Lofoten Seminary 2021

The path to a Nucleic Acid vaccine

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Overview

- Intro Elanco Aqua
- Vaccines – definition, how they work, their importance, development, challenges, regulations
- Nucleic acid vaccines:
  - RNA vaccines to fight COVID-19
  - DNA vaccines for fish
- Prescriber importance and post marketing surveillance

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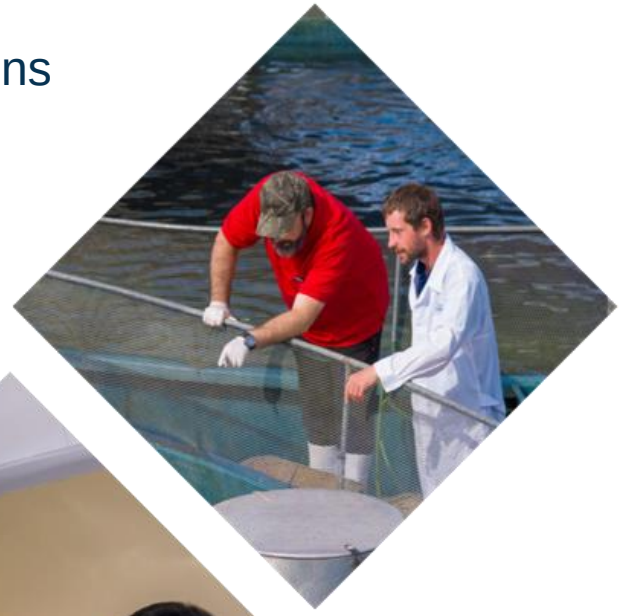
Elanco Aqua Overview

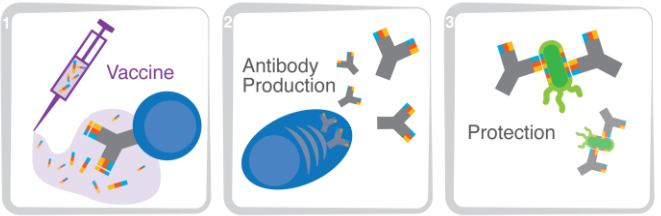
- Internal R&D facilities and active collaboration with external research institutions
- Several products marketed in Global Aquaculture
- Focused on salmonids and warm water (mainly shrimp)
- Expertise in Parasitology, Therapeutics, Microbiology and Vaccines
- Expertise in technical services in all major salmon farming regions
- Strong diagnostic capabilities



Vaccines and how they work

Vaccine trains the immune system to create antibodies, just as it does when it's exposed to a disease. However, they do not cause the disease.

- **Individual immunity**: a fish gets vaccinated against a disease, their risk of infection is reduced (also less likely to transmit the virus or bacteria to others).
- **'Herd immunity' = 'population immunity':** when individuals who are not immune but live in a community with a high proportion of immunity, have a reduced risk of disease as compared to non-immune individuals living in a community with a small proportion of immunity.



Vaccine types:

- Killed/Inactivated Vaccines: viral or bacterial pathogen
- Live Vaccines
  - Modified/attenuated naturally or via genetic manipulations
  - "Natural" infection generates protective antibodies and cellular immune response
- Toxoids: Contain inactivated toxins
- Subunit: Contain only the part of the pathogen that generates immunity
- Nucleic acid vaccines: Contain genetic information that results in production of immunogenic protein of pathogen

https://www.who.int/news-room/q-a-detail/vaccines-and-immunization-what-is-vaccination
https://www.vaccines.gov/basics/types

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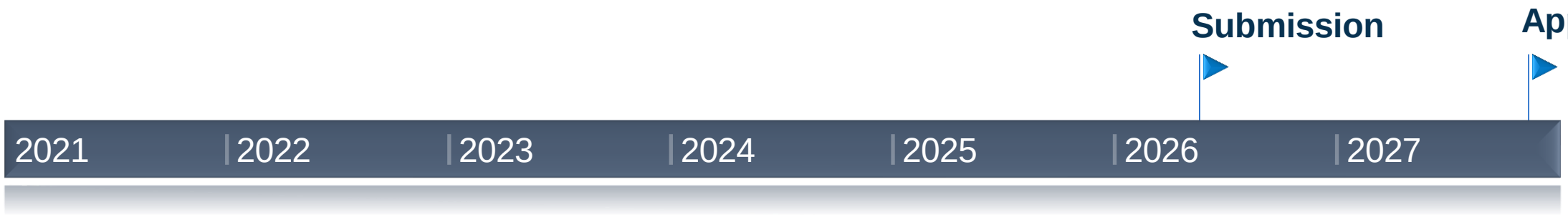
Vaccine development simplified workflow



Acquisition of Relevant Strains/Isolates

Generation of Investigational Vaccine Product(s) & development of challenge model

Dose Determination

Duration Of Immunity study

Laboratory safety study

Shed and spread study

Demonstration batches

Efficacy study in the target species

Field Safety Study

Stability monitoring program

Complete EU Dossier

Aqua healthcare industry challenges

Product development challenges

- **Average time-to-market +9 years** – an increase of 5 years within the last 20 years
- **Increased cost to support existing products** – between 16% (US) and 51% (Europe) of R&D resources spent on maintaining registrations
- It costs a company up to **€ 150 million** to develop a major new product
- This means that the costs have increased by **157%** in real terms over the last 15 years.
- **Multidisciplinary efforts:** Sales, Technical, Marketing, R&D, Regulatory, Manufacturing, Supply chain, Finance…
- Conducting studies to meet **different regional and national legal/regulatory requirements**

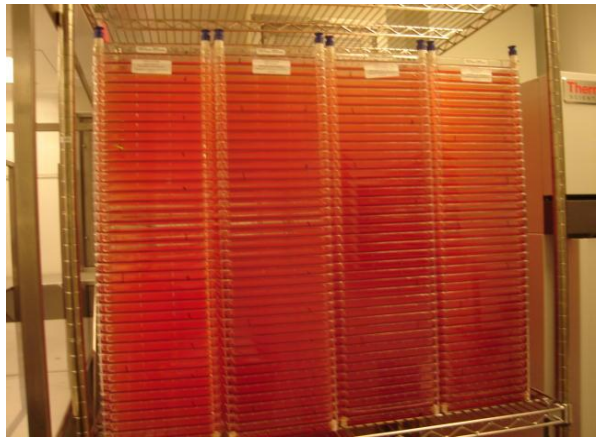
https://www.animalhealtheurope.eu/annual-report-2014/
https://www.bft-online.de/fileadmin/bft/aktuelles/IEvaccstate_final__2_.pdf

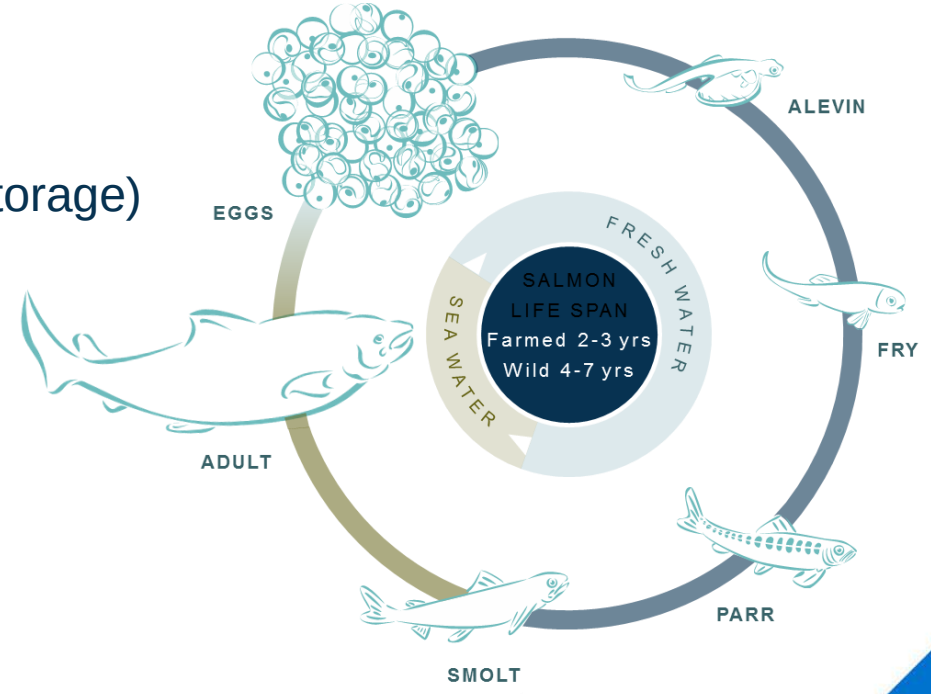
Challenges with Vaccines

- Monovalent vs. multivalent: Antigen interference may cause issues with efficacy & potency
- Complexity of antigen production
  - Biological systems (e.g., eggs, cell culture)
  - Undefined media
  - Undefined immunological antigens
- Vaccines may require special storage conditions (usually cold storage)

- Species-specific
- Vaccine strategy: type, dose, route, injection timepoint, …

Up scale
→





Regulations & Vaccine Licensing Requirements

EU-Regulated by European Medicines Agency (EMA),
Committee for Medicinal Products for Veterinary Use (CVMP)

The **Norwegian Medicines Agency** (NoMA)

- **Licensing requirements:**
  - ✓ Purity
  - ✓ Potency
  - ✓ Efficacy
  - ✓ Safety
  - ▪ Duration of Immunity (DOI)
  - ▪ Stability
- Both products and facilities are licensed
- Assays must be validated in a Good Manufacturing Practice (GMP) facility
- Release controls: Manufacturers control release of each batch through the Qualified Person

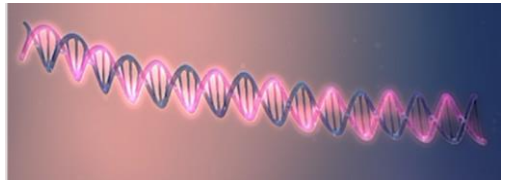
https://rr-africa.oie.int/wp-content/uploads/2000/11/szabo.pdf

Nucleic acid vaccines

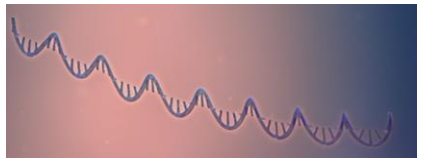
Nucleic acids = large biomolecules that create, encode, and store information essential to all known forms of life. Composed of nucleotides*, which are made of 3 components: a phosphate group, a 5-carbon sugar and a nitrogenous base / nucleobase.

2 main classes of nucleic acids:

deoxyribonucleic acid (**DNA**) its sugar = deoxyribose;



ribonucleic acid (**RNA**) its sugar = ribose



Strings of nucleotides bond to form helical backbones (2 for DNA, 1 for RNA), assembled into chains of base-pairs selected from 5 nucleobases: adenine, cytosine, guanine, thymine (only in DNA) and uracil (only in RNA). The nucleobase-pairs sequence stores and transmits coded instructions as genes (gene product = RNA / protein).

Identify vaccine candidates in genomic sequences based on the assumption that antibodies are more readily able to access surface and secreted than cytoplasm proteins; as such, they represent ideal vaccine candidates. **Reverse vaccinology**, uses several bioinformatics algorithms to **predict antigen localization**.

Synthetic* messenger RNA-based vaccines challenges in adequate cellular uptake and expression, unstable and quite **expensive production**.

https://doi.org/10.1016/j.biori.2017.10.001

Nucleic Acid vaccines

- 1990's: RNA encoding for influenza antigen 1st use in mice, but lipid delivery system too toxic for humans[1]

➢ *2002–2004: 1st severe acute respiratory syndrome coronavirus (SARS-CoV) outbreak*[1]

- **2005**: 1st Marketing authorization (MA) for a DNA vaccine in Canada = Elanco vaccine against a significant **salmon** disease[2]

- 2012: 1st described lipid nanoparticle (LNP) encapsulated RNA vaccine[1]

- **2017**: 1st MA for a DNA vaccine in Europe (including Norway) = Elanco vaccine against a major **Atlantic salmon** disease[3]

➢ *2019: a 2nd severe acute respiratory syndrome coronavirus strain was identified. This new strain causes coronavirus disease 2019 (COVID-19), which brought about the pandemic → need to act fast!* [1]

- Now nucleic acid vaccines are solving a major problem for humanity.

We've used this technology in aquaculture, protecting each A. salmon with only 1 dose for over 16 years!

1 https://www.nature.com/articles/d41586-021-00019-w
2 https://www.int-res.com/articles/dao_oa/d122p213.pdf
3 https://www.ema.europa.eu/en/medicines/veterinary

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How were these vaccines developed so quickly?

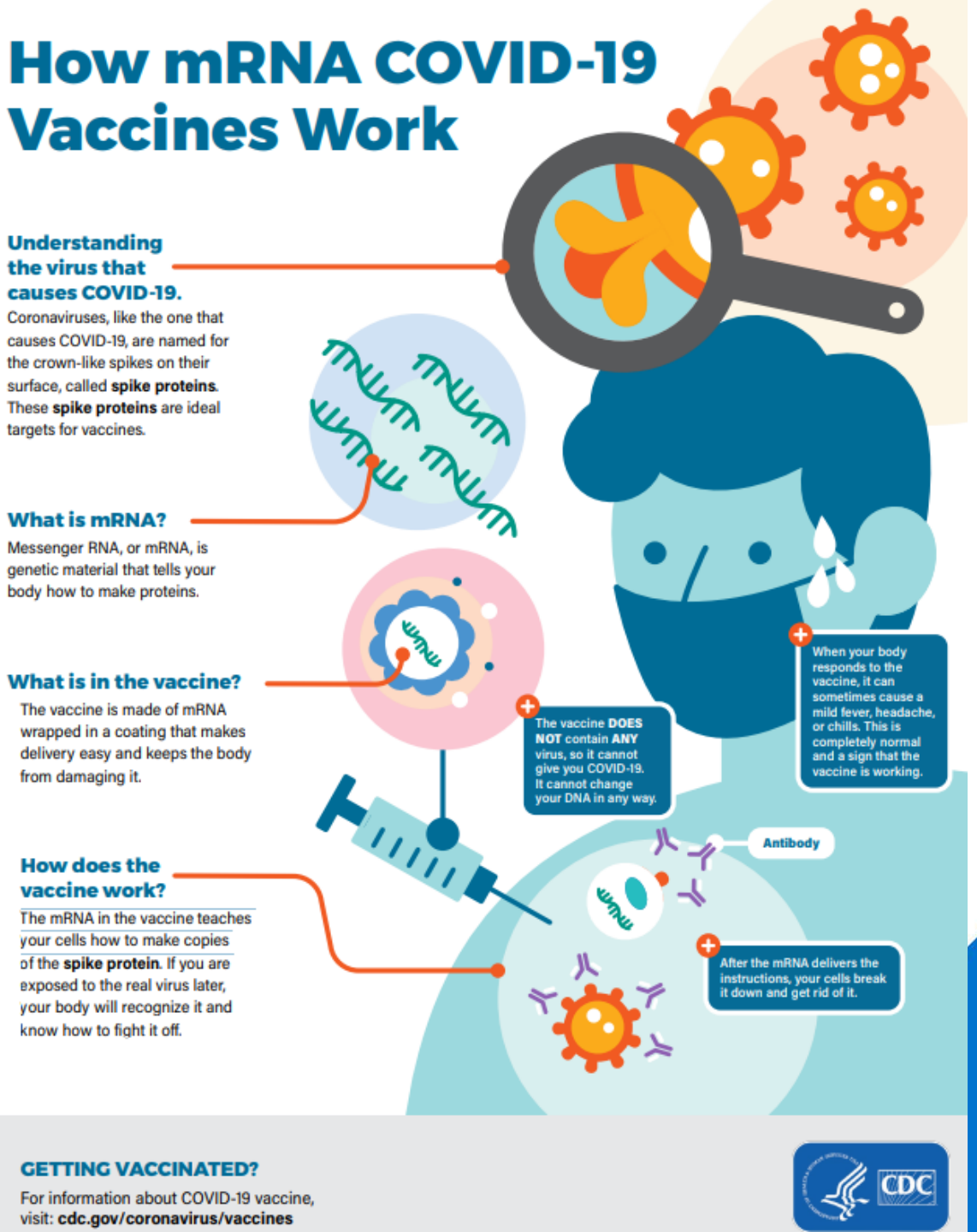
Public health emergency /pandemic → atypical development process

Governments:

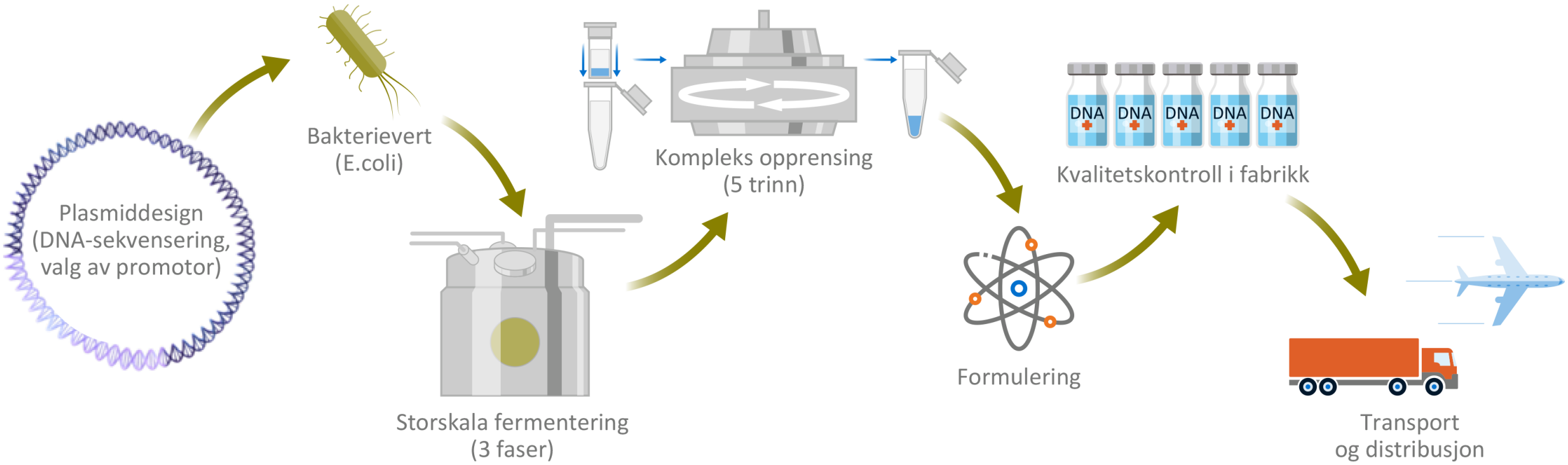
- joined government agencies, international counterparts, academia, nonprofit organizations and pharmaceutical companies to develop a **coordinated strategy for prioritizing and speeding development of the most promising vaccines.**
- made **investments** in the manufacturing capacity, giving companies confidence to invest aggressively in development and allowing faster distribution of an eventual vaccine.

https://www.fda.gov/vaccines-blood-biologics/vaccines/emergency-use-authorization-vaccines-explained

https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines/mrna.html



DNA vaccine: what it is, from production to the market



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DNA vaccines vs. conventional vaccines

Advantage	Specific benefit
Safety	• No infection risk • Purity, no oil adjuvant • Intra-muscular injection less risk of damage to internal organs
Efficacy	• Specificity of immune response • Innate, humoral and cell-mediated immunity • Long Duration Of Immunity (DOI) from single vaccination
Stability	• Plasmid stability: long product shelf-life, ease of storage and shipping
Reduced side effects	• Less loss of appetite and growth; less risk of melanin visceral adhesions

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Prescriber importance & Post marketing surveillance

- **Fish vaccines need to be prescribed in order to be sold.**

- The pharmaceutical work is not over after a sale, it needs to do **pharmacovigilance** (PV), i.e., gather information about safety profile of the product in clinical use.
  - Adverse reactions/events*
  - Interactions with other medicinal products
  - New effects
  - Lack of efficacy
  - Misuse

***Adverse Event** = any observation in animals, whether or not considered to be product related, that is unfavorable and unintended and that occurs after an animal is exposed to or any use of an approved or marketed product (off-label and on-label uses). Included are events related to a suspected lack of expected efficacy or noxious reaction in humans after being exposed to the marketed product.

https://legemiddelverket.no/english/pharmacovigilance/what-is-pharmacovigilance

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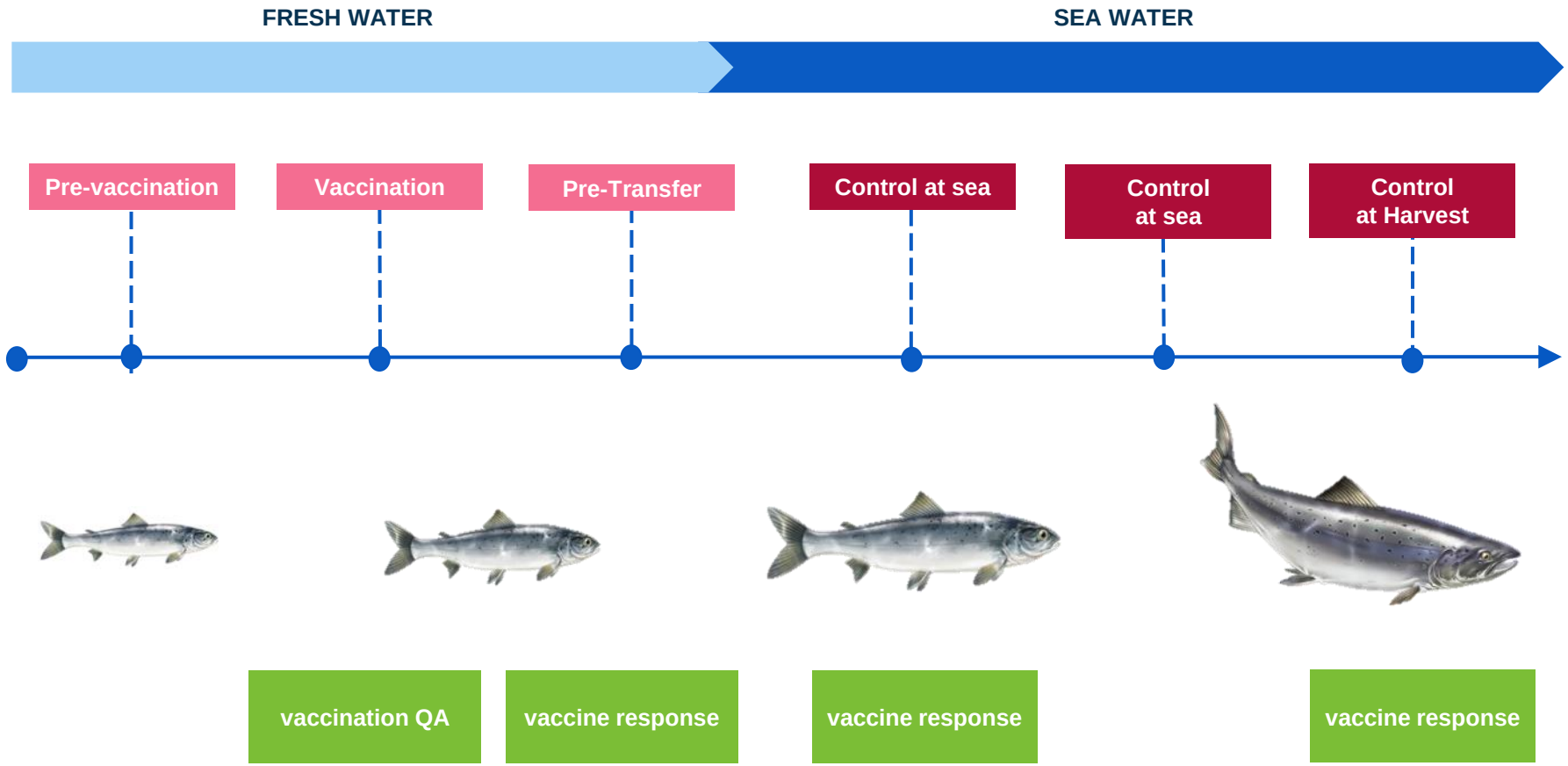
Post marketing Elanco service model for vaccines*



*Model can vary according to country regulations and local procedures

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Thank you!

Questions?

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