

# Vaccine Adjuvants



Bringing 80 years of  
expertise to you

Smart science to improve lives™

**CRODA**

# Dedication



## For more than 80 years our vaccine adjuvant business has been dedicated to safe and effective adjuvants suitable for use in both human and veterinary vaccines.

To this day, our focus has been to successfully develop, manufacture and market high-quality adjuvants for our pharmaceutical customers. This heritage makes our vaccine adjuvants unique in the industry. A heritage we are proud of.

Our industry-leading, Alhydrogel<sup>®</sup>, Adju-Phos<sup>®</sup> and Quil-A<sup>®</sup> are widely recognised in the vaccine industry for their unmatched track record when it comes to a proven history of safe and effective use.

### We offer you

- Industry experience as a world leading adjuvant specialist for vaccines serving the major human and veterinary vaccine producers globally
- Industry leading R&T capabilities resulting in a strong pipeline of innovative, next generation vaccine adjuvants
- Highest quality standards running the only aseptic and GMP certified manufacturing site for adjuvants globally

## Joining forces

We are proud of who we are, our values and our commitment to our customers. No other company can match our expertise in adjuvants, which is founded on an unprecedented 80-year heritage in the industry. Our focus today remains as it has always: we are dedicated to innovation and consistency in the quality of the products we supply to our customers.

The combination of a passionate team, strong adjuvant expertise, industry-leading aseptic production facilities and our own dedicated global sales network who is committed to understanding our customers' needs, will allow our vaccine adjuvant business better penetration into the pharmaceutical market to enhance vaccine development through our classic portfolio as well as through our rich development pipeline. Our commitment to the highest quality standards is a priority for us and our employees are continuously developing and manufacturing the highest quality of adjuvants in the business.

We all realise that the vaccines and blood products of tomorrow require new and innovative adjuvants. Our R&D department continuously dedicates their focus on innovation and working hard on the development of the next generation of adjuvants.

It is my sincere hope, that this brochure will give you a little more insight into what value we can offer you and your vaccine development, whilst sparking your interest to come and visit us. You will always be welcome at the Croda Denmark site in Frederikssund for a cup of coffee and a talk about your needs.

After all, we are here to collaborate with you!

A handwritten signature in blue ink, reading "Peter Tygesen".

**Peter H. Tygesen**  
Managing Director - Vaccine Adjuvants





We are committed to quality!

**Our quality system and production processes are designed keeping the intended end-use of the products in mind at all times.**

We want our products to be the most reliable, consistent and safe on the market. Our compliance with all applicable regulatory requirements is regularly audited by the Danish Medicines Agency.

**Sterility: A built-in quality attribute**

We aim to manufacture adjuvants with quality built into the process by design to meet the special requirements for the end-use in vaccines.

It may not be a formal requirement to use aseptically produced adjuvants in vaccine production and a terminal sterilisation of the vaccines will indeed ensure sterility of the final vaccine doses. However, we believe in striving towards the highest quality and safety standards. By choosing an aseptically produced sterile adjuvant, such as Alhydrogel or Adju-Phos, you will have the optimal starting point to meet the requirements for bioburden control throughout your vaccine manufacturing process - resulting in value for the patient.

Sterility is a critical quality attribute engineered into the production process for our Alhydrogel and Adju-Phos products. Our products are sterilised by heat during the production process and aseptically filled into the primary packaging.

## Alhydrogel - Aluminium hydroxide gel

- Best studied aluminium adjuvant product in the world
  - > 6,800 hits on Google Scholar
  - > 310 unique publications on PubMed.gov
- Over 80 year history of safe and effective use in commercial vaccines
- Produced in classified clean rooms to prevent contamination
- Sterilised and aseptically filled in a class A clean room
- EU GMP (Part I: Medicinal Products for Human and Veterinary Use) certified production of aseptically prepared sterile products
- Low levels of metals (Cu, Ni, Fe) limit antigen oxidation (Schlegl et. al, 2015)

### Product presentation:

Alhydrogel is a range of aluminium hydroxide gel products which have been specifically developed for use as an adjuvant in human and veterinary vaccines. The gel is a suspension of boehmite-like (aluminium oxyhydroxide) hydrated nano/micron size crystals in loose aggregates. The products have a very low conductivity as a result of the proprietary production process.

Alhydrogel products have a positive charge at neutral pH and effectively adsorb negatively charged antigens. The primary purpose of the adjuvant in vaccines is to boost the antibody-mediated (Th2) immune response to the antigens. Alhydrogel products can be combined with other adjuvants types (such as MPL - Monophosphoryl Lipid) to achieve a balanced Th1/Th2 immune response.

Alhydrogel was elected as the International Standard Preparation for aluminium hydroxide gels at an independent scientific workshop in Greece in 1988 and 1990 (Stewart-Tull 1989 and 1991).

Alhydrogel is supplied in concentrations of either 6.5 mg/ml or 10 mg/ml aluminium. A premium version (Alhydrogel "85") with approximately 20% higher protein adsorption capacity is also available.

### Main applications

- Human vaccines
- Veterinary vaccines
- Blood plasma fractionation (Example: Factor VIII purification)

### Standard packaging

Alhydrogel is supplied in the following standard HDPE container options:

- 250 ml infusion bottles equipped with a stopper/crimp closure
- 5 kg cans with screw caps
- 25 kg cans with screw caps



# Adju-Phos<sup>®</sup>

## Adju-Phos - Aluminium phosphate gel

- Best studied aluminium phosphate gel adjuvant in the world
  - > 729 hits on Google Scholar
- Over 40 year history of safe and effective use in commercial vaccines
- Produced in classified clean rooms to prevent contamination
- Sterilised and aseptically filled in a class A clean room
- EU GMP (Part I: Medicinal Products for Human and Veterinary Use) certified production of aseptically prepared sterile products

### Product presentation:

Adju-Phos is a range of aluminium phosphate gel products which have been specifically developed for use as adjuvants in vaccines. The gel is a suspension of hydrated amorphous aluminium hydroxyphosphate nano/micron size particles.

Adju-Phos products have a net negative charge at neutral pH and effectively adsorb positively charged antigens. The primary purpose of the adjuvant in vaccines is to boost the antibody-mediated (Th2) immune response to the antigens. Adju-Phos products can be combined with other adjuvant types (such as MPL) to achieve a balanced Th1/Th2 immune response.

Adju-Phos is supplied in two variants with pH-values at ~6.5 and at ~5.0. Both variants contain 0.9% NaCl (saline) to reduce injection site discomfort.

### Main applications

- Human vaccines
- Veterinary vaccines

### Standard packaging

Adju-Phos is supplied in the following standard HDPE container options:

- 250 ml infusion bottles equipped with a stopper/crimp closure
- 5 kg cans with screw caps
- 25 kg cans with screw caps

## Quil-A - Saponin vaccine adjuvant

- A highly concentrated and potent saponin adjuvant purified from bark extract of the Quillaja saponaria Molina tree.
- Well proven and extensively studied:
  - >16,300 hits on Google Scholar
  - > 370 unique publications on PubMed.gov
- Over 35 years of safe and effective use in commercial vaccines
- Stimulates both the cell-mediated (Th1) and the antibody-mediated (Th2) immune response to antigens-potential to protect against a wide range of bacterial and viral pathogens
- Cost-effective due to very low dose requirements (ie  $\leq 1$  mg/dose for cattle)
- The adjuvant efficacy of Quil-A is verified by vaccine tests for each raw material batch
- EU GMP (Part I: Medicinal Products for Human and Veterinary Use) certified production

### Product presentation:

Quil-A is a highly purified quillaja saponin product which has been specifically developed for use as an adjuvant in vaccines. Quil-A saponin was originally purified and characterised by Dr. Pharm. Kristian Dalsgaard in 1974 and adapted for commercial scale production in cooperation with Croda.

Quil-A consists of a complex mixture of ca. 25 major saponin molecules which have the triterpenoid backbone in common. It is a very versatile adjuvant due to its ability to induce a balanced immune response to protect against both intracellular (Th1) and extracellular (Th2) pathogens.

Quil-A saponin has the ability to form cage-like immunostimulating complex (ISCOM) particles together with cholesterol and phospholipids which can further increase the potency of the adjuvant and reduce local reactogenicity. Furthermore, novel nanoparticle adjuvants containing quillaja saponin as the active component are currently being developed.

Quil-A is supplied as a water-soluble lyophilised powder with minimum 95% dry matter. The product has been sterile-filtered prior to lyophilisation to ensure a low bioburden in the final product and has a long shelf life. The product is also available with the antioxidant ascorbic acid added which may improve stability of aqueous solutions of the product.

### Main applications

- Adjuvant in veterinary vaccines
- Active component of ISCOM and nanoparticle adjuvants
- Raw material for QS-21 and other saponin fractions

### Standard packaging

Quil-A is supplied in the following standard packaging options:

- 1 gram in tablet jar (HDPE) with tear-band cap (LDPE)
- 5 gram in tablet jar (HDPE) with tear-band cap (LDPE)
- 100 gram tablet jar (HDPE) with tear-band cap (LDPE)

# Listening and providing solutions

## Face-to-face with our customers

It is easy to write many pages about customer service and expertise. But it is a whole different story actually delivering it in a market as complex and changing as vaccine production.

That is why we take the individual needs of our customers very seriously. As no two customers require the same advice and service, we strive to personalise our advice to you in order to provide a comprehensive, custom-made solution, helping make your vaccine production process more efficient.

## Reliable all the way

Our manufacturing and laboratory facilities ensure that we can produce adjuvants to a consistent high quality that meets your requirements. The complete production flow from raw material and supplier control to packaging and release of the final adjuvants is strictly regulated and controlled to ensure that you can rely on our products to perform consistently and effectively in your vaccines.

We offer our adjuvants in multiple combinations of product versions and unit sizes to match many different needs from small-scale research to large-scale production.

# We are founded on research & development

## Innovation is in our DNA

We fully appreciate that knowledge and technology are never constant. The need for new and efficacious adjuvant systems to fight infectious and other diseases by prophylactic or therapeutic vaccines is growing. We are passionately developing new adjuvant technologies and we welcome partnerships with the vaccine industry to develop the vaccines of tomorrow.

Our R&D department consists of a multinational group of experienced and recognised vaccine adjuvant scientists, led by Dr. Erik Lindblad. Here you will find brief descriptions of a few of the exciting projects that are currently in our pipeline or have recently come through for commercialisation.

## NanoQuil® - The next-generation Saponin-based nanoparticle adjuvant

Saponin-based immunostimulating nanoparticles hold a highly promising potential in vaccinology. For example, ISCOMs have been known to the world since the original discovery by the Swedish scientist, Professor Bror Morein in 1984 [Morein et al., (1984). *Nature*; 308 (5958) : 457-60.].

Our vaccine adjuvant business is working to develop and commercialise a new generation of saponin-based nanoparticles under the brand name NanoQuil. NanoQuil consists of a series of immune-stimulating nanoparticles developed for use in both veterinary and human applications. NanoQuil exploits the benefits of previous generations of nanoparticles, such as ISCOMs, whilst simultaneously solving a number of issues around stability and production. NanoQuil belongs to a strong and potent adjuvant platform for new therapeutic and preventive vaccines.

At the moment, we are involved in developing prototype vaccines in collaboration with external experts and universities.

The first data from the testing of these nanoparticles have already been published: Novel G3/DT adjuvant promotes the induction of protective T-cells responses after vaccination with a seasonal trivalent inactivated split-virion influenza vaccine. (Van de Sandt et al. (2014). *VACCINE* 32 : 5614-5623).

## QS-21 to be made available in GMP-quality

QS-21 is a defined molecule of the triterpenoid saponin fraction extracted from the bark of the South American tree, *Quillaja saponaria* Molina. The fraction was originally isolated and characterised by Dr. Charlotte Kensil more than 25 years ago [Kensil et. al, 1991, J. Immunol. 1991;146: 431–37] and demonstrated to possess an optimal balance of high immunostimulation and low local reactogenicity.

Vaccines containing QS-21 are now commercially available and used to prevent diseases such as malaria, which it was previously not possible to develop effective vaccines against.

High quality QS-21 is available and suitable for use in human vaccines meeting the associated regulatory and registration requirements. Samples of QS-21 are available for evaluation and testing.

## Adju-Phos® ZP – Enhanced antigen adsorption and product characteristics

The original Adju-Phos, a sterilised hydrated aluminium hydroxyphosphate colloid gel, is a classic product in vaccine adjuvant product portfolio and it has been used as an adjuvant in vaccines for human use by leading international vaccine producers for more than 40 years.

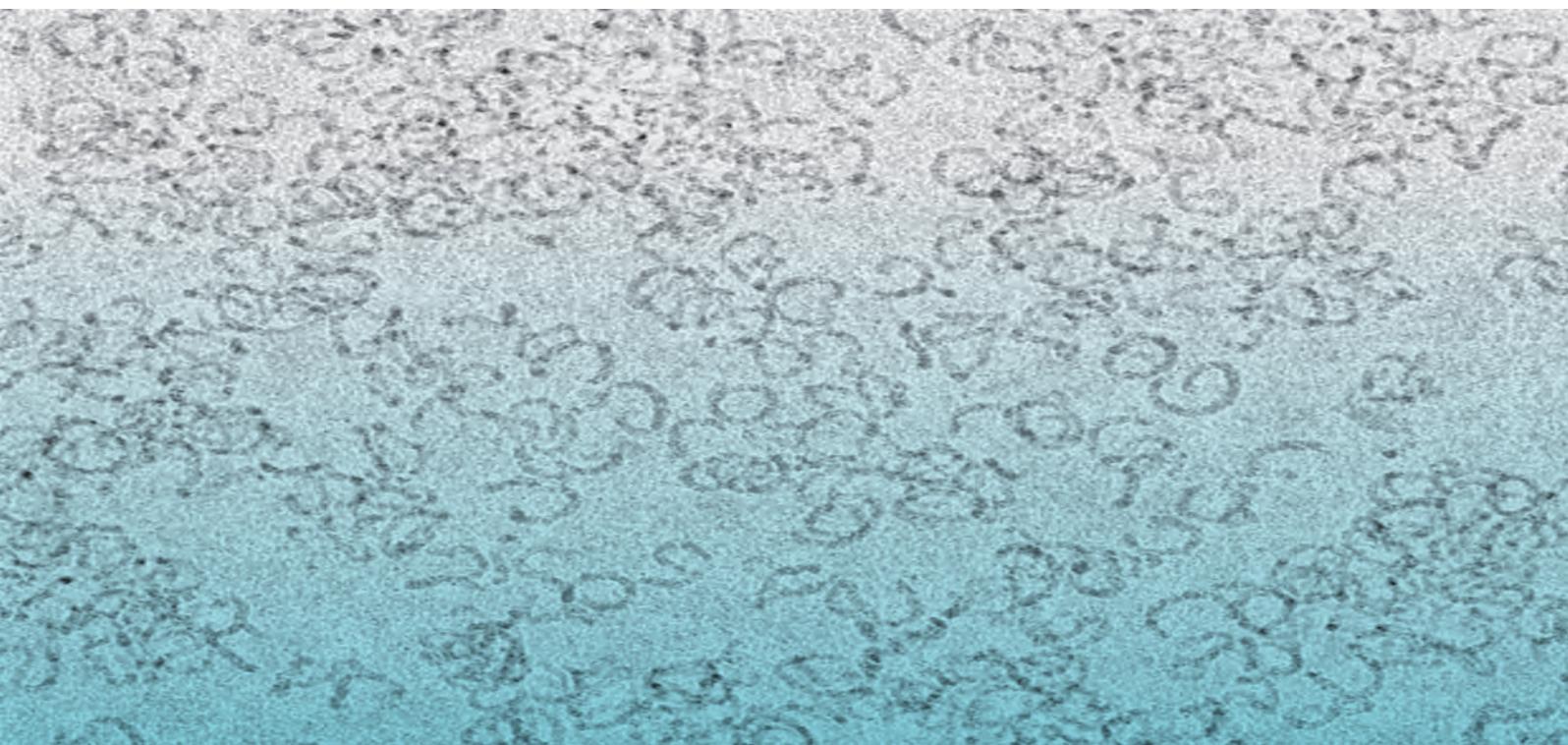
At physiological pH, Adju-Phos is negatively charged and is therefore able to adsorb positively charged protein antigens by electrostatic attraction. To minimise vaccination discomfort, vaccines normally should have pH values at or close to physiological pH.

In recent years there has been a quest to make multivalent vaccines protecting against a larger number of infectious agents and diseases than previously. To meet this quest we have developed a modified Adju-Phos which we have named Adju-Phos ZP.

With Adju-Phos ZP we have modified the surface characteristics to enhance the zeta-potential of the gel particles. This modification leads to the ability to adsorb more protein antigen. This is generally the case with positively charged protein antigens possessing an alkaline isoelectric point, as exemplified and demonstrated by the model protein lysozyme (IEP=11).

We see an attractive potential for Adju-Phos ZP in the development of new and improved multivalent vaccines.

Samples of Adju-Phos ZP are available for evaluation and testing.



## Our reason to be

**We are committed to bringing our unprecedented expertise and know-how in adjuvants and aseptic manufacturing of high-quality adjuvants to our customers in the vaccine and blood fractionation industry.**

We are the leading global manufacturer of premium quality vaccine adjuvants and solutions meeting the individual requirements for the human and veterinary vaccine industry.

It is our vision to supply high quality vaccine adjuvants and bring new and innovative next-generation adjuvant technologies to the market.

It is our goal to be your preferred partner and create value for your business.





#### Fact box

- Vaccine Adjuvants are a highly diverse collection of compounds that only share one characteristic: that of being able to enhance immune responses
- Roughly 2 billion human vaccine doses are produced annually containing our vaccine adjuvants
- Roughly 23,000 scientific hits on Google Scholar involving our vaccine adjuvant products
- More than 680 unique peer-reviewed publications on Pubmed.gov involving our vaccine adjuvant products

# Contact us



“We stand for quality, reliability and transparency.  
We are all about creating partnerships.”

**Peter H. Tygesen**  
Managing Director - Vaccine Adjuvants

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