PHARMAQ
part of zoetis

ALPHA JECT® micro 1 PD

An efficacious and safe monovalent vaccine against Pancreas Disease (PD) proven to be suitable for co-injection with other PHARMAQ vaccines

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WE MAKE AQUACULTURE PROGRESS

YOUR PARTNER IN FISH HEALTH

PHARMAQ, now part of Zoetis, is pleased to offer a new vaccine against Pancrease Disease for fish farmers in Norway and the UK. As of today, Pancreas Disease continues to be one of the major fish health challenges, affecting fish in the seawater phase of the production cycle. Farmers report that PD results in significant economic loss through mortality, reduced growth, downgrading at slaughter and increased susceptibility to other diseases. Fish carrying the virus are more sensitive to handling and stress which in turn might lead to outbreaks of the disease.

ALPHA JECT® micro 1 PD is a new tool in the battle against PD. The vaccine is well documented based on quality, safety and efficacy according to requirements set by the authorities, and is an example of PHARMAQ's constant focus on bringing new and innovative products to the market, to continue supporting our customers in building a sustainable and profitable salmon industry.

Morten Nordstad
President PHARMAQ a business of Zoetis

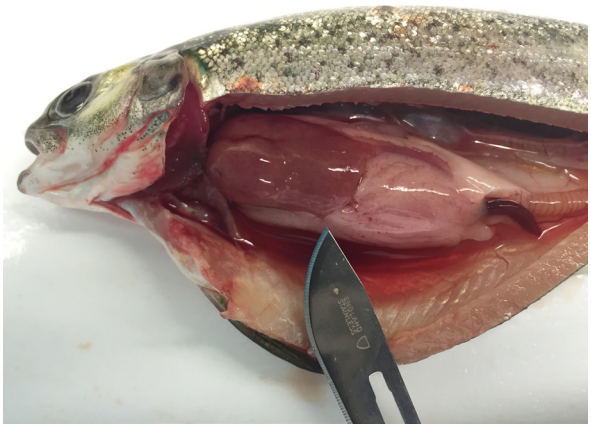
PANCREAS DISEASE (PD)

In the last decade, Pancreas Disease (PD) has been the most economically damaging viral disease for the Norwegian, Scottish and Irish salmon farming industries.

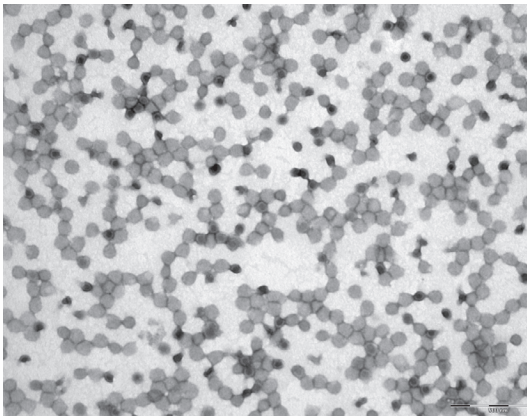
PD is caused by Salmonid Alphavirus (SAV) which exists as several different subtypes. In Norway the predominant subtype is SAV 3 south of Hustadvika, whereas SAV 2 is now endemic from Hustadvika (Mid Norway) throughout the whole of Sør-Trøndelag (Hjortaas *et al.* 2013). SAV1, 2, 4 and 5 have been identified to cause disease in Scotland whereas SAV 1, 4 and 6 is found in Ireland (Graham *et al.* 2012). SAV transmits horizontally from fish shedding virus into the water, and ocean currents are believed to be a significant mechanism of viral spread between marine farms (Viljugrein *et al.* 2009).

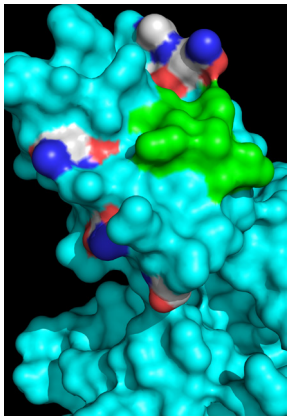
The infection causes necrosis in the pancreas and severe cardiac and skeletal myopathies (Ferguson *et al.* 1986). In Norway, 137 outbreaks of PD were detected in 2015 (Fiskehelserapporten).

Intensive surveillance and control are important tools to reduce the impact of PD. The establishment of separate control zones in Norway for SAV 3 and SAV 2 respectively, are examples of restrictions that have been implemented by the authorities in an attempt to prevent further spread of the disease. Other measures that have been introduced are restrictions on transport of smolts in and out of the control zones, transport of infected fish to slaughter houses, restrictive contact between infected sites and fallowing of sites. North of the SAV 2 zone the authorities require infected farms to slaughter their fish, or to move infected fish into the PD zone (Fiskehelserapporten). In addition, vaccination can become an important tool to reduce the transmission of PD virus.



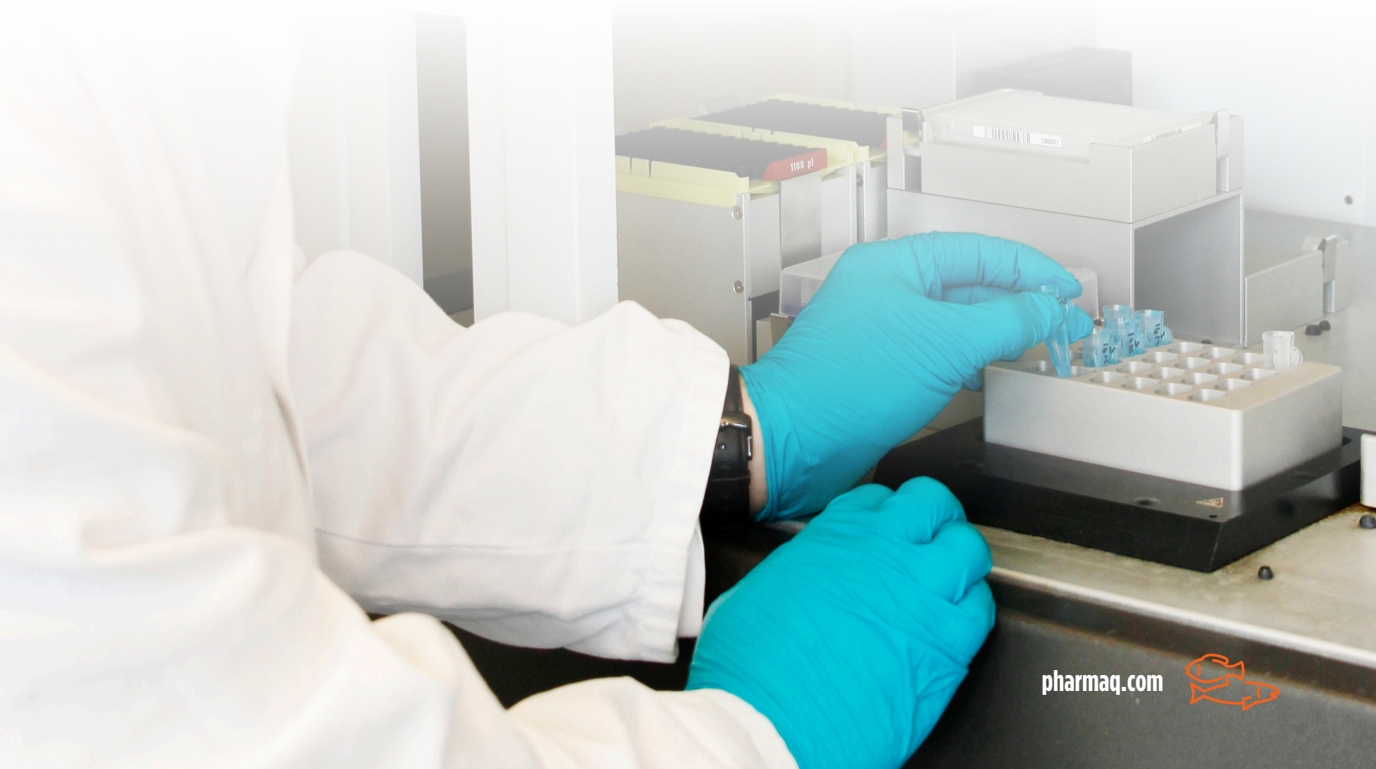
Typical pathology in PD diseased fish. Left: A PD diseased compared to a healthy salmon above it. Right: Typical petecial haemorrhaging in internal organs.





Left: Purified PD virus seen under electron microscopy. Photo: Trygve Eliassen (PHARMAQ). Right: The picture shows a structural model of the E2 protein in the SAV strain used as a vaccine antigen in ALPHA JECT® micro 1 PD. A known neutralizing epitope is shown in green. Model: Professor Richard Eng (University of Tromsoe)

Surveillance and screening for PD in the field is important in guiding the right preventive actions.



ALPHA JECT® micro 1 PD

ALPHA JECT® micro 1 PD is a monovalent vaccine developed for use in Atlantic salmon, *Salmo salar* L. It contains inactivated SAV 3 and is documented for use either alone, or simultaneously with PHARMAQ multivalent vaccines.

ALPHA JECT® micro 1 PD has been optimized through extensive research to reduce mortality, lesions in the heart and pancreas and impaired growth caused by PD. The efficacy of the vaccine is dependent on the antigen concentration, and the vaccine composition is determined based on clinical trials in fish.

ALPHA JECT® micro 1 PD is presented in 500 ml and 250 ml UVO injection bags for multidose delivery and the dose volume is 0.05 ml.

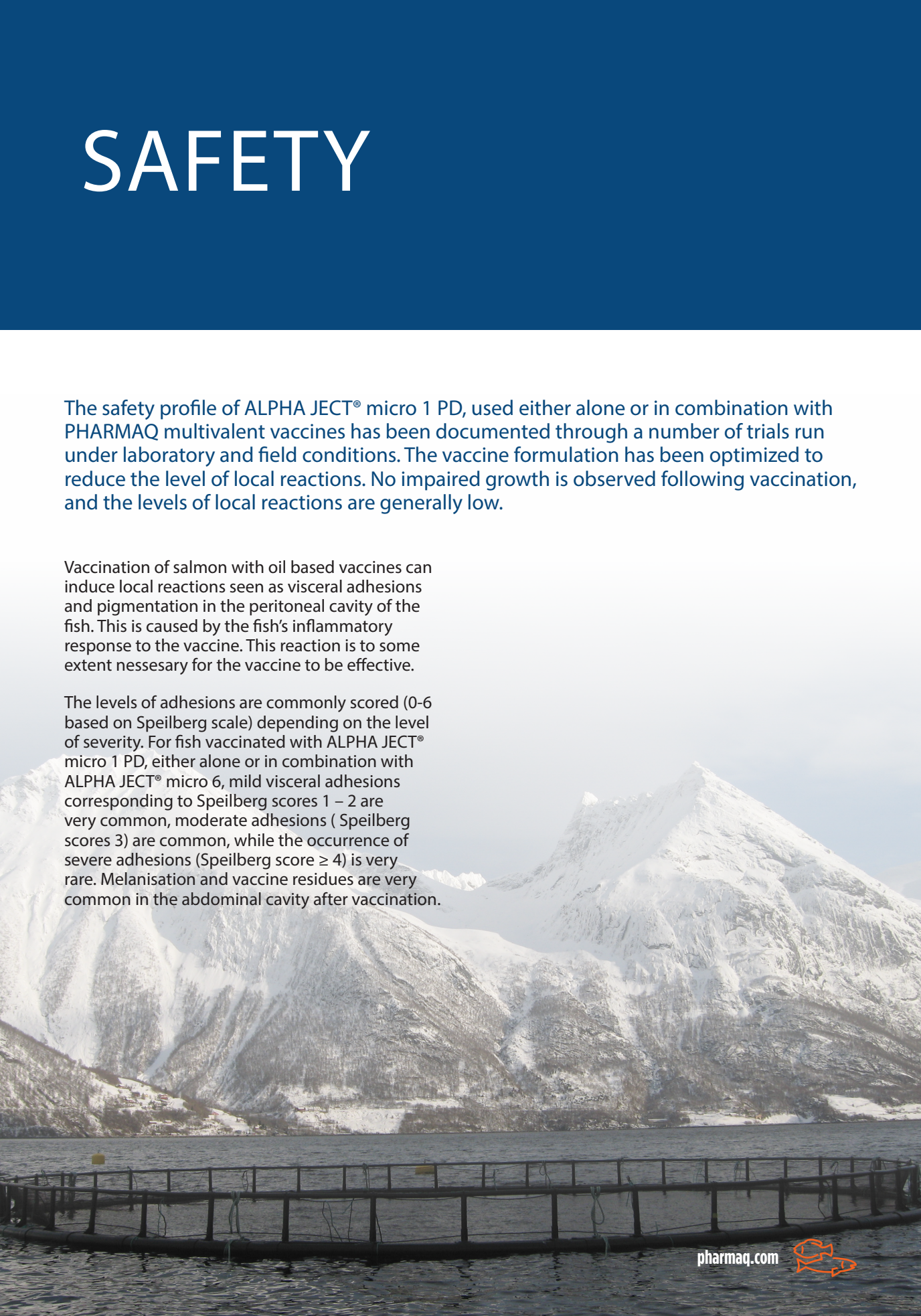
ALPHA JECT® micro 1 PD was granted a Marketing Authorization (MA) in 2015. An MA secures that the product meets the EU regulatory standards with regard to quality, safety and efficacy for veterinary vaccines, and is considered to have a positive benefit/risk balance.

SAFETY

The safety profile of ALPHA JECT® micro 1 PD, used either alone or in combination with PHARMAQ multivalent vaccines has been documented through a number of trials run under laboratory and field conditions. The vaccine formulation has been optimized to reduce the level of local reactions. No impaired growth is observed following vaccination, and the levels of local reactions are generally low.

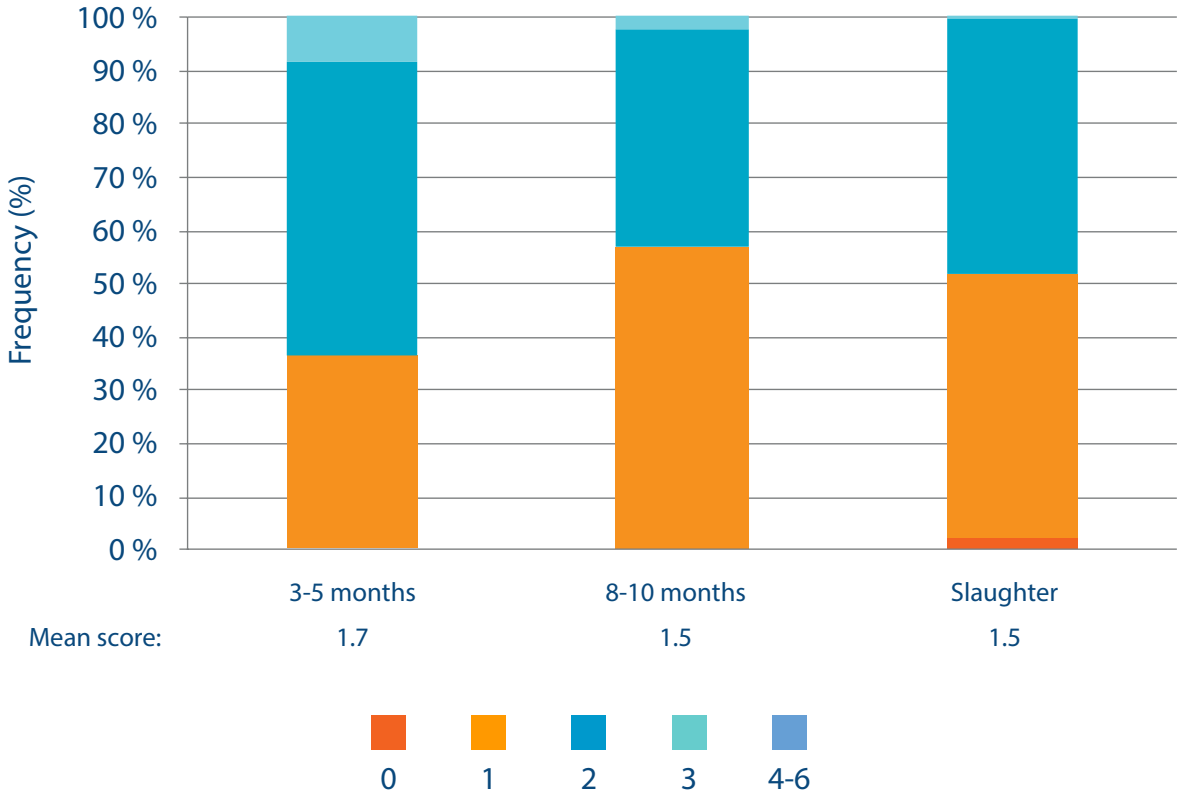
Vaccination of salmon with oil based vaccines can induce local reactions seen as visceral adhesions and pigmentation in the peritoneal cavity of the fish. This is caused by the fish's inflammatory response to the vaccine. This reaction is to some extent nessesary for the vaccine to be effective.

The levels of adhesions are commonly scored (0-6 based on Speilberg scale) depending on the level of severity. For fish vaccinated with ALPHA JECT® micro 1 PD, either alone or in combination with ALPHA JECT® micro 6, mild visceral adhesions corresponding to Speilberg scores 1 – 2 are very common, moderate adhesions (Speilberg scores 3) are common, while the occurrence of severe adhesions (Speilberg score ≥ 4) is very rare. Melanisation and vaccine residues are very common in the abdominal cavity after vaccination.



LOCAL REACTIONS

Data from field trials where salmon were co-injected with ALPHA JECT® micro 1 PD and PHARMAQ six component vaccine, show mild local reactions in the form of visceral adhesions.

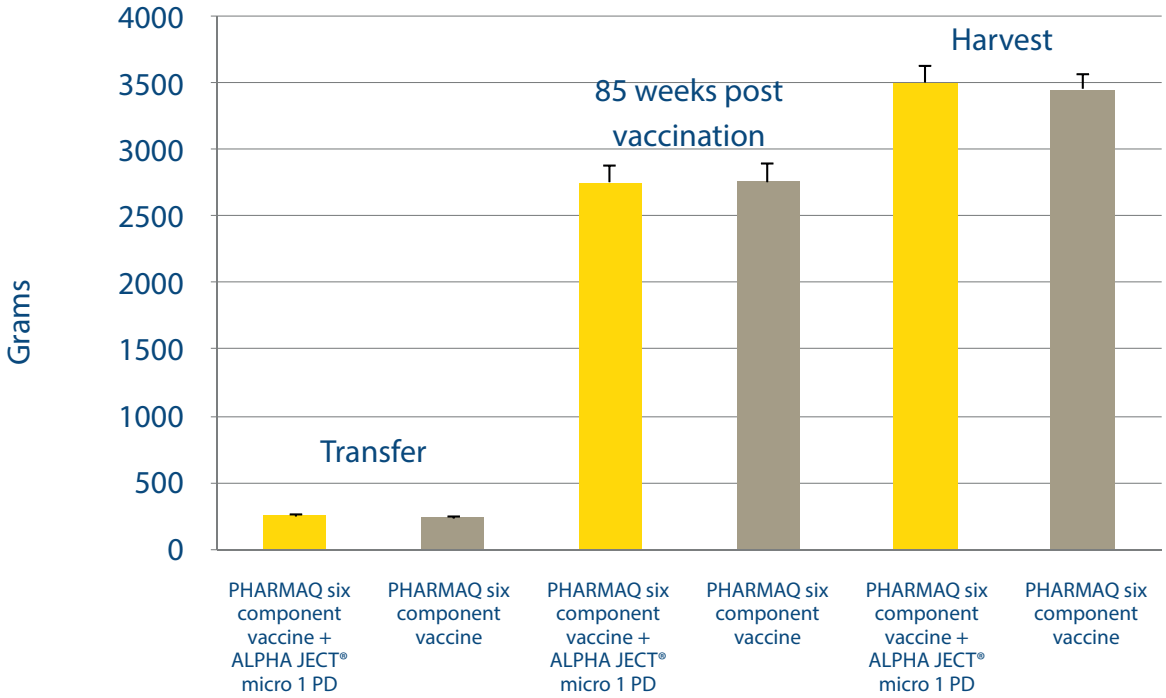


Frequency plots for adhesion scores for fish gathered from 3 different locations (n=394), where fish were vaccinated with a combination of ALPHA JECT® micro 1 PD and PHARMAQ six component vaccine.

In an extensive field trial with ALPHA JECT® micro 1 PD, fish in some cages appeared to develop a new type of local reaction the spinal column associated with fibriosis in the muscle close to the vertebrae. A follow-up study designed to investigate the causes of these side effects and to optimise the vaccine composition was subsequently carried out. Results are available that show that fish co-injected with ALPHA JECT® micro 1 PD and PHARMAQ six component vaccine do not have a higher incidence of these side effects than fish vaccinated with PHARMAQ six component vaccine alone. More information is available upon request.

GROWTH

Fish vaccinated with ALPHA JECT® micro 1 PD in combination with PHARMAQ six component vaccine grow as well as fish vaccinated with PHARMAQ six valent vaccine alone



Weight registered throughout the production cycle for salmon vaccinated either with ALPHA JECT® micro 1 PD alone or in co-injected with PHARMAQ six component vaccine. The figure shows that no differences in growth were found between the groups at any time point. The fish were tagged and kept in the same cage in seawater during the study. Growth (n=100 per group) was recorded at three time points during the production cycle.

No differences in growth between the same groups was observed in laboratory trials 6 weeks after vaccination, nor in a seperate field trial, where growth was recorded from vaccination until harvest.

EFFICACY

ALPHA JECT® micro 1 PD is documented to reduce mortality, lesions in pancreas and heart and weight loss during infection with PD, both when administered alone, or together with PHARMAQ six component vaccine. Vice versa, ALPHA JECT® micro 1 PD does not affect the potency of the six component vaccine.

Different prototypes of ALPHA JECT® micro 1 PD have been tested in challenge studies during development to ensure the best possible efficacy under laboratory conditions. The vaccine has performed very well in laboratory efficacy studies, however the ultimate proof of vaccine efficacy is obtained from natural outbreaks of PD during field trials. ALPHA JECT® micro 1 PD has been tested extensively under field conditions in a large field trial where the survival of vaccinated fish was significantly higher than in the control group vaccinated with another commercial PD vaccine.

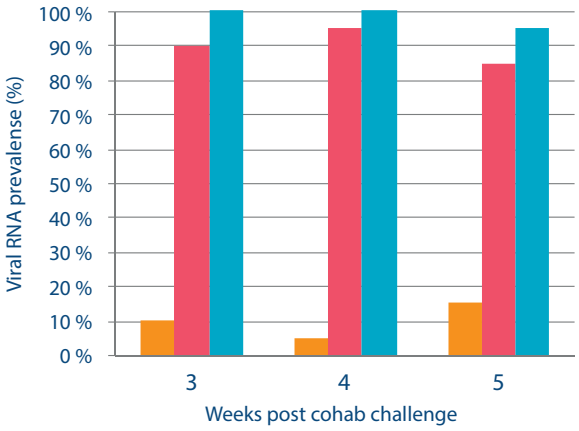
CHALLENGE MODEL

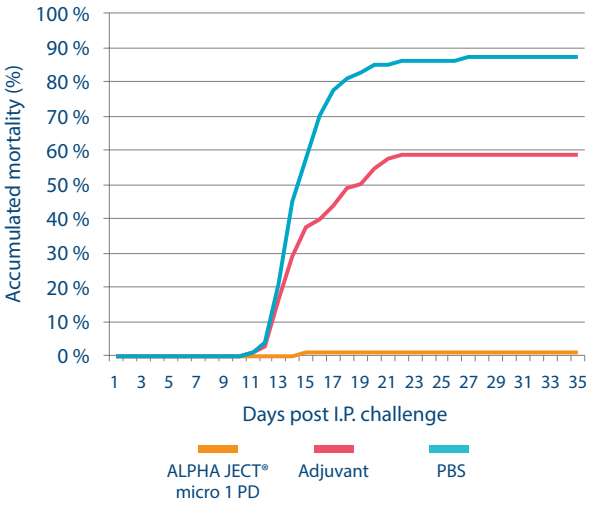
Two different challenge models for pancreas disease in Atlantic salmon have been used during the development of ALPHA JECT® micro 1 PD. Administration of the virus to the fish by intraperitoneal injection (I.P. model) secures a coordinated and predictable disease outbreak resulting in typical clinical signs and high levels of mortality in unvaccinated groups. However, as I.P. administration represents an artificial route of entry for the virus, this challenge model is quite different from a natural challenge.

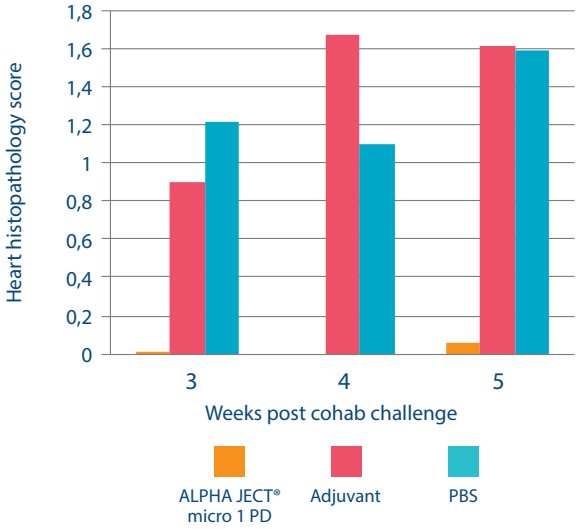
Fish challenged by adding I.P. infected 'shedder' fish to the tank containing vaccinated groups (cohabitant model) produces a waterborne route of infection, and thus more closely mimics the natural route of entry of the virus. However, in contrast to the I.P. model, mortalities seldom reach more than a few percent in the cohabitation model. Comparison of clinical signs developed in fish challenged by the two models is however closely correlated. Both models are able to discriminate between vaccines with variable degrees of efficacy. The efficacy of ALPHA JECT® micro 1 PD has been verified in both models (Karlsen *et al.* 2012).

REDUCTION OF MORTALITY AND PREVALENCE OF VIRUS IN FISH

Vaccination of salmon with ALPHA JECT® micro 1 PD alone or in combination with a PHARMAQ six component vaccine leads to a significant reduction of mortality, prevalence of virus positive fish and pathology in heart and pancreas compared to control fish.

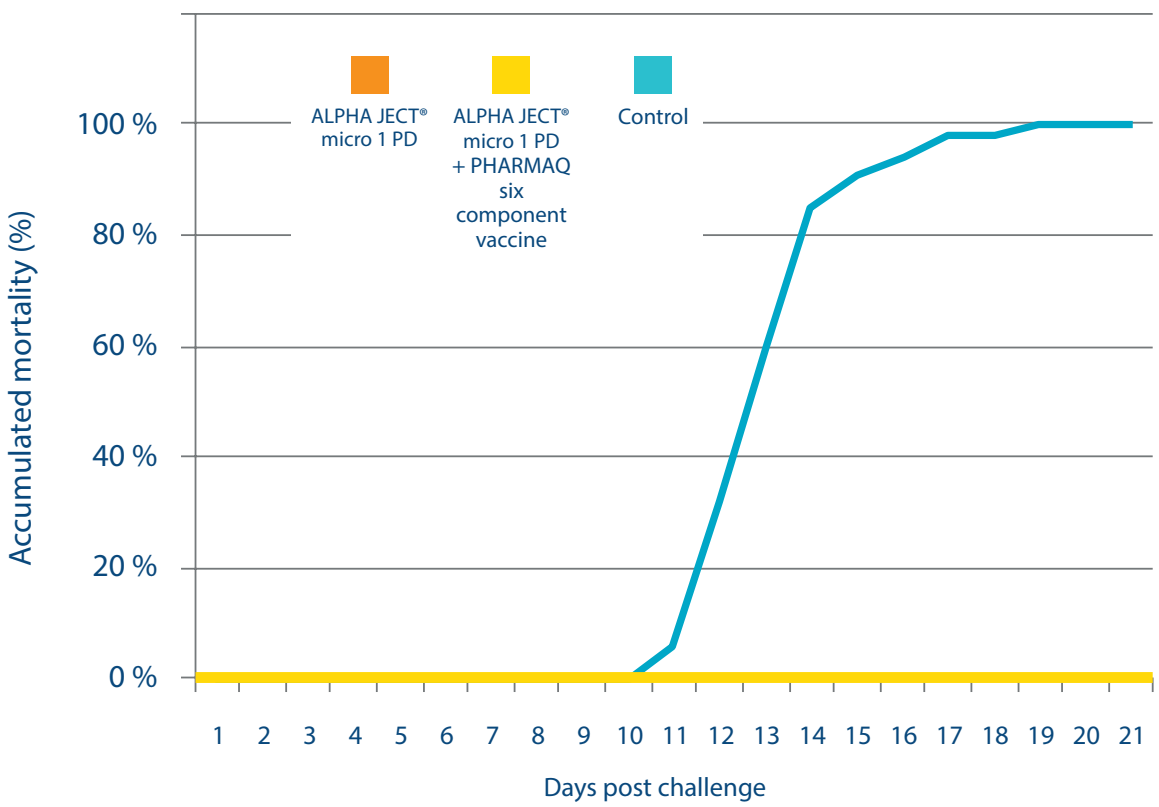






Three groups of Atlantic salmon (38g, n=40 per group per tank) were vaccinated either with ALPHA JECT® micro 1 PD, a vaccine without antigen (adjuvant only) or PBS and held in freshwater at 12°C. The fish were transferred to sea water 6 weeks post vaccination and then challenged with SAV either by cohabitation or I.P. In the I.P. challenged fish the outcome was measured as reduction of mortality and in the cohabitation challenged fish it was measured as amount of virus by PCR and histopathology score in the heart 3, 4 and 5 weeks post challenge (Karlsen *et al.* 2012).

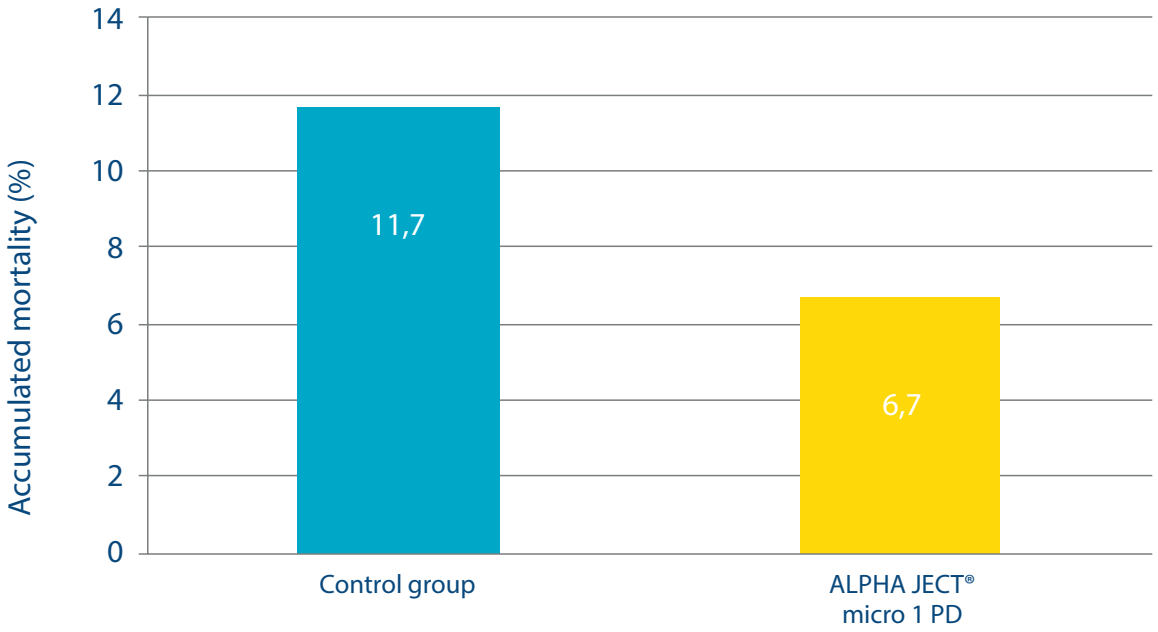
CO-INJECTION



Reduction of mortalities caused by PD is demonstrated following co-injection of ALPHA JECT® micro 1 PD and PHARMAQ six component vaccine (n=35 per group). The fish were immunised for 6 weeks at 12°C and were thereafter I.P. challenged with SAV.

FIELD EFFICACY

ALPHA JECT® micro 1 PD is efficacious in the field for a minimum 15 months post vaccination.



The efficacy of ALPHA JECT® micro 1 PD co-injected with PHARMAQ six component vaccine was investigated in a large field trial in the period 2011-2013. The trial included 17 different locations in Norway, 16 in the SAV 3 zone and one in the SAV 2 zone. The control group was vaccinated with a commercially available monovalent PD vaccine in combination with ALPHA JECT® micro 6 (16 locations) or Norvax Minova 6 (1 location). During the test period six of the locations had outbreaks of PD, but due to impaired quality of the data from three of the locations, only three ot the outbreaks provided data usable for statistical analysis. The overall mortality was significantly reduced in the group vaccinated with ALPHA JECT® micro 1 PD compared to the control group, confirming the results obtained in laboratory efficacy studies. The last outbreak started 15 months after vaccination and the results from this location therefore support duration of immunity of the vaccine for a minimum of 15 months under field conditions.

ALPHA JECT® micro 1 PD

Vaccine for fish. MA number: VM21714/4005

Emulsion for injection, vaccine for Atlantic salmon: 1 dose (0.05 ml) contains: Formaldehyde-inactivated culture of Salmon Pancreas Disease Virus (SPDV) strain AL V405, RPSend ≥80%. See also SPC.

Properties:
Classification: Inactivated viral vaccine. Immunological properties: Stimulates the development of active immunity to pancreatic disease (PD). Reduction of mortality during clinical outbreaks of Pancreas Disease has been documented up to 15 months post vaccination under field conditions.

Indications for use:
For active immunisation of Atlantic salmon to reduce mortality, lesions in the heart and pancreas, and impaired growth caused by PD. Onset of Immunity occurs no later than 516 degree days (DD) after vaccination. Duration of immunity: The vaccine reduces mortality, lesions in the heart and pancreas and impaired growth caused by SPDV infection for up to at least 12 months after vaccination.

Adverse reactions:
Adhesions, discolouration (melanisation) and vaccine residues in the abdominal cavity are very commonly observed following the use of oil-based vaccines. After use as a stand-alone vaccine or in combination with a multivalent vaccine from Pharmaq are mild adhesions (Speilberg score 1-2) very common, moderate adhesions (Speilberg score 3) common, while severe adhesions (Speilberg score ≥ 4) are very rare.

Precautions:
Fish with clinical symptoms of disease should not be vaccinated. Vaccination should preferably be performed at water temperatures of ≤15°C. Vaccination at water temperatures of <1°C or > 18°C is not recommended. Avoid vaccination during smoltification. See the enclosed leaflet for special precautions to be taken by those administering the vaccine. In the event of personnel accidentally being injected with this product, seek medical help immediately.

Interactions:
Safety and efficacy data show that this vaccine can be administered simultaneously with Pharmaq's multivalent oil-based vaccines containing the following antigens: *Aeromonas salmonicida, Listonella anguillarum* serotype O1 and O2a, *Vibrio salmonicida, Moritella viscosa* and Infectious Pancreatic Necrosis Virus (IPNV). The vaccines are administered intraperitoneally of anaesthetised fish, either simultaneously (1 injection) or in immediate succession (2 injections). No information is available on the safety and efficacy of this vaccine when used with any other veterinary medicinal product except the products mentioned above. A decision to use this vaccine before or after any other veterinary medicinal product therefore needs to be made on a case by case basis.

Gestation/lactation:
Vaccination of broodfish is not recommended and should be subject to a risk benefit evaluation of the prescribing veterinarian/fish health biologist.

Dosage:
0.05 ml per fish at a minimum weight of 28 g. Administration: The vaccine should be left to slowly reach 15-20°C by keeping it at room temperature and mixed thoroughly before use. The entire dose of vaccine should be administered by intraperitoneal injection at the midline, about one finlength anterior to the base of the pelvic fin. Fish should be anaesthetised prior to vaccination. It is recommended to starve the fish for at least 48 hours prior to vaccination.

Overdosing:
Administration of the vaccine in 0.1 ml (double dose) shows no other adverse reactions than those described above.

Withdrawal periods:
0 degree days.

Storage and shelf life:
Store and transport refrigerated (2°C - 8°C). Do not freeze. Protect from light. If the vaccine bag has been opened, use within 10 hours. The vaccine should not be used if the vaccine shows signs of a brownish water phase in the bottom of the container. Only administer if the vaccine appears as a homogenous white to cream coloured emulsion.

Pack size: 250 ml and 500 ml.

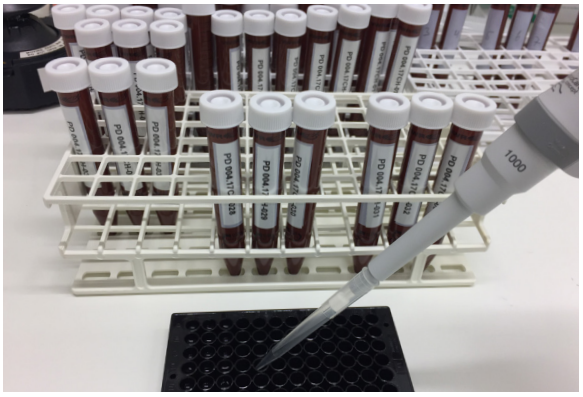
Based on SPC approved on 17.12.2015

TWINJECTION

Twinjection is PHARMAQ`s system for the simultaneous administration of two vaccines. Twinjection will reduce handling, stress and the operational cost of the vaccination procedure compared to sequential injection. Twinjection is thus beneficial for both the fish and the farmer.

Clearly it is important to ensure that correct doses of each vaccine are injected with Twinjection. PHARMAQ has tested the most common vaccination equipment in use today in order to assure secure and precise injection of each vaccine when co-injected. We can help to make specific recommendations and give guidance on best practice for each machine and gun.

PHARMAQ can also help manage the vaccination process if requested by a customer.

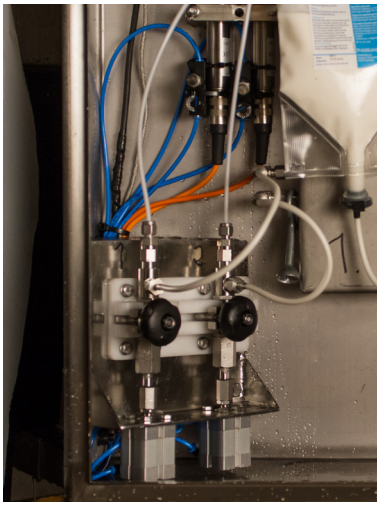


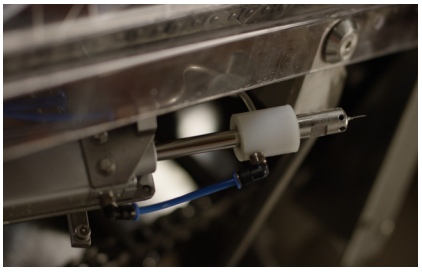
Testing of Twinjection technology.

TWINJECTION

NOW YOU HAVE A CHOICE!

With Twinjection you will have greater flexibility in deciding what vaccine antigens to use on your farm.





Twinjection allows two vaccines to be injected simultaneously into the fish visualized here using the NFT 20 vaccination machine and a manual gun from Henke Sass Wolf (illustration).

PD DIALOGUE

PHARMAQ has a proven track record in the provision of products and services to support the global aquaculture industry. We strongly believe in the value of open and collaborative dialogue to help us understand our customer's needs and so optimize the benefit they derive from using our products and services.

To support the launch of our ALPHA JECT® micro 1 PD we see that it is important for us to follow the performance of the vaccine from the point of administration until the fish is harvested. We propose to do this through "PD Dialogue".

PD Dialogue is the framework through which we will monitor the performance of ALPHA JECT® micro 1 PD in field. This will be done through close communication and collaboration with our customers and by measuring parameters such as the quality of the vaccination operation and further assessments of possible side effects after vaccination, at seawater transfer and at harvest. We can also measure growth, FCR and monitor the health status of your fish. If PD is suspected, we can offer RT-PCR analysis and histology through PHARMAQ Analytiq to confirm disease .

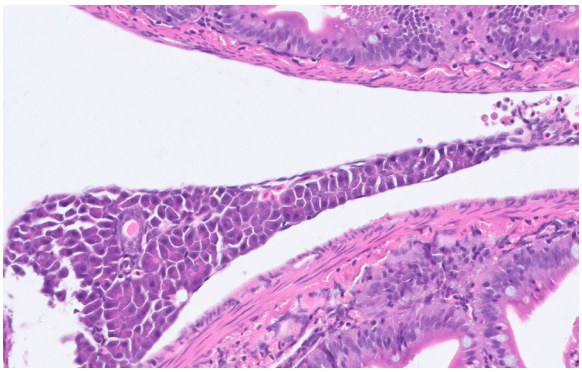
Concurrently we also offer screening for SAV in the market to gain as much knowledge as possible about the presence and distribution of the PD-virus.

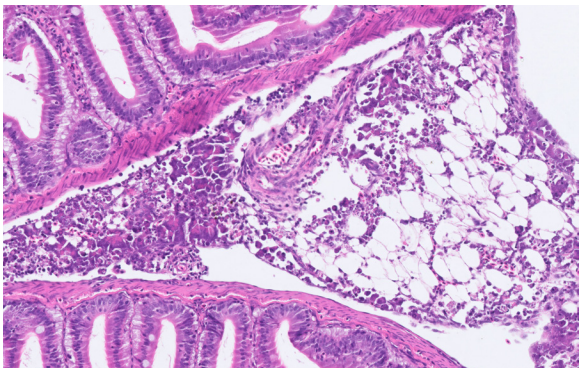
PD DIALOGUE

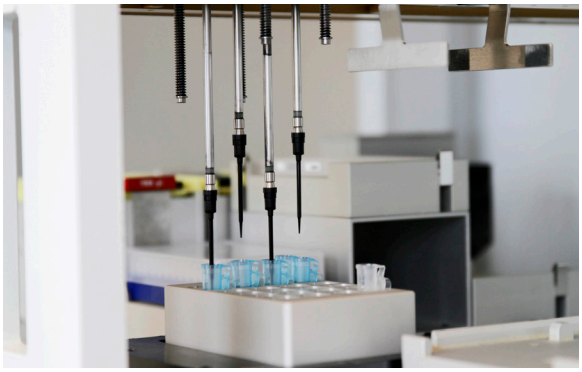
We will start a dialogue on how to best support our customers with the use of ALPHA JECT® micro 1 PD. We will tailor-make our PD Dialogue to fit each customer's need in order to learn as much as possible about the disease situation and the performance of our vaccine in the field. Data given to us will remain anonymous to others and will only be used for external purposes in agreement with the owner of the data.

The Pharmacovigilance system in PHARMAQ is an integral part of post marketing activities for veterinary medicinal products. If any unfavorable and unintended effect is observed after treatment or vaccination using a veterinary medicinal product supplied by PHARMAQ, please contact pharmaqcovigilance@pharmaq.no for advice.

The key to PHARMAQ's success is our constant focus on delivering high quality, safe, efficacious fish health products to our customers. A high focus on quality is paramount to PHARMAQ thoughout the value chain from the characterization of pathogens from diseased fish, research, development and registration of products, through to the production and supply of environmentally sound, safe and efficacious health products to aquaculture operators all over the world. We make aquaculture progress!







Picture on the top shows normal pancreas tissue. In the middle we see pancreas with acute necrosis. This is seen in an early stage of SAV infection. In later stages of the disease the pancreatic tissue may be totally absent (atrophy) before it is reconstituted if the fish survive. Histology can therefore give a picture on both how comprehensive the tissue damages are as well as indicate the stage of the disease. Bottom: RT-PCR screening is an efficient tool to confirm PD virus in fish.

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