and changing) sample sizes,⁷⁵ noted the “sparse” primary data in regard to the molecular characterization of GE salmon⁷⁶ and criticized the agency’s failure to fully investigate the gene insertion process.⁷⁷ VMAC committee members also questioned why AquaBounty engaged in culling of fish prior to physical inspection for abnormalities⁷⁸ and criticized the agency’s proposal to address safety through post-market surveillance as not appropriate and “heartburn” inducing.⁷⁹

Clearly there exists a genuine dispute among the scientific community regarding the safety of gene manipulation in animals, primarily because the outcomes cannot be controlled. Further, the GEP of AquAdvantage salmon must be presumed unsafe because the Secretary has not prescribed any regulations for its safe use and because ABT has not conducted any of the required toxicological studies on the GEP such as “human, animal, analytical, and other scientific studies...appropriate to establish the safety of [the] substance” for review by the scientific community.⁸⁰ Indeed, a further look into ABT’s studies reveal serious risks resulting

⁷³ *Id.* (citing Halina M. Zbikowska et al., *Fish can be first-advances in fish transgenesis for commercial application*. 12 *Transgenic Research* 379-389 (2003)).

⁷⁴ Food and Drug Administration, *Transcript of Veterinary Medicine Advisory Committee Meeting on AquAdvantage Salmon*, Monday, September 20, 2010 at 355. (hereinafter, “Transcript.”) (Attached as Exhibit Y).

⁷⁵ *Id.* at 373.

⁷⁶ *Id.* at 151.

⁷⁷ *Id.* at 150-153.

⁷⁸ *Id.* at 340, 342; Briefing Packet at 26-33 (Attached as Exhibit A).

⁷⁹ Transcript at 342-343 (Attached as Exhibit Y).

⁸⁰ 21 C.F.R. § 170.3(h)-(i) (2011) (Attached as Exhibit Q).

from its gene manipulation of Atlantic salmon, namely elevated levels of IGF-1 and potentially higher allergenicity. Therefore, the GEP of AquAdvantage salmon cannot possibly be GRAS.

1. *The GEP is a potentially harmful substance because it elevates the levels of IGF-1 in AquAdvantage salmon, which may cause an increased risk of cancer, premature sexual development, and reproductive senescence.*

In particular, the elevated levels of IGF-1 found in AquAdvantage salmon, caused solely by the GEP insertion, have the potential to cause serious and unintended consequences, including, but not limited to, an increased risk of multiple types of cancer. Scientific studies have concluded that, while IGF-1 occurs naturally in the human body, elevated levels are known to increase the risk of breast, prostate, lung, and colorectal cancers.⁸¹ Other symptoms include early puberty, increased reproductive aging and reduced lifespan in rodents.⁸² This is a serious cause for concern because the precise tolerance levels at which IGF-1 functions as a cancer promoter are still unknown and because consumers are ingesting greater amounts of IGF-1 through other sources of food, such as cow's milk treated with the artificial growth hormone rBGH.

Some early evaluations of Monsanto's NADA for its rBGH product, Posilac, suggested that the body's stomach acids protect the body from IGF-1 in milk from cows treated by rBGH by destroying it prior to digestion.⁸³ But more recent research indicates that IGF-1 binds to casein, the prominent protein found in milk, and is absorbed through the bloodstream.⁸⁴

⁸¹ Herbert Yu and Thomas Rohan, *Role of the Insulin-Like Growth Factor Family in Cancer Development and Progression*, 92 *Journal of the National Cancer Institute*, 1472-1489 (2000) (Attached as Exhibit S).

⁸² Holly M. Brown-Borg, *Hormonal control of aging in rodents: The somatotrophic axis*, 299 *Molecular and Cellular Endocrinology*, 64-71 (2008) (Attached as Exhibit T).

⁸³ Food & Water Watch, *rBGH How Artificial Hormones Damage the Dairy Industry and Endanger Public Health*, 5 <http://documents.foodandwaterwatch.org/rBGH.pdf> (last visited April 8, 2011) (Attached as Exhibit U).

⁸⁴ Toshikuro Kimura, et al., *Gastrointestinal absorption of recombinant human insulin-like growth factor-1 in rats*, 283 *Journal of Pharmacology and Experimental Therapeutics*, 611-618 (1997) (Attached as Exhibit V); Pascale Anderle, et al. *In Vitro Assessment of Intestinal IGF-1 Stability*, 91 *Journal of Pharmaceutical Sciences*, 290-300

Therefore, many consumers are already ingesting higher levels of IGF-1 through the milk they drink. To subject consumers to even more foods with elevated levels of IGF-1 would be a failure on the Agency's part to protect public health.

CVM has been tasked to review ABT's NADA based on only two studies that compare the levels of growth hormone and IGF-1 in GE salmon and non-GE salmon: a peer-reviewed publication from 1992 and an ABT study from 2004.⁸⁵ The 1992 study found that GE salmon had a 41.5 percent and 94.6 percent greater mean concentration of growth hormone than non-GE siblings and control salmon, respectively.⁸⁶ Furthermore, ABT's study, despite an impermissibly small sample size, showed a 39.8 percent greater level of IGF-1 in diploid salmon than the control group.⁸⁷ What's more, the company has not conducted one study that researches the health effects of consuming salmon with artificially elevated levels of IGF-1.

2. *The GEP is a potentially harmful substance because it may cause elevated levels of, or entirely new, allergens due to the insertion of the GEP.*

AquAdvantage salmon may also cause elevated levels of, or entirely new, allergens after insertion of the GEP. The allergenicity levels found even from the small sample sizes provided by ABT were considered significant in diploid salmon with the GE construct.⁸⁸ The limited data presented do not allow a conclusion to be drawn about triploids.

Research has shown that predicting allergenicity in GE foods is nearly impossible because manipulating a plant or animal's genetic makeup cultivates unpredictable and uncontrollable results. For example, in a study published in the *New England Journal of*

(2002) (Attached as Exhibit W); Michael Hansen, Ph.D, et al. *Potential Public Health Impacts of the Use of Recombinant Bovine Somatotropin in Dairy Production*, Consumers Union, (1997) (Attached as Exhibit X).

⁸⁵ Briefing Packet at 65-69 (Attached as Exhibit A).

⁸⁶ *Id.* at 66 (Attached as Exhibit A).

⁸⁷ *Id.* at 68.

⁸⁸ *Id.* at 103.

Medicine, researchers found that GE soybeans modified with Brazil nut proteins caused allergic reactions for individuals with Brazil nut allergies.⁸⁹ In another significant study, a GE pea caused allergy-related lung damage and skin complications in mice. As the authors pointed out, “...transgenic expression...in a pea can lead to the synthesis of a modified form of the protein with altered antigenic properties. These investigations...demonstrate that transgenic expression of non-native proteins in plants may lead to the synthesis of structural variants with altered immunogenicity.”⁹⁰ In other words, foods that are not typically allergens can become so when genetically altered. For foods that are already allergens, such as salmon, this study indicates that those foods may become hyper-allergens, possibly affecting consumers who were not originally allergic to salmon, but who become so after continuing to consume GE salmon over time.

Indeed, the allergenic potency for both triploid and diploid AquAdvantage salmon was, on average, between 19.5 and 52.5 percent higher, respectively, than non-GE salmon.⁹¹ While ABT also looked at the potential allergenicity of the Chinook growth hormone separate from AquAdvantage salmon and found there to be no significant different amino acid sequences from those in its computer database, this analysis does not take into consideration that the manipulation of genes is highly unpredictable. Regardless, ABT’s research still showed cause for concern from the allergenicity of the genetically engineered salmon, despite the unreliability of its determination.

In sum, there are multiple independent, peer-reviewed scientific studies relating the dangers and unknown variables to GE foods. They demonstrate that there is a lack of general

⁸⁹ Julie A. Nordlee et al., *Identification of a Brazil-Nut Allergen in Transgenic Soybeans*, 334 *New Eng. J. Med.* 688-692 (1996) (Attached as Exhibit Z).

⁹⁰ Vanessa E. Prescott et al., *Transgenic Expression of Bean α -Amylase Inhibitor in Pea Results in Altered Structure and Immunogenicity* 53 *J. Agric. Food Chem.* 9023-9030 (2005) (Attached as Exhibit AA).

⁹¹ Briefing Packet at 103 (Attached as Exhibit A).

recognition among qualified experts that the GEP of AquAdvantage salmon would be safe.

Likewise, given that ABT has not conducted the necessary toxicological studies necessary for determining the safety of the GEP and, furthermore, has not addressed the serious potential risks of elevated levels of IGF-1 and allergens, AquAdvantage salmon cannot possibly be considered GRAS.

D. OFAS cannot conclude that AquAdvantage salmon or the GEP is GRAS based on CVM's evaluation because ABT bears the burden of showing that its product is safe, CVM's evaluation was insufficient for approval of the AquAdvantage salmon rDNA construct as a new animal drug, and ABT's research was not adequate or well-controlled.

OFAS cannot utilize either CVM's review of ABT's NADA or ABT's research to determine that AquAdvantage salmon is GRAS, for at least four distinct reasons. First, the producer, not the Agency, must prove that the food additive is safe by conducting in-depth toxicological studies. Second, CVM did not evaluate any in-depth toxicological studies under the food additive provisions to determine whether the substance is safe. Third, CVM's evaluation of ABT's NADA was insufficient because it failed to conduct a comprehensive analysis of AquAdvantage salmon. Finally, ABT did not provide adequate or well-controlled studies as required by the Agency's regulations. Rather, the studies are so flawed and incomplete that they cannot be used to determine whether either AquAdvantage salmon or the GEP is safe. It would be unreasonable for OFAS to rely on any of CVM's evaluations of ABT's research or ABT's research alone for making its determination on the safety of either AquAdvantage salmon or the GEP.⁹²

OFAS must require that ABT prove its product is GRAS. The Food Additive Amendment of 1958 was established in order to prohibit the use of food additives that had not

⁹² A court must determine "whether the agency's decisionmaking was 'reasoned.'" National Treasury Employees Union v. Horner, 854 F.2d 490, 498 (1988) (citing American Horse Protection Ass'n v. Lyng, 812 F.2d 1, 5 (1987)).

been properly tested. It was intended to place the burden of proof on the processor to show the food additive was safe to consume. “The amendment was enacted in reaction to existing law which permitted a food processor to endanger the public’s health by using an untested additive for as long as it might take for the government to suspect the additive, to research it, and to determine its safety.”⁹³ Because the burden is on ABT to show that AquAdvantage salmon and the GEP are safe, OFAS is not in the position to review and affirm CVM’s evaluation of ABT’s NADA to determine whether or not either is GRAS, and to do so would violate the Agency’s food additive regulations.⁹⁴

CVM has thus far failed to conduct a proper safety-assessment review of ABT’s NADA that would be consistent with the Codex Guidelines. When reviewing ABT’s NADA, CVM essentially only utilized a substantial equivalence test, which is just a small part of a necessary comprehensive analysis. Substantial equivalence is “[a] concept...that maintains that a novel food, for example, one that derives from genetic modification or engineering, should be considered the same as and as safe as a conventional food if it demonstrates the same characteristics and composition as the conventional food.”⁹⁵ This concept is not a viable method for evaluating the safety of foods. “The concept...is not a safety assessment in itself; rather it represents the starting point, which is used to structure the safety assessment of a new food relative to its conventional counterpart.”⁹⁶

⁹³ *Burke Pest Control, Inc. v. Joseph Schlitz Brewing Co.*, 438 So. 2d 95, 98 (Fla.App. 2 Dist. 1983) (referencing S.Rep. No. 2422, 85th Cong., 2d Sess.).

⁹⁴ “A petition may be regarded as incomplete unless it includes full reports of adequate tests reasonably applicable to show whether or not the food additive will be safe for its intended use. The reports ordinarily should include detailed data derived from appropriate animal and other biological experiments in which the methods used and the results obtained are clearly set forth.” 21 C.F.R. § 171.1(E) (2011) (Attached as Exhibit BB).

⁹⁵ Jasper Womach, Cong. Research Serv., RL 97-905, *Agriculture: A Glossary of Terms, Programs, and Laws 247-48* (2005) available at <http://www.congress.gov/erp/lists/agglossary.html>. (last visited May 13, 2011) (Attached as Exhibit CC).

⁹⁶ Codex Guidelines at 9 (Attached as Exhibit I).

The Joint Food and Agriculture Organization/World Health Organization Expert Consultation on Foods Derived from Biotechnology report published in 2000 reiterates this point, saying, “it must be stressed that the comparative approach is not a safety assessment per se, but *part* of a strategy to establish whether the new product is as safe as a traditionally bred food with an acceptable history of safe use.” (emphasis original).⁹⁷ The issue of substantial equivalence should be considered as a starting point for considering the safety of a genetically engineered food product, not an endpoint. To thoroughly assess the safety of the AquaAdvantage salmon, the Agency must do more than consider the substantial equivalence.

OFAS must demand that ABT conduct the appropriate conventional toxicological studies on the safety of AquaAdvantage salmon and its GEP as food additives, not only because ABT’s studies do not meet the more rigorous requirements under the food additive provisions, but also because ABT’s studies submitted to CVM are not adequate or well controlled and are, therefore, in violation of the Agency’s own new animal drug regulations. These regulations require adequate, well-controlled research before a new animal drug can be approved. “The primary purpose of conducting adequate and well-controlled studies of a new animal drug is to distinguish the effect of the new animal drug from other influences, such as spontaneous change in the course of the disease, normal animal production performance, or biased observation.”⁹⁸

But, as illustrated below, ABT did not provide adequate or well-controlled studies. On the contrary, ABT’s research reveals multiple flaws and inconsistencies, such as including sample diploid fish in studies that are not and will not be the subject of NADA approval, intentionally removing fish that exhibited morphological problems, and conducting studies using

⁹⁷ Joint FAO/WHO Expert Consultation on Foods Derived from Biotechnology: *Topic 5: Profiling Techniques to Identify Differences between Foods Derived from Biotechnology and their Counterparts*, 1 (2000), <ftp://ftp.fao.org/es/esn/food/Bio-07.pdf>. (last visited April 28, 2011) (Attached as Exhibit DD).

⁹⁸ 21 C.F.R. § 514.117(a) (2011) (Attached as Exhibit EE).

extremely small sample sizes of fish, which cannot possibly demonstrate the true statistical significance of the effects of the GEP on AquAdvantage salmon.

1. *ABT's research is flawed because multiple studies were conducted on sample fish that were not the product under review for NADA approval.*

ABT's application is for all-female triploid Atlantic salmon, but the company evaluated diploid salmon as well.⁹⁹ Males were also included in some studies.¹⁰⁰ When comparing the vitamin, mineral, amino acid and free- and fatty-acid content of AquAdvantage salmon to two other controls, for example, the analysis was for male and female and diploid and triploid salmon.¹⁰¹ And only if ABT found a difference between its GE salmon and the control salmon would it perform a statistical analysis based on ploidy (diploid and triploid),¹⁰² further decreasing the already small sample size. Furthermore, the Agency was given experimental data on the level of IGF-1 in diploid salmon,¹⁰³ but it is not clear if any of the data were from triploid salmon,¹⁰⁴ the product under review for approval.

Under the Codex Guidelines, “[t]he comparator(s)...should ideally be matched in housing and husbandry conditions, breed, age, sex, parity, lactation, or laying cycle (where appropriate).”¹⁰⁵ Yet, CVM has thus far accepted ABT's application, based on incomplete and biased data, as conclusive.¹⁰⁶ And, despite the extremely small sample size of all types of AquAdvantage salmon, ABT still found there to be a statistically significant difference in

⁹⁹ Transcript at 231 (Attached as Exhibit Y).

¹⁰⁰ Food and Drug Administration, *Center for Veterinary Medicine: Phenotypic Characterization of AquAdvantage Salmon*, <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/VeterinaryMedicineAdvisoryCommittee/UCM230037.pdf> (last visited April 24, 2011) (hereinafter “Characterization of ABT”) (Attached as Exhibit FF).

¹⁰¹ Briefing Packet at 79, 80 (Attached as Exhibit A).

¹⁰² *Id.* at 88.

¹⁰³ *Id.* at 74.

¹⁰⁴ Indeed, the Agency has not investigated the impact of triploidization on GE salmon, including the interactions that this process may have on the genetic construct and GEP.

¹⁰⁵ Codex Guidelines at 69 (Attached as Exhibit I).

¹⁰⁶ Transcript at 140 (Attached as Exhibit Y).

Vitamin B6 for its diploid salmon and yet reasoned that the level still fell below the suggested daily dose.¹⁰⁷ Furthermore, the Agency was given experimental data on the level of IGF-1 in diploid salmon, but it is not clear if any of the data were from triploid salmon, the product under review for approval.¹⁰⁸

2. *ABT performed a culling process for its animal safety study whereby it removed AquAdvantage salmon that were unfit for the study, further tainting its research.*

ABT reported in its animal safety study that, of the 12 female and male triploid AquAdvantage salmon studied, a third of them exhibited jaw erosion.¹⁰⁹ ABT provides no explanation as to why such abnormalities exist in its salmon. Instead, the company simply says that triploidy is typically associated with an increase in the risk of abnormalities, namely jaw erosion and gill, fin, and heart abnormalities without considering the reasons.¹¹⁰

The Codex Alimentarius Commission states that, “[a] variety of data and information are *necessary* to assess unintended effects, because no individual test can detect all possible unintended effects or identify, with certainty, those relevant to human health.” (emphasis added).¹¹¹ But rather than provide better data by removing any diploids or male salmon and adding more triploid female Atlantic salmon to the sample size, ABT instead selectively removed over 20 AquAdvantage salmon from the study because of mortality, morbidity, or non-viability.¹¹²

¹⁰⁷ Briefing Packet at 91, tbl. 27 (Attached as Exhibit A).

¹⁰⁸ Le Curieux-Belfond study at 176 (Attached as Exhibit J) (citing J.T. Cook, et al., *Growth rate, body composition and feed digestibility/conversion of growth-enhanced transgenic Atlantic salmon (Salmo salar)*, 188 *Aquaculture* 15-32 (2000)).

¹⁰⁹ Transcript at 173 (Attached as Exhibit Y).

¹¹⁰ *Id.* (ABT admits that the likely cause of jaw erosion in AquAdvantage salmon is due to the rDNA construct insertion). See also Briefing Packet at 28, tbl. 4 (Attached as Exhibit A). These defects should also mean that these fish require more antibiotics and antifungals to rear. The company provided only one page on antibiotic use with no data. More analysis is needed to determine if these fish will require more antibiotics.

¹¹¹ Codex Guidelines at 61 (Attached as Exhibit I).

¹¹² Characterization of ABT (Attached as Exhibit FF).

Moreover, ABT makes an unfounded and simply false assumption that the irregularities found in AquAdvantage salmon will decrease over time, basing that assumption on just two years of data. ABT provided data on its triploidy salmon (male and female) over the course of five years, beginning in 2003.¹¹³ From 2003 to 2004, slight to moderate irregularities as well as severe irregularities increased. In 2005, there was an exponential increase in severe irregularities between AquAdvantage salmon and non-GE salmon. It is unclear why the company chose to outright ignore this dataset, relying solely on its 2006 and 2007 data, which was the first dataset to show a decrease in the percentage of irregularities in two consecutive years.¹¹⁴

3. *ABT's studies on IGF-1 were insufficient because they were conducted using an extremely small sample size of fish.*

ABT's studies showed significant differences in IGF-1 between Atlantic salmon and AquAdvantage salmon, despite the fact that the company used extremely small sample sizes. For instance, in four of six analyses on hormone levels, sample sizes of at least one of the comparator groups ranged from zero to six fish.¹¹⁵ These salmon were selected from a larger group of 100 to 200 fish, but the report is silent on whether the selection was made randomly.¹¹⁶

In sum, OFAS cannot conclude that either AquAdvantage salmon or the GEP is GRAS based on CVM's evaluation of ABT's research because it is the responsibility of ABT to prove that its product is safe. Additionally, the Codex Guidelines and the Agency's regulations mandate that OFAS subject AquAdvantage salmon and its GEP to the food additive provision's more rigorous safety-assessment standard in order to be determined GRAS. Indeed, CVM's own review process of ABT's NADA does not even meet the standards for evaluating the safety of a

¹¹³ Briefing Packet at 28, tbl. 4 (Attached as Exhibit A).

¹¹⁴ Id.

¹¹⁵ Id. at 68, tbl. 15.

¹¹⁶ Characterization of ABT (Attached as Exhibit FF).

substance as outlined by the Codex Guidelines. Finally, ABT's research is grossly insufficient because the company failed to study the appropriate ploidy and sex of its GE salmon. This is not to mention that far too few studies were submitted in support of the application and not all of the studies were peer reviewed. Thus, were OFAS to utilize ABT's research in any way or accept CVM's evaluative process of ABT's research to make its determination on the safety of AquAdvantage salmon or its GEP, it would be acting arbitrarily and capriciously for failing to give reasonable consideration to the glaring problems with ABT's research.¹¹⁷

IV. CONCLUSION AND SIGNATURE (corresponding to FDA Form 3503 Parts VI and VII)

The Agency's regulations and past guidelines dictate that OFAS must review AquAdvantage salmon and its components under the Act's food additive provisions because Atlantic salmon is a substance traditionally regarded as safe that has undergone significant alteration due to breeding or selection through genetic engineering to create the AquAdvantage salmon, and this change is reasonably expected to alter the nutritive value or the concentration of the Atlantic salmon's constituents. It should be subjected to closer inquiry, including pre-market evaluation, because the alteration raises safety concerns. And despite the fact that the Agency has made the decision to regulate GE animals containing rDNA constructs as new animal drugs, nothing precludes it from regulating some of its components as a food additive.

In this instance, the GEP, if not other components of the AquAdvantage salmon, fall under the food additive provisions because the GEP is a substance that has been intentionally added to become a component of AquAdvantage salmon. The GEP affects the characteristics of AquAdvantage salmon by changing its nutritional qualities and increasing its maturity rate.

¹¹⁷ See Nat'l Treasury Employees Union v. Horner, 845 F.2d 490, 498 (1988) (citing Motor Vehicle Mfrs. Ass'n, 463 U.S. at 43 (finding that "[t]he reviewing court must satisfy itself that the agency has "examine[d] the relevant data and articulate[d] a satisfactory explanation for its action including a 'rational connection between the facts found and the choice made.'")).

Further, OFAS must not only find that the GEP satisfies all the requirements of a food additive, but it must also find the GEP to be an added substance under the Act's adulteration provisions because it is poisonous or deleterious and may render AquAdvantage salmon injurious to health.

Finally, OFAS must find there is no consensus among the scientific community that the GEP is safe based on the sheer uncontrollable and unpredictable results that arise from genetically engineering animals. Furthermore, ABT's own studies illustrate potentially dangerous effects from the GEP insertion, including elevated levels of IGF-1 and potentially high allergenic potency. OFAS may not rely on any of CVM's conclusions from its review of ABT's NADA nor any of ABT's research to make its determination on the safety of AquAdvantage salmon or its GEP because, first and foremost, it is the responsibility of ABT to prove the safety of its product. Additionally, CVM's review of ABT's NADA is not satisfactory under the Agency's new animal drug provisions and the Codex Guidelines. Lastly, ABT's own studies fail to meet the Agency's requirements on adequate and well-controlled studies.

Therefore, Petitioners ask the OFAS to review and regulate AquAdvantage salmon, particularly the GEP, as an unsafe food additive,¹¹⁸ and to render the GEP of the AquAdvantage salmon an added substance under the Act's adulteration provisions. Please do not hesitate to contact Zach Corrigan, Senior Staff Attorney for Food & Water Watch, at 202-276-0159, should you wish to discuss this petition further. All further correspondences should be sent to Food & Water Watch at the post address below.

21 C.F.R. § 171.1 CERTIFICATION

¹¹⁸ This petition does not itself require an environmental assessment or environmental impact statement, pursuant to 21 C.F.R. § 25.32 (m) (2011).

Pursuant to 21 C.F.R. § 171.1, the undersigned certifies that, to the best of their knowledge and belief, this petition includes all information and views on which it relies and it includes representative data and information known to the Petitioners that are unfavorable to the petition.

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