DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NOV 19 2015

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Re: Docket # FDA-2011-P-0448

Dear Ms. Desai and Mr. Roady:

This letter responds to the citizen petition concerning AquaBounty Technologies' (ABT) AquAdvantage Salmon that you submitted to the Food and Drug Administration (FDA or the agency) on May 25, 2011 on behalf of Ocean Conservancy, Friends of the Earth, Center for Food Safety, Food & Water Watch, Center for International Environmental Law, and Greenpeace. The citizen petition requests that FDA "(1) refrain from taking final action on ABT's application for approval of AquAdvantage Salmon, a GE animal intended for human consumption, until FDA has completed a comprehensive environmental impact statement (EIS) that fully assesses the potential environmental impacts associated with GE salmon, and (2) amend its regulatory framework to specifically define the Agency's oversight of GE food animals in a manner that provides greater and necessary environmental protection and is consistent with NEPA" [the National Environmental Policy Act of 1969 or "NEPA"].

For the reasons explained below, FDA is denying your requests under 21 CFR § 10.30(e)(3). In this response, we explain why FDA's approval of ABT's new animal drug application (NADA) for AquAdvantage Salmon (ABT application)[1] does not require FDA to complete an EIS under NEPA. We further explain why FDA declines to amend its regulatory framework implementing NEPA in response to your request.

I. NEPA does not require FDA to prepare an EIS with respect to FDA's approval of the ABT application

NEPA requires federal agencies to consider the environmental consequences of "major federal actions significantly affecting the quality of the human environment." 42 U.S.C. § 4332. The

[1] The NADA is for approval of the integrated α-form of the opAFP-GH-c2 construct at the α-locus in the EO-1α line of triploid, hemizygous, all-female genetically engineered Atlantic salmon. For ease of reference, we may refer to the NADA as seeking approval of AquAdvantage Salmon. AquAdvantage Salmon are a subset of ABT salmon, which are defined as any GE Atlantic salmon from the E0-1α lineage irrespective of ploidy, zygosity, or gender (i.e., the set of Atlantic salmon that includes diploid GE salmon that may be used as broodstock, as well as AquAdvantage Salmon). (See Technical Terms, Environmental Assessment).

Council on Environmental Quality (CEQ) has issued regulations under NEPA that apply to all agencies of the federal government. 40 CFR § 1507.1. The CEQ regulations provide for the evaluation of the environmental effects of a major federal action. Under these regulations, major federal actions require preparation of an EIS or an environmental assessment (EA) unless the action is categorically excluded from the requirement to prepare an EIS or EA. 40 CFR §§ 1508.4, 1508.9, 1508.11. Consistent with these regulations and FDA's implementing regulations in 21 CFR Part 25, FDA prepared an EA for the specific conditions of use in the application, and concluded that approval of the ABT application will not have a significant effect on the quality of the human environment, and presented its findings in a "finding of no significant impact."[2] Therefore, FDA's approval of the ABT application is not an action for which an EIS is needed.[3]

A. FDA's approval of the ABT application will not have a significant effect on the quality of the human environment.

The term "significantly as used in NEPA requires considerations of both context and intensity." 40 CFR § 1508.27. "[I]ntensity . . . refers to the severity of impact." 40 CFR § 1508.27 lists 10 considerations for an agency to evaluate in determining the intensity of an action. You assert that the considerations listed in subparts (b)(4), (5), and (6) "weigh heavily in favor of the preparation of an EIS." CP at 5. We disagree.

The first of the considerations upon which you rely is "[t]he degree to which the effects on the quality of the human environment are likely to be highly controversial." 40 CFR § 1508.27(b)(4). You assert that "uncertainties associated with ABT's application have generated ongoing controversy among a broad-range of experts, lawmakers, and consumer health and environmental advocates, both within the United States and abroad," and cite to several letters, an email, and proposed federal, state and Canadian legislation. CP at 5 & n.3. These letters, email, and proposed legislation, however, reflect only general concern about or opposition to the concept of genetically modified[4] salmon.[5] With the exception of internal September 30, 2010 and October 6, 2010 U.S.

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[2] Your citizen petition is based on the 2010 EA prepared by ABT. Subsequent to the filing of this petition, FDA prepared its own draft EA and in December 2012, made its draft EA and preliminary finding of no significant impact (FONSI) for AquAdvantage Salmon available to the public for comment, and finalized these documents on November 12, 2015. Although the two documents are similar in that they reflect the same fundamental containment approach (primary reliance on physical containment at the PEI breeding facility and multiple, redundant forms of containment, including physical, biological, geophysical, and geographic, at the grow-out facility in Panama), FDA's own draft EA is considerably more complete. It included updated information on the practices at both ABT's egg production and grow-out facilities, the results of agency inspections and site visits, interactions with other federal agencies, and a more formalized risk analysis than that provided by the sponsor.

[3] *Am. Bird Conservancy, Inc. v. FCC*, 516 F.3d 1027, 1033 (D.C. Cir. 2008) and *Scientists' Institute for Public Information, Inc. v. Atomic Energy Com.*, 481 F.2d 1079, 1088-1089 (D.C. Cir. 1973), upon which you rely (CP at 4), do not mandate preparation of an EIS under the circumstances present here. In *Am. Bird Conservancy,* the court held that, where there was no real dispute that certain towers "may" have a significant environmental impact, Federal Communication Commission (FCC) regulations required the completion of an EA before the FCC could determine not to prepare a programmatic EIS. Here, FDA prepared an EA and, based on that analysis, concluded that approval of ABT's NADA will not have a significant impact on the environment. *Scientists' Institute for Public Information* involved the question whether NEPA applied to a nuclear reactor research and development program. There is no dispute here as to NEPA's applicability to NADA approvals.

[4] FDA refers to these salmon as "genetically engineered," while others may refer to them as "genetically modified" or "transgenic." We are assuming that these latter terms refer to the use of modern biotechnology in the production of AquAdvantage Salmon.

Fish and Wildlife Service (FWS) documents (CP Attachment 1),[6] none of the documents you cite is specific to FDA's evaluation of the likelihood of any significant impact to the environment of the United States via the potential exposure pathways from the production and grow-out facilities in Prince Edward Island, Canada (PEI), and Panama, and FDA's finding of no significant impact (FONSI) on the environment of the United States. The September 30 and October 6, 2010 FWS documents, moreover, were followed by FWS's December 16, 2010 determination that FDA's "no effect" determination in its environmental review under NEPA "seems well supported for this approval." See CP Attachment 1.

General misgivings about genetically engineered fish and generalized "questions regarding potential environmental threats" are not the type of controversy that are required to be considered under 40 CFR § 1508.27(b)(4). Rather, as the CEQ regulation makes clear, it is the effects on the environment that must be controversial. The term "controversy" in the NEPA context refers to cases "where a substantial dispute exists as to the size, nature or effect of the major federal action rather than to the existence of opposition to a use." *Rucker v. Willis*, 484 F.2d 158, 162 (4th Cir. 1973). See also *Fund for Animals v. Frizzell*, 530 F.2d 982, 988 (D.C. Cir. 1975) ("certainly something more is required besides the fact that some people may be highly agitated and be willing to go to court over the matter"). Moreover, "[C]ontroversy is not decisive but is merely to be weighed in deciding what documents to prepare." *Hillsdale Envtl. Loss Prevention v. U.S. Army Corps of Eng'rs*, 702 F.3d 1156, 1181 (10th Cir. 2012), *quoting Town of Marshfield v. FAA*, 552 F.3d 1, 5 (1st Cir. 2008). "When specialists express conflicting views, an agency must have discretion to rely on the reasonable opinions of its own qualified experts ..." *Marsh v. Oregon Natural Resources Council*, 490 U.S. 360 (1989).

The second consideration upon which you rely is "[t]he degree to which the possible effects on the human environment are highly uncertain or involve unique or unknown risks." 40 CFR §

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[5] These include internal emails dated September 28 and 29, 2010, among U.S. Fish and Wildlife Service employees opining that fish escape, but without any specific reference to the containment conditions proposed for AquAdvantage Salmon (CP Attachment 2). We note that the views of lower-level agency employees do not necessarily reflect an agency's ultimate position. *See, e.g., Paralyzed Veterans of Am. v. D.C. Arena L.P.*, 117 F.3d 579 (D.C. Cir. 1997) ("A speech of a mid-level official of an agency . . . is not the sort of 'fair and considered judgment' that can be thought of as an authoritative departmental position."); *N.Y. State Dep't of Soc. Serv. v. Bowen*, 835 F.2d 360, 365 (D.C. Cir. 1987) (contrasting agency's "informal statements" with "position officially articulated"). In addition, the cited materials include a letter dated September 28, 2010 from members of the U.S. Senate to then-FDA Commissioner Hamburg expressing general concerns and urging review by FDA's Center for Food Safety and Applied Nutrition of the product's potential health effects on humans (CP Attachment 3); a letter dated September 29, 2010 from members of the U.S. House of Representatives to Commissioner Hamburg expressing general concerns with FDA's review process (CP Attachment 4); a letter dated September 16, 2010 from members of the California Legislature to Commissioner Hamburg expressing concern that approval will lead to other applications to grow genetically modified fish in other production systems such as open net-pen culture in marine and freshwater habitats (CP Attachment 5); a bill introduced into the U.S. Senate on January 31, 2011 to amend the Federal Food, Drug, and Cosmetic Act (FD&C Act) to prevent approval of transgenic fish (CP Attachment 6); a bill introduced into the U.S. House of Representatives on February 8, 2011 to amend the FD&C Act to prevent approval of transgenic fish (CP Attachment 7); a California bill dated January 2, 2011 to require labeling of all transgenic salmon sold or produced in California (CP Attachment 8); and a Canadian House of Commons Motion dated March 1, 2011 to prevent the introduction into the Canadian food system of genetically modified salmon (CP Attachment 9).

[6] These documents provide comments from regional FWS employees on the materials made available for the 2010 Veterinary Medicine Advisory Committee Meeting. The documents do not specify the intended recipient of these comments. The documents include the names of the FWS employees, but do not include their signatures FDA has no record of receiving these documents from the FWS.

1508.27(b)(5). In support of this assertion, you cite the statements of "leading transgenic fish experts" and uncertainties reflected in letters and emails that you raise elsewhere in your petition, CP at 5, 10, 11. FDA has addressed the authorities you cite in its discussion of those other portions of your petition. See infra at 7, 2-3. FDA's assessment concluded that approval of ABT's application will not result in a significant impact on the environment of the United States. As stated in the EA, "[t]he geographical and geophysical conditions present in the aquatic environments surrounding both the PEI broodstock and the Panama grow-out facilities are sufficiently inhospitable to limit the potential establishment and spread of AquAdvantage Salmon or diploid ABT salmon to other locations. In the unlikely event that an escape were to occur, the likelihood of survival of AquAdvantage Salmon or diploid ABT salmon would be a function of the life stage(s) of the animal escaping and the location into which it escapes. This is particularly true for the earliest life stages (eggs and embryos) in PEI, which would be unlikely to survive if exposed to high salinity and low temperature conditions in the nearby aquatic environment, and for all life stages of these salmon in Panama, which would be unlikely to survive the high temperature conditions in the lower reaches of the watershed." EA, Section 7.3.2. Moreover, "the combination of triploidy and an all-female population is expected to render AquAdvantage Salmon effectively and functionally sterile resulting in complete reproductive containment." EA, Section 7.4.2. The EA goes on to conclude that no data or information indicate "that escape or release of GE salmon . . . from the egg production facility would result in significant effects on the environment of the United States," or that "escape or release of AquAdvantage Salmon as a result of grow-out would result in significant effects on the environment of the United States." EA, Sections 7.5.1.1.3 and 7.5.1.2.3.

The third consideration you cite is "[t]he degree to which the action may establish a precedent for future actions with significant effects." 40 CFR § 1508.27(b)(6) Specifically, you state that "this application has the potential to establish a precedent for other transgenic animals intended for human consumption." However, the approval of the NADA related to AquAdvantage Salmon is an individual action, just as approval of any other NADA is an individual action, with its own particular, potential environmental risks, and therefore does not set precedent for approval of future NADAs. Furthermore, you have not provided evidence that such future actions would necessarily have significant effects on the environment.

B. <u>As described in FDA's Environmental Assessment, FDA has concluded, based on substantial evidence and analysis, that an EIS is not needed.</u>

Your citizen petition asserts that, for the following three reasons, FDA must prepare an EIS prior to taking final action on ABT's petition:

(1) ABT's application "admits serious environmental risks;" (CP at 9)
(2) Scientists you cite "have expressed deep concern regarding the deficient science surrounding the ABT application"; (CP at 10) and
(3) "ABT has announced plans to expand production" of AquAdvantage Salmon to the U.S. and abroad. (CP at 12)

We disagree for the reasons set forth below.

1. Environmental Risks: Triploidy Process

ABT's application has not "admitted serious environmental risks," as you state in your citizen petition.

Your citizen petition maintains that because the triploidy induction process is not 100% effective and some AquAdvantage Salmon may not be triploid, and because there is a lack of specific data demonstrating that AquAdvantage Salmon are indeed sterile, "serious questions [are raised] about the sufficiency and reliability of ABT's plan to mitigate the risks presented by the potential escape of the [AquAdvantage Salmon]," which "must be carefully evaluated in an EIS." CP at 9. First, it is important to note that the induction of triploidy, is consistently, on average, 99.8% effective for AquAdvantage Salmon.[7] EA, Section 5.3.2.3. The statement in the EA that you cite concerning an absence of data on sterility, moreover, is followed by an extensive discussion of the scientific evidence that triploidy does indeed result in effective reproductive sterility in Atlantic salmon and other fish. EA, Section 7.4.1.3 ("Although …there are no specific data demonstrating that triploid AquAdvantage Salmon are indeed sterile…there are several reasons why this is believed to be the case….[B]ased on the available evidence, FDA has concluded that triploidy would ensure functional sterility and reproductive incompetence in the sponsor's all-female populations of AquAdvantage Salmon."). See EA Section 7.4.1.3.[8]

More importantly, your focus on triploidy in isolation gives an incomplete picture of the containment measures specified in the AquAdvantage Salmon NADA approval. There are numerous biological, physical, and geographical/geophysical methods of containment. The EA notes that "no single containment measure will be effective at all times and should not be considered to exist outside the context of multiple, independent and complementary measures in series….By combining containment measures with different stringencies, attributes, and modes-of-action, the compromise of aggregate containment by the failure of a single measure becomes increasingly unlikely." EA, Section 2.6. As a consequence, under the conditions established in the approval, ABT must have multiple and redundant forms of biological, physical, and geographical/geophysical containment in place. These complementary and redundant biological, physical, and geographical/geophysical methods of containment, in addition to others described in the EA, support FDA's conclusion that the likelihood of escape of any ABT salmon, diploid or triploid, and at any life stage is extremely low, and that, even if any diploid ABT Salmon did escape, it is extremely unlikely that they could survive and establish themselves in the wild. EA, Section 7.8.

There are two forms of biological containment in place for AquAdvantage Salmon: triploidy and an all-female genotype. Although, as noted, a very small fraction of AquAdvantage Salmon may not be triploid, the second form of biological containment, production of an all-female fish population, is 100% effective in preventing reproduction. In this case, triploidy is an intrinsic component of the redundant forms of containment that are applied to ensure that, in the highly unlikely event AquAdvantage Salmon escape from physical containment, they cannot reproduce or establish in the environment. "The combination of triploidy and an all-female population is expected to render AquAdvantage Salmon effectively and functionally sterile resulting in complete reproductive containment." EA, Section 7.4.2. Further, any possibility of establishment either near

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[7] The conditions established in the approved application specify that, based on testing, a minimum of 95% of the AquAdvantage Salmon eyed-eggs would be triploid but, "[b]ased on the results of multiple method validation studies, the actual average percentage of triploidy is consistently at 99.8%." EA, Section 7.4.2.

[8] You also point to FDA's statement in its Briefing Packet for the Veterinary Medicine Advisory Committee, dated September 20, 2010, that ABT's characterization of AquAdvantage Salmon as "'sterile'" was "'potentially misleading'" because "'sterility has not been explicitly verified in these fish and up to 5% of the eggs sold for grow-out may be non-triploid and still within release specifications.'" CP at 9. Sterility, however, cannot be explicitly verified without destroying all the eggs, and, as, FDA further explained, "AquAdvantage Salmon will be effectively sterile, with fertility greatly reduced or eliminated as a result of triploidy…." Briefing Packet at 115. See also EA, Section 7.4.1.3.

the broodstock or grow-out facilities is precluded because there are no wild Atlantic salmon populations nearby in Panama or in any of the watersheds near the PEI facility with which even diploid ABT salmon could attempt to spawn. EA, Sections 7.4.1.6, 7.4.2.

In addition to biological containment, ABT's production and grow-out plan and the conditions established in the NADA include physical and geographical/geophysical containment that apply to AquAdvantage Salmon and all other ABT salmon. Upstream of these redundant and complementary biological containment measures, the PEI egg production and Panama grow-out facilities have been designed to have multiple redundant physical containment measures (i.e., barriers) in place to prevent escape of ABT salmon, including AquAdvantage Salmon. At PEI, all areas have at least four independent forms of physical or mechanical containment, and at the ABT Panama facility containment methods include use of multiple, redundant screens on pipes and drains throughout the facility, and net coverings on tanks. EA, Section 5.4.2, Table 2, and Figure 6; Section 5.5.2, Table 4, and Figure 7.

Geographical/geophysical features of the ABT facilities and their surrounding environment will also deter establishment of ABT salmon, including AquAdvantage Salmon, in the environment. In the watersheds surrounding the PEI facility, there are no wild Atlantic salmon populations despite repeated attempts to introduce them. Features of the surrounding watershed that have prevented salmon population recovery are believed to be stream sedimentation caused by agriculture and other land-use activities and blockages from beaver dams. EA, Section 6.1.1.3. The geographical/geophysical features at the Panama facility that would prevent establishment of AquAdvantage Salmon include water diversion from the adjacent river that results in a poor habitat for salmonids; water temperature in the mid- to lower-parts of the adjacent river that exceeds the upper lethal limit for salmon; and a large dam on the river that presents an obstacle to fish passage. EA, Section 6.1.2.

In addition to maintaining that the lack of 100% effectiveness of triploidy requires preparation of an EIS, you also state that "two studies have found that in certain circumstances, transgenic fish can out-compete wild fish to the point of total population collapse" and that these studies "underscore the need for a comprehensive EIS." CP at 10, n. 7 & 8. These studies concern the "Trojan gene hypothesis," which explored the possible extinction of populations of the Japanese ricefish, medaka (*Oryzias latipes*), a species that is commonly used in the laboratory for testing purposes, through the flow of a gene that confers a reproductive advantage while also rendering offspring of those fish less able to survive in the natural environment. EA, Section 7.5.1.1.1. As you acknowledge, however, the originator of that hypothesis has said that this is not the case with respect to AquAdvantage Salmon. See EA, Section 7.5.1.1.1 ("the data conclusively shows that there is no Trojan Gene effect as expected. The data, in fact, suggest that the transgene will be purged by natural selection…..[and that] the long-term risk of GE salmon is close to zero as no fitness advantages in any component were demonstrated, resulting in a purge scenario for the transgene.").

Nonetheless, you assert that "the theory's relevance should not be dismissed outright" because "[o]ther studies note that background genetics or behavior can change the likelihood of the Trojan gene effect…." CP at 10, n.8. With respect to the two "other studies" you cite, we note that both are mathematical models, and not environmental studies. Further, in both papers, the requisite conditions for the Trojan gene hypothesis to apply to GE salmon so as to cause alterations in population dynamics are the introduction of growth-enhanced GE salmon into the environment by intent or escape, and mating of these GE salmon with wild-type conspecifics. FDA's EA determined that the probability of diploid ABT salmon escaping from the PEI facility is highly unlikely and there are no conspecifics in the local watershed with which mating could occur. The EA also determined that conditions at the grow-out facility in Panama make escape highly unlikely,

and there are no conspecifics in the local waters with which to interact and reproduce. Because the two requisite conditions for the models in these papers do not exist at either location, the models do not have relevance to the specific conditions specified in the AquAdvantage Salmon approval.

2. Concern Regarding Science

You state in your citizen petition that FDA must take into account "concerns that notable transgenic fish experts have expressed," in particular that "'there is a high scientific uncertainty in predicting overall fitness and ecological effects of growth enhanced transgenic fish,'" and that that there is a "dearth of information relating to how transgenic salmon will behave in the wild, including how they will interact with native salmon." CP at 10, 11. The EA addresses in detail these issues with respect to the two facilities at which the conditions established in the NADA allow ABT to develop and grow AquAdvantage Salmon and diploid ABT salmon. EA, Section 7.0 et seq.

Your petition cited studies concerning transgenic fish in general in support of the assertion that uncertainty requires gathering additional data. As explained below, hypotheses regarding genetically engineered fish in general are non-specific and lack relevance to the particular conditions under which AquAdvantage Salmon will be developed and grown.

To the extent there is any "uncertainty" with respect to fitness, ecological effects, and interaction with native salmon, these are all dependent on escape from physical confinement. As discussed in the EA, it is highly unlikely that AquAdvantage Salmon or diploid ABT salmon, could escape confinement and, in the highly unlikely event that they did, that they could establish in the local environment because of the absence of native Atlantic salmon in surrounding waters and other factors elaborated upon in the EA.

For example, at the PEI facility, there are two overarching reasons why FDA does not believe that diploid ABT salmon would enter the surrounding waters and establish. The first is that due to a minimum of three to five redundant containment measures at each point of potential escape, the simultaneous and complete failure of all of the physical containment systems in the facility is extremely unlikely. EA, Section 7.5.1.1. Second, it is highly unlikely that escaped or released diploid ABT salmon would be able to reproduce and establish in the local environment or farther afield. The river system located adjacent to the PEI facility has been reported to not have a wild salmon population since sometime before 2002, and all of the other river systems in the general vicinity of the PEI facility no longer have populations of Atlantic salmon. EA, Section 7.5.1.1.1. The disappearance and main impediments to wild Atlantic salmon on PEI are believed to be due to stream sedimentation (mainly through agricultural runoff) and barriers to migration such as beaver dams. These dams and other blockages cause summer temperatures to exceed tolerable levels for salmonids, and oxygen levels fall well below minimum accepted concentrations. Finally, water quality is compromised in much of the main stem of the river down to the head of the tide near the PEI facility. Over-winter habitat is lacking in many stream reaches, and blockages that may affect in-stream movement or migration patterns are common in most rivers in that area. Finally, water quality problems resulting from soil erosion and agricultural runoff are present in some watercourses. EA, Section 7.5.1.1. For all of these reasons, FDA has concluded that, even in the extremely unlikely event that ABT Atlantic salmon escape from the PEI facility and could survive the impediments described above, the possibility of interaction with wild Atlantic salmon is extremely remote, as there are no existing Atlantic salmon in surrounding waters.

With respect to the grow-out facility in Panama, similar multiple and redundant physical and mechanical barriers exist to preclude the escape of the triploid, all female, sterile AquAdvantage Salmon. And, to an even greater degree, in the highly unlikely event that AquAdvantage Salmon

did escape the physical containment of the Panama facility, the presence of turbid waters, the low dissolved oxygen, and temperatures lethal to the survival of any Atlantic salmon in the lower watershed render the issue of survival extremely unlikely. EA, Section 7.3.1.2. Further, there are no Atlantic salmon in the local watershed and no related salmonids with which they could interbreed even if a small percentage of the all female fish were diploid. EA, Section 7.4.1.6.

Your petition cites comments from several scientists regarding the uncertainty associated with predicting how transgenic fish will affect the environment where they have not been studied, or interact with other native salmon. CP at 10-11. FDA notes that that there will always be some level of uncertainty surrounding any risk estimation, including that made specifically for AquAdvantage Salmon. One reason is that, as with all fish, the phenotype of AquAdvantage Salmon is influenced not only by their genotype, but by the particular environment in which they are found. For example, the phenotype of fish raised in tanks in a laboratory will differ from that of fish that live in the wild, even if they share identical genomes. This phenomenon is referred to as a genome by environment (G X E) interaction.
Further, because to date, there have been no approvals for AquAdvantage Salmon, or free releases of AquAdvantage Salmon into the environment, risk assessors and regulators must extrapolate outcomes from studies conducted under laboratory or simulated natural conditions, including mesocosms or simulated streams. Generating additional data in laboratory studies or even mesocosms could somewhat reduce but not eliminate uncertainty due to all of the uncontrolled conditions in the environment. The analysis in the EA focuses first and foremost on the adequacy and redundancy of containment, as the conditions specified in the approval require extensive and redundant physical and biological containment.[9]

Thus, although the scientists cited above may have identified additional research that could add to the general knowledge base concerning the behavior of GE fish in the wild, including salmon (although we note that much of the seminal work in this field has been done on Coho salmon, a different species than Atlantic salmon[10]), such research is not necessary to determine that there is no significant impact on the environment under the particular conditions specified in the NADA for AquAdvantage Salmon because, as explained above, even if ABT salmon were to escape despite multiple methods of containment at the PEI and Panama facilities, it is highly unlikely that they would be able to reproduce and establish in the local environment or farther afield. Moreover, in the extremely unlikely event that they could survive the impediments described above, the possibility of interaction with wild Atlantic salmon is extremely remote, as there are no existing Atlantic salmon in surrounding waters. See EA Section 7.5.

3. ABT Plans to Expand

Your citizen petition notes that "ABT's Chief Executive Officer, Dr. Ron Stotish, has publicly expressed ABT's intention to increase production of AquAdvantage Salmon throughout the U.S. and around the world," and you assert that NEPA requires FDA to assess these expansion plans in an EIS. You assert that FDA is required to prepare an EIS "that evaluates all known potential

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[9] For a detailed discussion of uncertainties associated with estimating risks of genetically engineered fish in various environments, including mesocosms, see Moreau, D. T.R. 2014. Ecological risk analysis and genetically modified salmon: Management in the face of uncertainty. *Annu. Rev. Animal Biosci* 2:515-533.

[10] Coho salmon are of a different genus than Atlantic salmon (*Onchorynchus kisutch* vs *Salmo salar*), and the particular coho salmon that have been studied most extensively have a different growth hormone construct under a different promoter (Mori, T. and R. Devlin 1999. Transgene and host growth hormone gene expression in pituitary and nonpituitary tissues of normal and growth hormone transgenic salmon. *Molecular and Cellular Endocrinology* 149: 129-139.). Thus, results are difficult to extrapolate.

scenarios in which the AquAdvantage Salmon may be produced, raised, and released..." CP at 13. You also cite 40 CFR § 1508.25(a)(2)-(3), which relates to the scope of an EIS and specifies that "cumulative actions" should be considered together. CP at 13.

The CEQ regulation you cite is specific to determining the scope of an EIS; this regulation does not address whether an EIS needs to be prepared. Cumulative impacts are but one factor in determining whether an action has a significant impact on the environment. "Significantly as used in NEPA requires considerations of both context and intensity." 40 CFR § 1508.27. CEQ regulations provide 10 considerations for an agency to evaluate in determining the intensity of an action, including "Whether the action is related to other actions with individually insignificant but cumulatively significant impacts. Significance exists if it is reasonable to anticipate a cumulatively significant impact on the environment. Significance cannot be avoided by terming an action temporary or by breaking it down into small component parts." 40 CFR § 1508.27. CEQ's regulations define cumulative impact as "the impact on the environment which results from the incremental impact of the present action when added to other past, present and reasonably foreseeable future actions . . . ." 40 CFR 1508.7. *National Wildlife Federation v. FERC*, 912 F.2d 1471, 1478 (D.C. Cir. 1990) ("[A]n EIS need not delve into the possible effects of a hypothetical project, but need only focus on the impact of the particular proposal at issue and other pending or recently approved proposals that might be connected to or act cumulatively with the proposal at issue."); *Society Hill Towers Owners' Ass'n v. Rendell*, 210 F.3d 168, 182 (3d Cir. 2000) (future development identified in planning documents did not need to be considered in an EA for a hotel-parking garage project because it was "not at all certain that the proposed 'mega' entertainment complex or any of the projects included in the planning documents will ever be completed.").

At present, discussions of possible facilities in the United States are purely speculative. FDA has no other applications or proposals from ABT to develop and grow AquAdvantage Salmon anywhere but in the Canadian and Panamanian facilities covered by the current NADA. Any other facilities that ABT might propose to open in the future, including any in the U.S., are not within the scope of this NADA approval, and are not part of the action FDA is taking in approving this NADA. Furthermore, possible future FDA actions with respect to applications for such facilities are not reasonably foreseeable, and thus are not cumulative impacts to be considered under 40 CFR § 1508.27.

Furthermore, FDA could not analyze environmental impacts of such possible facilities without knowing specifics about them such as their location, the biological, hydrological, and geological features of the area, and any containment conditions that would be proposed. Specifics about a facility's location, such as whether it is located near the ocean within the range of native Atlantic salmon, or inland and away from any water source that is a possible salmon habitat would have a significant influence on any analysis of potential environmental impacts.

If ABT were to propose to produce AquAdvantage Salmon in the United States (or at additional locations outside of the United States with the intent to import food from them into the United States), they would first have to submit a supplemental NADA for the new production facilities. Any such supplemental application would require its own NEPA analysis of potential environmental impacts of those facilities. Supplemental NADAs are required for any "major" changes to an approved application. 21 CFR 514.8(b)(2). Contrary to your assertion, it is not possible for ABT to avoid this requirement "for major alterations to its facilities or containment measures...." CP at 13.

Under these regulations, major changes include any change in the "controls, equipment, or facilities that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug as these factors may relate to the safety or effectiveness of the drug."

A new facility to produce AquAdvantage Salmon may affect its identity and quality. For example, a new broodstock and egg production facility must have in place controls necessary to produce triploid, all female fish. Conditions at new grow-out facilities, including water quality and water temperature, may affect the growth and quality of fish. Additionally, we note that submission of a supplemental NADA for changes in manufacturing facilities is also a condition of the AquAdvantage Salmon NADA approval. Consequently, establishment of a new facility to produce AquAdvantage Salmon either in the U.S., or in a foreign country for import into the U.S., would require prior FDA approval of a supplemental NADA, which would trigger NEPA review requirements. Moreover, any foreign facilities that ABT might open in the future to supply fish outside the U.S. are not within the scope of FDA's authority if the fish produced by those facilities never enter the United States.

II. Request to Amend Regulations

Your citizen petition requests that FDA "amend its regulatory framework to specifically define the Agency's oversight of GE food animals in a manner that provides greater and necessary environmental protection and is consistent with NEPA."[11] Specifically, you request that FDA "promulgate new regulations specific to GE food animals that *at least* address the following deficiencies, which render the existing framework wholly unsuitable for effective oversight of ABT's application." CP at 6. These include: (1) Environmental Safety, (2) Inter-Agency Coordination and Consultation, (3) Increased Public Participation; and (4) Increased Transparency. CP at 6-8. As explained below, we decline to amend our regulations as you request.

FDA's current regulations concerning environmental review at 21 CFR Part 25 are consistent with the Council on Environmental Quality's NEPA regulations at 40 CFR Parts 1500-1508. Both the CEQ and FDA NEPA regulations apply to all major FDA actions, including major actions concerning any GE animals, including those intended for food use. Furthermore, our new animal drug regulations expressly incorporate our obligations under NEPA to consider the potential environmental impacts of approval of an NADA or a supplemental NADA. 21 CFR § 514.1(b)(14). NEPA requirements apply to major FDA actions, to the extent that they do not conflict with requirements of the FD&C Act or other applicable statutes, without the necessity for specific regulations. Thus, the regulations you request are not necessary for FDA to comply with NEPA. For example, the requirement you cite that agencies "shall consult with and obtain the comments of any Federal agency which has jurisdiction by law or special expertise with respect to any environmental impact involved," CP at 6, citing 42 U.S.C. § 4332(c) and 40 CFR § 1501.6, is already applicable to FDA actions.[12]

Similarly, with respect to public participation, FDA's regulations at 21 CFR § 25.50, already provide for public involvement "to the extent not protected from disclosure by existing law applicable to the agency's operation." FDA limits public participation, when required to do so by law, not under NEPA, but under the Trade Secrets Act, 18 U.S.C. § 1905 (which prohibits the disclosure of confidential information), and section 301(j) of the FD&C Act (which prohibits the revealing of any information acquired under the authority of the new animal drug provisions of the FD&C Act) [21 U.S.C. § 331(j)]. This is consistent with NEPA's mandate to interpret "public laws

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[11] We are constrained to note that, despite your assertion that FDA's regulation of GE animals produced for human food under the Federal Food, Drug, and Cosmetic Act is "improper" CP at 1, you nonetheless request amendments to FDA's regulations for review of applications related to these animals.

[12] The provision of NEPA you cite is specific to a "detailed statement" required for "major Federal actions significantly affecting the quality of the human environment." It is not applicable in those circumstances where FDA determines that an action does not significantly affect the quality of the human environment, as it has done with respect to AquAdvantage Salmon.

of the United States" to fullest extent possible" in accordance with the policies set forth in NEPA. 42 U.S.C. § 4332.

III. Conclusion

FDA concludes that the arguments presented in your citizen petition do not raise new issues. These arguments do not change the agency's conclusion in its EA and determination in its FONSI that approval of the NADA for AquAdvantage Salmon grown under the conditions described in the application, including multiple, redundant forms of containment, will not have a significant impact on the environment of the United States. These conditions do not trigger a requirement under NEPA that FDA prepare an EIS. We are, therefore, denying your request to prepare an EIS for this NADA.

FDA is also denying your request to amend FDA's regulations. You have failed to provide information that your proposed changes are needed to fulfill FDA's obligations under NEPA and the FD&C Act.

Sincerely,

Leslie Kux
Associate Commissioner for Policy