Appendix I

Divergent position on a CVMP opinion on the granting of a marketing authorisation for CLYNAV (EMEA/V/C/002390/0000)

The undersigned wish to express a divergent position to the CVMP opinion on the application for the marketing authorisation of CLYNAV, a DNA-vaccine for Atlantic salmon to "reduce impaired daily weight gain, and reduce mortality, and cardiac, pancreatic and skeletal muscle lesions caused by pancreas disease following infection with salmonid alphavirus subtype 3 (SAV3)".

The undersigned is of the opinion that the potential benefit of the vaccine; reduction of clinical signs and mortality caused by pancreas disease (PD) for two months after vaccination, does not outweigh the potential risks of the vaccine with regards to:

- target animal safety and welfare
- the possible lack of protection against clinical disease beyond two months after vaccination.
- the possible interactions between CLYNAV and other mandatory vaccines used in Atlantic salmon farming in the EU/EEA
- the possible reduction of fillet quality due to injection site reactions

The laboratory studies presented do not satisfactorily document safety and efficacy for the vaccine, and they are furthermore not considered to be of sufficient clinical relevance for the Atlantic salmon farming industry in Norway. For example, field trials are considered pivotal to document safety and efficacy of the vaccine under various field conditions, and to confirm the findings from the limited laboratory trials. A positive conclusion on the benefit / risk assessment can therefore not be reached with the current documentation presented for the product.

Further elaborations on the divergent position:

PD is a significant infectious disease affecting salmon farming in Norway. Approximately 1/3 of all salmon in Norway are vaccinated against this disease. Under field conditions, SAV-3 is a virus that can infect fish during the entire production cycle at sea, and not only a short period after sea transfer. Clinical disease of PD is seen all year round, but the majority of outbreaks occur during the summer months. Clinical disease has substantial consequences for animal welfare and the economy in fish farming. PD-vaccination is an important part of the measures to control the disease. Therefore, it is very important to have vaccines on the market, for which satisfactory safety and efficacy have been established by a sufficient number of good quality laboratory studies and confirmed under relevant field conditions. Norway is, for the time being, the only market for CLYNAV in Europe, as it is indicated only against SAV3 infection.

In the undersigned’s opinion, there are potential risks related to safety and efficacy for the product, which have not been properly addressed. The issues of special concern are:

- No field trials have been performed with CLYNAV. Field trials are considered pivotal for two reasons:
  - PD is a very important disease, both from a fish welfare and an economical point of view. It is therefore considered necessary to confirm sufficient safety and efficacy for all
vaccines to be used for control of this disease, in order to reduce suffering and economic losses caused by PD.

The undersigned is of the opinion that the laboratory studies presented for CLYNAV do not document adequate safety and efficacy for the vaccine as well as the clinical relevance for Atlantic salmon farming in Norway. The laboratory trials cannot replace field trials.

- This is the first DNA-vaccine for fish in Europe. PD is included in the CVMP MUMS-list (EMA/CVMP/IWP/123243/2006-Rev.2). For products intended for MUMS, reduced data requirements may apply. However, a precautionary principle should have been followed for documentation of adequate safety and efficacy for this new vaccine concept, for which we have no experience in fish in Europe. The MUMS guideline should not take precedence over the precautionary principle for such a novel product.

- Duration of immunity (DoI) after vaccination. DoI has only been demonstrated in a laboratory challenge study for three months after vaccination. Therefore, it has not been proven that CLYNAV will protect fish for the major part of the production cycle at sea (approximately 2 years) when clinical disease is likely to occur. Hence, serious animal welfare concerns and economic losses cannot be excluded after the use of the vaccine under field conditions.

- A negative impact on target animal safety and welfare following the intra-muscular injection and the high volume of CLYNAV to be injected. A volume of 0.05 ml is to be injected intramuscularly in the epaxial muscle ("back loin"), central to the dorsal fin and above the mid-line in fish, from the weight of 25 grams. Relative to the minimum fish size this is a large volume injected intramuscularly. Both local and general reactions to the vaccination were common or very common in the laboratory studies. As the indication implies routine treatment of a large number of fish, then it is not acceptable that a possible negative impact on target animal welfare caused by the injection volume and injection site of CLYNAV has not been adequately addressed in the documentation.

- Possible interactions between CLYNAV and other vaccines that are mandatory for Norwegian salmon farming. In particular, neither long-term efficacy nor safety in fish also vaccinated with other, mandatory vaccines have been studied under field conditions. The risk of interactions can therefore not be excluded.

- Long term effects on the quality of the fillet at the injection site. Although claimed by the applicant not to be a problem for a similar DNA-vaccine in Canada, this aspect has not been studied under field conditions after treatment with CLYNAV.

London, 21 April 2016

Hanne Bergendahl

Keith Baptiste