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Leslie Kux
Division of Dockets Management (HFA–305)
Food and Drug Administration
5630 Fishers Lane
Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2010-N-0385, "Food Labeling; Labeling of Food Made From AquAdvantage Salmon; Public Hearing; Request for Comments," 75 Fed. Reg. 52,602 (August 26, 2010)

Dear Ms. Kux:

Food & Water Watch is a national consumer advocacy organization. Our members are extremely concerned about the potential approval of genetically engineered (GE) salmon for human consumption and we urge the agency to carefully evaluate the health, environmental, and other impacts of this proposal. We offer the following comments on the question of whether AquaBounty's AquAdvantage salmon, if approved, should be labeled.

I. Introduction

AquaBounty's genetically engineered salmon, if approved by the FDA, clearly requires labeling. It is a different fish, whose differences appear to pose a threat to consumer health. In addition to being unhealthy for consumers, unlabeled GE salmon is also unfair, as it leads to consumers paying full price for an inferior product. While the FDA continues to consider the separate issue of whether to approve GE salmon, the issue of labeling is clear: The AquAdvantage salmon is a different fish than Atlantic Salmon, and FDA must require these differences to be labeled.

The fish exhibits a multitude of material differences, evident in measures of allergenicity, hormone levels, fatty acids, amino acids, vitamins and minerals. In fact, in every food safety aspect considered by the FDA, the agency found double-digit differences between GE salmon and control groups. Disconcertingly, as members of the FDA's Veterinary Medicine Advisory Committee (VMAC) repeatedly pointed out during their meeting in September, the FDA's scientific approach and statistical analysis were conducted in such a way that these differences largely went unacknowledged and unexamined by the agency.

But even the pervasive flaws in FDA's process cannot mask the ubiquitous differences in GE salmon. Of the 60 nutrition analytes that FDA considered – including fatty and amino acids,

vitamins and minerals – more than a third of these showed double-digit differences compared to control groups. And the GE salmon exhibited triple-digit differences in the content of four fatty acids.

Indeed, the overall picture from the data is one of GE salmon being high in fat – though not higher in beneficial omega fats—and lower in protein. Because salmon are prized for having high protein content and healthy fat levels, a point even the president of AquaBounty acknowledges,[1] these differences are of particular interest to consumers.

But perhaps even more troubling to consumers are the potentially dangerous levels of allergenicity and hormone content found in the GE salmon. An extremely small sample size of GE salmon (triploid and diploid) exhibited allergenic potency rates that were 19.5 to 52.5 percent greater than non-GE salmon. Similarly, despite small sample sizes (four of six studies included at least one group with between 0 and 6 subjects),[2] GE salmon still evidenced a 39.8 percent greater level of the hormone IGF-1 than the control group.[3] A separate, peer-reviewed study of the salmon showed GE salmon have 41.5 and 94.6 percent greater mean concentrations of growth hormone.[4]

As detailed in these comments, because all of the differences between AquaBounty's AquAdvantage salmon and Atlantic Salmon, FDA is required under the Federal Food, Drug, and Cosmetic Act to mandate the labeling of the product. Atlantic Salmon cannot be used as the market name of the GE salmon because it is not its common or usual name. Alternatively, because of the differences in key nutrient values, FDA's regulations require that it be labeled as an "imitation." In addition, AquAdvantage salmon must be labeled to reveal facts that are material to the consumer about consequences from the product's use, including the fact that it poses health risks from its IGF-levels and allergic potency. Moreover, the GE salmon needs to be labeled to inform consumers who may be wary of purchasing or consuming a product that has been so radically altered from Atlantic Salmon. Finally, the law requires that the agency mandate labeling to reflect the nutritional differences in the genetically engineered product, as well as the fact that it is likely to have a high fat content that will affect its texture, taste, and how it is processed. All of these differences are material and overwhelmingly supported by public opinion.

Though the science is indeed telling, it is also inadequate. The FDA seemingly has already drawn conclusions about the lack of material differences of AquAdvantage salmon[5] based on an extremely flawed Environmental Assessment conducted by AquaBounty, even though this assessment was designed to demonstrate the safety and effectiveness of the salmon, not differences or similarities in material identity. For this reason, many material

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[1] Food and Drug Administration. Transcript of Veterinary Medicine Advisory Committee Meeting on AquAdvantage Salmon. Monday, September 20, 2010 at 100. (hereinafter, "Transcript.")
[2] Food and Drug Administration Center for Veterinary Medicine. Veterinary Medicine Advisory Committee. "Briefing Packet: AquAdvantage Salmon." September 20, 2010 (pre-released September 3, 2010) at 103. (hereinafter, "Briefing Packet.")
[3] *Id.* at 68.
[4] *Id.* at 66.
[5] *Id.* at 108.

differences that might be present in the GE salmon – for example, with regards to organoleptic properties – have simply not been studied.

If the FDA wants to seriously analyze material differences in AquaBounty salmon, it should insist that AquaBounty conduct new studies that specifically address this question, and then release full data sets to the public. The best place to do this may be through a full environmental impact assessment, which can approach these issues through long-term studies that correct major deficiencies found in the environmental assessment, such as feeding studies and survival studies. We believe that a full EIS is imperative for GE salmon.

Despite the many problematic aspects of the data reported by the FDA and obvious deficiencies in overall science, there is still sufficient data to demonstrate myriad material differences in the GE salmon. Indeed, a failure to require labeling would be arbitrary, capricious, an abuse of discretion, or otherwise not in accordance under the Administrative Procedures Act.

II. Background

A. FDA Process

AquaBounty's AquAdvantage salmon, if approved, will be the first genetically engineered animal to enter the food supply. This landmark regulatory decision has generated great concern from consumers, who have witnessed FDA's flawed regulatory approach and weighed in by the hundreds of thousand, telling the FDA not to approve the GE salmon and insist that it be labeled if it is approved.

The FDA has asked that the public comment specifically on whether there are material differences in available data regarding "composition of the food, or its nutritional, functional or organoleptic properties," though, as described below, labeling requirements are not limited to these specific types of differences.

Additionally, though the FDA has not yet made a decision on labeling, it appears to have already made a decision on the material identity of GE salmon, which forms the basis for its regulatory decision on labeling. In its briefing packet, the FDA concludes that there were no material differences with the regards to its composition as a food or its allergenicity.[6] Making such a determination seems premature in view of the larger regulatory process, which is designed to include independent input from members of the public, scientists, and other government agencies. It is equally troubling that the FDA made this decision given the enormous number of measurable differences between GE salmon and non-GE salmon.

Furthermore, it is unclear how the FDA expects members of the public to comment on such differences given the agency's lack of transparency in data reporting. The FDA has not released full data sets to allow a comparison between the material aspects of triploid GE salmon, the subject of AquaBounty's new animal drug application, and conventional

[6] *Id.* at 108.

salmon. The FDA's current data set appears to combine values of diploid and triploid GE salmon into a summarized sample, apparently averaging their values along different analytes. By pooling the data of diploid and triploid GE salmon, the FDA has inexplicably introduced an enormously confounding variable, triploidization, into its assessments of GE salmon. Equally disconcerting, it appears that the FDA has used its flawed, summary data sets as the basis for its own assessment of material differences.

In the very few places where the FDA gives data specific to triploid GE salmon (found in the appendix of the FDA briefing packet), we see striking differences that amplify the need for labeling. Triploid GE salmon exhibited 73 percent greater values of the fatty acid docosapentaenoic than the sponsor control, and 27 percent higher values than the farm control.[7] In measurements of free fatty acids, the triploid GE salmon showed 29 percent and 80 percent higher values; for folic acid, the differences are 16 and 37 percent lower; for iron, the differences are 20 percent lower than the sponsor control and 15 higher than the farm control.[8]

Elsewhere in FDA's briefing packet, where the FDA appears to average together values for diploid and triploid GE salmon, the differences are legion. As just three of dozens of examples that are described later in this document, GE salmon expressed 200 percent greater content of the fatty acids arachidic and eicosatrienoic compared to the sponsor control, while its free fatty acid content was 125 percent and 29 percent greater than farm and sponsor controls.[9] Notably, some of the food safety studies were conducted on sample sizes as small as two fish, weakening the power of these studies and rendering some of these massive differences not "statistically different," according to the FDA's analysis.[10]

As an additional difficulty, the FDA has not published any data on some key aspects of the material identity of GE salmon, including its organoleptic properties—defined by the FDA as "those that stimulate the sensory organs, such as texture or aroma."[11] Though the FDA has said that these organoleptic properties are a key factor in its decision-making on the labeling question, there is no indication that the agency has investigated this issue; moreover, the FDA's public documents on GE salmon provide no data on any aspect of GE salmon's taste, texture, smell or other organoleptic aspects.

Weaknesses in science abound in all of the public documents that the FDA has released on GE salmon, including AquaBounty's Environmental Assessment and the associated briefing packet by the FDA. The independent scientists that comprised the FDA's VMAC criticized myriad aspects of the FDA's use of data. In their own words, members called the science on

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[7] *Id.* at Food Safety Appendix D
[8] *Id.* at Food Safety Appendix D
[9] *Id.* at Food Safety Appendix D
[10] *Id.* at Food Safety Appendix D
[11] Food and Drug Administration. "Background Document: Public Hearing on the Labeling of Food Made from the AquAdvantage Salmon." Available at http://www.fda.gov/Food/LabelingNutrition/FoodLabelingGuidanceRegulatoryInformation/Topic-SpecificLabelingInformation/ucm222608.htm#_ftnref22 and on file. Accessed October 18, 2010. (hereinafter, "Background Document.")

which FDA is basing its assessment "a mess,"[12] "equivocal,"[13] "preliminary,"[14] "ad hoc,"[15] and likened it to the work of a neophyte graduated student struggling to grasp the big picture of the scientific method.[16]

VMAC member James McKean noted during the concluding discussion, "…it leaves a cloud that is not—it is not partly sunny necessarily in the weather. That there are questions that have not been answered by the data that has been presented in the last two days."[17]

The VMAC's criticism of the FDA's work on GE salmon, which frequently mentioned insufficient sample sizes, equivocal data and inappropriate scientific approaches, speaks volumes to the inadequacy of the FDA's overall approach to the GE salmon – and the issue of labeling.

Senior scientists at the United States Fish and Wildlife Service echoed the comments of VMAC, calling the FDA process "ineffective," and skewering AquaBounty's Environmental Assessment as "overly simplistic" and potentially "very misleading." These scientists, who go on to warn the FDA that its process threatens to create a regulatory environment where "Economics and development take priority…," also express that the Fish and Wildlife Service was inappropriately excluded in the FDA process.[18]

In summary, the FDA's premature conclusion that there are no material differences is based on extremely flawed science, including a paradigm of investigation that seems designed to overlook the very real material differences in the AquAdvantage salmon. As the agency continues to receive new criticism about its regulatory process from countless stakeholders – other government agencies, independent scientists, and hundreds of thousands of consumers—the agency must step up and acknowledge the numerous conspicuous material differences in GE salmon, which seem apparent to everyone but the FDA. The AquAdvantage salmon is a different fish, and if the FDA erroneously decides to approve it for human consumption, its differences must be disclosed to consumers through labeling.

[12] Transcript at 215.
[13] Transcript at 346.
[14] Transcripts at 355.
[15] Transcript at 366.
[16] Transcript at 361-362.
[17] Transcript at 354.
[18] Comments from documents received through Freedom of Information Act request to United States Fish and Wildlife Service. Letter from USFWS Conservation Genetics Community of Practice (COP) to unknown recipients. October 6, 2010.

B. Consumer Opposition

Over the past two months, hundreds of thousands of consumers have formally objected to FDA's review of GE salmon, submitting comments that criticize the agency's regulatory process, express concern over the safety of the salmon as a food, and insist that the fish be labeled. These comments are bolstered by two recent polls, which have revealed overwhelming opposition to the approval of GE salmon. An October survey sponsored by National Public Radio, found that almost two-thirds (65 percent) of consumers would not eat GE fish and 93 percent of consumers want it labeled.[19] This mirrors the results of a September poll commissioned by Food & Water Watch, which found that 78 percent of consumers oppose GE salmon.[20]

Loudly and clearly, consumers have voiced their opinion that they see GE salmon as a different fish, whose differences deserve better regulation—better science, more transparency, independent testing, a full Environmental Impact Statement, and mandatory labeling if the FDA does approve it.

C. International Acceptance

An additional concern that the FDA should consider are consumers abroad, who may reject the U.S. salmon industry, which exported $35 million worth of Atlantic salmon in 2008,[21] if the FDA approves the GE salmon without a label. Consumers in Europe, Japan and elsewhere have pressured their governments to ban or highly restrict genetically engineered food. If the FDA decides that the AquAdvantage salmon does not require labeling, it could spell the end of salmon exports—or could potentially ruin the salmon export market through the inadvertent intermingling of GE and non-GE product, which has become a major problem for U.S. crop exporters.[22]

D. Law Applicable to FDA's Labeling Decision

The law governing the agency's labeling authority is the Federal Food, Drug, and Cosmetic Act ("FFDCA" or the "act"), 21 U.S.C. § 301-399b (2006), which provides that a food is to be deemed misbranded if, for among other reasons, "its labeling is false or misleading in any particular." 21 U.S.C. § 343(a)(1).

Among other reasons, food is misbranded under the act, "if it is offered for sale under the name of another food[;] *id.* at § 343(b); . . . [i]f it is an imitation of another food, unless its

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[19] Thomson Reuters. "National Survey of Healthcare Consumers: Genetically Engineered Food." October 1-13, 2010.
[20] Lake Research Partners. "Attitudes Toward the FDA's Plan on Genetically Engineered Fish." September 20, 2010.
[21] National Marine Fisheries Services, Fisheries Statistics. "Imports and Exports of Fishery Products; Annual Summary." 2009 at Exports of Domestic Fishery Products, 2008-2009.
[22] Government Accountability Office. "Genetically Engineered Crops. Agencies are proposing changes to improve oversight, but could take additional steps to enhance coordination and monitoring." November 2008 at 14-16.

label bears, in type of uniform size and prominence, the word 'imitation' and, immediately thereafter, the name of the food imitated[;] *id*. at § 343(c); . . .[;] and " . . . [u]nless its label bears . . . the common or usual name of the food, if any there be . . .." *Id.* at § 343(i).

Advertising and labels can also be misleading if they either fail to reveal facts "material in the light of such representations or material with respect to consequences which may result from the use of the articles to which the labeling or advertising relates under the conditions of use prescribed in the labeling or advertising thereof or under such conditions of use as are customary or usual." *Id.* at § 321(n). In other words, 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. For AquAdvantage salmon, the agency indicates that material information is that which, without such information being disclosed, would lead the consumer to assume that a food, because of its similarity to another food, has nutritional, organoleptic, or functional characteristics of the food it resembles when in fact it does not. 75 Fed. Reg. 52,602, 52,603 (Aug. 26, 2010). Further, it has been a long-held agency policy requiring labeling to advise consumers of special health risks from the food under § 321(n).[23]

Pursuant to the FFDCA and its regulations, the agency's "Draft Guidance for Industry: Voluntary Labeling Indicating Whether Foods Have or Have Not Been Developed Using Bioengineering" ("2001 draft guidance") dictates the labeling of genetically engineered food in four circumstances:

> 1) if a bioengineered food is significantly different from its traditional counterpart such that the common or usual name no longer adequately describes the new food, the name must be changed to describe the difference; 2) if an issue exists for the food or a constituent of the food regarding how the food is used or consequences of its use, a statement must be made on the label to describe the issue; 3) if a bioengineered food has a significantly different nutritional property, its label must reflect the difference; and 4) if a new food includes an allergen that consumers would not expect to be present based on the name of the food, the presence of that allergen must be disclosed on the label.[24]

As detailed extensively below, because all of these conditions and those spelled out in the FFDCA are met with AquaBounty's AquAdvantage salmon, FDA is required under the FFDCA to mandate the labeling of the product. A failure to do so would be arbitrary, capricious, an abuse of discretion, or otherwise not in accordance under the Administrative Procedures Act (APA). 5 U.S.C. 706(2)(A) (2006). For example, it would violate the APA's

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[23] Statement by Robert E. Brackett, Ph.D., Director, Center for Food Safety and Applied Nutrition, Food and Drug Administration, on The Regulation of Dietary Supplements: A Review of Consumer Safeguards, before The Committee on Government Reform, U.S. House of Representatives, March 9, 2006.

[24] Food and Drug Administration. "Guidance for Industry Voluntary Labeling Indicating Whether Foods Have or Have Not Been Developed Using Bioengineering Draft Guidance." http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodLabelingNutrition/ucm059098.htm (hereinafter "FDA 2001 Draft Guidance.")

requirement that the process by which an agency reaches a conclusion be logical and rational. *NetCoalition v. SEC*, 615 F.3d 525, 538–39 (D.C. Cir. 2010). And, even while courts usually provide great deference to agency determinations that are based upon highly complex and technical matters, they will not "'defer to the agency's conclusory or unsupported suppositions.'" *Id.* (quoting *McDonnell Douglas Corp. v. U.S. Dep't of the Air Force,* 375 F.3d 1182, 1187, (D.C. Cir. 2004).

Here, the record clearly establishes that labeling of AquaBounty's product is warranted. And a failure to do in the face of this evidence would be arbitrary and capricious. *Cf. Pub. Citizen v. Heckler*, 653 F. Supp. 1229, 1240 (D.D.C. 1986) (internal quotation omitted). (Finding arbitrary and capricious a failure to promulgate a rule where the Secretary of Health "has indeed offered an explanation for her decision that runs counter to the voluminous evidence to the contrary she had before her.")

Therefore, Food & Water Watch urges the FDA to require the mandatory labeling of AquaBounty's AquAdvantage salmon.

III. Arguments for Requiring Labeling

A. AquAdvantage salmon is so different from Atlantic Salmon that the latter term does not adequately describe the former; to allow the genetically engineered product to be sold or advertised as such would constitute misbranding under 21 U.S.C. § 343(b) & (i).

As demonstrated below, AquAdvantage salmon is materially different from Atlantic Salmon in a number of its characteristics, and therefore must be labeled under 21 U.S.C. § 321(n). But, even apart from this determination, FDA should conclude that AquaBounty's insertion of recombinant genetic material, derived from the ocean pout and Chinook Salmon species,[25] is intended to induce changes to the Atlantic Salmon's very nature so that it is no longer Atlantic Salmon as consumers know it. The FDA has found that AquAdvantage salmon exhibit altered behaviors, a unique physiology, and materially different characteristics. Therefore, it cannot be labeled or advertised as Atlantic Salmon or it would be misbranded under the FFDCA, which requires food to bear a label of what it is, by its common or usual name, and that it cannot bear the name of a different food.[26] *See* 21 U.S.C. § 343(b), (i).

For example, the AquAdvantage salmon showed statistically significant differences in composition, including protein values (albumin, globulin, total protein, albumin:globulin ratio),[27] calcium, cholesterol, phosphorous, total bilirubin,[28] aspartate aminotransferase

[25] Briefing Packet at vii.
[26] This stands in contrast to FDA's principles document "describing the relevant legal principles and related questions specific to the labeling of foods from AquAdvantage Salmon," which incorrectly suggests that labeling on genetically engineered food is only required if it "differs in nutritional quality, taste," from the traditional product.
[27] *Id.* at 35.
[28] *Id.*

and glucose.[29] And, according to the FDA, "lipid and energy were significantly lower in the genetically engineered salmon pre-smolts relative to comparators, while moisture content was significantly higher."[30]

FDA has also concluded that the new gene construct in AquAdvantage salmon was likely responsible for morphological irregularities found in the GE salmon, including higher rates of jaw erosion and focal inflammation.[31] The FDA, noting the potential bias involved with AquaBounty's "selective culling" of fish prior to physical examination, admitted that there may be a difference in the physical performance of GE salmon, which the agency would monitor with post-market surveillance.[32] One member of the Veterinary Medical Advisory Committee (VMAC), charged with advising the agency on AquaBounty's application, said this policy gave him "heartburn."[33]

In terms of behavior, AquAdvantage salmon exhibit greater feeding and oxygen needs – eating as much as five times more food than non-GE salmon[34] and consuming 1.7 times more oxygen.[35] The GE salmon also showed behavioral differences including a willingness to feed in the presence of predators,[36] reduced disease resistance, and reduced schooling tendency.[37] Finally, AquaBounty's new animal drug application is founded on the claim that the GE salmon can grow larger than the non-GE sibling when adequate food is available.[38]

The hormonal activity of the GE salmon is far different from traditional Atlantic Salmon as well. AquaBounty submitted two studies examining hormones to the FDA. One found that GE salmon exhibited 41.5 and 94.6 percent greater levels of growth hormone as two groups of non-GE salmon.[39] The second study found that the GE salmon showed much higher mean levels of IGF-1 and of 11-keto testosterone – 39.8 percent higher and 20.7 percent higher, respectively, than non-GE comparators.[40]

In addition, studies conducted on the food safety of GE salmon clearly show material differences in the nutritional quality of the fish as a food. The food safety studies by AquaBounty compare the rates of 19 fatty acids, 18 amino acids, eight vitamins, ten minerals and five other nutrition analytes, including total fat and protein – a total of 60 analytes. Compared to the sponsor control, GE salmon expressed double-digit differences

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[29] *Id.*
[30] *Id.* at 44.
[31] *Id.* at 41.
[32] *Id.* at 33.
[33] Transcript at 342.
[34] AquaBounty Technologies, Inc. "Environmental Assessment for AquAdvantage® Salmon." Submitted to the Food and Drug Administration Center for Veterinary Medicine. August 25, 2010. At 36. (hereinafter "Environmental Assessment.")
[35] *Id.* at 34.
[36] *Id.* at 36.
[37] *Id.* at 38.
[38] *Id.*
[39] Briefing Packet at 66.
[40] *Id.* at 68.

in 22 of these analytes, notably including a 57.8 percent greater total fat content.[41] In an additional three analytes, all fatty acids, the GE salmon expressed triple-digit increases.[42] Compared to the farm control, the GE salmon expressed double-digit differences in nineteen analytes, and in one measure, free fatty acids, the GE salmons' levels were 125.0 percent greater.[43]

Such fundamental changes to the core make-up of the fish transforms the Atlantic Salmon into a separate food that is different than its common name, and, therefore, its advertising and labeling must indicate this under 21 U.S.C. § 343(b) & (i). This is especially true if the insertion of the genetically engineered material changes the original DNA of the salmon, which is unclear based on the FDA's presentation to the VMAC.[44] VMAC member Craig Altier pressed the FDA to provide evidence that the insertion of rDNA into Atlantic Salmon did not unintentionally delete existing DNA. The FDA was unable to provide data to demonstrate this.[45]

To not require labeling would be contrary to FDA's regulations, which provide that:

> [t]he common or usual name of a food, which may be a coined term, shall accurately identify or describe, in as simple and direct terms as possible, the basic nature of the food or its characterizing properties or ingredients. The name shall be uniform among all identical or similar products and may not be confusingly similar to the name of any other food that is not reasonably encompassed within the same name. Each class or subclass of food shall be given its own common or usual name that states, in clear terms, what it is in a way that distinguishes it from different foods." 21 C.F.R. § 102.5 (emphasis added).

As the agency expressed itself in its 2001 draft guidance, the FFDCA, 21 U.S.C. § 343(b) & (i), applies to genetically engineered food, so that "[i]f a bioengineered food is significantly different from its traditional counterpart, such that the common or usual name no longer adequately describes the new food, the name must be changed to describe the difference."[46]

Concluding that such differences require a different name for a genetically engineered product is not novel for the agency. For example, the agency allowed DuPont to use the common or usual name "High Oleic Soybean Oil" for oil derived from a new genetically engineered soybean variety due to the fact that the product did not meet the specifications for soybean oil in the Food Chemical Codex (FCC, Committee on Food Chemical Codex, 1996). The agency made this decision simply based on the compositional differences of the oil and its intended use as a replacement for hydrogenated soybean oils: "a new common

[41] *Id.* at Tables 21 to 25.
[42] *Id.*
[43] *Id.*
[44] Transcript at 150-153, comments and questions from Dr. Craig Altier.
[45] Personal correspondence with Craig Altier.
[46] FDA 2001 Draft Guidance.

or usual name (High Oleic Soybean Oil) is appropriate to distinguish this oil from soybean oil as defined by FCC."[47]

Likewise, with the case of AquAdvantage salmon, such significant differences between Atlantic Salmon are present. Indeed, these differences are also apparent when GE salmon is compared to farmed salmon found in the United States Department of Agriculture (USDA) nutrient database, which offers 53 comparable data points on the nutritional value of Atlantic farmed salmon (raw). GE salmon manifested double-digit differences in 31 analytes and triple-digit differences in three analytes compared to the USDA's nutrient data.[48] (See attached, Chart 1.)

The FDA seemingly has already concluded that the GE salmon is essentially the same as the Atlantic Salmon based on its assessment of the lack of differences in the Isoelectric Focusing and 2- dimensional gel electrophoresis fingerprints. To make the determination that because of these similarities that AquAdvantage salmon can be called Atlantic Salmon would be to confuse the scientific test for determining whether a specimen is of a certain species with the test for determining the proper name of the product. FDA's own labeling guidance indicates that the proper market name is one that is "nationally recognized in the U.S. and commonly used by consumers to identify a species."[49] Therefore, even if the AquAdvantage salmon are technically the same species as Atlantic Salmon, if the the agency were to allow AquaBounty to use the name Atlantic Salmon to refer to its novel product, it would be allowing misbranding because consumers do not commonly recognize and use this term to describe such a product.

Similarly, even if the AquAdvantage salmon was to technically carry the same scientific common name of Atlantic Salmon, AquaBounty cannot use such name as its market name where it would be misleading under the FDA regulations:

> The common or usual name of a food shall include a statement of the presence or absence of any characterizing ingredient(s) or component(s) and/or the need for the user to add any characterizing ingredient(s) or component(s) when the presence or absence of such ingredient(s) or component(s) in the food has a material bearing on price or consumer acceptance or when the labeling or the appearance of the food may otherwise create an erroneous impression that such ingredient(s) or component(s) is present when it is not, and consumers may otherwise be misled about the

[47] Food and Drug Administration. "Biotechnology Consultation Note to the File BNF No. 000039." December 5, 1996. http://www.fda.gov/Food/Biotechnology/Submissions/ucm161157.htm

[48] *Id.*; USDA Nutrient Database. "Fish, salmon, Atlantic, farmed, raw." http://www.nal.usda.gov/fnic/foodcomp/cgi-bin/list_nut_edit.pl Accessed November 5, 2010. (hereinafter "USDA Nutrient Database. Atlantic Salmon.")

[49] Food and Drug Administration. "Guidance for Industry: The Seafood List - FDA's Guide to Acceptable Market Names for Seafood Sold in Interstate Commerce." September 1993; Revised: January 2009. http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/Seafood/ucm113260.htm

presence or absence of the ingredient(s) or component(s) in the food.
21 C.F.R. § 102.5(c) (emphasis added).[50]

As discussed below, the sale of AquAdvantage salmon without identifying that it has been genetically engineered would be misleading because its genetic engineering would have a material bearing on price and consumer acceptance, due to its additional growth hormones, greater fatty acid content, and lack of certain nutrients, including protein, among other reasons. Therefore, given this material bearing on price and consumer acceptance, Atlantic Salmon cannot be used as the proper market name for the product – even if it were construed as the proper scientific name of the animal.[51]

In sum, given that the record clearly demonstrates the AquAdvantage salmon's exhibition of altered behaviors, a unique physiology, and materially different characteristics, it cannot be labeled or advertised as Atlantic Salmon. To do so would allow the sale of misbranded product under 21 U.S.C. § 343(b) & (i).

B. In the alternative, AquaBounty must only be allowed to advertise AquAdvantage salmon as imitation product as such under 21 U.S.C. § 343(c).

Food is misbranded if "it is an imitation of another food, unless its label bears, in type of uniform size and prominence, the word 'imitation' and, immediately thereafter, the name of the food imitated." 21 U.S.C. § 343(c). FDA defines an imitation food as a food that "is a substitute for and resembles another food but is nutritionally inferior to that food." 21 C.F.R. § 101.3(e)(1) (2010). Nutritional inferiority, among other measures, is determined by comparing the percentage of "essential nutrients" in the substitute to those in the food for which it substitutes. "Nutritional inferiority includes . . . *[a]ny* reduction in the content of an essential nutrient that is present in a measurable amount . . . . 21 C.F.R. § 101.3(e)(4) (2010) (emphasis added).

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[50] *See also*, Lara Beth Winn, "Special Labeling Requirements for Genetically Engineered Food: How Sound Are the Analytical Frameworks Used by FDA and Food Producers?" 54 Food Drug L.J. 667, 673 (concluding that a broad interpretation of the term "characterizing component" is warranted to encompass genetic material. The author also determines that "as applied to biotech food, this provision suggests that if genetic material introduced into a host organism through human intervention is a characterizing component that has a material bearing on consumer acceptance of the food, and if consumers may be misled about the presence of new genetic material introduced through human intervention, in the absence of information to the contrary, biotech food should carry a common or usual name that differs from the common or usual name of its traditional counterpart.")

[51] To allow the sale of AquAdvantage salmon as Atlantic Salmon given these differences would also be to illegally sanction economic adulteration. Economic adulteration is a process

1) a) by which less expensive ingredients were substituted, or b) the proportion of more expensive ingredients diminished, 2) so as to make the product, although not in itself deleterious, inferior to that which the consumer expected to receive 3) when purchasing a product with the name under which it was sold. *Federal Security Administration v. Quaker Oats Co.,* 318 U.S. 218, 230 (1943).

The "essential nutrients" include protein and the following:

> Vitamin A, Vitamin C, Calcium, Iron, Vitamin D, Vitamin E, Vitamin K, Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Biotin, Pantothenic acid, Phosphorus, Iodine, Magnesium, Zinc, Selenium, Copper, Manganese, Chromium, Molybdenum, and Chloride. 21 C.F.R. 101.9(c)(8)(iv) (2010).

Should the substitute contain less of any essential nutrient than in the food it is substituting for, the substitute must be labeled with the word "imitation." 21 U.S.C § 343(c).

AquAdvantage salmon clearly demonstrates differences in essential nutrients. Looking at the USDA database,[52] the GE salmon has 23.6 percent less Vitamin C, 52.9 percent less Iron, 7 percent less Vitamin B12, 8.6 percent less Magnesium, and 29 percent less Pantothenic acid. Last, the GE salmon's mean values of total protein were 5.1 and 6.3 percent lower than both the sponsor control and the USDA nutrient database.[53] For at least three essential nutrients, protein, B12, and Pantothenic acid, the differences were large enough to be considered measurable under FDA's regulations,[54] and, thus, the product must be considered an imitation. 21 C.F.R. § 101.3(e)(4)(i)-(ii) (2010).

Given the pronounced inferiority of the GE salmon in terms of essential nutrients, if FDA concludes that AquAdvantage can be labeled Atlantic Salmon, it can only do so if it is advertised and sold as imitation Atlantic Salmon. A failure to do so would render the product misbranded under the FFDCA and FDA's regulations.

C. AquAdvantage salmon must be labeled pursuant to 21 U.S.C. § 321(n) to reveal facts that are material to the consumer about consequences from the product's use, either from the uses that are customary or usual.

1. AquAdvantage salmon should be labeled because of its elevated IGF-1 levels, which pose special health risks.

It is not unusual for FDA to require products be labeled, pursuant to FFDCA § 321(n), so that consumers can be warned of the health risks in products. Such warnings have been required even though the agency did not find that such labels were needed for the safe use of the product. See, for example, 61 Fed. Reg. 3,118, 3,161 (January 30, 2006) (requiring the disclosure of the gastro-intestinal (GI) effects of Olestra to "preclude unnecessary concerns about the origin of GI effects, were they to be observed, and may also prevent unnecessary or inappropriate medical treatment of those symptoms.")

Likewise, FDA has required labeling of health risks when there is simply the possible presence of a deleterious substance that would cause harmful effects. See, for example, 63 Fed. Reg. 20,486, 20,487 (April 24, 1998) (proposing warning labels on unpasteurized

[52] USDA Nutrient Database. Atlantic Salmon.
[53] USDA Nutrient Database. Atlantic Salmon; and Transcript at Table 21.
[54] Calculation based on a 100-gram sample of Atlantic Salmon.

juice: "[g]iven the possible presence of pathogens in untreated juice, and the potential consequences of consumption of these beverages, the fact that juice may contain harmful pathogens and the fact that a product has not been treated to control such pathogens are material facts regarding the consequences that may result from use of these juice products." (emphasis added)); 63 Fed. Reg. 37,030, 37,033. (stating for the final juice rule: "The evidence available at this time documents that there is a risk of foodborne illness from consumption of untreated juice. The agency does not contend, nor does the validity of the juice labeling proposal require, a showing that all unpasteurized juice is adulterated.")

The agency must follow suit and require warning labels on AquAdvantage salmon because of the health risks from IGF-1. Recent research shows that when present in the human body at elevated levels, IGF-1 increases the risk of breast, colon, prostate, and other cancers,[55] although scientists still do not fully understand why. Early research into the impact of IGF-1 levels from the use of rBGH, a hormone used in the dairy industry, had suggested that even if humans ingested IGF-1 from treated cows' milk, the human digestive process would destroy it. But more recent research indicates that most IGF-1 actually survives digestion. IGF-1 binds to casein, the main protein in milk, and may be absorbed into the human bloodstream along with it.[56]

The only study that AquaBounty performed on levels of IGF-1 in its AquAdvantage salmon showed troublingly high rates. It found that the GE salmon has rates of IGF-1 that were 39.8 percent higher than those in the control group.[57] The presence of this potentially dangerous hormone must be disclosed to consumers.

Not only does the agency have the authority to require the labeling of AquAdvantage salmon because of the health risks from IGF-1, the agency's failure to do so based on the record before it would be arbitrary and capricious. AquaBounty claims that there are no significant differences in the levels of IGF-1. But the AquaBounty study used insensitive instrumentation in its measurements of hormones, allowing the company to detect IGF-1 levels in a total of six GE salmon of a total of thirty, all of which were diploid.[58] This is problematic for many reasons, perhaps most prominently because AquaBounty has not measured IGF-1 levels in triploid GE salmon, which is the product that AquaBounty intends to sell based on its new animal drug application.

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[55] Yu H. and Rohan T. "Role of the Insulin-Like Growth Factor Family in Cancer Development and Progression." Journal of the National Cancer Institute, Vol. 92, No. 18, September 20, 2000, at 1472-1489; Moschos S. and Mantzoros C. "The Role of the IGF System in Cancer: From Basic to Clinical Studies and Clinical Applications." Oncology. Vol. 63 No. 4, November 4, 2002, at 317-332.

[56] Kimura, Toshikiro, Murakawa, Yusuke, Ohno, Misako, Ohtani, Seiji, and Higaki, Kazutaka. "Gastrointestinal absorption of recombinant human insulin-like growth factor-1 in rats." Journal of Pharmacology and Experimental Therapeutics. Vol. 283 No. 2, July 1997 at 611-618; Anderle, Pascale, Langguth, Peter, Rubas, Werner, and Merkle, Hans. "In Vitro Assessment of Intestinal IGF-1 Stability." Journal of Pharmaceutical Sciences, Vol. 91 No. 1, January 2002, at 290-300; Hansen, Michael, Ph.D, et al. "Potential Public Health Impacts Of The Use Of Recombinant Bovine Somatotropin In Dairy Production." Consumers Union. September 1997.

[57] Briefing Packet at 68.

[58] *Id.* at 67-69.

Moreover, FDA's subsequent margin of exposure analysis was conducted in such a way as to paper over these differences. For reasons the FDA does not explain, the agency selected data points for its margin of exposure test that made levels of IGF-1 appear higher in non-GE salmon and lower in AquAdvantage salmon, thus reducing the differences between the two groups. [59]

The only statistician on the VMAC, Jodi Ann Lapidus, skewered this data set, saying that the control group would need to manifest "differences on the order of 16…..to have called that statistically significant."[60] She also attacked the weak sample sizes in Table 15 of the FDA's hormone analysis, saying: "To have a difference of the sort that is shown on the first table in to be relevant, you are probably going to need on the order of magnitude of like 100 samples in each group to show those and it to be statistically significantly different."[61]

FDA's approach to the labeling question is too reliant on a faulty scientific approach that attempts to find large (statistically significant) differences between very small samples sizes, which is virtually impossible to do. In this way, the FDA's research paradigm almost seemed designed, intentionally or not, to find no differences between GE salmon and non-GE salmon.

Clearly the science surrounding the assessment of IGF-1 in AquAdvantage salmon is inadequate, and the FDA's current conclusions about the safety and similarity of the GE salmon's hormone levels compared to non-GE salmon[62] are based on a highly flawed data set that has been manipulated in a scientifically irresponsible manner. For the agency to conclude that, based on its failure to adequately examine the levels of IGF-1, this absence of evidence constitutes an evidence of absence would be an unreasonable judgment that would likely not survive judicial review.

Notwithstanding the problem with the agency's science, the danger of IGF-1 and the likely presence of it in the product – akin to the risk of pathogens in unpasteurized juice – is sufficient evidence for the agency to require that such health risks be disclosed to consumers, and a failure to do so would be arbitrary and capricious.

2. AquAdvantage salmon should be labeled because its allergenic potency poses special health risks

Similarly, the risks of exposing consumers to a product that, according to all indications, can spur allergic reactions mean that FDA must require labeling of the AquAdvantage salmon under 21 U.S.C. § 241(n).

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[59] *Id.* (As evident from Tables 15 and 16, the FDA unnecessarily included a seventh GE salmon sample, set at the lowest level of quantification, which reduced its mean value. Additionally, though the non-GE sponsor control group evidenced 11 fish with detectable levels of IGF-1, the FDA only chose seven – and chose the seven with the highest mean values).

[60] Transcript at 373.

[61] Transcript at 374; FDA also ignored that the range of IGF-1 levels in GE diploid fish were enormous, the highest of which (18.428) dwarfed the highest non-GE salmon (12.235) by 50.6 percent, calling into question the value of the data. Briefing Packet at Table 16.

[62] *Id.* at 74 and 75.

In its draft guidance on genetically engineered food, the agency indicated: "If a new food includes an allergen that consumers would not expect to be present based on the name of the food, the presence of that allergen must be disclosed on the label."[63] Likewise, FDA has required labeling in substances that are allergens even when it has concluded that the substances are otherwise safe, such as carmine and cochineal extracts. See, for example, 74 Fed. Reg. 207, 209. ("FDA has concluded that the labeling requirements established by this regulation will provide consumers adequate information that will enable them to avoid carmine and cochineal extract. . . . The labeling required by this regulation will help consumers and health professionals more quickly identify people with sensitivities to these color additives.")

According to the information presented to the VMAC, AquAdvantage salmon showed between 19.5 and 52.5 percent (triploid and diploid) greater average "allergenic potency" than non-GE salmon.[64] The diploid GE salmon's differences were considered statistically significant.[65]

This alone is grounds for the FDA to require that AquAdvantage salmon be labeled so that consumers can avoid the potential allergenic product.[66] But the agency should act with special care given that the AquAdvantage salmon is genetically engineered with protein from several aquatic species,[67] and the need to carefully consider the allergenic implications of these recombined genes with salmon DNA. This is supported by the wide and growing body of scientific literature showing the unique allergenicity of genetically engineered food. A New England Journal of Medicine study found that soybeans engineered with Brazil nut proteins caused allergic reactions for consumers with Brazil nut allergies.[68] In another case, a harmless protein found in certain beans, which acts as a pest deterrent, became dangerous once it was transferred to a pea, causing allergy-related lung damage and skin problems in mice.[69] Even genetically engineered livestock feed may have some impact on consumers of animal products. Italian researchers found biotech genes in the milk from dairy cows fed a genetically engineered food diet, suggesting transgenes' ability to survive pasteurization.[70]

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[63] FDA 2001 Draft Guidance.
[64] Briefing Packet at 103.
[65] *Id.* at 103.
[66] Protection would include 6,600,000 Americans, who are allergic to seafood, one of the most common allergies in the world. See Sicherer, S.H. et al. "Prevalence of seafood allergy in the United States determined by a random telephone survey." Journal of Allergy Clinical Immunology. July 2004 at Abstract; Do, T. et al. "Allergy to fish parvalbumins: Studies on the cross-reactivity of allergens from 9 commonly consumed fish." Journal of Allergy Clinical Immunology. December 2005 at Introduction.
[67] Ocean pout are an eel-like aquatic animal that is of very distant relation to the salmon, only as similar as a manatee and human being are. World Registry of Marine Species. Search for Ocean pout, Atlantic salmon, Manatee and Human Being. http://www.marinespecies.org/aphia.php?p=taxdetails&id=159267 and http://www.marinespecies.org/aphia.php?p=taxdetails&id=127186 Accessed September 16, 2010.
[68] Nordlee, J. et al. "Identification of a Brazil-Nut Allergen in Transgenic Soybeans." The New England Journal of Medicine. March 14, 1996.
[69] Young, E. "GE pea causes allergic damage in mice." *New Scientist*. November 21, 2005.
[70] Agodi, A. et al. "Detection of genetically modified DNA sequences in milk from the Italian market." International Journal of Hygiene and Environmental Health. January 10, 2006.

It would be absolutely arbitrary and capricious for FDA to conclude that the allergenicity risks of AquAdvantage salmon are minimal given a lack of evidence. Again, the agency would be committing the very basic logical fallacy of believing that the seeming absence of statistically significant evidence is somehow a statistically significant evidence of absence. The agency already seems to be veering in this direction by dismissing the allergenicity data of triploid salmon because of the lack of statistically significant differences due to the small sample sizes. This conclusion was teamed with an equally problematic conclusion that it need not determine the safety of diploid GE salmon, which exhibited statistically significant 52.5 percent higher rates of allergenic potency – even with the miniscule sample sizes – because AquaBounty only intends to sell triploid GE salmon.[71] Of course the only reasonable conclusion would be that more evidence is needed,[72] not that it is somehow safe.

Moreover, the agency's analysis ignores the agency's own durability plan for AquAdvantage salmon, which contains lax rules that will allow up to five percent of AquaBounty's GE salmon to remain diploid (because up to five percent will not successfully undergo the triploidization process).[73] This means that consumers will be exposed to a salmon with enormously higher rates of allergenic potency. The FDA has a clear indication that some number of the GE salmon, which exhibit high allergenic potency, will enter the food supply based on the current proposal from AquaBounty. Therefore, it should require the product to be labeled to inform consumers of this health risk.

Likewise, FDA acknowledges its lack of sufficient data to make conclusions regarding the AquAdvantage salmon's content of parvalbumin, a major allergen.[74] Meanwhile, the FDA completely threw out one entire allergenicity study conducted by AquaBounty because it was so technically flawed.[75]

Clearly, this lack of evidence cannot counter the evidence that AquAdvantage poses a serious allergenicity risk and should be labeled to allow consumers to know of these risks.

3. The AquAdvantage salmon must be labeled because it has different nutritional, organoleptic, and functional characteristics than Atlantic Salmon.

In addition to the health risks from AquAdvantage salmon, there are a number of nutritional, organoleptic, and functional characteristics of the genetically engineered product that require it to be labeled under 21 U.S.C. § 321(n).

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[71] Briefing Packet at 103 and 105.
[72] As one member of the VMAC noted, "And I do not think that with the information that we got, we could say that is a valid assay to measure what they are trying to measure. . . . So I do not think there is much that can be said with regard to the allergenicity in any sort of objective way based upon the studies that were done." Transcript at 359.
[73] Briefing Packet at 50.
[74] *Id.* at 105.
[75] *Id.* at 104.

Material Functional Differences. First, it must not be overlooked that purchasing decisions may result from the use of the food to which the labeling relates. This is quite different than saying that the agency is requiring labeling simply because consumers want such information, or believe they have the right to know. Rather, labeling is needed because of the differences between the GE salmon and non-GE variety, of which, without labeling, consumers would accidentally be unaware of at the time of purchase. And the agency has required labeling when doing so will contribute to customers' purchasing decisions. See, for example, 61 Fed. Reg. 3118, 3162 (Jan. 30, 1996) (requiring mandatory labeling for Olestra and saying that "FDA believes that this information will be used by consumers both in their decisions on purchases and to help them adjust their consumption to minimize side effects")

As discussed above, AquAdvantage salmon are a fundamentally different and inferior product than Atlantic Salmon. This will affect consumers' purchasing decisions, and this is a consequence that is material under § 321(n) that mandates labeling.

For example, labeling is needed to alert people who wish to avoid foods because of religious or moral reasons. This was one of the reasons that the agency has required the source of protein hydrolysate found in food. See 56 Fed. Reg. 28,592 (June 21, 1991) ("First, for religious or cultural reasons, some consumers wish to avoid foods or food ingredients that are of animal origin because their dietary convictions prohibit or discourage the consumption of such foods. If, for example, hydrolyzed casein, a protein hydrolysate derived from the milk protein casein, were used as an ingredient in a food, the name used to declare this ingredient would have to convey the animal origin of the protein source to adequately inform such an individual of the nonacceptability of the food in his/her diet.")

In its guidance, Food Labeling; Foods Derived From New Plant Varieties, 58 Fed. Reg. 25,837 (April 28, 1993), the agency seemingly distinguished the hydrolysate example from genetically engineered food, generally. But such distinguishing factors are not applicable to genetically engineered AquAdvantage salmon.

The agency found that genetically engineered plants were different from hydrolysate because:

> The agency's conclusion that the food source of a protein hydrolysate is information that must be revealed in labeling was reached in the context of the addition to food of food ingredients directly derived from animal or microbial sources. . . . That situation is different from the biotechnology context, which involves the presence in a plant chromosome of deoxyribonucleic acid (DNA) that was originally derived from an animal or microorganism but is now an inherent constituent of a plant. When using recombinant DNA techniques, scientists do not infuse the plant with the original genes that were removed from the animal. The animal genes are used to produce copies in the laboratory. Once the copies are transferred to

> the plant, they become an integral part of its genetic information, just like thousands of other genes that are present in the plant chromosome. There is a scientific basis to conclude that such genetic alterations do not change the essential nature of the plant, nor do they confer "animal-like" characteristics to the plant. For example, a tomato does not become "fish-like" following the addition of a copy of a fish gene that causes the production of a freeze-tolerant protein. This difference in context may bear directly on whether special labeling should be required for such "genetically engineered" products. 58 Fed. Reg. 25,839.

This is commonly known as the inherent-gene-copy theory. It is important to note that the agency says that its theory's application is dependent on context, meaning its applicability and relevancy has to be assessed for each and every genetically engineered product.

It is also important to note that the agency did not simply say that the duplication and synthesizing of the genetic material for insertion makes it exempt from labeling. Nor could the agency have determined this, as it would render a nullity the FFDCA requirements that imitation products be labeled. After all, many products that are imitation are simply synthetic copies of the original food product. Rather, the key for the agency was that, with genetically engineered food derived from plants, the copied synthetic genetic material becomes inherent in the host plant, and that these inherent genes "do not change the essential nature of the plant."[76] *Id.*

With AquAdvantage salmon, on the other hand, the insertion of the recombinant genetic material does "change the essential nature" of the recipient. As demonstrated above, AquAdvantage Salmon exhibits an extensive list of altered behaviors, a unique physiology, and materially different characteristics. According to the FDA's own guidance, such differences mean that the inherent-gene-copy-theory is inapplicable.

Many of these changes, such as the high fatty acids, lower omega levels, and lower protein levels are relevant to consumers' purchasing decisions. In addition, purchasers may simply have moral, cultural, or dietary issues with purchasing or consuming a product that is so dramatically altered from the common Atlantic Salmon. Indeed, recent polls indicate that close to 65 percent of all people would not eat genetically engineered fish.[77] Because of

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[76] The insertion of the genetic material may also confer certain characteristics to the Atlantic Salmon that make it more pout-like. To FWW's knowledge, no such studies have been conducted to conclude that this is not likely. This is the second situation in which the agency's guidance states that inherent-gene- copy theory would not apply.

[77] Thomson Reuters. "National Survey Of Healthcare Consumers: Genetically Engineered Food" October 2010; It is worth noting that under the hydrolysate example, the agency never questioned the validity of the desires of those who sought to avoid food product derived from certain sources. Rather, it simply determined that since some people do not want to purchase or consume animal-derived products, they would benefit from labeling. Likewise, under FDA's guidance, once a genetically engineered product, like the AquAdvantage salmon, is determined to be so dramatically different from the original product that its inherent nature is changed, and thus the inherent-gene-copy-theory of ingredients is inapplicable, it does not matter what dietary, cultural, or moral reason consumers may have to avoid or pay less for the product. All that matters is that consumers wish to avoid the product. This is a functional effect that must be labeled.

these functional differences and their relevance to consumers, the agency should require labeling of the AquAdvantage salmon.

Material Nutritional Differences. All of the differences mentioned above under Section III. A. and B. are material nutritional differences that mandate that AquAdvantage salmon be labeled. A few are worth further discussion.

First, in terms of hormones, the two studies AquaBounty submitted both revealed material differences. Unfortunately, these studies also reveal serious problems in their application of science that demand more testing on the GE salmon for its safety.

One peer-reviewed study from the 1990s examined hormone levels in fish that had average weights of less than 50 grams[78] – about one-eightieth of the weight of an average market-weight salmon. Even at that miniscule size, GE salmon exhibited 94.6 percent greater levels of growth hormone than one control group, and 41.5 percent greater growth hormone levels as the non-GE sibling comparator group.[79] Tellingly, these enormous differences were not statistically significant because of low sample sizes (between five and seven salmon in each group).[80]

The other study that AquaBounty utilized showed enormously higher levels of two hormones: IGF-1 at 39.8 percent higher than the sponsor control and 11-keto testosterone at 20.7 and 56.0 percent greater than the sponsor and farm controls, respectively.[81] The FDA chose only to further examine the levels of IGF-1, and did so using only six genetically engineered diploid salmon,[82] which was problematic because of the small sample size, and also because the diploid genetically engineered salmon are not the subject of the animal drug application.

Not only did FDA's analysis of hormone levels suffer from insufficient sample sizes – using as few as six fish (three groups of two fish) in one assessment[83] – it was also problematic because the instrumentation that AquaBounty used to measure hormone levels were so imprecise that scientists were unable to quantify levels of many hormones in the salmon. For example, AquaBounty reported no growth hormone in any of the salmon studied, and only six salmon exhibited detectable levels of T4.[84]

It would be absolutely inappropriate to conclude, however, that the lack of statistically significant data is grounds not to require labeling. To do so would be arbitrary and capricious. Despite a completely inappropriate scientific approach and problematic sample size, FDA's study of hormones still showed compelling differences. The range of IGF-1 levels in GE diploid fish were enormous, the highest of which (18.428 nanograms/gram)

[78] Briefing Packet at 66.
[79] *Id.*
[80] *Id.*
[81] *Id.* at Table 15.
[82] *Id.* at Table 16
[83] *Id.* at Table 15, See T4.
[84] *Id.* at 68.

dwarfed the highest non-genetically engineered variety (12.235 nanograms/gram) by 50.6 percent.[85] These huge nutritional differences demand that FDA require AquAdvantage Salmon to be labeled.

The material differences in fat content of AquAdvantage Salmon serve as another basis for mandatory labeling. Of the nineteen fatty acids examined, the FDA found statistically significant differences in nine when comparing triploid GE salmon.[86] These statistically significant differences were evident despite extremely small sample sizes.

In all nineteen fatty acids measured, the GE salmon manifested higher values than the sponsor control, with most differences greater than 50 percent; and all fatty acid analytes appeared in levels at least 15 percent higher in the GE salmon.[87] GE salmon showed double or triple-digit differences compared to farm control on eleven of nineteen analytes. Comparing these analytes to the USDA nutrient database, which provide for comparisons on 16 fatty acid analytes, 12 showed double or triple-digit differences.[88]

Not surprisingly, GE salmon exhibited far greater levels of total fatty acids than non-GE salmon. Triploid GE salmon, which AquaBounty intends to market, showed almost twice as much fatty acid content as the sponsor control salmon that AquaBounty used – and this difference was found to be statistically significant.[89] Equally troubling, GE salmon showed a much greater variance in total fat content than non-GE salmon, ranging from 3.6 to 24.1 percent.[90] This means that one particularly obese GE salmon exhibited nearly 25 percent total fat—a full 62.8 percent fatter than the heaviest sponsor control salmon.[91]

Total fatty acids of triploid GE salmon were 61.9 percent greater than the sponsor control group (diploid) and 17.7 percent greater than farmed salmon, according to the USDA nutrient database.[92]

The GE salmon was even 3.9 percent fattier than diploid farm control salmon, which serves as a very poor comparator for fat content because this group was fed an unknown diet, which even the FDA acknowledges as "limiting the extent to which comparisons could be made."[93] Because diet is the main determinant in a salmon's total fat content and total fatty acids,[94] this omission calls into question the validity of the farm control.

Meanwhile, when compared to non-GE fish fed a similar diet (sponsor control),[95] GE salmon had total fat levels (related to but distinct from total fatty acids) that were an

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[85] *Id.* at Table 16.
[86] *Id.* at 93.
[87] *Id.* at Table 25.
[88] *Id.* at Table 25; USDA Nutrient Database. Atlantic Salmon.
[89] Briefing Packet at 170.
[90] *Id.* at 80, Table 21.
[91] *Id*.
[92] *Id*. at 93 and Food Safety Appendix D, page 170; USDA Nutrient Database. Atlantic Salmon.
[93] *Id.* at 94.
[94] *Id.* at 94
[95] *Id.* at 94-95.

amazing 57.7 percent higher, and protein levels that were 5.1 percent lower. Again, this suggests that the GE salmon is not just a far fattier fish, but it is missing five percent or more of the protein content that consumers seek out in salmon.

FDA does not tell us what the total fat content of triploid GE salmon was, but we can infer that it was higher than all other fish, because it's total fatty acid content was higher than all other fish measured, and the FDA acknowledges that that total fatty acid is directly proportional to total fat content.[96]

All of this data strongly supports the conclusion that that AquAdvantage salmon are a far fattier fish than non-GE salmon. This material difference in fat content is of special importance to consumers because GE salmon's fat content does not contain the beneficial omega fat content highly sought after by consumers. That is, though higher overall in fatty acids, AquAdvantage Salmon actually expressed 14 percent lower omega rates than farmed fish (according to independent studies) and 200 percent less than wild-caught salmon.[97] Because the FDA does not supply complete data on fatty acids based on ploidy, it is impossible to discern the omega levels of triploid GE salmon versus diploid comparators. In any event, the GE salmon's excessive fatty acid content teamed with lower omega rates is exactly the type of food that many American consumers seek to avoid in their diets, and such material nutritional differences need to be disclosed to consumers.

AquAdvantage Salmon also exhibited lower mean levels of amino acids compared to genetically similar non-GE salmon raised in the same environment (sponsor control). In all 18 amino acids examined by AquaBounty and the FDA, GE salmon had lower levels. And using the USDA nutrient database as a comparator, GE salmon had lower levels in all but one amino acid. Additionally, the GE salmon also manifested greater variance in amino acid levels, with its standard deviation larger than control groups in all but one analyte.[98]

Because amino acids are the building blocks of proteins, lower amino levels spell another material difference of special concern to consumers who seek out salmon as a good source of protein. That is, the GE salmon is not simply fattier, it is also lower in protein. The GE salmon's mean values of total protein were 5.1 and 6.3 percent lower than both the sponsor control and the USDA nutrient database. Though GE salmon did have 1.5 percent greater protein content than the farm control, the merits of this comparison is highly questionable because, as mentioned before, the diet of the farm control remains unknown, which even the FDA acknowledges as highly confounding.[99] The best comparison, between GE salmon and its sponsor control, which were raised in a similar manner with similar diets, evidences greater than a five percent difference in protein, a crucial finding that the FDA has not examined closely enough.

[96] *Id.* at 93.
[97] *Id.* at Table 28, page 95.
[98] *Id.* at Table 24.
[99] *Id.* at 94.

Such material differences should be disclosed to consumers though labeling. Indeed, this is underscored by AquaBounty itself, which acknowledges that consumers prize salmon because it is "a high protein food, high in Omega-3 fatty acids, a heart healthy food for the American diet."[100]

Finally, the AquAdvantage Salmon generally exhibited large differences in vitamin and mineral values compared to non-GE salmon – often lower levels – and such material nutritional differences must be disclosed in labels. In 12 of the 18 vitamin and minerals measured, GE salmon showed lower levels compared to sponsor controls. In five of these analytes, the GE salmon showed double digit differences. Compared to the farm control, the GE salmon expressed eight double-digit differences in vitamin and mineral content. Again, because sample sizes were so small, these differences did not always present statistically significant findings. The USDA nutrient database provides data points for 15 of 18 of the vitamin and mineral analytes that AquaBounty examined. Eleven of these 15 manifested double or triple-digit differences between GE and non-GE salmon.

Moreover, the FDA's analysis of nutrients found that three vitamins, seven minerals and one amino acid were, according to some quantitative measurement, different from the control groups. Of these, the FDA found serine, potassium, and Vitamin B6 to be statistically significantly different.[101] Triploid GE salmon showed differences with regards to niacin, magnesium and phosphorous.[102] The agency concluded that three analytes were statistically significantly different, including Vitamin B6, folic acid and niacin.[103]

It is not entirely clear why the FDA decided to rule out the findings of statistical significance of folic acid and niacin. It would appear that the FDA disregarded folic acid levels because the statistically significant differences were drawn from comparisons between diploid (for both GE and non-GE) fish, which are not the subject of AquaBounty's new animal drug application. But for the purposes of determining material differences, FDA states that it designed its comparisons to look at GE salmon's food safety values relative to "salmon normally consumed by humans,"[104] which an FDA official has acknowledged as being diploid.[105]

This suggests that the FDA would want to consider a comparison between triploid GE salmon, the subject of AquaBounty's new animal drug application, and diploid non-GE salmon. The FDA does not report this data in the briefing packet; troublingly, when this comparison is made for folic acid, triploid GE salmon showed 37.4 percent and 15.8 percent lower values of folic acid compared to diploid farm and sponsor control salmon[106] - far greater differences in values than those that the FDA would have considered with its diploid-diploid and triploid-triploid comparisons. Certainly, a consumer needs to know if

[100] Transcript at 100.
[101] Briefing Packet at 88-89.
[102] *Id.*
[103] *Id.*
[104] *Id.* at 87.
[105] *Id.*; Transcript at 222, comments from Kathleen Jones.
[106] Briefing Packet at Food Safety Appendix D, page 167.

his or her fish contained different levels of vitamins, minerals, or amino acids, and the agency should require labeling to provide them this information.

Material Organoleptic Differences. For decades private industry has developed a grading system for salmon based on qualities like color, which determine price.[107] Because consumers prefer redder salmon meat, coloring agents have been added to salmon, and graders indicate that salmon that is too pale can have little to no commercial value.[108] Additionally, salmon can vary widely in texture and firmness, depending on genetics, husbandry practices, slaughter, and processing.[109] Salmon with too soft a texture will be rejected from consumer markets as well.[110]

The FDA considers these organoleptic properties of salmon – defined as "those that stimulate the sensory organs, such as texture or aroma"[111] – as material aspects of the Atlantic Salmon identity,[112] which could help determine the need for labeling the product. Given that the sight of salmon – particularly its redness – is of such great importance to consumers and the marketplace, FDA should have examined this aspect of the GE salmon determine if it constitutes a material difference. Similarly, texture and firmness should also be evaluated in a matter that reflects both industry and FDA standards. Such a failure to do so should preclude the agency from making any determinations that the AquAdvantage salmon is not organoleptically different than the non-GE variety.

The fat content of salmon also has great importance on the material make-up of the fish. Domesticated salmon exhibit average fat content of between 10 and 15 percent, according to industry standards,[113] while the USDA says the average fat level is between 12.3 percent (cooked) and 13.4 percent (raw).[114] The fat content of salmon can have impact on organoleptic properties critical to fish's commercial value, such as texture and taste, as well as determining if and how it can be used in different processing (filets, smoking, canning, etc.).[115] Processors of salmon, for example, typically request a fat content of between 8 and 12 percent.[116]

AquaBounty's data clearly shows the triploid GE salmon's exceedingly high fat content, with total fatty acid that was 61.9 percent greater than the sponsor control group and 17.7 percent greater than farmed salmon, according to the USDA nutrient database.[117] This fatty

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[107] DSM Nutritional Products. "Salmonid Pigmentation Guide." http://www.dsm.com/en_US/downloads/dnp/51643_aqua.pdf Accessed October 18, 2010.
[108] Steine, G. et al. "The Effect of Color on Consumer WTP for Farmed Salmon." Marine Resource Economics. 2005 at 218.
[109] Ashton, T. et al. "A Novel Tensile Test Method to Assess Texture and Gaping in Salmon Fillets." Journal of Food Science: Sensory and Food Quality. Vol. 75, No. 4, 2010. at Introduction.
[110] *Id.* at 189.
[111] Background Document at Footnote 1.
[112] *Id.* at Introduction.
[113] Stead, S. et al. "Handbook of salmon farming." Springer. 2002 at 191-192. (hereinafter "Handbook.")
[114] USDA Nutrient Database. Atlantic Salmon.
[115] Handbook at 191-192
[116] *Id.*
[117] Briefing Packet at Food Safety Appendix D, page 170.

acid content represents not just a nutritional difference that consumers are concerned about, but also will affect a difference in texture and taste and a change in how the AquAdvantage Salmon can be used in the marketplace (e.g., processing).

It is also important to consider other factors impacting the fat content of salmon, which include seasonality and size of fish.[118] Were the agency not to require labeling, its conclusion would suffer from the fatal and capricious flaw that an analysis was not done on a number of factors. For example, the GE salmon that AquaBounty intends to put on the market could actually contain even greater levels of fat. FDA acknowledged that AquaBounty had failed to control for the potentially confounding variable of seasonality in other parts of the company's environmental assessment.[119] In addition, AquaBounty harvested fish for its fat analyses at an unspecified market weight (2.0 to 7.5kg), leaving it unclear what the true fat percentage of GE salmon will be in a commercial setting.[120] Such a wide variation in harvest weight could have an impact on measure of fat between fish. For example, if AquaBounty harvested its salmon at an extreme weight, 2.0 or 7.5 kilograms, for the purposes of the study, but, in practice, plans to harvest them at three or four kilograms, the fat percentage may change. Unfortunately, the FDA did not investigate the entire life cycle of genetically engineered salmon, and has not released full data sets that may help explain apparent weaknesses in data.

As an additional concern related to salmon color, domesticated salmon growers frequently add costly coloring agents, such as astaxanthin and canthaxanthin, to salmon feed that enhance the color of the fish.[121] Around fifteen percent of feed costs actually go to these coloring agents, [122] clearly suggesting the importance to the industry of producing appropriately reddened salmon. But given that the AquAdvantage salmon has been altered through the inclusion of DNA from foreign organisms, including the highly unrelated ocean pout, it remains unclear if or how these coloring agents will work with genetically altered salmon. Will the salmon's flesh redden to meet consumer expectations? Will these reddening agents interact with the GE salmon in a unique way that causes physical changes? These questions remain unexamined by the FDA.

Finally, perhaps the greatest organoleptic test, regarding taste, has not been conducted. There have been no credible feeding tests or other appropriate measures of taste or smell.

In sum, there is adequate evidence that there will be material difference in organoleptic characteristics in AquAdvantage Salmon that require labeling based on fat content alone. And any agency failure to require labeling because it cannot find any differences will be arbitrary and capricious, stemming from the fact that it simply did not adequately look for them.

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[118] Handbook at 191-192.
[119] Transcript at 187.
[120] Briefing Packet at 78.
[121] Steine, G. et al. (2005). At 212.
[122] *Id.*

4. AquAdvantage Salmon should be labeled because consumers nearly unanimously support its labeling

Because there are differences between Atlantic Salmon and GE salmon, it is proper to consider consumer opinion as to whether such changes are material. See Stauber v. Shalala, 895 F. Supp. 1178, 1193 (W.D. Wis. 1995). Consumer opinion dictates the need for labeling:

- 93 percent of respondents indicated that they wanted genetically engineered food to be labeled in an October 2010 poll by Reuters.[123]
- 95 percent of respondents in a 2008 poll conducted by Consumers Union believed that food products made from genetically engineered animals should be labeled as such.[124]
- 93 percent of respondents in a 2001 poll conducted by ABC News believed that genetically engineered foods should be labeled.[125]
- 93 percent of respondents in a 1997 poll by Novartis, Inc. wanted foods that are genetically altered to be clearly identified with labels.[126]

Therefore, because AquAdvantage Salmon is materially different from Atlantic Salmon, presenting special health risks of which consumers should be advised, as well as different nutritional, organoleptic, and functional characteristics than the Atlantic Salmon with which consumers are familiar – and because consumers strongly support the labeling of the product –FDA should mandate its labeling under 21 U.S.C. § 321(n). A failure to do so would be to disregard the extensive evidence in the record, rendering the decision arbitrary and capricious, and thus illegal under the APA.

IV. Conclusion

An analysis of GE salmon demonstrates in myriad ways the FDA's obligation to require GE salmon to be labeled, should it be approved for consumer consumption. Genetically engineered salmon exhibits large differences in measures of allergenicity, hormone levels, amino acids, fatty acids, vitamins, minerals and total content of protein and fat. AquAdvantage salmon also display greater frequency of health problems, differences in composition, and differences in behavior. Of great importance, many of the differences found in GE salmon pose a threat to consumer health, either through the introduction of hormones and allergens into the diet or through the fish's inferior protein and high fat content.

Meanwhile, the organoleptic properties of GE salmon, which are a basis for the FDA's determination of material differences, have been completely overlooked by the FDA.

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[123] Thomson Reuters.
[124] Consumer's Union. "Food Labeling Poll." Consumer Reports National Research Center, Yonkers, NY. November 11, 2008. http://www.greenerchoices.org/foodpoll2008/. Accessed September 20, 1010.
[125] Langer, G. "Behind the Label Many Skeptical of Bio-Engineered Food." ABC News. June 19, 2001.
[126] Consumers Union. "Summary of Public Opinion Surveys Related to Labeling of Genetically Engineered Foods." http://www.consumersunion.org/food/summpollny699.htm Accessed September 20, 2010.

Indeed, a major deficiency underscoring the FDA's entire risk assessment and approach to the labeling issue is the inexcusably weak science, rife with errors, omissions and a lack of transparency that disables the public from fully participating in the FDA's public rule-making process.

Notwithstanding the weaknesses in FDA's evaluation, there is substantial data to demonstrate material differences—and to demonstrate the FDA's legal requirement to mandate labeling of GE salmon under the Federal Food, Drug, and Cosmetic Act. Atlantic Salmon cannot be used as the market name of the GE salmon because it is not its common or usual name. Alternatively, because of the differences in key nutrient values, FDA's regulations require that it be labeled as an "imitation." In addition, AquAdvantage Salmon must be labeled to reveal facts that are material to the consumer about consequences from the product's use, including the fact that it poses health risks from its IGF-levels and allergic potency. Moreover, the genetically engineered salmon needs to be labeled to inform consumers who may be wary of purchasing or consuming a product that has been so radically altered from Atlantic Salmon. Finally, the law requires that the agency mandate labeling to reflect the nutritional differences in the genetically engineered product, as well as the fact that it is likely to have a high fatty content that will affect its texture, taste, and how it is processed.

All of these differences are material and overwhelmingly supported by public opinion. The FDA's role is one of a public health protector and watchdog for consumers, but its actions so far on GE salmon seem at stark odds with that mission. The public is rightfully suspect of biotechnological applications for food, which too often leave the public on the outside of the decision-making process. This is certainly the case with AquaBounty's AquAdvantage salmon.

The FDA's management and administration of AquaBounty's new animal drug application for the AquAdvantage salmon has been far too opaque. The problems with the FDA's science and regulatory process have received overwhelming criticism from members of the FDA's Veterinary Medicine Advisory Committee, fellow scientists at the U.S. Fish and Wildlife Service and hundreds of thousands of citizens. The FDA must require AquaBounty to conduct a full Environmental Impact Statement to fully address the safety and effectiveness of AquAdvantage salmon. When that process is complete, if it approves GE salmon, the agency must require labeling of the fish in light of the many, substantial differences in genetically engineered fish.

Chart 1: Differences in Nutritional Content between GE Salmon, Farm Control Salmon, Sponsor Control Salmon, and USDA Salmon Nutrient Data

	Percent Difference GE vs Farm Control	Percent Difference GE vs Sponsor Control	Percent Difference GE vs USDA
Fatty Acids			
Arachidic	0.00	200.00	36.36
Arachidonic	12.50	50.00	-2.17
Docosahexaenoic	-2.74	47.92	28.62
Docosapentaenoic	13.64	85.19	27.23
Eicosadienoic	20.00	50.00	-3.23
Eicosapentaenoic	-5.98	86.44	27.61
Eicosatrienoic	50.00	200.00	66.67
Eicosenoic	-41.76	15.22	100
Free fatty acids	125.00	28.57	
Gamma linolenic	0.00	50.00	50
Heptadecanoic	0.00	100.00	-6.98
Linoleic	10.45	45.10	-17.78
Linolenic	27.78	76.92	37.72
Myristic	-12.00	65.00	18.71
Oleic	14.58	64.18	
Palmitic	-6.28	67.29	-4.64
Palmitoleic	-9.18	58.93	
Pentadecanoic	-20.00	33.33	-13.04
Stearic	7.69	75.00	-15.15
Amino Acids			
Alanine	0.92	-5.98	-13.45
Arginine	2.83	-5.22	-10.73
Aspartic acid	2.25	-6.19	-10.12
Cysteine	4.76	-4.35	0.46
Glutamic acid	0.00	-7.22	-13.78
Glycine	1.08	-7.84	-2.08
Histidine	3.92	-3.64	-3.46
Isoleucine	3.53	-4.35	-9.09
Leucine	1.43	-6.58	-12.07
Lysine	1.22	-6.21	-11.23
Methionine	3.70	-5.08	-10.54
Phenylalanine	2.78	-6.33	-12.43
Proline	1.49	-6.85	-5.69
Serine	0.00	-6.17	-15.18

Threonine	3.95	-4.82	-8.14
Tryptophan	5.88	-5.26	-13.87
Tyrosine	4.84	-4.41	-14.36
Valine	2.02	-5.61	-8.76
Vitamins			
Folic acid	-24.14	-12.00	
Niacin	9.64	9.93	12.38
Pantothenic acid	-17.91	-16.16	-28.89
Vitamin B1	16.67	-12.50	
Vitamin B12	0.00	0.00	-7.12
Vitamin B2	6.93	-4.42	
Vitamin B6	16.92	6.53	20.59
Vitamin C	7.58	-25.13	-23.59
Minerals			
Calcium	-12.45	-8.19	206.33
Copper	33.33	14.29	77.78
Iron	0.00	8.33	52.94
Magnesium	-3.40	-8.42	-8.56
Manganese	0.00	0.00	172.72
Phosphorous	-1.65	-4.44	6.83
Potassium	-1.84	-6.40	1.54
Selenium	-15.00	-5.56	-29.17
Sodium	0.18	-9.16	-44.86
Zinc	-10.53	-1.92	41.67
Nutrition Other			
Carbohydrate	-17.39	2.70	
Ash	0.88	-3.39	0.88
Moisture	1.24	-5.92	0.47
Protein	1.49	-5.11	-6.32
Total Fat	-4.94	57.77	7.45

Source: Food & Water Watch analysis of data in FDA Briefing Packet.

Chart 2: Differences in Allergenicity between GE Triploid Salmon, Non-GE Salmon, and GE Diploid Salmon

	Percent Difference	Percent Difference
	GE Triploid vs Non-GE	GE Diploid vs Non-GE
Allergenicity	19.46	52.49

Source: Food & Water Watch analysis of data in FDA Briefing Packet.

Chart 3: Differences in Growth Hormones between GE Salmon, Non-GE Salmon, Farm Control Salmon, and Sponsor Control

	Percent Difference	Percent Difference
Hormones		
Study 1	GE vs Non-GE Sibling	GE vs Control
Growth Hormone	41.49	94.63
Study 2	GE vs Sponsor control	GE vs Farm Control
IGF-1	39.78	
11-keto testosterone	20.71	55.98

Source: Food & Water Watch analysis of data in FDA Briefing Packet.