Croda Pharma

Empowering biologics delivery

Addressing the challenges of vaccine formulation

Excipients | Lipids | Adjuvant Systems

Smart science to improve lives™

Avanti® Polar Lipids
Part of Croda International Plc

CRODA

The building blocks for vaccine delivery systems

Combining our unique product portfolios and expertise, Croda Pharma and Avanti Polar Lipids are empowering the development and manufacturing of next generation vaccines. With strong expertise in high quality excipients, a culture of innovation and specialist scientific knowledge, we support our customers with the development of new and effective adjuvant systems and ingredients for vaccines.

We are passionately driving our innovation pipeline to expand our unique and comprehensive offer to our customers in both commercial and academic organisations worldwide.

Our world-class high purity excipients and lipids, together with the diverse portfolio of vaccine adjuvants and immunomodulators, provide a unique combination of building blocks to develop new adjuvant systems and vaccine delivery systems. Leveraging over 80 years of expertise, our scientists collaborate with vaccine developers and manufacturers to create solutions for vaccine formulation challenges.

We put quality at the heart of everything we do

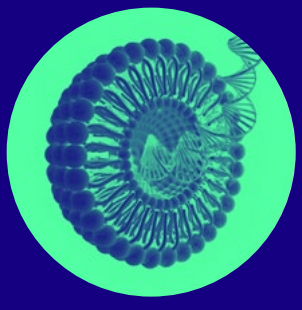
This commitment goes beyond products and consistency of the ingredient systems we bring to market. Our high standards encompass all levels of customer relationships. We provide customised advice and solutions and welcome partnerships across industry and research institutions.

This brochure provides insight into our offering for vaccine development across all platforms in Croda Pharma. Discover here how we can support you in the development of the next generation vaccines.

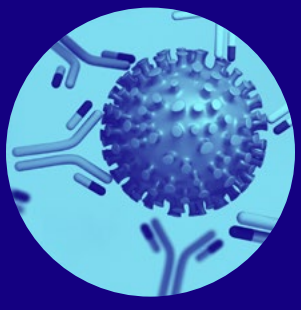
Empowering biologics delivery

Small Molecule Delivery

Protein Delivery



Nucleic Acid Delivery



Adjuvant Systems

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Our journey to Croda Pharma

Founded almost 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.

Leveraging over 80 years of expertise in vaccine adjuvants development and manufacturing, Croda Pharma's industry-leading brands of aluminium-based adjuvants, Alhydrogel™ and Adju-Phos™, as well as the saponin-based Quil-A™ are widely recognised for their unmatched safety and effectiveness in both human and veterinary vaccines. This portfolio of essential products was acquired into the business along with an impressive GMP manufacturing site from Biosector in 2018, including sterile production and aseptic filling.

The year 2020 marked another important milestone in the evolution of the business. 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 (MPLA) derivatives.

And now, it manufactures multiple synthetic analogues of MPL containing a single molecular species. These are as effective and safe at inducing an immune response as their natural product predecessor.

Over the past decade, Avanti has concentrated on developing high purity lipids for liposomal delivery systems including Lipid Nanoparticle (LNP). LNP delivery technology helps solve the stability and delivery issues associated with mRNA-based vaccines and therapeutics, as well as gene editing technology.

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

Alongside our partners, we continue to develop adjuvants to target new diseases and pathogens such as cancer, Alzheimer's, malaria, tuberculosis, HIV, *Staphylococcus aureus*, amongst others.

We are committed to the United Nations Sustainable Development Goals (SDGs). By the end of 2030, our technology will be part of at least 10 clinical phase III trials across at least 25% of the WHO-listed pipeline vaccines.

Offering for vaccines development

Enabling breakthrough innovation

Our vaccine adjuvant portfolio is founded on strong research and development. We recognise the need for new and efficacious adjuvant systems to fight diseases with prophylactic and therapeutic vaccines. Therefore, we develop new adjuvant systems and welcome partners who share our passion, to create the vaccines of tomorrow.

A unique blend of support and expertise

Our combined experience is based on decades 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.

A focus on scientific endeavour

We are committed to enabling next generation drug delivery systems. Leveraging innovation, formulation and application, we are determined to deliver better excipients, lipids and adjuvants systems for biopharma, to unlock more treatments.

R&D is our foundation

With our leading R&D capabilities, we are advancing our strong pipeline of innovative next generation adjuvants, lipids and high purity excipients.

We recognise that only an R&D focus will allow us to develop the new, innovative vaccine adjuvants that are required to deal with challenging infectious diseases and pathogens.

Dedicated production sites

Our production site located in Denmark has been dedicated to safe and effective adjuvants for use in human and veterinary vaccines for more than 80 years. Our expertise in this area is simply unmatched. We support the major human and veterinary vaccine producers through an experienced team operating the only cGMP certified manufacturing site including aseptic filling globally, for commercially available aluminium-based adjuvants.

Another major production site is located in Alabama, USA. With decades of combined experience in formulating lipids, the teams there support vaccine formulation and development activities. Further, formulation services for both pre-clinical and clinical development using our own cGMP manufactured lipids are offered. Batches can be scaled from a few millilitres to >100 litres to accommodate your stage of clinical development.

Across our other facilities for vaccine components, we work in partnership with our customers to provide a seamless transfer of the formulation for scale-up and manufacturing.

Adjuvants

Alhydrogel™

Alhydrogel is a range of aluminium hydroxide gels specifically developed for use as adjuvants in human and veterinary vaccines.

Alhydrogel has very low conductivity due to the absence of buffering ions and is positively charged at neutral pH. This allows the product to effectively adsorb negatively charged antigens.

Alhydrogel products can be combined with other adjuvant types (such as monophosphoryl lipids) to achieve a well-balanced Th1/Th2 immune response.

Alhydrogel is supplied in two concentrations: Alhydrogel 1.3% and Alhydrogel 2%. A premium version (Alhydrogel “85”) with higher protein adsorption capacity is also available.

The range is manufactured according to EU GMP (Part I: Medicinal Products for Human and Veterinary Use) certified production of aseptically prepared sterile products.

Adju-Phos™

Adju-Phos is a range of aluminium phosphate gel products specifically developed for use as adjuvants in vaccines.

Adju-Phos products have a net negative charge at neutral pH and effectively adsorb positively charged antigens.

Like Alhydrogel, Adju-Phos products can be combined with other adjuvant types (such as monophosphoryl lipids) to achieve a well-balanced Th1/Th2 immune response.

It is supplied with two variants of pH-values to reduce injection site discomfort.

Adju-Phos is manufactured according to EU GMP (Part I: Medicinal Products for Human and Veterinary Use) certified production of aseptically prepared sterile products.

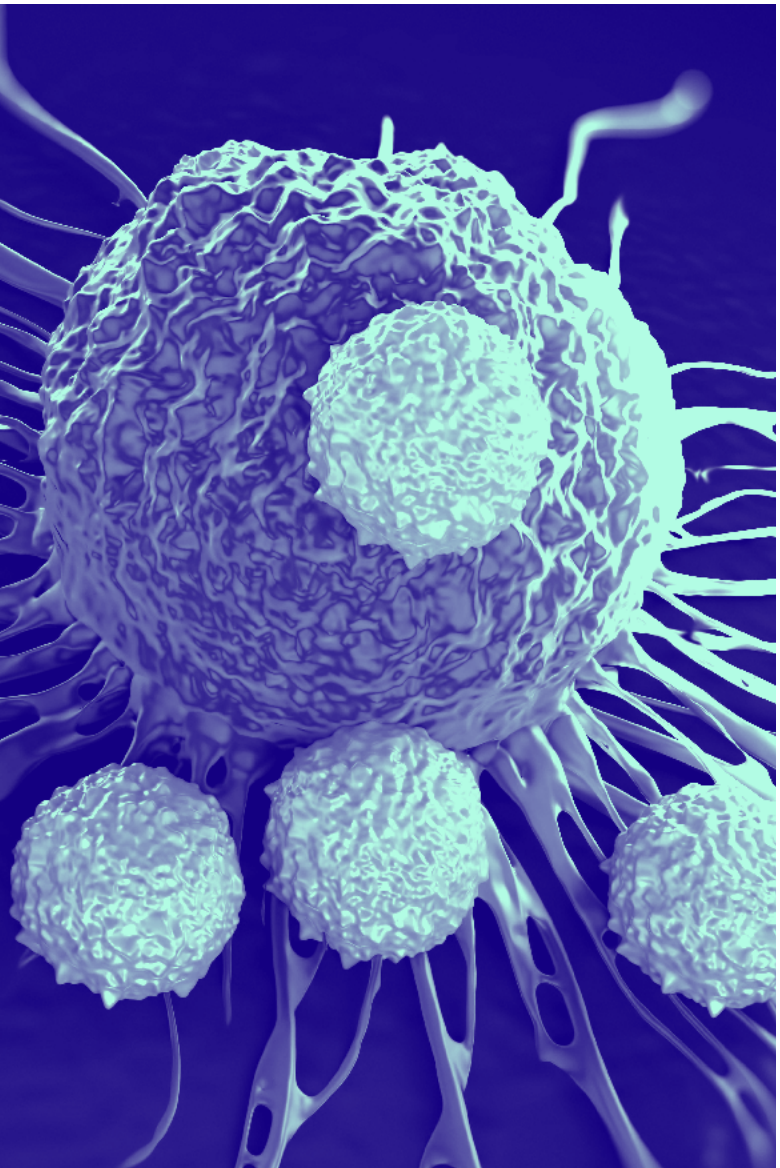
PHAD™

PHAD, Phosphorylated HexaAcyl Disaccharide, is the first synthetic equivalent to bacterial-derived monophosphoryl lipid A (MPLA) used as an adjuvant in vaccines.

It boosts the immune system through activation of the toll-like receptor 4 (TLR4) resulting in production of proinflammatory cytokines and antigen-specific effector CD4+ and memory CD8+ T-cells.

Also referred to as GLA, PHAD, has been administered to over a thousand human subjects without serious adverse events.

PHAD is available in bulk quantities for vaccine development and commercial manufacturing.



3D-PHAD™

A highly pure PHAD, 3D-PHAD provides a homogeneous synthetic equivalent for the 3-deacylated MPLA derived from bacterial LPS (lipopolysaccharides).

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.

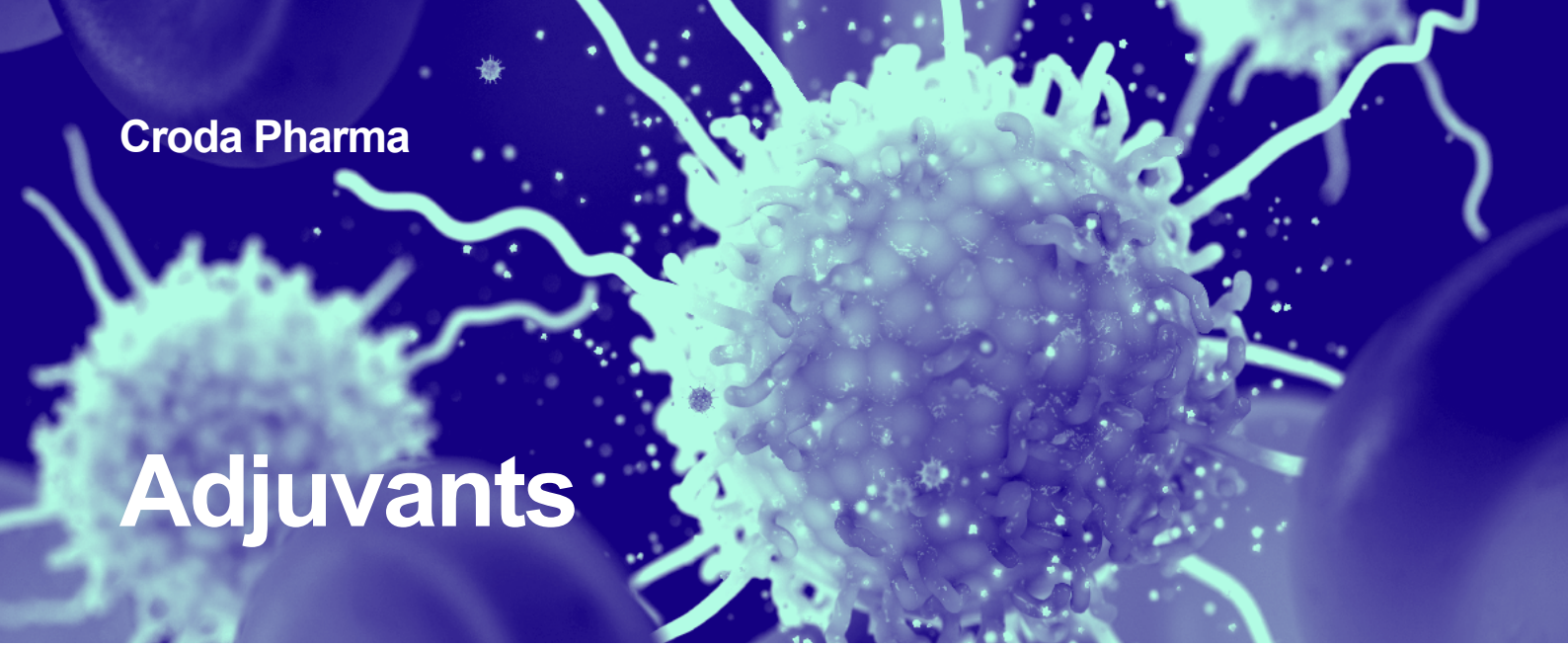
3D-PHAD is protected under US Pat No. 9,241,988. Licensing opportunities are available for vaccine or immunotherapy commercialisation.

3D-(6-acyl)-PHAD™

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

This adjuvant is structurally homogeneous and highly purified. It mimics the TLR4 agonist activity of bacterial MPLA.

PHAD, 3D-PHAD, and 3D-(6-acyl)-PHAD have been tested extensively in animals using a variety of antigens. In all cases, these adjuvants exhibit a similar activity and safety profile to bacterially derived MPL.



Croda Pharma

Adjuvants

Squalene

Squalene is a natural lipid belonging to the terpenoid family. It is an important component in some vaccine formulations. Its most common use in licensed vaccines is in seasonal and pandemic influenza vaccines.

Vulnerable people like the elderly are at higher risk of complications and benefit particularly well from the availability of efficient vaccines. Squalene-based adjuvants increase the immunostimulating effect of a vaccine significantly, hence they are used in seasonal influenza vaccines for elderly.

Furthermore, there are clinical trials in progress for prophylactic vaccines against tuberculosis, HIV, malaria, shingles, and other severe diseases using squalene in combination with a TLR4-agonist.

It has been shown that squalene-based emulsions in vaccine formulations can help to improve the immune response. For instance, they increase vaccine antigen uptake and enhance activation and recruitment of various immune cells at the injection site.

Further benefits relate to an established safety profile, a high tolerance in both adults and children, and a dose sparing effect.

Squalene has traditionally been sourced from shark liver oil, leading to the search for sustainable alternatives.

We will be able to provide a sustainably sourced squalene based on a proprietary bio fermentation process. Not only is this squalene molecularly identical to that harvested from sharks, but it is produced using yeast isoprenoid pathway engineering, which also ensures higher purity exceeding EP monograph requirements. Comparative studies in adjuvant systems have demonstrated identical stability.

QS 21

QS 21 is a water-soluble purified triterpenoid saponin molecule fraction from the bark of the South American tree *Quillaja saponaria* Molina.

As an amphiphilic surfactant, it has demonstrated optimal balance of enhanced immunostimulatory properties and tolerable reactogenicity and has found its way into human applications.

Human vaccines containing QS 21 are now commercially available and used to prevent diseases such as malaria and shingles. Before this development, it was not possible to develop effective vaccines against malaria.

The adjuvant activity of quillaja saponins was reported as early as 1925. They have been used in veterinary vaccines since the 1970s. Croda has manufactured Quil-A for veterinary vaccines since 1982.

Croda's QS 21 is derived from Quil-A and is a highly purified immunostimulant obtained by successive chromatographic purification cycles.

It is manufactured according to GMP requirements for Investigational Medicinal Product of the EU and is intended "for investigational use only". It is supplied as a lyophilised product in 5 mg vials and dispatched frozen.

Sustainable sourcing

Our ambition to become the most sustainable supplier of innovative ingredients and aligning our approach with the United Nations Sustainable Development Goals (SDGs) drives us to search for alternatives ensuring both the high quality requirements for a pharmaceutical ingredient and a secure supply chain.

Find out more for QS 21 in the **Adjuvants development pipelines** section.

Lipids for LNPs

Lipid Nanoparticles (LNPs) have been shown to be effective at delivering mRNA vaccines. Traditionally, LNP systems include four lipid components: Cationic lipid, PEG lipid, structural/neutral lipid, and cholesterol.

The ionizable 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 and decreases particle aggregation.

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

Explore some of the lipids from our GMP portfolio.

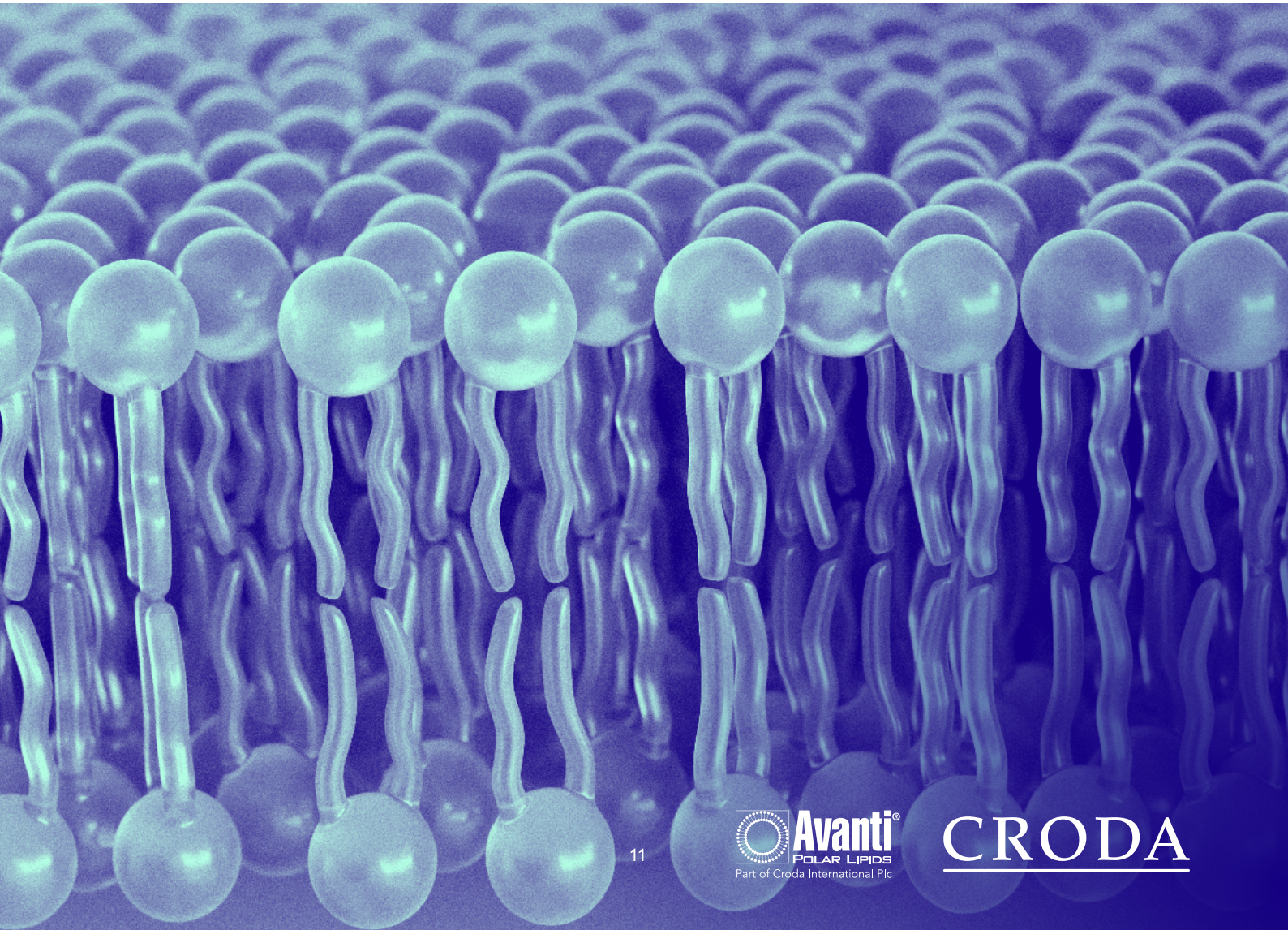
Phospholipids:

- **DSPC**
- **DMPC**
- **DOPC**
- **DMPG**

Additional lipids:

- **ALC-0315**
- **ALC-0159**

Further research grade materials are available through the Avanti website **www.avantilipids.com**



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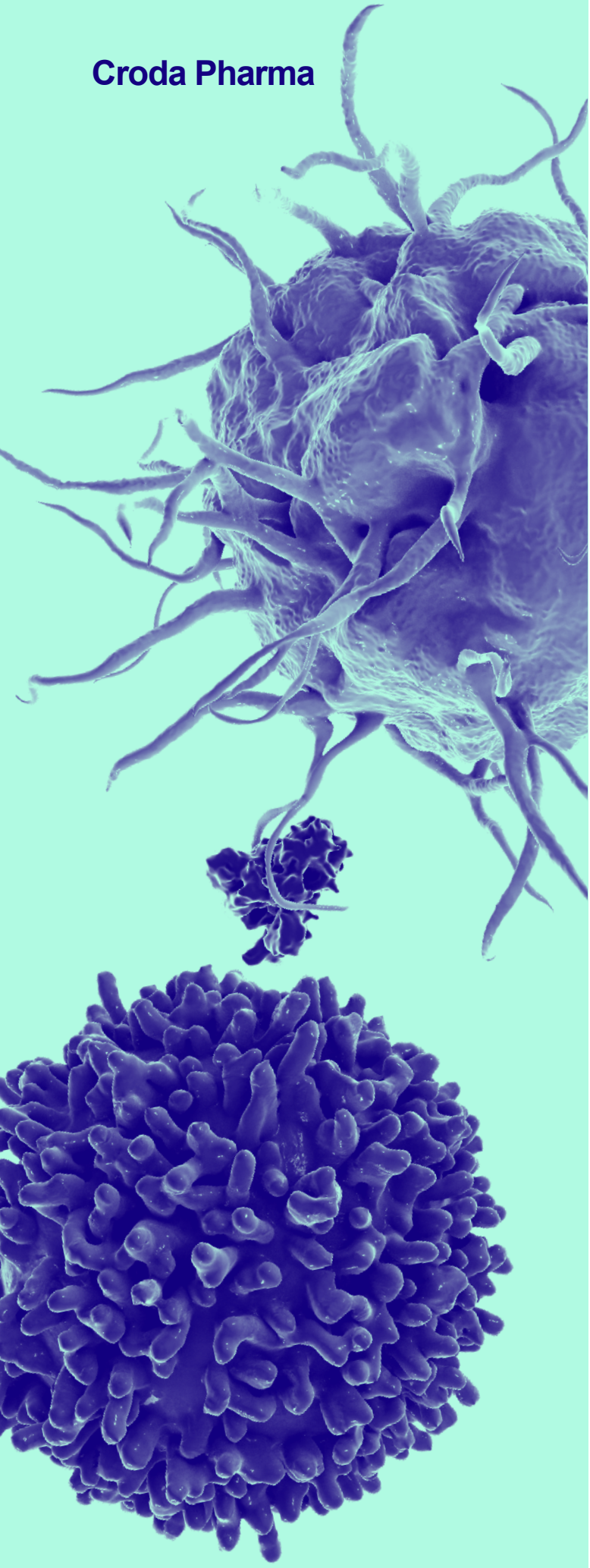


Adjuvants development pipeline

Cationic Adjuvant Formulation CAF®

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

Croda Pharma continuously increases its offering in innovative vaccine adjuvant systems. The strategic collaboration with SSI (Statens Serum Institut, 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 new, patented, CMI inducing cationic liposomal adjuvants. Over the past decade, clinical trials have shown these to be powerful immunostimulators in tuberculosis, chlamydia, HIV, malaria, pandemic flu and specific cancer studies.

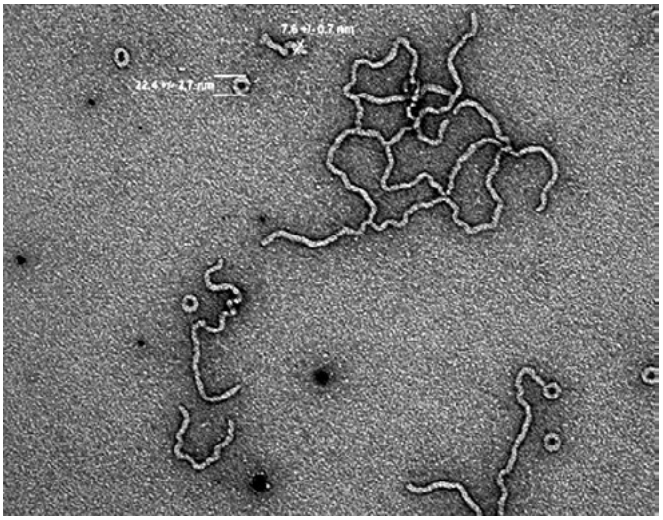
Croda will manufacture and commercialise two CAF adjuvants:

- **CAF01** – a two component liposomal suspension which induces strong antibody and T-cell (Th1/Th17) responses in vaccines for infectious diseases. The potent neonatal adjuvanticity in preclinical studies suggests that it is fulfilling the requirements for novel vaccines to be used in early life.
- **CAF09b** – a second generation, three component cationic liposomal adjuvant used in cancer immunotherapy trials, facilitating strong production of antigen specific CD8 + T-cells after vaccination in combination with peptide or protein-based antigens.

CAF01 induces systemic immunity, facilitating mucosal booster responses after mucosal administration of antigens alone. Preclinical studies indicate CAF09b could be a potent adjuvant for mucosal applications directly priming the immune response.

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.



Electron micrograph of NanoQuil

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.

Sourcing sustainable alternatives

Saponins

A recent collaboration agreement* enables our customers access to the most sustainable source of saponins in contrast to conventional methods. Our partner developed a unique and innovative process to grow *Quillaja saponaria* Molina biomass in their labs and then extracting the QS 21 fraction from these young plants.

Our goal is to secure supply independent from harvest yields and in a scalable way in line with our customers' demand.

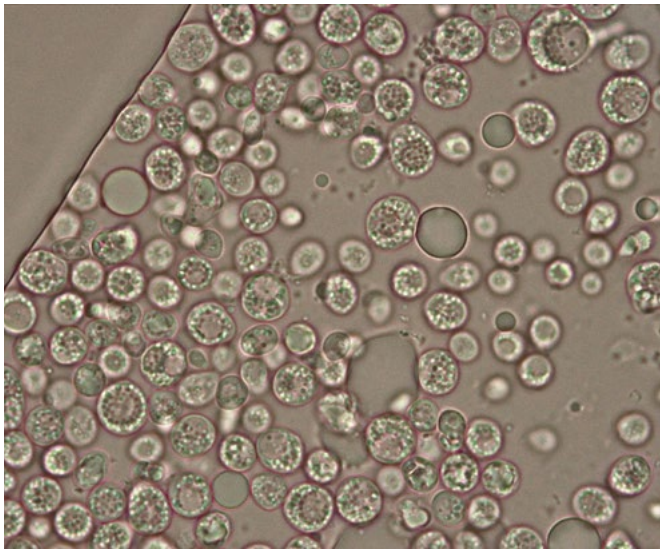
Further efforts are ongoing to expand sustainable sourcing to our saponin-based adjuvants for veterinary application.

*Partnership agreement with Botanical Solution Inc. (BSI)

Squalene

Traditionally, the natural lipid which is an important component of adjuvant systems is obtained from shark-liver. An innovative and proprietary bio fermentation process* delivers high-purity squalene appropriate for use in vaccine formulations. The method enables a secure and scalable supply chain.

*Partnership agreement with Amyris Inc.



Micrograph of yeast full of squalene

Discover more on sustainably sourced squalene in the **Adjuvants** section.

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Additional ingredients for vaccine development

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 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.

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. It is the first o/w adjuvant approved for human influenza vaccines and under clinical evaluation for HIV and CMV.

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

Plant derived cholesterol

Cholesterol is an essential ingredient in a wide range of technologies from adjuvants systems, lipid nanoparticles for mRNA delivery to cell culture media. 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.

Virodex™

The Virodex range has been developed as a replacement for Triton™ X-100 with equivalent performance. The range includes two compendial grade variants with known parenteral applications. They are REACH-compliant and cGMP EXCiPACT-manufactured to meet the highest standards in biopharmaceutical manufacturing.

Contact our teams for more information on our sustainable bioprocessing solutions, including our Virodex range for viral inactivation and cell lysis.

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 the entire biologics development lifecycle through local support and worldwide manufacturing capabilities, helping to bring new vaccines and biologic therapies to market faster and at scale.

We engage with customers through our global network of Croda employees around the world and welcome close cooperation to develop the products of tomorrow.

To discuss your needs or for any further product information, such as monograph compliance, please contact your sales representative or email us at:

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

North America:
pharma.usa@croda.com

Latin America:
pharma.latam@croda.com

Asia Pacific:
pharma.asia@croda.com

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