November 12, 2015

U.S. Food and Drug Administration

FINDING OF NO SIGNIFICANT IMPACT

AquAdvantage Salmon

In support of an approval of a New Animal Drug Application related to AquAdvantage Salmon, which are triploid, hemizygous, all-female Atlantic salmon (*Salmo salar*) bearing a single copy of the α-form of the *opAFP-GHc2* recombinant DNA construct at the α-locus in the EO-1α lineage

November 12, 2015

Prepared by

Center for Veterinary Medicine
United States Food and Drug Administration
Department of Health and Human Services

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Finding of No Significant Impact (FONSI)
for Proposed Action to Approve New Animal Drug Application related to AquAdvantage Salmon

AquaBounty Technologies, Inc. (ABT or the sponsor) has provided data and information to the Food and Drug Administration's (FDA's) Center for Veterinary Medicine (CVM) in support of a New Animal Drug Application (NADA 141-454) for a genetically engineered (GE) Atlantic salmon[1] to be produced and grown only under the conditions specified in the application. This resulting line of fish, referred to as AquAdvantage Salmon, is designed to exhibit a rapid-growth phenotype that allows it to reach smolt size (100 g) faster than non-GE farm-raised Atlantic salmon.

As a part of the NADA review and approval process under the Federal Food, Drug, and Cosmetic Act (FD&C Act), and consistent with the mandates in the National Environmental Policy Act of 1969 (NEPA), 42 U.S.C. § 4321 et seq. and FDA's environmental impact considerations regulations (21 CFR part 25), FDA has thoroughly evaluated the potential environmental impacts of this proposed action[2] (the approval of an NADA for AquAdvantage Salmon), issued a draft environmental assessment (EA) for public comment, taken relevant comments under consideration, and prepared the attached final EA dated November 12, 2015. This FONSI is based on the analyses and findings presented in the November 12, 2015 EA for AquAdvantage Salmon, including a consideration and evaluation of alternatives. In this case, several alternatives were considered, but the only alternative specifically evaluated was the no action alternative (i.e., a decision not to approve the NADA).

Approvals by FDA of NADAs related to GE animals are limited to the specific set of conditions enumerated and described in the NADA and the approval letter, with the GE animal remaining under FDA regulatory oversight as long as it is produced and marketed. FDA has determined that for this proposed action (i.e., approval of this NADA), FDA's approval of the AquAdvantage Salmon NADA would be for the specific set of conditions described in ABT's NADA and as enumerated in FDA's approval letter. These include appropriate controls on the production of the AquAdvantage Salmon, including appropriate physical and biological containment measures to ensure the identity, quality, and purity of the animal lineage. Many of these controls are relevant to the potential impacts on the environment. Under the specific conditions of the NADA for AquAdvantage Salmon, these fish are defined as triploid[3], all-female populations that would be produced as eyed-eggs at a single specific facility on Prince Edward Island (PEI) in Canada. Eyed-eggs would be shipped to a single, specific land-based grow-out facility in the highlands of Panama, where they would be reared to market size and harvested for processing for food[4] use (e.g., preparation of eviscerated whole fish, fish fillets, steaks, etc.) in Panama prior to retail

[1] The NADA is for approval of the α-form of the *opAFP-GHc2* recombinant DNA construct at the α-locus in the EO-1α line of triploid, all-female Atlantic salmon under the conditions of use specified in the application. For ease of reference, this document refers to the application as being for approval of the AquAdvantage Salmon.

[2] For the purposes of this FONSI, "action" and "approval" may be used interchangeably.

[3] With reference to AquAdvantage Salmon, and throughout the EA, "triploid" means that, based on sampling, at least 95% of released eyed-eggs have three complete sets of chromosomes per cell with a probability of 0.95 (i.e., the probability that these eggs are not at least 95% triploid is less than 0.05) (see EA, Section 7.4.1.2).

[4] For the purposes of this FONSI, "food" refers to food for humans and animals, including animal feed.

sale in the United States. The conditions that would be established in the NADA would require that there be processes in place to ensure the genetic integrity of the eggs, as well as the success of the process to produce triploidy if the application were to be approved. The conditions would specifically limit breeding and rearing of AquAdvantage Salmon to those two locations. In addition, the conditions would not include raising AquAdvantage Salmon in ocean net pens, or their production or growth in the United States.

FDA's approval of the AquAdvantage Salmon NADA would be for the specific set of conditions described in the drug sponsor's NADA and as enumerated in FDA's approval letter. No other conditions of production and use of AquAdvantage Salmon would be within the scope of the approval,[5] as no others would be approved by FDA under this NADA. The approval of the NADA is therefore described as the preferred alternative. Any production or use outside the scope of the approval would be unapproved and would, therefore, render the product unsafe under section 512(a) of the FD&C Act and adulterated under section 501(a)(5) of the FD&C Act. The sponsor must notify FDA about proposed changes in any conditions established in an approved application and obtain FDA approval of a supplemental application for the change where necessary. 21 CFR 514.8. Major and moderate changes require the filing and review of a supplemental NADA. Approvals of such supplemental applications would constitute major agency actions and trigger additional environmental analyses under NEPA, unless otherwise excluded.

As part of the NADA review process under the FD&C Act, but separate from the environmental analysis itself, FDA has evaluated both the direct and indirect food safety impacts of AquAdvantage Salmon and any potential impacts of the rDNA insertion on target animal safety. With respect to food safety, in 2010 FDA released its preliminary conclusion that food from AquAdvantage Salmon is as safe as food from non-GE Atlantic salmon, and that there is a reasonable certainty of no harm from consumption of food from AquAdvantage Salmon. Further, FDA's preliminary conclusion was that no significant food consumption hazards or risks have been identified with respect to the phenotype of the AquAdvantage Salmon. In the event of an approval, this finding would be finalized and FDA would post a summary of its review at http://www.fda.gov/animalveterinary/products/approvedanimaldrugproducts/foiadrugsummaries/ucm056939.htm.

As the NADA approval would only permit production and grow-out of AquAdvantage Salmon at facilities outside of the United States, the areas of the local surrounding environments that are most likely to be affected by the action lie largely within the sovereign authority of other countries (i.e., Canada and Panama). Because NEPA does not require an analysis of impacts in foreign sovereign countries[6], effects

[5] Several additional alternatives, including rearing of AquAdvantage Salmon under other production conditions (e.g., ocean net pens), were considered in the EA, but were rejected for further evaluation (see EA, Section 4.3).

[6] See, e.g., See, e.g., *Natural Resources Defense Council, Inc. v. Nuclear Regulatory Com*., 647 F.2d 1345, 1366 (D.C. Cir. 1981); *Consejo de Desarrollo Economico de Mexicali v. United States*, 438 F. Supp. 2d 1207, 1234 (D. Nev. 2006), vacated and remanded on other grounds, 482 F.3d 1157 (9th Cir. 2007). CEQ has issued guidance on NEPA analyses for actions taking place within the U.S. that may have transboundary effects extending across the border and affecting another country's environment. This does not apply here because would be no effects that cross the border from the United States into other countries from AAS. https://ceq.doe.gov/nepa/regs/transguide.html. Canada and Panama exercise regulatory authority over ABT facilties in their respective countries. See Canadian Science Advisory Secretariat Summary of the

on the local environments of Canada and Panama have not been considered and evaluated in the EA except insofar as it was necessary to do so in order to determine whether there would be significant effects on the environment of the United States due to the origination of exposure pathways from the production and grow-out facilities in Canada and Panama.[7]

In addition, social, economic, and cultural effects of the proposed action on the United States have not been analyzed and evaluated because the analysis in the EA indicates that the proposed action will not significantly affect the physical environment of the United States. Under NEPA, social and economic effects must be considered only once it is determined that the proposed agency action significantly affects the physical environment. 40 CFR 1508.14; see *Olmstead Citizens for a Better Community v. U.S.*, 793 F.2d 201 (8th Cir. 1986) ("an impact statement generally should be necessary only when the federal action poses a threat to the physical resources of the area…."). See also *Metro. Edison Co. v. People Against Nuclear Energy*, 460 U.S. 766, 774 (U.S. 1983).

FDA's approach to analysis in the EA is based on a characterization of hazards, an evaluation of potential exposure pathways, and a consideration of the likelihood of any resulting risk. The environmental analysis of consequences in the EA incorporates the principles described by the National Research Council as well as the U.S. Environmental Protection Agency's (EPA) approach to ecological risk assessment. The potential hazards and harms addressed in the EA center on the likelihood and consequences of diploid AquaBounty Technologies (ABT) salmon[8], and AquAdvantage Salmon, escaping, surviving, and becoming established in the environment, and then dispersing or migrating such that there might be an exposure pathway to the United States, and subsequently causing an adverse outcome (the risk) to the environment of the United States. These hazards are addressed for the production of eyed-eggs and grow-out to market size, within the framework of a conceptual risk assessment model, and the following series of risk-related questions:

1. What is the likelihood that AquAdvantage Salmon will escape the conditions of confinement?
2. What is the likelihood that AquAdvantage Salmon will survive and disperse if they escape the conditions of confinement?
3. What is the likelihood that AquAdvantage Salmon will reproduce and establish if they escape the conditions of confinement?
4. What are the likely consequences to, or effects on, the environment of the United States should AquAdvantage Salmon escape the conditions of confinement?

Environmental and Indirect Human Health Risk Assessment of AquAdvantage Salmon (CSAS Summary), http://www.dfo-mpo.gc.ca/csas-sccs/Publications/ScR-RS/2013/2013_023-eng.html.

[7] Under Executive Order 12114, FDA considered whether the proposed action would have significant impacts on the environment of the global commons or of foreign nations not participating or otherwise involved in the action and, has determined that there would be no significant impacts. See http://www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/GeneticEngineering/GeneticallyEngineeredAnimals/ucm466350.htm.

[8] ABT salmon are 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).

For the purposes of the environmental assessment, although AquAdvantage Salmon that will provide food for export into the United States is an all-female, triploid fish from the EO-1α lineage, the EA encompasses risks associated with all other lifestages (i.e., gametes through adults), and all of the zygosities and ploidies associated genotypes and phenotypes (i.e., diploids, triploids, hemizygotes, homozygotes females and masculinized females) that are required for the production of the triploid, all-female AquAdvantage salmon to be used for food. In general, when it is important for the purposes of assessing a specific environmental risk, the EA specifies whether an animal is assumed to be reproductively competent, and the term "diploid ABT salmon" is used.

Based on this analysis, FDA considers the likelihood that AquAdvantage Salmon and diploid ABT salmon could escape from containment, survive, and become established into the local environments of either the PEI or Panamanian facilities to be very low.This is consistent with the conclusions of Canadian authorities based on their qualitative Failure Mode Analysis of the physical barriers and operational procedures involving containment at both the PEI and Panamanian facilities. The Canadian officials concluded that the potential for both acute failure of physical containment and chronic release of AquAdvantage Salmon is negligible at the PEI facility and low for the Panamanian facility, with at least reasonable certainty.[9] Given this very low likelihood of escape, survival, and establishment in the environments local to the PEI and Panamanian facilities, it is also highly unlikely that GE fish could disperse and migrate such that there would be an exposure pathway to the environment of the United States.

Should unintentional release occur, the environmental conditions in the geographic settings of the egg production and grow-out sites and farther afield (e.g., the tropical Pacific Ocean) would afford additional means of containment of any escaped eggs or fish, given that these conditions would be generally hostile to their long-term survival, reproduction, and establishment. In Canada, this is evidenced by the lack of Atlantic salmon in the vicinity of the egg production facility even though these fish are native to this area and have been intentionally stocked there in the past. These environmental conditions will greatly limit, or in the case of Panama, essentially preclude the possibility of a complete exposure pathway by which diploid ABT salmon or AquAdvantage Salmon could reach the United States.

In addition, because the production process for AquAdvantage Salmon ensures that populations produced will be triploid (effectively sterile), all-female animals, the possibility of their reproducing in the wild is likewise extremely remote. The greatest potential risk to the environment of the United States would occur in the event of the escape of diploid ABT broodstock from the PEI facility. These fish are reproductively competent and some will be homozygous for the *opAFP-GHc2* gene. Nonetheless, given that growth enhanced Atlantic salmon in general do not have a reproductive advantage compared to non-GE Atlantic salmon, and sometimes are disadvantaged (Moreau and Fleming, 2011; Moreau et al. 2011a), the lack of existing Atlantic salmon populations in the surrounding waters, and, most importantly, the stringent physical containment at that site, the probability of establishment is very low. The Canadian government reached a similar conclusion (See Reference 8).

[9] The Canadian Science Response (DFO). (2013). Summary of the environmental and Indirect Human Health Risk Assessment of AquAdvantage Salmon. *DFO Can Sci. Divis. Sec. Sci. Respon. 2013/023*) refers to all life stages as AquAdvantage Salmon. ("Although the proposed AquAdvantage Salmon product for export to Panama is all-female triploid eyed-eggs from the EO-1α line….other life stages (gametes through to sexually mature adults), genotypes (i.e., diploids, triloid, hemizygotes, homozyotes) and gender (females and masculinized females) are required for the production of the eyed-eggs and are therefore included in the risk assessment").

Because risk is the product of two probabilities, the probability of exposure, and the conditional probability of harm given that exposure has occurred (NAS 2002), if exposure is negligible, then even if the probability of harm is larger, the overall risk is negligible. The analysis in the EA indicates that there is a very low likelihood of escape from either the PEI or Panama facilities. Given the additional redundant containment measures in place (e.g., biological, geographical, and geophysical), the combination of these factors results in an extremely low likelihood that AquAdvantage Salmon could escape into the wild and migrate to and cause effects on the environment of the United States. FDA therefore concludes that the development, production, and grow-out of AquAdvantage Salmon under the conditions specified in the application and as described in the accompanying EA would not result in significant effects on the quality of the human environment in the United States, including populations of endangered Atlantic salmon.

FDA has considered the no action alternative for this action, that is, a decision not to approve the NADA for AquAdvantage Salmon. There are two general likely scenarios to consider as a result of the no action alternative: (1) the sponsor would cease production of AquAdvantage Salmon, and (2) the sponsor would continue to rear AquAdvantage Salmon at the existing locations outside the United States, and/or at new suitable locations outside of the United States (and could decide to sell the eggs, fish, or the technology to producers outside of the United States), with no intent to directly market food from these fish in the United States. There are no potential environmental impacts arising from the first general scenario. If no AquAdvantage Salmon are produced, there will be no production sites and no potential for escape or release of these fish to the environment, and therefore no effects on the environment of the United States. For the second general scenario, production of AquAdvantage Salmon at locations outside the United States for marketing outside the United States (i.e., outside the jurisdiction of FDA)[10], an assessment of potential effects on the environment becomes highly uncertain as the conditions and effects are not reasonably foreseeable. Because production of AquAdvantage Salmon would be possible at any number of locations worldwide, under different containment conditions and levels of regulatory oversight, and potentially within areas where native Atlantic salmon or other salmonid species are present, there are far too many variables and unknowns to define specific scenarios and perform a comprehensive risk assessment for them. A further set of unknowns includes the extent and nature of regulatory decisions in sovereign foreign countries with the authority to regulate either the technology of genetic engineering or the products thereof. Thus, it is impracticable to make any accurate predictions with respect to potential environmental impacts on the United States other than to state that should production occur with less restrictive physical or biological containment conditions than those specified in the NADA, adverse environmental impacts to the United States could be more likely to occur because escape, reproduction, establishment and migration of the AquAdvantage Salmon would be more likely. The same would be expected if production were to occur in locations where there would be less regulatory oversight than would occur under an FDA NADA approval.

As a result of the review of the materials submitted in support of an NADA approval for AquAdvantage Salmon, FDA has made a “no effect” determination under the Endangered Species Act (ESA), 16 USC §

[10] This scenario, production of AquAdvantage Salmon outside the jurisdiction of the United States, is possible regardless of whether or not FDA approves the NADA. It appears more likely to occur if FDA does not approve the NADA because ABT would need to produce AquAdvantage Salmon outside FDA’s jurisdiction, i.e. outside the U.S. without importing food from such fish in the U.S., if it wished to market food from its GE salmon without FDA regulation.

1531 et seq., i.e., when produced and reared under the conditions in the application, and as described within FDA's EA, AquAdvantage Salmon would not jeopardize the continued existence of United States populations of threatened or endangered Atlantic salmon, or result in the destruction or adverse modification of their critical habitat. The two federal agencies responsible for administering the ESA, the National Marine Fisheries Service (NMFS) of the National Oceanic and Atmospheric Administration (Department of Commerce) and the U.S. Fish and Wildlife Service (FWS) of the Department of Interior, have been provided with this "no effect" determination and the underlying information in support of it. Based on their statutory authorities and regulations, both of these agencies have either concurred with, or indicated no disagreement with, FDA's "no effect" determination. [See Appendix D of the EA]

The Council for Environmental Quality's NEPA 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. There would be no "incremental impact" because this would be the first NADA approval for AquAdvantage Salmon and FDA is not aware of any specific reasonably foreseeable future FDA actions on NADAs for GE fish at this time. As a result, there would be no cumulative impacts on the environment of the United States for the action to approve this NADA for AquAdvantage Salmon.

NEPA Decision and Findings

We have carefully considered the potential environmental impacts of both the proposed agency action to approve the NADA for AquAdvantage Salmon (the preferred alternative) and the No Action Alternative, as described and evaluated in the EA. Based on our evaluation and analysis, and taking into consideration the specific conditions that would be established in the NADA, we have made the finding that the action to approve the NADA for AquAdvantage Salmon would not individually or cumulatively have a significant effect on the quality of the human environment in the United States. Based on that finding, FDA has decided not to prepare an environmental impact statement for this proposed action.

Bernadette M. Dunham -S

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Date

Bernadette Dunham, D.V.M. Ph.D.
Director, Center for Veterinary Medicine
Food and Drug Administration

Attachment:
Environmental Assessment for AquAdvantage Salmon dated November 12, 2015