Comments to the legal framework for using ovulation triggers to produce caviar without killing the sturgeon

Sources: Regulation 2019/6 EC effective 28.01.2022
Directive 2001/82/EC
Regulation 2016/429//EC
Letter of the EUROPEAN COMMISSION, DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY
Ref.Ares (2020) 7855400 -22/12/2020

Introduction: The status of the sturgeon as an endangered species has become particularly worrying over the past thirty years due to illegal fishing and habitat destruction from pollution and weir construction. Sturgeons can live up to 60-100 years old. They have a record of more than 250 million years, so they are older than the dinosaurs.

Since 1998, most sturgeon species have been protected by the Washington Convention on the Protection of Species by CITES *(Appendix II; Convention on International Trade in Endangered Species)*, some like the beluga sturgeon even under *Appendix I*. Since 2007, the trade in caviar from wild-caught sturgeon has been completely prohibited with the exception of the USA and Canada. Despite this fact, poaching of the heavily reduced stocks is still flourishing and large quantities of illegal caviar are still being sold in the black market, although this is severely punished.

The international efforts of restocking programs to reproduce sturgeons and to bring them back to their original habitats as juveniles have so far shown little success, as the juveniles are very sensitive to anthropogenic environmental stress factors, as reported at the International Sturgeon Symposium ISS8 in Vienna in 2017 by China.

Today almost all legal caviar is produced in aquaculture. Bronzi et al. (2019)[1] identified 2329 commercial sturgeon farms worldwide. However, the production numbers of over 3000 t / year of caviar in the 1980s could not be compensated for by the slowly growing sturgeon aquaculture with only 250-350 t / year of caviar.

Until now, most sturgeon aquaculture farms slaughter their females in order to obtain caviar. Since the Alfred Wegener Institute for Polar and Marine Research in Bremerhaven patented a new process for stabilizing mature eggs, the sturgeons no longer must be slaughtered, which is an enormous advantage both economically and qualitatively.

However, with the new process of treating mature stripped eggs for caviar production, the responsible veterinarians are faced with the task of helping a cohort of ready-to-spawn female sturgeon with ovulation triggers to release their eggs painlessly and safely and to reduce mortality due to egg binding.

Statement by the EU Commission on the use of ovulation triggers in sturgeon:

The EU Commission was asked by the lawyer´s office Castringius, Bremen, to provide information on the off-label-use of ovulation agents that are approved in another EU member state for the same application but different species. Off-label-use means in this case that there is a drug registered in the EU member state Ireland for the fish “trout” with a waiting time of zero days. The questions to the EU are aimed in particular at the definition of a waiting times for the production of food (caviar) from the fish sturgeon. For this purpose, the responsible EU Directorate for Health and Food Safety was addressed in particular with regard to the setting of a waiting time for food production. To this end,

[1] Sturgeon meat and caviar production: Global update 2017 Paolo Bronzi et al. 2019 J Appl Ichthyol. 2019; 35: 257-266

the Commission was asked to answer five questions that relate to both Directive 2001/82 / EC, which is still in use, and Regulation 2019/6 / EU, which will apply as of 28 January 2022.

Note for the reader: *The comments refer to Articles 114 and 115 of Regulation 2019/6 / EU, the letter from the Commission of December 22nd, 2020, appendices to this guide and Regulation (EU) 37 / 2010. It makes reading easier when you have these texts in front of you.*

In **question 1** Castringius asked for information as to whether Art. 114 applies to the use of an ovulation trigger for caviar extraction. The commission quotes Art. 114 (1) with emphasis on the personal responsibility of the attending veterinarian and the avoidance of suffering when choosing the appropriate medication. In particular, it recommends that the veterinarian include scientific aspects when assessing the active substances, and notifications from the responsible authorities about possible risks.

Answer 1 from Brussels
SANTE/E5/AK/ acr Ares (2020) 8772757
"...where there is no authorised veterinary medicinal product in a Member State for an indication concerning a food-producing aquatic species, the veterinarian responsible may, under his or her direct personal responsibility, and in particular to avoid causing unacceptable suffering..."

Comment: With the drug Receptal®, there is a drug that meets the requirements of Art. 114 (1) (a), because it is approved in Ireland for use as an ovulation agent in trout. The legality of the use of Receptal® is therefore beyond question and the examination of other options in Art. 114 (1) is not applicable. The task now arises for the veterinarian to determine a waiting time on their own personal responsibility.

Question 2 therefore asks about the legal provision that should be used when determining the waiting time. The Commission replies that, in accordance with Art. 115 (1), the waiting time specified for the animal species in question in the product information for the medicinal product must first be used. If there is none specified, the veterinarian must determine a waiting time taking into account Art. 115.

Answer 2:
*If a medicinal product has a withdrawal period provided in its summary of the product characteristics for **the animal species in question**, this withdrawal period is to be applied;*
Otherwise, veterinarian must set a withdrawal period in accordance with the criteria set in Article 115.

Comment: In the summary of specific product characteristics (SPC) for Receptal®, both "trout" and "rainbow trout" are named as animal species for which the approval applies. On the website of the manufacturer MSD Ireland you can find the information[2]: "An injectable hormone containing Buserelin for use in cattle, horses, **fish**, and rabbits." In the following paragraphs, the text is specifying the target species as trout (4.1) respec-tively rainbow trout (4.2)[3]. It is obvious that pharmacokinetic and -dynamic in fish is determined by

[2] https://www.msd-animal-health.ie/products/receptal/

[3] For the complex taxonomy of fishes, named as "trout", see e.g. https://en.wikipedia.org/wiki/Trout
If there had ever been the idea of applying a biological or taxonomic understanding of fish at the level of the species term in drug legislation, the challenge would have been to deal e.g., with 3000 species of carp. Even for the case of sturgeon, there would still be approval procedures for 27 sturgeon species necessary.

water temperature. For example, rainbow trout spawns in winter at 6-15 oC, sturgeon at 9-18 oC in freshwater in spring/early summer. As the degradation rates for Buserelin are not essentially different in both species at same temperatures, the interpretation of sentence 1 of Art. 115 is not trivial and could offer the responsible veterinarian the option to set the same waiting time for sturgeon on the basis of scientific information and the SPC for the use of Receptal® from Ireland.

A narrow, biologic species term does therefore not correspond to the spirit of the new European regulation 2019/6, especially not for **fish**, where there are no "major species" and extremely few medicinal products.

Answer 3:

The withdrawal periods are determined for each veterinary medicinal product during its authorisation, in order to ensure that no residues that may constitute a hazard for consumers are present in foodstuffs obtained from treated animals. The withdrawal periods for the veterinary medicinal product are calculated based on the entry for the active substance in the Commission Regulation (EU) No 37/2010 on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin.

Question 3 relates to the waiting time in connection with ensuring food safety for human consumption. The waiting time must be long enough for residues of the agent to fall below the maximum residue level for pharmacologically active substances according to Regulation 37/2010. The Commission's answer here is rather general and not related to the specific case of using Receptal® with the active ingredient Buserelin, for which "no maximum residue limit" is required according to Regulation 37/2010.

Comment: It is not clear how the waiting time was calculated in the specific case of the approval of Receptal® for trout and rainbow trout in Ireland. **If there is no maximum residue limit (MRL) for Buserelin** required according to regulation 37/2010, any amount of Buserelin does not pose a risk to the consumer, even if it is consumed for a lifetime. The Commission, however, sees the need for a safety factor to be introduced in the case of off-label-use without any substantial argument. After all that has been said before, the safety factor can actually only be zero. The Commission does not comment on this contradiction in the answer to question 3.

Answer 4:

In case of using a medicinal product outside the terms of the marketing authorisation it is for the veterinarian responsible to set a withdrawal period. When doing so, the veterinarian responsible should follow the criteria set in Article 11(2) of Directive 2001/82/EC (and, as of 28/01/2022, in Article 115 of Regulation (EU) 2019/6).

Question 4 deals with whether the application of Receptal® to sturgeon is at all an application outside the market approval (off-label-use), since the approval was not specifically for a taxonomic species, but rather for fish in general (e.g. like for Receptal® in Switzerland). See the comment on question 3.

Question 5 is specifically aimed at the selection of the specific provision from the various possibilities of Art. 115, in particular whether caviar should be treated like eggs, i.e. according to Art. 115 (1) (c) (i). The Commission clearly refers to Art. 115 (1) (d), since here, in contrast to the previously valid Directive 2001/82 / EC, a regulation for aquatic animals is formulated. Art. 115 (1) (d) reads:

"For aquatic animal species whose meat is intended for human consumption, the waiting time is not less than:

(i) The longest waiting time specified in the technical information, regardless of the aquatic animal species for which it is specified, multiplied by a factor of 1.5 and expressed as the number of degree days,

(ii) If the medicinal product is approved for food-producing terrestrial animal species, the longest waiting time specified in the product information for food-producing terrestrial animal species, multiplied by a factor of 50 and expressed as the number of degree days, but not longer than 500 degree days.

(iii) 500 degree days if the medicinal product is not approved for use in the production of food for the animal species,

(iv) 25 degree-days if the longest waiting time for any species is zero. "

Answer 5:

In case of using a medicinal product outside the terms of the marketing authorisation it is for the veterinarian responsible to set a withdrawal period. Please note that Regulation 2019/6/EU, unlike the current Directive 2001/82/EC, provides for specific rules on the use of medicinal products outside the terms of the marketing authorisation ***in aquatic species*** *(Article 114 and corresponding criteria for setting a withdrawal period –****Article 115(1)(d))****.*

The information for Receptal® specifies waiting times without naming species in question:

Meat and offal: Zero days
Milk: Zero hours

Art. 115(1)(d)(i) results in a zero day waiting period. The same would result from (ii). (iii) is not applicable. Because of its reference to aquatic species, the conditions for setting 25 degree-days according to (iv) are met. In practice, the calculation of the waiting time according to paragraph (iv) results in fractions of days (e.g. at 15 degrees water temperature 5/3 days), which according to Art. 115 (2) should not be rounded up in the case of Art. 115 (1) (d) (iv). A precise calculation is therefore required for the waiting time, e.g. in a number of hours (at 15 ° C that is 40 h).

Conclusion:

The EU Commission emphasizes the personal responsibility of the veterinarian when prescribing and administering a drug, thereby considering the actual scientific knowledge and notifications from the responsible authorities regarding possible risks of the use as food.

In the event that Receptal® is used to induce ovulation, the EC regulation 2019/6/EU, effective from January 28, 2022 on, must be observed in accordance with its Article 115 (1) (d) (iv) when calculating the waiting time.