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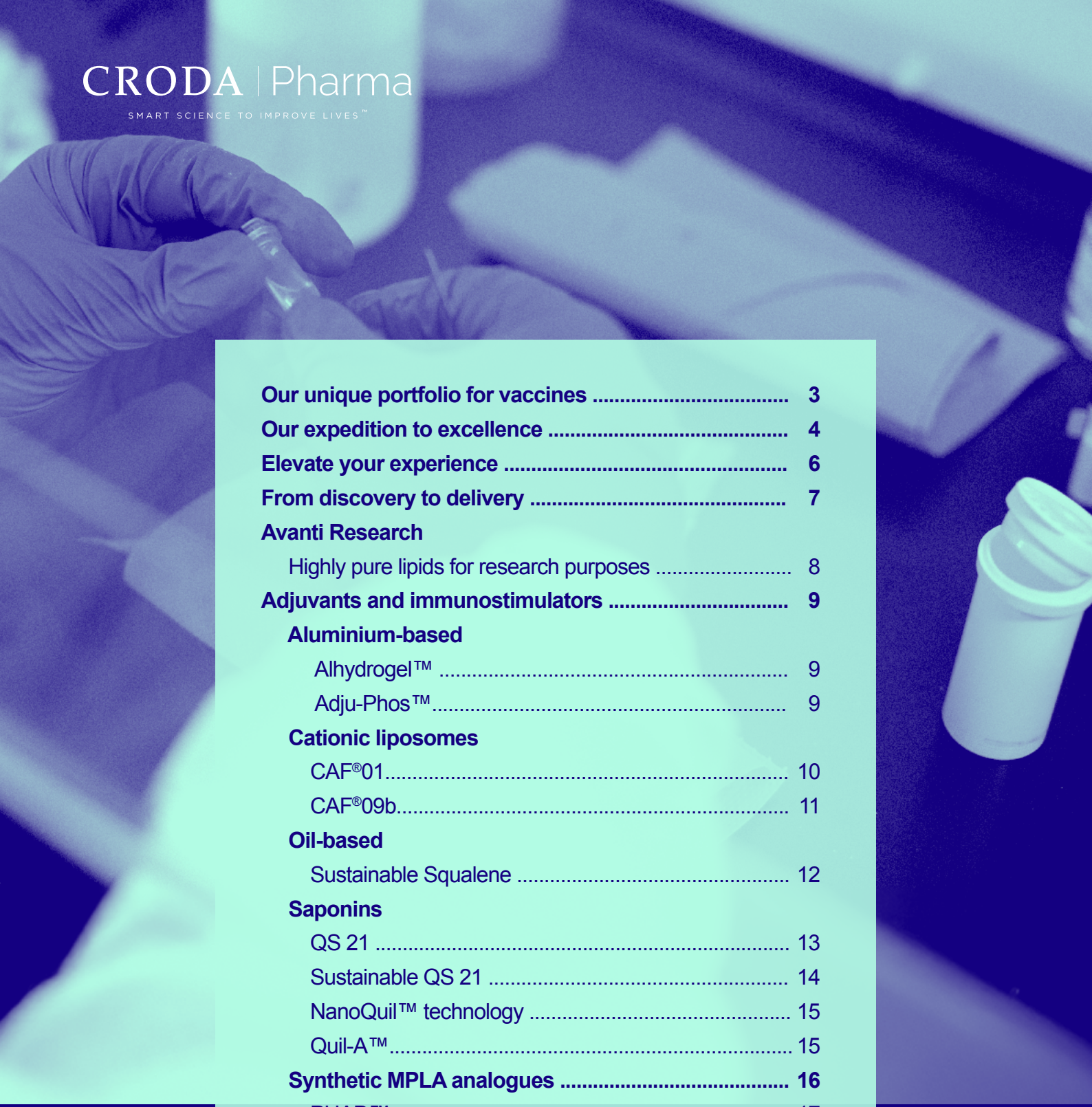
Avanti Research

A CRODA BRAND

# Empowering the development of tomorrow's vaccines

## From research to commercialisation

www.crodapharma.com



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# Bringing together 250 years of adjuvants expertise with an even broader and unique portfolio for vaccines

**Vaccine development can span decades of extensive research, testing, and regulatory processes. And while recent advancements and pandemics have driven these timelines down, this has only highlighted the need for better and more secure access to vaccine ingredients and a powerful supply chain to support these advancements.**

This need is further amplified by the call for more sustainable and nature-positive alternatives for traditional vaccine ingredients such as non-shark derived squalene and saponins that do not contribute to deforestation.

## Our offering

**Unlocking new administration routes**

**More secure supply chain**

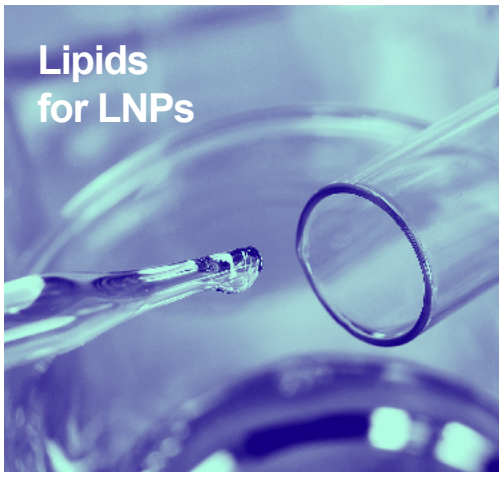
**Nature-positive alternatives**

Leveraging our long history of adjuvants manufacturing and our innovation culture, our scientists are collaborating with vaccine developers and academia **to develop new and effective adjuvant systems and ingredients for the vaccines of the future**.

**The Croda Pharma and Avanti Research portfolio** includes high purity research grade materials for early-stage research, novel adjuvant systems and sustainable, innovative immunomodulators and excipients for clinical development phases and large-scale GMP production.

**Explore our capabilities and discover how we can help accelerate your future vaccine development.**





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# Our expedition to excellence: the steps we have taken

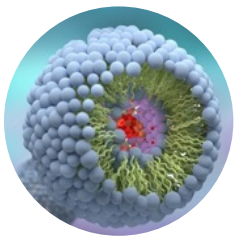
Founded 100 years ago, Croda understands the central role science plays in our everyday lives. Today, that means using our **Smart science to improve lives™.**

Croda Pharma is at the forefront of pharmaceutical science, with the ability to deliver high quality excipients, quickly and at scale. The company has proven to be crucial for the rapid rollout of many COVID-19 vaccine programmes. Today we are a global, innovative, and application science-led business that positively impacts the health of millions of people.

## Some significant milestones have marked this development

### 2018

Acquisition of Biosector with over 80 years of adjuvants expertise and their industry-leading brands of aluminium-based adjuvants, **Alhydrogel™** and **Adju-Phos™**, as well as the saponin-based **Quil-A™** along with an impressive GMP manufacturing site including sterile production and aseptic filling.



### 2020

Avanti Polar Lipids, (Avanti) joined the Croda group. Founded in 1967, Avanti is a global leader in the manufacture and supply of the highest purity lipids for research and pharmaceutical product development. Avanti revolutionised vaccine development with the introduction of synthetic Monophosphoryl Lipid A derivatives, known under their intensely investigated and cited **PHAD™**-range.

## Enabling access to innovative technologies and sustainable supply chains

At Croda Pharma, we recognise the need for novel adjuvant systems to respond to the challenges in vaccine development. We are dedicated to unlocking the potential of new technologies to enhance our portfolio of safe and effective vaccine adjuvants. Our goal is to make novel adjuvant systems available for clinical development and commercial manufacturing. To achieve this, we have established several strategic partnerships.

### 2022

STATENS SERUM INSTITUT

Partnership with the renowned **Statens Serum Institut** (SSI) in Copenhagen, Denmark, which focuses on preventing and controlling infectious diseases. We exclusively manufacture, and commercialise two **CAF®**-adjuvants, **CAF®01** and **CAF®09b**. Over the past decade, clinical trials have demonstrated their effectiveness as powerful vaccine adjuvants.

## 2023

Partnership with **Amyris Inc.**, USA, a pioneer and leader in synthetic biology who has developed an innovative method to enable access to squalene. This key component of seasonal and pandemic influenza vaccines is traditionally harvested from the liver of deep-sea sharks. Amyris's sustainable, reproducible and scalable process combined with our expertise in purification, brought the **award-winning Sustainable Squalene** to the market.

## 2023

Partnership with **Botanical Solution Inc.** (BSI), USA, enabling access to the high-performing **immunostimulator QS 21**. This saponin fraction, found in the bark of *Quillaja saponaria* Molina, a Chilean tree, is traditionally obtained from bark extracts. To address the depletion of natural resources and make supply chains independent of weather and harvest conditions, BSI has developed a technology based on plant cell cultures, allowing for the sustainable and scalable production of kilograms of QS 21. Together, Croda and BSI are making this crucial component for highly efficient adjuvant formulations available to the vaccine industry.

## 2024

Avanti Research (formerly Avanti Polar Lipids) was founded to meet the demand for highly purity lipids in scientific research. Over the decades, these lipids have built a world-renowned reputation. Now a part of the Croda family, the Avanti Research brand leads the way with highly purified lipids and services for fundamental and pharmaceutical development including novel lipids for vaccine adjuvant research and next-generation delivery systems. With an innovative portfolio boasting over 2,000 lipids, Avanti Research offers solutions to offer academic, biotech, and pharma researchers. The comprehensive range of high-purity lipids for clinical development and commercial manufacturing has been integrated into the Croda Pharma brand.

Driven by sustainability, innovation, and our portfolio of market-leading products, Croda Pharma and Avanti Research, much like the whole Croda organisation, is committed to having a positive impact on the environment and society.

In our Pharma business commercial opportunities focused on vaccines for diseases affecting the world's most vulnerable populations have been prioritised, with 16 commercial vaccines for four priority diseases (Hepatitis B, Meningitis, Pneumococcal infections and Malaria) containing our technologies.

## Discover our outstanding offerings and capabilities to support you in developing the next generation of vaccines.


# Elevate your experience: Our differentiators

**Powered by culture of innovation**

- We recognise the **need for new and efficacious adjuvant systems** to fight diseases with prophylactic and therapeutic vaccines
- We are advancing our rich **pipeline of innovative next generation adjuvants**, lipids and high purity excipients
- We use our **strong network with innovative research institutes** to expand our offering and bring novel adjuvant systems into clinical research and commercial application

**Unique blend of expertise**

With **over 250 years** of combined experience **Croda Pharma** and **Avanti Research** offer a wealth of formulation knowledge with pharmaceutical excipients, lipid-based formulations, and aluminium- and saponin-based adjuvants

- We make use of our entire knowledge to ensure quality and consistency to make your project successful

**Longstanding commitment to sustainability**

We are committed to be **the most sustainable supplier of innovative ingredients**, demonstrated by the recent launch of our **Sustainable Squalene**.

- We prioritise sustainable supplies to **ensure access** to existing vaccines and the **vaccines of tomorrow**
- We are working tirelessly to **scale up** alternative and **innovative manufacturing** processes and thereby ensure continuous and **secure supply**

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# From discovery to delivery: Support every step of the way

| Exploratory | Early clinical | Late clinical | Market |
|---|---|---|---|
| Research-grade | GMP for clinical development | | GMP commercial production |

- We provide comprehensive support for all phases of vaccine development, from preclinical research through clinical trials to commercial manufacturing. Our expertise includes developing novel adjuvants and adjuvant formulations in collaboration with our customers
- A prime example is our PHAD™ range, synthetic Monophosphoryl Lipid A derivatives, which have shown promising results in phase II vaccine development studies
- Our in-licensed Cationic Adjuvant Formulations, CAF®01 and CAF®09b, are demonstrating encouraging outcomes in clinical trials for chlamydia and personalised neoantigen melanoma vaccine candidates
- Our market-leading aluminium-based adjuvants, Alhydrogel™ and Adju-Phos™, are available in the highest quality and aseptically filled for commercial vaccine production

**Explore our portfolio to see how we can best support your next vaccine development project.**


# Avanti Research - Highly pure lipids for research purposes

## It starts with Avanti Research...

Proven adjuvants have been used in vaccine research for decades. However, they no longer meet the requirements for new and more powerful adjuvants needed to develop new, more effective vaccines. Research activities have therefore intensified, and new mechanisms are being investigated. Highly pure molecules are required even in the discovery phase.

For early-stage research, the Avanti Research portfolio is the perfect starting point.

We are proud to leverage Avanti's world-leading position in the delivery of high-quality lipids. But we are also committed to empowering scientists and researchers with innovative solutions beyond lipids. This vision is at the heart of our brand transformation from Avanti Polar Lipids to **Avanti Research**, a Croda brand.

**Avanti Research** will continue to innovate and enable access to novel lipids for vaccine adjuvant research while evolving to offer a broader range of solutions to enable the next generation of safe and effective vaccines.

The research-use-only (RUO) adjuvant and immunostimulator offering is the ultimate toolbox enabling access to a wide range of molecules to build a system tailored to the specific disease target.

Catalogue materials are available in smaller pack sizes, offering flexibility, minimising waste, and reducing costs.

## It continues with Croda Pharma….

Croda Pharma takes research material to the next level. Research-use-only grades are transitioned into GMP material suitable for clinical development stages under the Croda Pharma umbrella.

Croda Pharma supports your vaccine development projects from discovery to delivery every step of the way. Our comprehensive portfolio of components combined with decades of expertise accelerates the production of complete adjuvant systems and enables access to novel and high-performing adjuvant systems for the vaccines of tomorrow.

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# Adjuvants and immunostimulators

## Aluminium-based

### Alhydrogel™

Manufactured since 1939, Alhydrogel is one of the most widely used vaccine adjuvants in approved vaccines such as for tetanus, diphtheria, meningitis and poliomyelitis as well as in developmental vaccines such as for SARS-CoV-2, herpes zoster or HPV.

#### Key features of Alhydrogel:

**Immune response enhancement:**
Alhydrogel primarily elicits effective Th2 immune response, which is crucial for antibody production.

**Versatility:** It can be used with a wide range of antigens, making it suitable for diverse vaccine formulations.

It also can be combined with immunostimulators such as Monophosphoryl Lipid A (MPLA) or CpG to achieve a well-balanced Th1/Th2 response.

**Safety profile**: It has a long history of clinical use, demonstrating high safety in human and veterinary applications.

**Physico-chemical properties:** At pH 6-8, it has a positive charge, so it effectively adsorbs negatively charged antigens.

It tolerates re-autoclaving, but its colloidal structure is destroyed if frozen.

**Available grades:**
Alhydrogel 1.3% (6,5 mg/ml aluminium)

Alhydrogel 2% (10 mg/ml aluminium)

Alhydrogel “85”, a premium version with higher protein adsorption capacity making it more suitable for multivalent combined vaccines.

**Manufacturing:** The range is manufactured according to EudraLex – Volume 4 (EU GMP) certified production of aseptically prepared sterile products (Annex 1: Manufacture of Sterile Medicinal Products).

### Adju-Phos™

Adju-Phos is an aluminium-based vaccine adjuvant with over 40 years history of use in commercial vaccines. It is used in various vaccines including those for pertussis, hepatitis B, tetanus and diphtheria.

#### Key features of Adju-Phos:

**Immune response enhancement:**
Adju-Phos primarily elicits effective Th2 immune response, which is crucial for antibody production.

**Versatility:** It can be used in vaccines for both bacterial and viral infections and continues to be explored in clinical development trials.

Like Alhydrogel, Adju-Phos product can be combined with other adjuvant types to imprint a different immune fingerprint and increase immune response stimulation.

**Safety profile:** It has a well-established safety profile with minimal side effects such as local inflammation at the injection side. Adju-Phos contains 0,9% NaCl to reduce injections site discomfort.

**Physico-chemical properties:**
Adju-Phos is an amorphous aggregate of nanometre-size hydrous crystallites. At neutral pH, it has a net negative charge and effectively adsorbs positively charged antigens.

**Available grades:**
It is supplied with two variants of pH-values to allow flexibility during the manufacturing process.

**Manufacturing:** The range is manufactured according to EudraLex – Volume 4 (EU GMP) certified production of aseptically prepared sterile products (Annex 1: Manufacture of Sterile Medicinal Products).

# Cationic liposomes

A common challenge for adjuvants is that they significantly increase the humoral response to vaccine antigens but induce only very weak-cell-mediated immune (CMI) responses. There is therefore a need for vaccine adjuvants that prime T-cell immunity, for effective vaccines against especially intracellular pathogens, but also to support improved antibody responses.

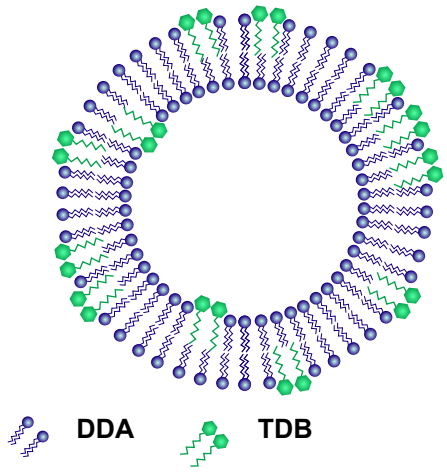
Croda Pharma continuously increases its offering in innovative vaccine adjuvant systems. The strategic collaboration with Statens Serum Institut (SSI), leading Danish governmental life-science research institute, enables us to offer an even more diverse adjuvant portfolio.

The CAF® technology platform is a range of novel, patented, CMI inducing cationic liposomal adjuvants. Over the past decade, clinical trials have shown these to be powerful immunostimulators in tuberculosis, chlamydia, HIV, malaria, and specific cancer studies.

Currently, Croda collaborates with SSI to exclusively manufacture and market two CAF®-adjuvants, CAF®01 and CAF®09b.

## CAF®01

CAF®01 is a fully synthetic two-component liposomal suspension composed of dimethyldioctadecyl ammonium (DDA) and C-type lectin receptor agonist trehalose dibehenate (TDB).




### Key features of CAF®01

**Immune response enhancement:**
CAF01 drives both humoral and cellular immune responses. It has an exceptional ability to induce memory CD4+ T-cell responses, shown in both mice and humans.

DDA acts as a delivery vehicle serving to promote uptake and presentation of the vaccine antigen in the relevant subset of antigen-presenting cells (APCs), whereas TDB is a MINCLE ligand that thus activates APCs through the SYK-CARD9 signalling pathway thereby inducing highly potent Th1/Th17 and B-cell responses.

Potent neonatal adjuvanticity in preclinical studies suggests that it is fulfilling the requirements for novel vaccines to be used in early life by which many vaccine adjuvants fail to do.

**Versatility:** It can be used with a wide range of pathogens such as proteins, peptides, inactivated vira, split virions and antigen isolates. It is suitable for vaccines against intracellular pathogens such as *Mycobacterium* tuberculosis or *Chlamydia* trachomatis.

**Safety profile:** CAF01 has a proven safety and tolerability profile with no residual tissue damage or nodule formation at injection site.

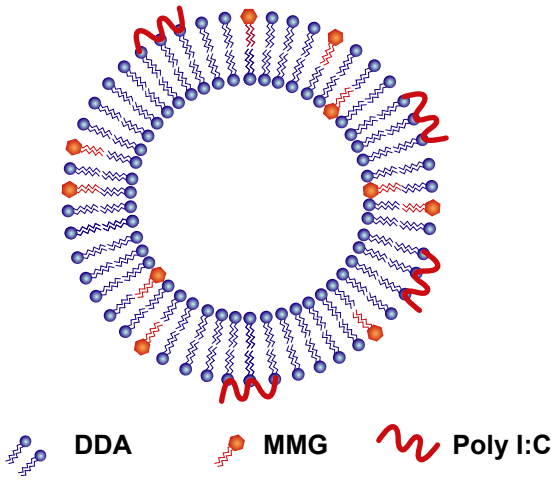
**Physico-chemical properties:**

- Well characterised liposome
- Long-term stability
- Can be freeze-dried
- Simple mixing/reconstitution of antigen with adjuvant system

**Supply chain:** CAF®01 is available in technical grade for pre-clinical development. It is manufactured by an up-scalable manufacturing process. Product suitable for use in investigational medicinal products can be made to order.

# CAF®09b

CAF®09b is a fully synthetic three-component liposome-based adjuvant system. The delivery system is built by the cationic surfactant dimethyldioctadecyl ammonium (DDA) combined with the immunostimulatory C-type lectin receptor agonist monomycoloyl glycerol (MMG) and the TLR3 agonist poly I:C (polyinosinic-polycytidylic acid).




## Key features of CAF®09

**Immune response enhancement:**
CAF®09b drives strong CD8+ T-cell responses obtained through simultaneous stimulation of MINCLE and TLR3 receptors.

In cancer immunotherapy trials, CAF®09b has been shown to induce strong production of antigen specific CD8+ T-cells through cross-priming in combination with peptide- or protein-based antigens.

Further preclinical studies indicate CAF®09b could be a potent adjuvant for mucosal applications directly priming the immune response. Highest CD8+ T-cell potency is thus obtained by intraperitoneal administration e.g. utilised in clinical cancer immunotherapy trials and by intranasal administration e.g. utilised preclinically with corona vaccine trials to obtain local immunity and prevention of infection.

**Versatility:** It is a highly versatile adjuvant system, that can be combined with different types of antigens, including peptide-based neoantigens for personalised vaccines, protein subunits, inactivated vira, or split virions. It is suitable for vaccines against intracellular pathogens such as *Mycobacterium* tuberculosis or *Chlamydia* trachomatis.

**Safety profile:** CAF®09b is evaluated safe in toxicology and human clinical trials.

Clinical trials demonstrate better tolerability in comparison to poly I:C alone, the most used adjuvant in therapeutic cancer vaccine trials.

**Physico-chemical properties:**

- Well characterised liposome
- Long-term stability
- Can be freeze-dried
- Simple mixing/reconstitution of antigen with adjuvant system

**Supply chain:** CAF®09b is available in technical grade for pre-clinical development. It is manufactured by an up-scalable manufacturing process. Product suitable for use in investigational medicinal products can be made to order.

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# Oil-based

## Sustainable Squalene

**Squalene is a key component in emulsion adjuvants for seasonal and pandemic influenza vaccines. It is a natural lipid belonging to the terpenoid family. Initially, it was identified as a component of shark liver oil.**

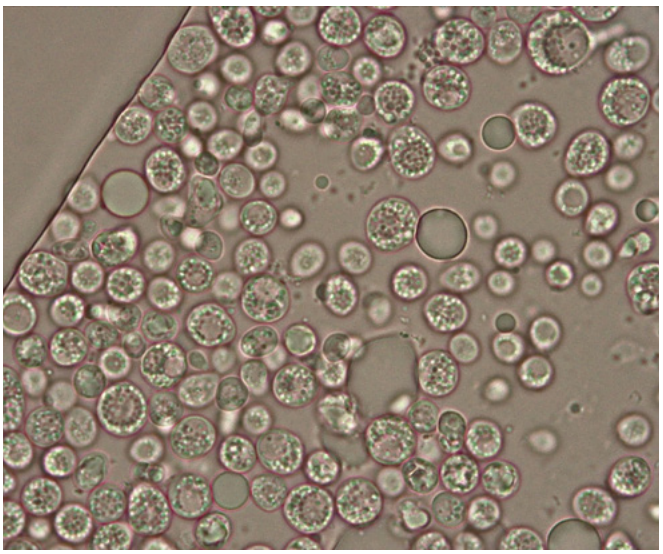
**Squalene demonstrates remarkable bioactive properties which are widely recognised.**

### Origin

The current primary source of squalene is shark liver oil, which raises ecological concerns. Sharks are vital to maintaining marine ecosystems and they are under threat from overfishing and habitat loss. Harvesting squalene from deep-sea sharks exacerbates this issue and poses a significant challenge for sustainability.

Synthetic biology paved the way to an innovative fermentation-based process to produce squalene.

The resulting squalene is molecularly identical with shark-derived squalene and has been demonstrated to have equivalent stability in emulsion adjuvants.



Micrograph of yeast full of squalene (green circles)

### Award-winning production process

The innovative production method combined with purification excellence results in Sustainable Squalene with superior purity of at least 99% meeting stringent requirements for vaccines.

### Key features of Sustainable Squalene:

**Immune response enhancement:** Squalene-based emulsions establish an immunocompetent environment at the site of injection

- Induce the release of DAMP (Damage-Associated Molecular Pattern) signals
- DAMP signals recruit innate immune cells
- Trigger cytokine and chemokine cascades
- Lead to Antigen-Presenting Cell (APC) activation, enhanced antigen uptake and presentation to adaptive immune cells

Squalene emulsion adjuvants generate robust antibody and memory B-cell responses.

**Safety profile:** Squalene has a well-established safety profile and shows high tolerance in both adults and children. Therefore, it is of particular importance for vulnerable patients.

**Sustainability benefits:**

- Conservation of shark populations, benefitting marine ecosystems and blue carbon
- Raw materials with low land impact and land utilisation
- Detailed study of Product Carbon Footprint on GMP grade manufacturing process

**Available grades:**
Sustainable Squalene is available in two grades: one with vitamin E and one without, both filled under a nitrogen blanket.

**Supply chain:** Proven commercial scalability (Excipient GMP) and perennial availability of raw material source provide security of supply

# Saponins

## QS 21

**QS 21 is a purified triterpenoid saponin molecule fraction from the bark of the South American tree *Quillaja saponaria* Molina. The adjuvant activity of quillaja saponins was reported as early as 1925. In the 1970s, a purified saponin-mixture of quillaja saponins was introduced for use in veterinary vaccines (see Quil-A).**

In 1991, Dr. Charlotte Kensil et al. isolated and named QS 21 as a component of the triterpenoid quillaja saponins. This highly purified fraction demonstrated an optimal balance of enhanced immunostimulatory properties and tolerable reactogenicity. The QS 21 fraction comprises different isomeric forms.

### Key features of QS 21:

**Immune response enhancement:**

- QS 21 elicits a broad activation of the adaptive immune system
- It enhances the activation of dendritic cells and macrophages, which are crucial for initiating the immune response
- It improves the presentation of antigens to T-cells and can induce a strong cell-mediated response against intracellular infections
- Through stimulation of Th1 and Th2 cytokine secretion, it helps regulating the immune response
- It further can act synergistically with other components such as Monophosphoryl Lipid A (MPLA) to increase the overall potency of a vaccine

**Versatility:** QS 21 is a highly versatile immunostimulator due to its ability to enhance both humoral and cell-mediated immune responses.

It is used in adjuvant systems with synthetic MPLA analogues (see Synthetic MPLA analogues) in clinical development for vaccines against malaria, tuberculosis and HIV among others.

**Safety profile:** The safety profile of QS 21 has been extensively studied and generally shows it to be safe and well-tolerated. It is recommended to formulate QS 21 with a lipid to neutralise the surfactant activity and improve the tolerance of QS 21 containing formulations.

**Physico-chemical properties:**

- QS 21 is supplied as a lyophilised product in 5mg vials and dispatched frozen
- QS 21 is known to undergo hydrolytic degradation, which can affect its stability and efficacy as a vaccine adjuvant
- To mitigate hydrolysis, it is recommended to formulate QS 21 with lipids or phospholipids, which help stabilise the adjuvant and maintain the high adjuvant potency of the final vaccine

**Storage conditions:**

- Store frozen in the lyophilised state
- Recommended pH in aqueous stock solutions:
  - pH 5.5 to 6.5
  - Hydrolytic splitting of the acyl chain fragment compromises the adjuvant effect and occurs spontaneously, especially at a pH ≥ 7.4 and at elevated temperatures

**Manufacturing:** It is available in investigational GMP quality for use in clinical development.

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# Sustainable QS 21

**At Croda, we are committed to become the most sustainable supplier of innovative ingredients. We are working towards a portfolio of products with proven, substantiated claims on their environmental footprint.**

Our strategic partnership with Botanical Solution Inc. (BSI), a leading producer of advanced botanical ingredients, secures access to the most sustainable source of pharmaceutical grade QS 21 suitable for use in vaccine formulations.

Botanical Solution Inc. has developed an award-winning technology based on juvenile plants from *Quillaja saponaria* Molina. The innovative in-lab cultivation and extraction process sustainably delivers QS 21 and secures consistent supply to produce kilogram-quantities of GMP QS 21.

## Benefits of Sustainable QS 21:

**Source:**

- One raw material source
- No deforestation
- Juvenile plants from *Quillaja saponaria* Molina are identical with traditional source of QS 21

**Technology:**

- Optimised biotechnological platform for increased efficiency
- Growth in meticulously controlled environment

**Supply chain:**

- Proven commercial scalability to deliver in the future kilogram quantities of QS 21

**Quality:**

- Highly purified GMP QS 21 for clinical development

Please contact your responsible Account Manager for information on availability.

Cultivation of juvenile plants of *Quillaja saponaria* Molina

# NanoQuil™ technology

**Saponin-based immunostimulating nanoparticles have potential for use in vaccinology. We are working on development and commercialisation of new generation saponin–based nanoparticles within the NanoQuil range.**

Saponins from the bark of *Quillaja saponaria* Molina show a potent activation of dendritic cells and induction of cytokines/chemokines resulting in a strong stimulation of cell-mediated (Th1) and antibody-mediated (Th2) immune response.

However, saponins are prone to hydrolysis and degradation at physiological pH at ambient temperatures. In addition, cell-lytic properties lead to local reactions at the injection site. This requires a balanced adjuvant dose between the immunostimulatory effect and the local reaction.

- NanoQuil technology has been developed to overcome the challenges of saponins while securing the benefits. It consists of a series of immunostimulating nanoparticles developed for use in both veterinary and human applications
- NanoQuil is based on incorporation of saponin in cholesterol resulting in increasing stability of saponins and reducing negative cell-lytic effect due to its low reactogenicity



# Quil-A™

**Quil-A is a highly purified quillaja saponin which has been specifically developed for use as an adjuvant in veterinary vaccines.**

Quil-A saponin was originally purified and characterised by Dr. Kristian Dalsgaard in 1974 and adapted for commercial scale production. It is a highly concentrated and potent saponin purified from bark extract of the Quillaja saponaria Molina tree, that consists of a complex mixture of more than 100 different saponin molecules.

## Key features of Quil-A:

**Immune response enhancement:**
Its mode of action involves stimulating both humoral (Th2) and cellular (Th1) immunity, leading to a more robust and sustained immune response.

Quil-A enhances the activation of dendritic cells, which play a pivotal role in initiating immune responses by presenting antigens to T-cells.

It induces the secretion of pro-inflammatory cytokines such as IL-1ß, which is essential for recruiting immune cells to the site of infection. It has been shown to contribute to increased levels of IFN-ɣ and CD8+ T-cells.

**Versatility:** It is suitable for both intracellular pathogens via a cell-mediated mechanism of action (Th1) and extracellular pathogens via an antibody-mediated mechanism of action (Th2).

Quil-A is used in various veterinary vaccines, for farm animals as well as companion animals, for example, cattle, pigs, sheep, poultry, cats, and dogs.

**Safety profile:** Quil-A is an extensively studied veterinary vaccine adjuvant and used for over 40 years in commercial veterinary vaccines.

**Physico-chemical properties:**

- It can form cage-like ISCOM (Immune Stimulating Complex) particles together with cholesterol and phospholipids
- Supplied as a lyophilised, concentrated, crystal-like powder
- Water-soluble
- Sterile filtered prior to lyophilisation to ensure a low bioburden in the final product

**Manufacturing:** Manufactured according to Eudralex Volume 4 (EU GMP) certified production.

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# Synthetic MPLA analogues – Our PHAD™ range

**As early as the late 1890s, there were observations that lipopolysaccharides (LPS) from gram-negative bacteria display adjuvant activity. LPS is a structural constituent of the outer membrane of such bacteria. Its toxicity, however, hindered its use in vaccines. LPS consists of a polysaccharide portion and a polyacylated diglucosamine lipid called lipid A. This constitutes the core active moiety of LPS.**

In the following decades, research continued, and it became apparent that Monophosphoryl Lipid A, MPLA, was non-toxic and yet immunostimulatory.

Only in the late 1990s, the Toll-like receptor 4 (TLR4)-agonist effects of LPS and lipid A derivatives were revealed and understood and paved the way for inclusion in vaccines. Eventually, the first vaccine containing MPLA in combination with the saponin-derived QS 21, known as the AS01 adjuvant system from GSK, was approved in 2017 by the U.S. Food and Drug Administration.

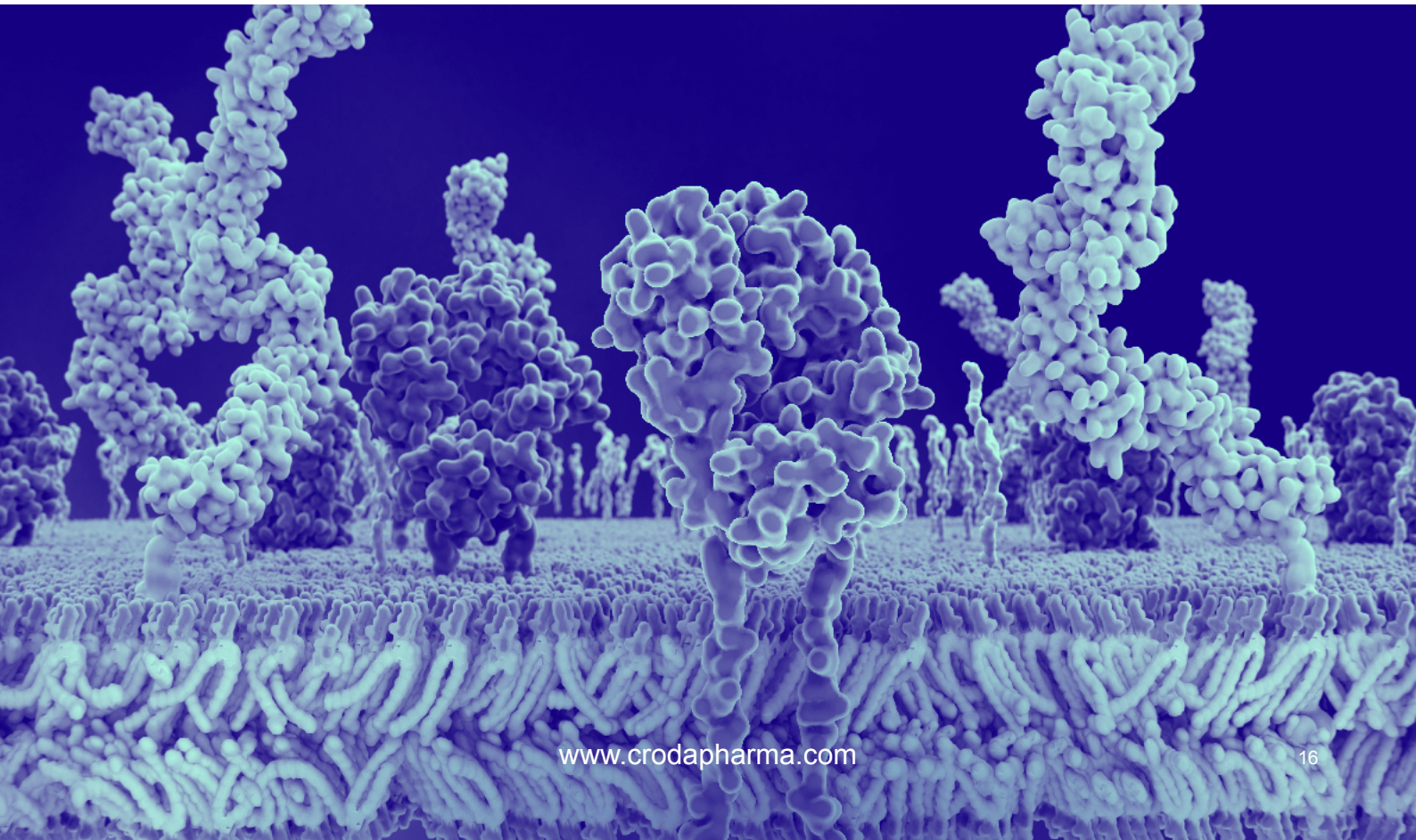
In parallel, research was ongoing on synthesis pathways to obtain structural analogues to the bacterial-derived MPLA.

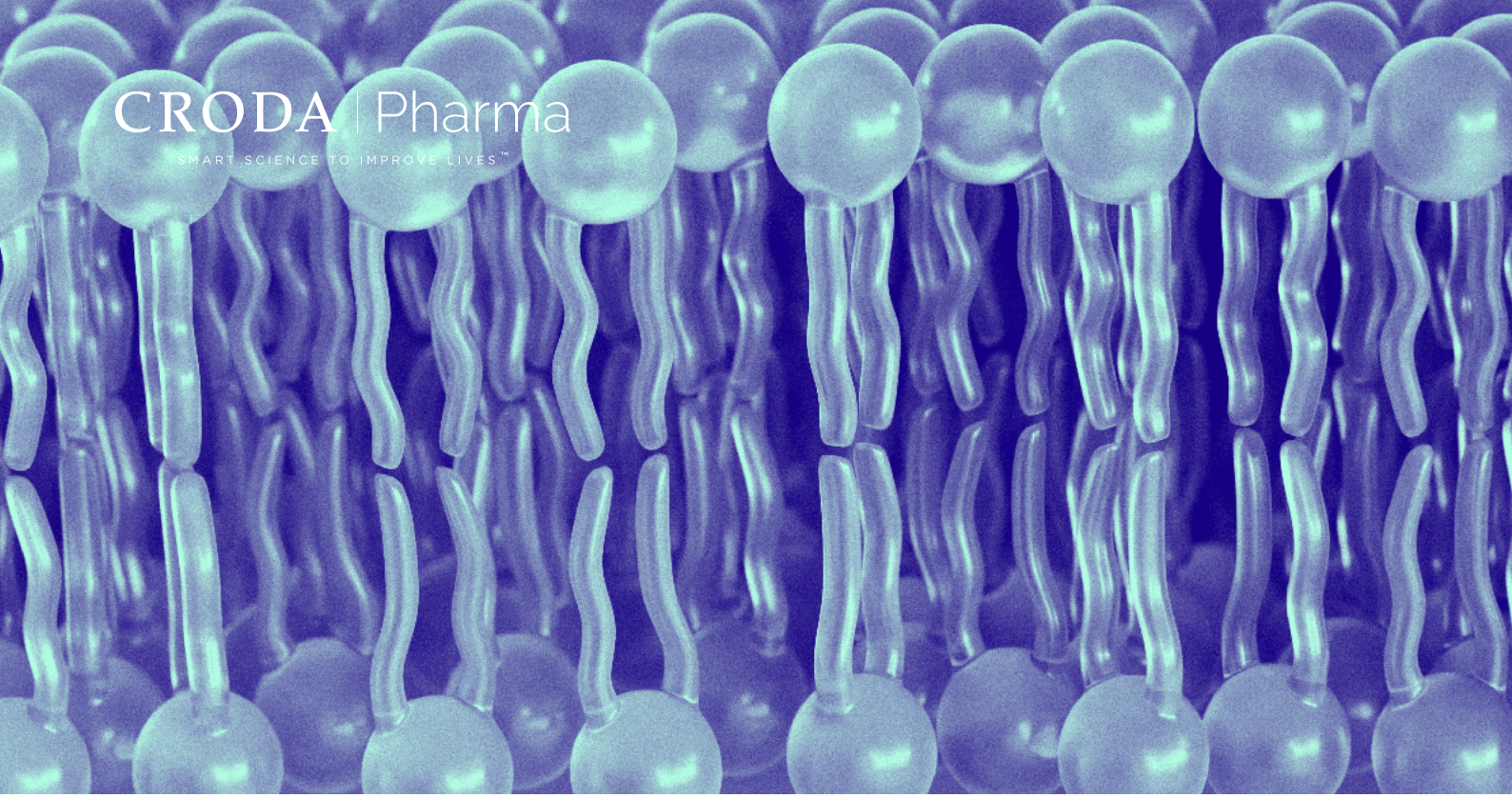
**Our portfolio includes the PHAD-range, a series of synthetic equivalents to MPLA.**

## Immune response enhancement:

The signalling pathway through which MPLA and synthetic analogues work is by stimulation through the TLR4-receptor. TLRs are transmembrane pattern recognition receptors (PRRs) that recognise pathogen associated molecular patterns (PAMPs). PAMPs are derived from micro-organisms and drive inflammation in response to infections. One such PAMP is LPS.

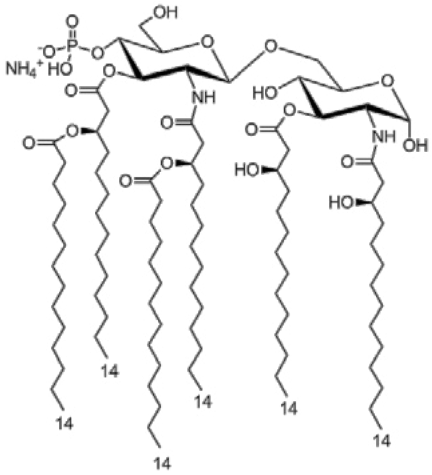
The activation of the TLR4 signalling pathway through synthetic MPLA analogues like PHAD, 3D-PHAD, 3D-(6-acyl)-PHAD and C10-PHAD results in production of proinflammatory cytokines and production of antigen-specific effector CD4+ and CD8+ T-cells. CD4 + cells are helper T-cells and CD8+ cells are cytotoxic T-cells.






## PHAD™

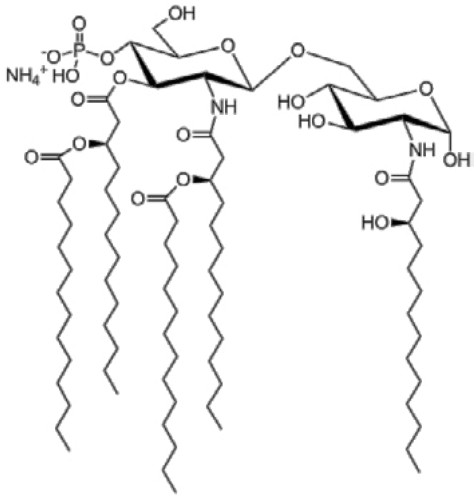
PHAD, Phosphorylated HexaAcyl Disaccharide, is the first synthetic equivalent to bacterial-derived Monophosphoryl Lipid A (MPLA) used as an immunostimulator in adjuvant systems in clinical development.



Also referred to as GLA (Glucopyranosyl Lipid Adjuvant), PHAD has been administered to over a thousand human subjects in clinical trials on a range of adjuvant formulations combining PHAD with saponins, squalene emulsions or aluminium-based adjuvants.

## 3D-PHAD™

3D-PHAD, synthetic monophosphoryl 3-deacyl lipid A, is a highly pure homogenous synthetic equivalent of the 3-deacylated MPLA derived from bacterial LPS. Less pyrogenic than its bacterial-derived mimic, it is comparable to bacterial MPLA and other synthetic MPLA analogues at eliciting an immune response in a liposomal adjuvant system.

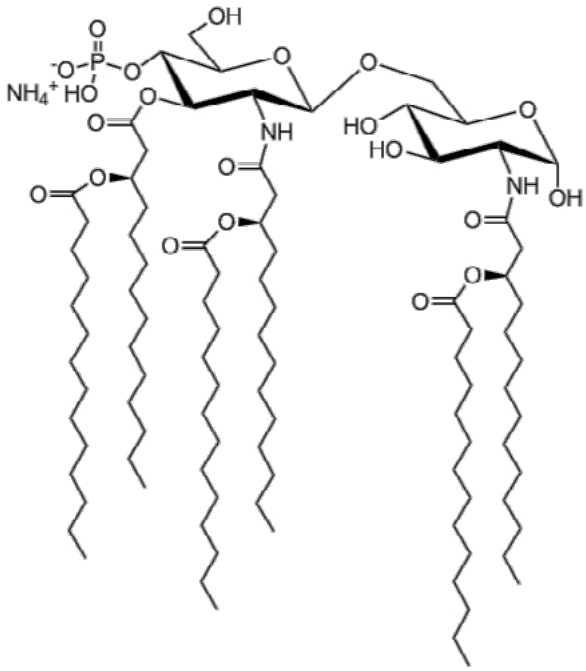


The product has demonstrated equivalency to PHAD during extensive preclinical testing, and human trials are scheduled for launch.

3D-PHAD is protected under US Pat No. 9,241,988. Licensing opportunities are available for vaccine or immunotherapy commercialisation.

## 3D-(6-acyl)-PHAD™

The synthetic and highly pure MPLA structural analogue, 3D-(6-acyl)-PHAD is most closely related to the reported structure of MPL® used in marketed liposomal adjuvant systems.



**Versatility:** PHAD, 3D-PHAD and 3D-(6-acyl)-PHAD are advanced adjuvant system components researched in more than a hundred pre-clinical and approximately eighty clinical studies.

In formulation with a variety of antigens, PHADs fight against a range of pathogens and diseases like malaria, tuberculosis, influenza, HIV, and many more.

PHADs are also used in next-generation treatments like microneedle platforms for seasonal influenza and dendritic cell-based cancer immunotherapies.

They are formulated in different adjuvant systems in combination with QS 21, squalene emulsions or aluminium-based adjuvants.

**Safety profile:** In all cases, these adjuvants exhibit a similar activity and safety profile to bacterially derived MPL.

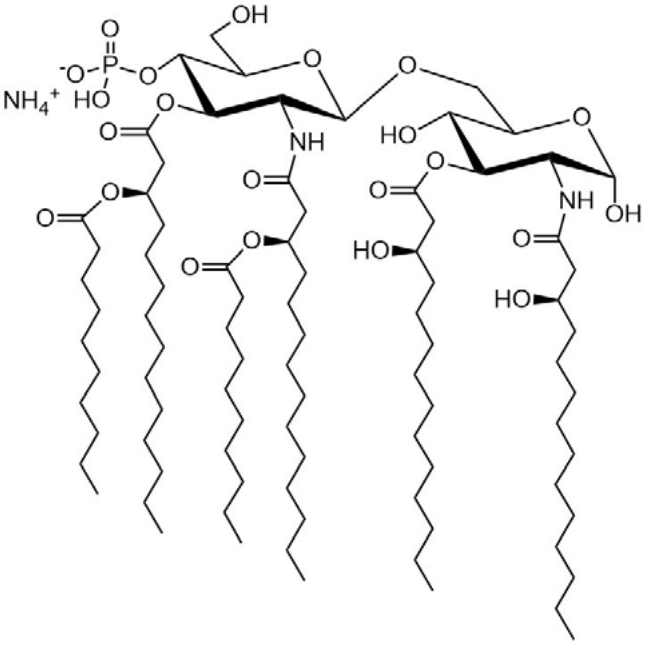
**Manufacturing:** Manufactured at an FDA registered facility. Compliant with 21CFR part 210/211, ICHQ7 and IPEC guidelines as applicable.

The PHAD range of products is available in GMP quality for clinical development.

## C10-PHAD™

C10-PHAD is a synthetic structural analogue designed for superior adjuvant performance. Based on structural analysis of the known ligand/receptor interactions, a second-generation lipid adjuvant (SLA) was designed to target the human receptor.

The lipid chains were shortened to develop a targeted immunostimulator made for human-receptor agonism.



Referred to as SLA, it has been used in pre-clinical studies across different species and a variety of pathogens, including bacteria and viruses, formulated in different adjuvant systems in combination with QS 21 and squalene emulsions.

Advancements in clinical development have been reported, suggesting promising adjuvanticity and good safety profiles.

**Manufacturing:** Manufactured at an FDA registered facility. Compliant with 21CFR part 210/211, ICHQ7 and IPEC guidelines as applicable.

C10-PHAD is available in GMP quality for clinical development.

Licensing opportunities are available for vaccine and immunotherapy commercialisation.

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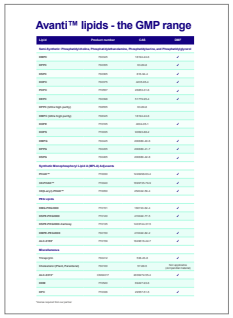
# Highly pure excipients

## Our Avanti™ lipids portfolio

**Through the Avanti lipids range, Croda Pharma supplies GMP manufactured lipids that will allow you to perfectly tailor your adjuvant formulation.**

The range includes essential components such as phospholipids and sterols which are used in licensed vaccine formulations and novel adjuvant systems in clinical development.


Avanti™ lipids - the GMP range

# Lipids for adjuvant systems

**Adjuvant systems like squalene-based water-in-oil emulsions or liposomal systems containing TLR4 agonists, saponins and aluminium-based adjuvants are formulated with further lipids such as:**

### Avanti POPC

1-palmitoyl-2-oleoyl-glycero-3-phosphocholine, or 16:0-18:1 PC (POPC), is a mixed-chain phospholipid featuring a 16-carbon saturated (palmitoyl) acyl chain at the sn-1 position and an 18-carbon monounsaturated (oleoyl) acyl chain at the sn-2 position. Thanks to a ~–2°C phase transition temperature and its physiological relevance, POPC is widely used in membrane biophysics, liposome formulations, and cell model systems.

### Avanti DOPC

1,2-dioleoyl-sn-glycero-3-phosphocholine, or 18:1 (Δ9-Cis) PC (DOPC), is an unsaturated phospholipid that features 18-carbon acyl chains with a cis-double bond at the ninth position. This phospholipid has a low phase transition temperature of around –17°C, enabling it to remain in a fluid, liquid crystalline state at physiological temperatures. This feature makes it an essential lipid in liposomal drug delivery, cell membrane research, and biophysical studies.

### Avanti DPPC

1,2-dipalmitoyl-sn-glycero-3-phosphocholine, or 16:0 PC (DPPC), is a saturated phospholipid with two 16-carbon acyl chains. This phospholipid is known for its critical role in liposomal formulations, pulmonary surfactant research, and advanced drug delivery systems. As such, DPPC is essential in both biomedical and pharmaceutical applications.

### Avanti DMPC

1,2-dimyristoyl-sn-glycero-3-phosphocholine, or 14:0 PC (DMPC), is a synthetic phospholipid with two 14-carbon saturated acyl chains at the sn-1 and sn-2 positions of glycerophosphocholine. The phospholipid's phase transition temperature (around 23°C) has helped make it a staple in membrane biophysics, liposome formulations, and lipid-based drug delivery systems. DMPC improves immune response and facilitates targeted antigen delivery, which makes it a vital component in lipid-based vaccine adjuvants.

Visit our website to explore our GMP lipids for large-scale production with pharmaceutical-grade solutions manufactured to meet the highest quality and regulatory standards for clinical and commercial applications.

### Avanti Cholesterol, plant

Cholesterol is an essential ingredient in a wide range of technologies from adjuvants systems, lipid nanoparticles for mRNA delivery to cell culture media. It is highly biocompatible, stabilises membranes, forms liposomes with increased rigidity, and promotes fusion process making it a perfect component of lipid-based drug delivery systems.

Cholesterol is traditionally derived from egg or animal sources. In the last few years, there has been increasing demand for cholesterol from a plant-based source.

Our plant-based and parental grade cholesterol provides a high-purity alternative to traditional egg and animal-based cholesterol and is USP/NF, JP and parenteral grade Ph. Eur. compliant. It is available for research and development work as well as parental applications.

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# Surfactants and stabilisers

**Croda offers a comprehensive range of high-quality pharmaceutical components. We continuously expand the range in response to market needs.**

All our components are designed and manufactured for pharmaceutical use, using current Good Manufacturing Practice (GMP) standards across all our platforms and manufacturing sites. We were one of the first excipient suppliers to receive EXCiPACT™ certifications across all our global sites and continue to pioneer new monograph approvals via our representation on global monograph industry forums.

We believe that having the highest quality and purest grades of components helps our customers formulate seamlessly and drive products to market quickly and efficiently. Croda's Super Refined™ range of highly purified excipients is manufactured through proprietary processes that remove impurities without affecting the fundamental structure in any way.



## Super Refined™ Polysorbate 20 and 80

It is widely reported in the scientific community that polysorbates can prevent proteins from denaturation, aggregation, surface adsorption and flocculant formulation during product thawing. They are also used in downstream and upstream processes as detergents, washing agents, splitting agents, blocking agents and for lysing cells.

Commonly found impurities in standard compendial grade excipients can negatively influence formulations. Several types of surfactants oxidise readily when exposed to the air or UV light, causing them to lose their properties and potency as solubilising agents. Purity is an incredibly important factor for successful vaccine development.

Polysorbate 20 and 80 (Tween™ 20 and Tween 80) are non-ionic surfactants which are widely used as excipients in the pharma industry; from oral, topical, and injectable applications to blood fractionating, vaccine development and formulation.

Super Refined Polysorbates have been developed to optimise the performance of pharmaceutical formulations and are recommended when the highest quality and purity is required. The level of impurities which are known to have an adverse effect on formulation stability has been reduced.

Super Refined Polysorbate 20 and 80 are manufactured according to GMP standards in EXCiPACT™ certified factories and comply with USP/NF, Ph. Eur., JP and ChP. Chinese DMFs are filed at CDE including for parenteral use.



## Super Refined™ Poloxamer 188

Poloxamer 188 is an industry recognised surface-active, non-ionic polymer and has known protein stabilisation applications in final biologic formulations. It is composed of a central hydrophobic block of polypropylene oxide flanked by two hydrophilic blocks of polyethylene oxide. This structure allows it to act as a surfactant, stabiliser, and solubiliser in various pharmaceutical applications.

Super Refined Poloxamer 188 meets the highest purity standards as a product belonging to our Super Refined range. It offers tightly controlled impurity profiles and molecular weight and undergoes rigorous quality testing. It complies with USP/NF, Ph. Eur. and JPE monographs with ChP status currently in progress.

Super Refined Poloxamer 188 is manufactured to GMP standards at an EXCiPACT™ certified production site. It is suitable for use as a parenteral excipient.

## Span™ 85 Pharma

Span 85 is a non-ionic low HLB surfactant widely used as dispersant, solubiliser, suspending and wetting agent. It is used in MF59 adjuvant system, together with squalene and Polysorbate 80. MF59 is the first o/w adjuvant approved for human influenza vaccines and under clinical evaluation for HIV and CMV (Cytomegalovirus) .

Croda's Span 85 Pharma complies with Ph. Eur. and is manufactured according to GMP standards in EXCiPACT™ certified factories.

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# Lipids for LNPs

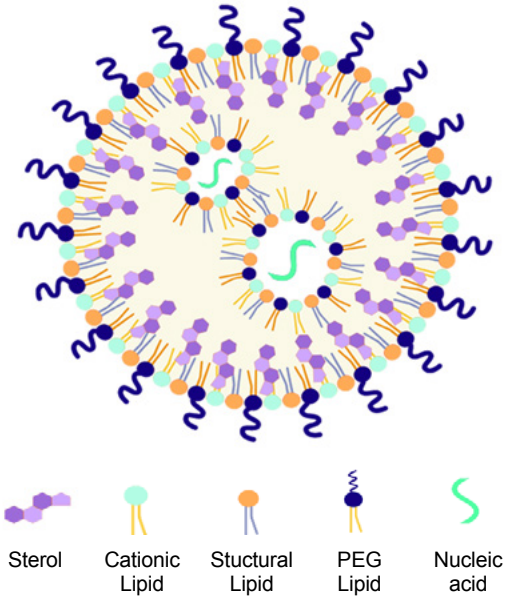
**Lipid Nanoparticles (LNPs) are lipid-based drug delivery systems that carry nucleic acid material. They have been shown to be effective at delivering mRNA vaccines. These systems primarily rely on four lipid components: an amino (cationic) lipid, PEG lipid, structural/neutral lipid, and cholesterol.**

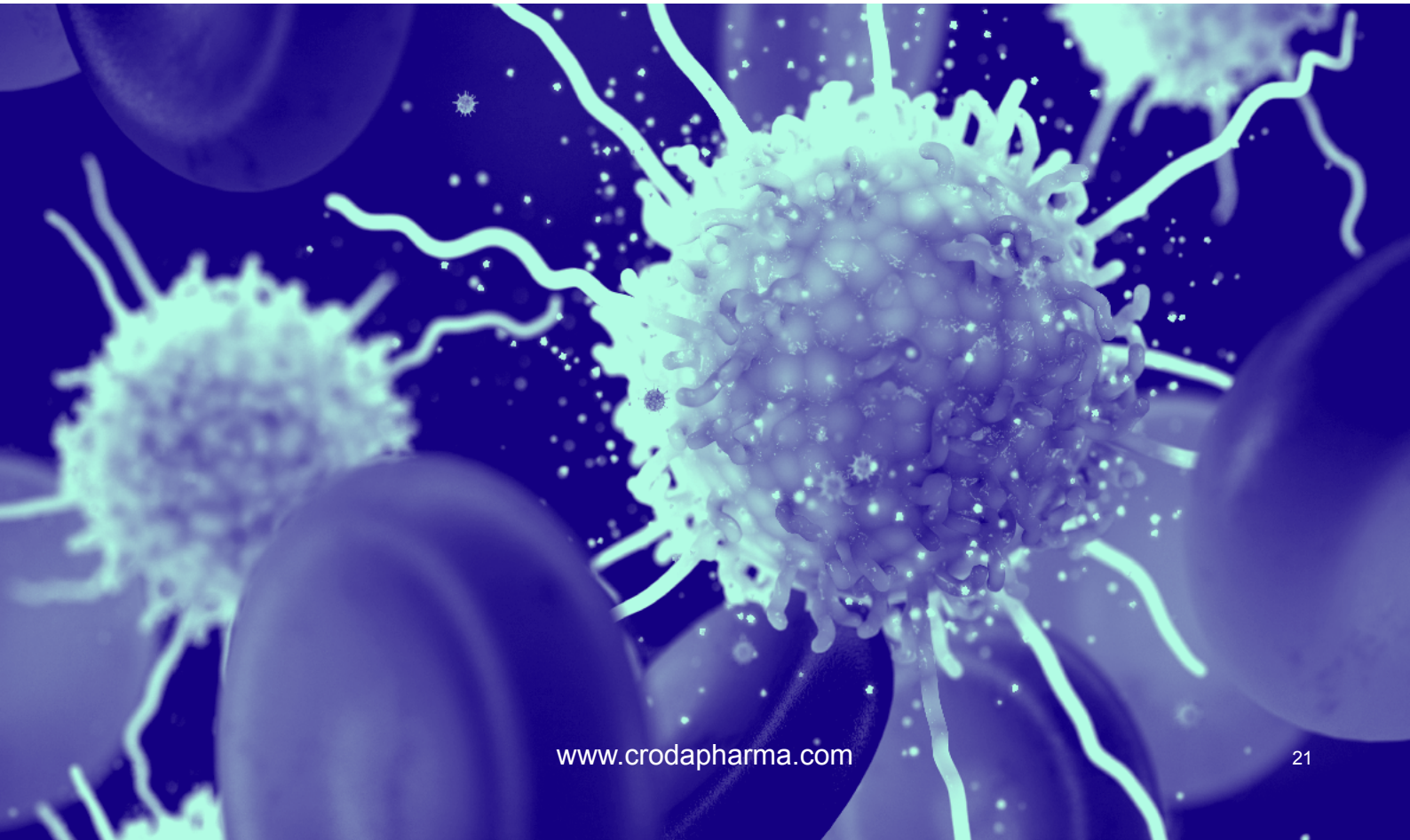
The ionisable cationic lipid sequesters the genetic material through a charge interaction and releases the material following a pH-change in the endosome. The PEG lipid component forms the exterior shell to protect the LNP, provides steric hindrance to prevent aggregation, and promotes small particle.

The structural/neutral lipid drives the formation of encapsulation, stabilises the LNP, and can prevent premature breakdown. Finally, cholesterol acts as a stability enhancer and assists in the transfection of RNA.

Genetic material is highly susceptible to RNAse activity, but the LNP protects the genetic material from degradation. The LNP also allows the genetic material to gain access to the cell and once inside, to be released. This allows the cellular machinery to translate the delivered genetic material into a cellular response.

**For more information on LNP technology contact your responsible Account Manager.**



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# Specialised manufacturing hubs

**We produce our adjuvants at manufacturing sites worldwide.**

## Zealand, Denmark:

- Over 80 years production of safe and effective adjuvants for human and veterinary vaccines
- Unmatched expertise and highly experienced team to support vaccine producers
- World's only GMP-certified manufacturing site with aseptic filling for commercially available aluminium-based adjuvants

## Staffordshire, UK:

- Excellence in lipid purification and home of our award-winning Sustainable Squalene
- Awarded a UK government grant in recognition of its contribution to delivering high-purity lipids used in COVID-19 vaccines

## Alabama, USA

- Decades of experience in formulation services to support both pre-clinical and clinical development using our cGMP-manufactured lipids
- Continuous research for novel adjuvant components to produce fully synthetic, high-purity compounds for discovery and research
- Scaling capabilities from millilitres to over 100 litres to meet clinical development needs

# Contact our experts

**Croda Pharma partners with world leading pharmaceutical organisations to solve the most complex health and well-being challenges our society faces in this millennium.**

We support you with our manufacturing capabilities and our global network of Croda employees around the world.

**Please contact your sales representative or email us at:**


**Europe, Middle East & Africa:**
pharma.emea@croda.com

**Latin America:**
pharma.latam@croda.com

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