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Was amorphous aluminium hydroxyphosphate sulfate adequately evaluated before authorisation in Europe?

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ABSTRACT

The Merck Sharp & Dohme Corp aluminium adjuvant 'amorphous aluminium hydroxyphosphate sulfate' (AAHS), primarily used in the Gardasil vaccines against human papilloma virus, has been criticised for lack of evidence for its safety. Documentation from Danish authorities and answers from the European Medicines Agency (EMA) suggest that AAHS may not have been sufficiently evaluated. Documentation from the Danish Medicines Agency shows discrepancies in the trial documents of two prelicensure clinical trials with Gardasil in 2002 and 2003. For both trials, the Agency seems to have authorised potassium aluminium sulfate as the adjuvant and not AAHS. In addition, the participants in the trial launched in 2002 were informed that the comparator was saline, even though the comparator was AAHS in an expedient consisting of L-histidine, polysorbate-80, sodium borate and sodium chloride. According to the EMA, AAHS was first introduced in Europe in 2004 as the adjuvant in Procomvax, a vaccine against the hepatitis B virus and Haemophilus influenza type b. The EMA reports that AAHS was introduced without any prelicensure safety evaluation. The adjuvant is described by the company to be both physically and functionally distinct from all other previously used aluminium adjuvants. There is a need for rigorous evaluation of benefits and harms of the adjuvant AAHS.

Introduction

Aluminium is considered an effective adjuvant in vaccines, but its safety may not have been sufficiently in focus.[1] Aluminium is a known neurotoxin and inflammagen,[2] and interferes with several biomolecules and biochemical pathways, for example, disturbs calcium metabolism, increases oxidative stress, binds to phosphate groups of nucleoside diphosphates and triphosphates such as ATP, and competes with iron and magnesium.[3 4] Several research groups have raised concerns about the health effects of using aluminium in vaccines.[1 5–10] However, both the US Food and Drug Administration Center for Biologics Evaluation and Research and the US Agency for Toxic Substances and Disease Registry concluded that traditional aluminium adjuvants are safe.[11 12]

Aluminium adjuvants have been associated with a number of adverse effects, including injection site pain and tenderness, persistent lumps, granulomas, contact dermatitis and postimmunisation headache,[13] but also more severe adverse events such as macrophagic myofasciitis[14] and the autoimmune/inflammatory syndrome induced by adjuvants.[15] Animal models have demonstrated the toxicity of aluminium adjuvants[16] and their translocation away from the injection site.[17 18]

Criticisms have been raised of the prelicensure randomised clinical trials, that forms the body of evidence for the approval of Gardasil, a Merck Sharp & Dohme Corp manufactured human papilloma virus (HPV) vaccine made of recombinant HPV types 6, 11, 16 and 18 L1 virus-like particles.[19–23] One criticism is the use of amorphous aluminium hydroxyphosphate sulfate (AAHS) as a comparator in the prelicensure trials.[20 23] However, the European Medicines Agency (EMA) and the WHO conclude high vaccine safety and efficacy.[24 25] AAHS produced by Merck has a short history prior to the use in the Gardasil vaccine. A recent study by Doshi *et al* found that participants in Gardasil trials were not adequately informed that the placebo was AAHS.[23] As AAHS is both physically and functionally distinct from all previously used aluminium adjuvants,[26] it is crucial to know the body of evidence regarding safety that constitutes the basis of approval of randomised clinical trials using AAHS by medicines agencies. Here we describe some discrepancies in the documents that constitute the foundation for authorisation of two Gardasil randomised clinical trials in Denmark.

It is important to stress that we are not against safe vaccines in general. However, inadequacies in the regulation of vaccine adjuvants may fuel concerns—rightly or wrongly—in the highly polarised environment that surrounds vaccine sciences. It is therefore imperative to ensure transparent documentation and adequate informed consent in randomised clinical trials.

The Future II and Future K trials

Some of the prelicensure randomised clinical trials with the Gardasil vaccine were conducted in Europe. Data access to detailed trial information for the Danish part of the Future II trial (501-015) and the Future K trial (501-018) was obtained from the Danish Medicines Agency and the Danish National Committee on Health Research Ethics. Access was permitted to Merck protocols, recruitment brochures, informed consent forms and to selected sections of the quality, manufacture and control section of the Investigational Medicinal

Table 1 Adjuvants and excipients in the experimental vaccine and the comparator used in the Danish part of the Future II trial (501-015) according to information from the Danish Medicines Agency and the Danish National Committee on Health Research Ethics

Agency/committee	Composition of the experimental vaccine	Composition of the comparator
Danish Medicines Agency Danish National Committee on Health Research Ethics	225 mcg aluminium as potassium aluminium sulfate 9.56 mg sodium chloride 0.78 mg L-histidine 50 mcg polysorbate 80 35 mcg borax	225 mcg aluminium as potassium aluminium sulfate 9.56 mg sodium chloride 0.78 mg L-histidine 50 mcg polysorbate 80 35 mcg borax
Protocol	225 mcg aluminium as amorphous aluminium hydroxyphosphate sulfate (Merck aluminium adjuvant)	Merck standard aluminium diluent (225 µg alum) in normal saline, unique selling proposition (NaCl 0.9%) or Merck aluminium adjuvant placebo
Recruitment brochure	No information	Saline
Informed consent form	No information	Saline

Product Dossier (IMPD) regarding the Future II trial, and composition tables for experimental vaccine and comparator regarding the Future K trial.

In the Future II trial launched in 2002, 12 167 women aged 16–23 years participated at 90 trial centres in 13 countries.[27 28] In the Future K trial launched in 2003, 1781 children aged 9–15 years participated at 47 trial centres in 10 countries worldwide.[29] Both the Future II and the Future K trials have been described elsewhere.[27–29]

What do the trial documents show?

The IMPD written by Merck dated April 2002 relates to the manufacture of three container lots of the experimental vaccine and four lots of the comparator used in the Nordic parts of the Future II trial.[30] In the section of drug description and in the section of adjuvant preparation, the adjuvant is described as AAHS in a solution with the excipients L-histidine, polysorbate-80, sodium borate and sodium chloride. However, in the remaining parts of the IMPD, the type of aluminium is described as potassium aluminium sulfate and not AAHS.[30] The document describes the required quality test based on potassium aluminium sulfate, and in the composition table of the experimental vaccine and the comparator, the adjuvant is also listed as potassium aluminium sulfate (table 1; online supplementary figure S1).[30]

Regarding the Future K trial, the Danish Medicines Agency only released the composition table for the experimental vaccine and the comparator (online supplementary figure S2), which showed that the adjuvant was listed as potassium aluminium sulfate and not AAHS (table 2). In all documents, the adjuvant was defined as an inactive component.

Regarding the recruitment brochures and informed consent forms, the use of an adjuvanted comparator was not mentioned and the comparator was defined as saline (tables 1 and 2). The Future II recruitment brochure stated that the trial was not a safety trial as the vaccine was already tested for adverse events.[31] It further stated that no adverse events were found except for light redness and tenderness at the injection site.[31]

In the Merck protocols, the adjuvant was specified as 225 mcg aluminium as AAHS (Merck aluminium adjuvant) (tables 1 and 2), but in the section that describes the clinical material in the Future II protocol, the comparator was specified as Merck standard aluminium diluent (225 µg alum) in normal saline, unique selling proposition (NaCl 0.9%). In other sections of the protocol, the comparator is described as Merck aluminium adjuvant placebo (table 1). For the Future K trial, a non-aluminium containing comparator was mentioned in the Merck protocol; however, the composition of the vaccine and the comparator was not specified (table 2). For both trials, the excipients were not mentioned in the Merck protocols, recruitment brochures or the informed consent forms (tables 1 and 2).

EMA's approval of AAHS

Two queries (ASK-50308 and ASK-53619) about how AAHS was approved and introduced by EMA were sent to EMA on 15 January and 4 April 2019. The answers show that the EMA has no specific safety studies comparing aluminium alone with an inactive comparator. The EMA stated in the answer that no new clinical safety studies were needed comparing aluminium alone versus inactive comparator for vaccines containing aluminium adjuvants (see the online supplementary file). The EMA explained that there was no need to further investigate an adjuvant alone when there are no new safety issues reported after decades of use. The EMA stated further that if the adjuvant is novel, then there should usually be enough safety data from the preclinical

Table 2 Adjuvants and excipients in the experimental vaccine and the comparator used in the Danish part of the Future K trial (501-018) according to information from the Danish Medicines Agency and the Danish National Committee on Health Research Ethics

Agency/committee	Composition of the experimental vaccine	Composition of the comparator
Danish Medicines Agency Danish National Committee on Health Research Ethics	225 mcg potassium aluminium sulfate 9.56 mg sodium chloride 0.78 mg L-histidine 50 mcg polysorbate 80 35 mcg borax	9.56 mg sodium chloride 0.78 mg L-histidine 50 mcg polysorbate 80
Protocol	225 mcg aluminium as amorphous aluminium hydroxyphosphate sulfate (Merck aluminium)	No aluminium
Recruitment brochure	No information	Saline
Informed consent form	No information	Saline

studies to allow for it to be given with antigen(s) from the outset (see the online supplementary file). In the answers, EMA specified that the applicability to established adjuvants (eg, aluminium hydroxide and aluminium phosphate) will vary on a case-by-case basis. EMA explained that no further non-clinical studies on the AAHS adjuvant were required, as AAHS is used in other vaccines approved in Europe. The EMA refers in the answer to the Guideline on Adjuvants in Vaccines for Human Use[32] (see the online supplementary file).

According to the EMA, AAHS was introduced in Europe in 2004, when the name of the adjuvant in the vaccine Procomvax was modified from aluminium hydroxide to AAHS (see the online supplementary file). The change was requested by the company to align the nomenclature of the adjuvant in all relevant authorised Merck vaccines at that time. The EMA explained that the adjuvant AAHS is the same chemical compound as the one initially called aluminium hydroxide. The change in name reflects a change in nomenclature that occurred after the initial authorisation of Procomvax. The change was accepted by the Committee for Medicinal Products for Human Use (see the online supplementary file).

Discussion

It was not possible to identify the type of aluminium adjuvant used in the Future II and the Future K trials from the accessed documents. None of the documents listed the composition of the vaccine and the comparator according to the Gardasil insert. It seems plausible that it was AAHS they used in the trials, as AAHS is the vaccine adjuvant in both trial protocols (tables 1 and 2). Doshi *et al* also came to the same conclusion that the comparator was AAHS.[23]

In the section for the clinical material description in the Future II protocol, the placebo is described as 'Merck standard aluminium diluent (225 µg alum) in normal saline, unique selling proposition (NaCl 0.9%)', which does not correspond to the description of AAHS. In other sections of the protocol, the placebo is described as 'Merck aluminium adjuvant placebo', but as aluminium hydroxide was used in Merck vaccines in 2002, and as AAHS according to the EMA was unknown by the authorities before 2004, we can speculate that the Committee on Health Research Ethics may have interpreted the placebo as being aluminium hydroxide.

The Danish Medicines Agency authorisation of potassium aluminium sulfate and not AAHS for both trials is noteworthy, as potassium aluminium sulfate (also referred as alum) is a different aluminium salt than AAHS, and it has no record of being used as an adjuvant in European human vaccines.[33] Even known aluminium adjuvants such as AlHydrogel (aluminium hydroxide) and AdjuPhos (aluminium hydroxyphosphate) react quite differently as adjuvants.[34] Therefore, equating potassium aluminium sulfate with AAHS is questionable. Indeed, the only published study on the adjuvant properties of AAHS, a Merck in-house study in mice, concluded that the formulation of aluminium adjuvants has significant implications for their biological activity.[26] The manufacturer of AAHS seems to have prevented independent studies of AAHS, though experts in the characterisation of aluminium adjuvants have speculated that the inclusion of sulfate moieties will increase the acidity at the injection site with likely concomitant increased toxicity.[34]

In both the Future II and Future K trials, the trial participants do not seem to have been informed about the use of AAHS, which is in line with the findings from Doshi *et al*.[23] In all documents, the comparator is described as an inactive component. This is also questionable as aluminium is potentially reactive both when administered alone and in a vaccine formulation.[35]

Gardasil is also composed of the excipients polysorbate-80, sodium borate and L-histidine in addition to AAHS. However, the excipients do not seem to have been described in the protocols, even though they were part of the vaccine and the comparator according to the IMPD (online supplementary figure S1). The excipients are added with the purpose of stabilising the virus-like particles, as they are unstable during long-term storage.[36] The missing information is of relevance, as the safety of the excipients has been questioned.[37–39]

The answers from the EMA on queries ASK-50308 and ASK-53619 suggest that Merck did not inform the EMA about AAHS (see the online supplementary file). Merck seems to have told EMA that AAHS was identical to aluminium hydroxide, and that they requested nomenclature changes for all approved vaccines to secure identical nomenclature. In 2002, neither the Danish Medicines Agency nor the EMA seems to know about the adjuvant AAHS. The manufacturer cannot claim that this was because of another use of nomenclature as the aluminium adjuvant was correctly declared for the vaccine in the Future II and Future K study protocols, except for the excipients.

Merck seems to have been aware of the chemical and functional differences between aluminium hydroxide and AAHS, as they have published an in-house study where they compare AAHS with more traditionally used adjuvants.[26] Therefore, the change in nomenclature suggests that Merck may have got AAHS authorised without following the guidelines for new adjuvants.

According to EMA's own guidelines, an adjuvant should be tested alone in minimum two species unless otherwise justified, as adjuvants themselves might be immunogenic.[32] Full tissue examination is recommended in the case of novel adjuvants with no prior non-clinical and clinical experience.[32] It can be argued that the AAHS should have been handled as a novel adjuvant by the agencies, as it is a new type of aluminium adjuvant with excipients that have not been used earlier in EMA authorised vaccines. As EMA seems to be unaware of any safety studies where AAHS is tested against an inert comparator (a real placebo), one can question the safety of AAHS containing vaccines. A recent PhD thesis from the Nordic Cochrane Centre concluded that it is unclear to what extent the benefits of the Gardasil vaccine outweigh its harms, as almost all of the Gardasil studies used AAHS as comparator.[40] In the light of our observations, the benefit–harm balance of the vaccine may need a re-evaluation.

The present cases regarding the Future II and Future K trials from Denmark emphasise that the clinical trial authorisation processes have not been able to secure proper vaccine and control descriptions and sufficient informed consent. Merck initiated trials with a design, where the placebo seems unknown both for the authorities, the investigators and the trial participants. Moreover, the trial design, using a novel adjuvant as the placebo, seems unapproved by the authorities. If this is the case, then the trials raise ethical concerns. Based on the present cases, EMA should re-evaluate the guidelines for clinical trial authorisations and close any possible holes in the regulations to secure future vaccine safety. Comparable actions of the national regulatory authorities and ethics committees are likely needed.

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Competing interests SBP was a trial participant in the Danish part of the Future II trial.

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SUPPLEMENTARY FILES

S1: Drug composition for the experimental vaccine and comparator in the Danish part of the Future II trial (501-015). Access to the Investigational Medicinal Product Dossier permitted by the Danish Medicines Agency [30].

II. DRUG PRODUCT

II.A. COMPOSITION OF DRUG PRODUCT

The targeted composition of the Quadrivalent HPV VLP Vaccine is presented in Table 22. The placebo contains the same quantity of inactive ingredients as the vaccine but contains no active ingredients (HPV L1 proteins). Release criteria for the excipients Polysorbate 80, L-histidine, sodium borate, and potassium aluminum sulfate are provided in Appendix 3.

Table 22. Targeted Composition of the Quadrivalent HPV VLP Vaccine

Description of Ingredients			Unit/mL	Unit/0.5mL Dose
Active Ingredients	HPV L1 Protein type (µg)	6	40	20
		11	80	40
		16	80	40
		18	40	20
Inactive Ingredients	Aluminum (µg)		450	225
	Sodium Chloride USP (mg)		19.12	9.56
	L-Histidine (mg)		1.55	0.78
	Polysorbate-80 (µg)		100	50
	Sodium borate (µg)		70	35
	Water for Injection USP		QS	QS

HPV: human papilloma virus.
VLP: virus-like particle.

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S2: Drug composition in Danish language for the experimental vaccine in the Danish part of the Future K trial (501-018). Access to the document permitted by the Danish Medicines Agency (Kaliumaluminiumsulfat = Potassium aluminium sulphate).

2611-575

LÆGEMIDDEL STYRELSEN

23 OKT. 2003

2/4

Kliniske forsøg

Skema til brug ved katalogisering af indholdsstofferne i farmaceutiske specialiteter m.v.

1) Præparatets navn: Human Papillomavirus Vaccine

2) Dispenseringsform/styrke (kun én dispenseringsform/styrke på hvert skema).: Injektionsvæske

3) Stofnavn*	4) Mængde pr. 0,5 ml dosis *	5) Specifikation*	6) Stoftype*
HPV L1 Protein type 6	20 µg	Intern	A
HPV L1 Protein type 11	40 µg	Intern	A
HPV L1 Protein type 16	40 µg	Intern	A
HPV L1 Protein type 18	20 µg	Intern	A
Kaliumaluminiumsulfat	225 µg	EP	C
Natriumchlorid	9,56 mg	USP	C
L-histidine	0,78 mg	USP	C
Polysorbate 80	50 µg	EP	C
Borax	35 µg	EP	C
Vand til injektionsvæske	q.s.	USP	C

From: AskEMA <askema-no_reply@ema.europa.eu>
Sent: 21. marts 2019 11:53
To: Christian Gluud <christian.gluud@ctu.dk>
Subject: Ask EMA - (ASK-50308) information on aluminium in vaccines

Re: EMA request reference ASK-50308

Dear Dr Gluud,

Thank you for your query of 15 January 2019 regarding studies underpinning the safety of aluminium in vaccines.
Please see below responses to your questions:

Question 1. Knowing that each adjuvant must be tested alone and in combination with each antigen (according to the guidelines), did the EMA assess clinical trials that demonstrate the safety of aluminium adjuvants used in any of the following vaccines (please provide separate answers to each vaccine)?
- Fendrix
- Cervarix
- Gardasil
- Silgard
- Prevenar 13
- Prevenar
- Synflorix
- Infanrix Hexa
- Trumenba
- Gardasil 9
- Vaxelis

Please kindly clarify to us when and how EMA assessed the safety of each aluminum adjuvant used in the vaccines approved by the Agency.

From previous correspondence you sent on 4th Dec to EMA following receipt of ASK-45800 (http://askema.eudra.org/browse/ASK-45800) and from the published Cochrane protocols, we understand that you would like to confirm whether EMA has assessed trials comparing aluminium adjuvants alone versus an inactive control, for each of the vaccines approved via EMA mentioned in question 1. Please see below some clarifications, which we hope are helpful to address your questions.

All the vaccines mentioned in question 1 are aluminium-adjuvanted. The safety of the aluminium adjuvant alone or in combination with the antigen has been established in the past, as aluminium has been in use for decades. Data generated from clinical trials with aluminium-containing vaccines worldwide and the safety data gathered from the use of aluminium-containing vaccines over six decades have shown that their safety profile is acceptable, with only local reactions as possible side effect linked to aluminium, which normally resolve in a short timeframe. In addition, a thorough safety and toxicology assessment in non-clinical studies is performed before any vaccine can enter clinical trials, including testing multiples of the human dose.

For marketing authorisation purposes, no new clinical safety studies are needed comparing aluminium alone versus inactive control for vaccines containing aluminium adjuvants that comply with the required limits in the European Pharmacopoeia (Ph.Eur.). In particular, the upper limit for the amount of aluminium in allergens and vaccines is 1.25 mg per dose. All authorised vaccines in the EU contain less than this maximum amount.

We would like to clarify that the applicability of the GUIDELINE ON ADJUVANTS IN VACCINES FOR HUMAN USE (EMEA/CHMP/VEG/134716/2004) to established adjuvants (e.g. aluminium hydroxide and aluminium or calcium phosphate) will vary on a case-by-case basis (please refer to page 5 of the guideline, under scope).

Thus, this guideline mainly applies to novel adjuvants – this is reflected in section 5.1. Even for novel adjuvants, the testing in humans of the adjuvant alone is generally not encouraged. Please see section 5.2.1 which states that: "It would not be envisaged that the adjuvant would have to be administered alone in these studies. If the adjuvant is novel, there should usually be sufficient safety data from the pre-clinical studies to allow for it to be given with antigen(s) from the outset. The same situation should apply to an established adjuvant when it is to be given at a higher dose than usual or by a new route of administration. However, if there is suspicion that an adjuvant might accumulate, consideration could be given to a pharmacokinetic evaluation in humans. If it is considered that the administration of adjuvant alone in clinical studies might be necessary, it may be appropriate to obtain further scientific /regulatory advice from EU Regulators."

Therefore, in line with the guideline, for the vaccines mentioned above, we do not have specific safety studies comparing aluminium alone to inactive control. This is because there is no need to further investigate an adjuvant alone when there are no new safety issues reported after decades of use, which means that there is no scientific value in conducting additional clinical studies with aluminium alone in the context of each specific vaccine development and could be challenged by Ethics Committees. In addition, sometimes there may be limitations in the feasibility of trials' conduct. For example, Trumenba contains aluminium for protein stability, so it was not possible to study the vaccine without aluminium. Only some trials in the development of Gardasil and Cervarix were conducted using aluminium alone as placebo in order to maintain the blinding.

Below we include extracts from the different EPARs for your information. For more details we would like to refer you to the documents published on our website.

Fendrix: In order to improve the immune response to the hepatitis B surface antigen (HBsAg), GlaxoSmithKline Biologicals (GSK Bio) has developed Fendrix, a hepatitis B vaccine containing HBsAg adjuvanted with 3-O-desacyl-4'-monophosphoryl lipid A (MPL) and aluminium phosphate. The adjuvant system used (aluminium phosphate and MPL) is called AS04C and enhances the immunogenicity of HBsAg. (page 1)
The quantity of 0.5 mg of aluminium chosen for the HB-AS04 vaccine formulation is already used in a commercially available HepB vaccine and was shown to be a safe and effective adjuvant dosage. The effect of a lower content of aluminium on the humoral response was studied in healthy subjects in two phase II HBV-MPL studies, Study HBV-MPL-004 and HBV-MPL-005. Both studies indicated that decreasing the aluminium content of the HB-AS04 vaccine would lower the effect of the antibody response. As the development of the HB-AS04 vaccine targeted an improved humoral response as compared to a commercially available HepB vaccine, the quantity of aluminium in Fendrix seems optimal (see page 12)

Cervarix: uses AS04 as adjuvant, already licensed in Fendrix. In efficacy studies HPV-001 and HPV-007, the control group received Al(OH)3 (aluminium hydroxide).

Gardasil includes amorphous aluminium hydroxyphosphate sulfate adjuvant. The Merck Aluminium Adjuvant (aluminium hydroxyphosphate sulphate adjuvant, 225ug) is used in other vaccines, which are approved in Europe, and it is agreed that no further non-clinical studies on the adjuvant are required according to the Guideline on adjuvants in vaccines for human use (CHMP/VEG/134716/2004) (page 8).
All studies were placebo controlled and the total population that received placebo included

9,701 subjects (the placebo was aluminium adjuvant in all studies except study 018 (pre-/adolescent safety study) which used a non-aluminium-containing placebo) (see page 10).

Gardasil 9: The HPV L1 VPLs are produced using the same manufacturing process as used for the applicant's licensed Gardasil. The VLPs are adsorbed on amorphous aluminum hydroxyphosphate sulfate (AAHS) adjuvant (500ug). The aluminium content per dose for the 9vHPV Vaccine (500 µg) is greater than for the 4-valent HPV vaccine formulation (225 µg). Previous clinical experience with an 8-valent formulation containing HPV Types 6, 11, 16, 18, 31, 45, 52, and 58 and 225 µg aluminium indicated that addition of new HPV types to the 4-valent HPV vaccine formulation may result in somewhat lower anti-HPV titres for HPV Types 6, 11, 16, and 18. In an effort to keep the immunogenic response for HPV Types 6, 11, 16, and 18 non-inferior to that induced by the 4-valent HPV vaccine, the adjuvant content was increased to 500 µg aluminium per dose (see page 17).
Toxicology studies of AAHS alone were not performed because this adjuvant has been used before in several other Merck vaccines and has an established safety profile (see page 24).
Clinical trials were conducted against an active placebo (Gardasil).

Prevenar is conjugated to the CRM197 carrier protein and adsorbed on aluminium phosphate (0.5 mg). The effect of aluminium phosphate as adjuvant on the antibody response of rabbits to 7 monovalent conjugate Pneumococcus C vaccines (each containing 5 mcg of saccharide) was evaluated. The results showed an enhancing effect of the adjuvant on the antibody response to 6 of the 7 serotypes present in Prevenar (not for 9V), after both one or 2 doses of vaccine. It was thus decided to include aluminium phosphate as adjuvant in the Prevenar vaccine. Aluminium and MPL as vehicle adjuvant were tested in toxicology studies in rabbits. Several multidose studies have been conducted in rabbits and mice without any evidence of systemic or local toxic effects. The only observed effect was transient local irritation and inflammation at the injection site.
In clinical trials, controls received licensed vaccines.

Trumenba contains aluminium phosphate, which is a known adjuvant but which in this case functions as formulation stabiliser (see page 12).
Due to the fact that aluminium phosphate is essential for the stability, it appeared not possible to manufacture a stable formulation of the rLP2086 vaccine without the addition of aluminium phosphate, and therefore the potential impact of aluminium phosphate as an immunological adjuvant could not be evaluated experimentally. Considering its properties, it is however likely that it will have adjuvant activity (see page 23, non-clinical section). Clinical trials evaluated the safety of the vaccine against a saline placebo or a different vaccine already authorised.

Infanrix hexa: contains 0.5 mg as aluminium hydroxide (Al(OH)3) and 0.32 mg as aluminium phosphate (AlPO4). To potentiate the immune response, D, T, pertussis antigens (PT, FHA and PRN), and HBsAg are adsorbed on aluminium salts (aluminium hydroxide and aluminium phosphate) which are well-known and universally accepted immunopotentiating agents. The IPV component, although not pre-adsorbed for formulation, does adsorb when mixed with the other antigens. The Hib component is adsorbed also (see page 1).
No novel excipients are included in this vaccine.
In clinical trials, control groups were administered similar authorised vaccines (DTPa vaccines) to compare immune responses and reactogenicity.

Vaxelis: PR5I [i.e. Vaxelis] is a fully liquid preservative free suspension for injection adjuvanted onto aluminium phosphate and amorphous aluminium hydroxyphosphate sulfate. The components are the same components as in vaccines that are currently licensed or were previously licensed in Europe (see page 12).
There are no novel excipients used in the finished product formulation (see page 23).
The approach for PR5I approval in Europe with respect to efficacy and safety has been to

demonstrate non-inferiority of PR5I when compared to Infanrix hexa or to separate administration of the US licensed individual component vaccines and comparable safety profile. In addition given the target age group for the product, subjects in the trials received concomitant routine vaccinations.

In the context of the assessment of the marketing authorisation applications, the approach taken for the above mentioned vaccines was found by the CHMP to be a reliable way for establishing the safety profile of the vaccines. In addition, please note that all vaccines are approved in the EU on the basis of a positive-benefit risk, and this balance is continuously monitored by authorities after vaccines are marketed.

The scientific evidence available to date on the safety of aluminium as adjuvant and the assessment of this evidence has been performed not only by EMA over many years (See: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/07/WC500108657.pdf), but also by other international and EU scientific public health authorities that continue to support the safe and effective use of aluminium adjuvants in vaccines such as:
WHO (See: http://www.who.int/vaccine_safety/topics/aluminium/statement_112002/en/index.html and http://www.who.int/vaccine_safety/reports/Jun_2012/en/index.html).
CDC: https://www.cdc.gov/vaccinesafety/concerns/adjuvants.html
FDA: CBER article published in Vaccine 2011, see: https://www.ncbi.nlm.nih.gov/pubmed/22001122

For the other vaccines that contain aluminium as adjuvant and are not listed in your question 1, we recommend that you refer to the related products' EPARs to find out how the safety of the vaccine was evaluated.

Question 2. When was the amorphous aluminum hydroxyphosphate sulfate (AAHS) adjuvant first tested in a clinical trial?

To the best of our knowledge, 'amorphous aluminum hydroxyphosphate sulfate' is used only for vaccines produced by Merck. The Merck adjuvant was first used and licensed in Europe through the centralised procedure for Procomvax (Hib-HBV; EU MA 1999; this vaccine was withdrawn and is thus no longer authorized for use in the EU). According to the latest PI for Procomvax published on the EMA website (see below), four clinical trials were conducted between 1992 and 2000: https://www.ema.europa.eu/documents/product-information/procomvax-epar-product-information_en.pdf

For more information with regards to the clinical development program of this vaccine, including the trials submitted for authorisation, please refer to the EPAR which is published here:
https://www.ema.europa.eu/en/documents/scientific-discussion/procomvax-epar-scientific-discussion_en.pdf

Question 3. When and in what vaccine was the AAHS adjuvant first introduced?

To our knowledge 'amorphous aluminum hydroxyphosphate sulfate' was first used and licensed in Europe through the centralised procedure for Procomvax (Hib-HBV; EU MA 1999). This vaccine is no longer available in the EU (the marketing authorisation expired in 2009).

We hope the above is of help towards carrying out your studies. We would be grateful if you could take part in a short survey on our service, which you can access through the following

link:
https://ec.europa.eu/eusurvey/runner/AskEMA

Kind regards,
R. Gonzalez
Stakeholder and Communication Division

Re: EMA request reference ASK-53619

Dear Dr Gluud,

Thank you for your query of 4 April 2019 which follows up to query 50308 on aluminium adjuvants in vaccines.

Question 1: In the above mentioned EPAR, amorphous aluminum hydroxyphosphate sulfate (AAHS) is reported nowhere. Instead, in the above mentioned EPAR, the trials conducted to approve Procomvax report that aluminium hydroxide is used as adjuvant. The Procomvax Summary that Gonzales suggested us and which is published here: https://www.ema.europa.eu/en/documents/product-information/procomvax-epar-product-nformation_en.pdf reports that Procomvax is approved with AAHS as adjuvant.
Could EMA please explain why the trials where conducted with Aluminium Hydroxide while the vaccine was approved with AAHS?

The adjuvant AASH is the same chemical compound as the one initially called 'aluminium hydroxide' used in trials leading to the initial authorisation as described in the EPAR. The change in name reflects a change in nomenclature that occurred after the initial authorisation of Procomvax.

In the product information (PI) adopted at the time of the initial marketing authorisation in May 1999 the adjuvant was listed as "aluminum hydroxide", in line with the assessment report (of note, the original PI is no longer publicly available on EMA's website but can be found on the EC's website https://ec.europa.eu/health/documents/community-register/html/h104.htm).

The name of the adjuvant was modified to AAHS in the SmPC during the renewal in August 2004 as part of renewal variation R-0015. The change was requested by the company to align the nomenclature of the adjuvant in all relevant, authorised Merck vaccines at that time.

The CPMP assessment report for the renewal of the marketing authorisation of Procomvax states: "In addition, both in the SPC, labelling and package leaflet, the MAH proposes to update the excipient name of aluminium hydroxide to amorphous aluminium hydroxyphosphate sulphate. This change was accepted by the CPMP."

The change was to replace 'aluminium hydroxide' by 'amorphous aluminium hydroxyphosphate sulfate' (described as the insoluble precipitate formed upon addition of a solution of sodium hydroxide to a solution of aluminium potassium sulfate (alum)).

Question 2: Could EMA please clarify to us the reasons why this vaccine withdrawn?
The marketing authorisation for this vaccine expired as the company decided not to renew the license. The company informed the Agency that this decision was not related to any safety concern. For more information you can read the public statement issued at the time:

https://www.ema.europa.eu/en/documents/public-statement/public-statement-procomvax-non-renewal-marketing-authorisation-european-union_en.pdf

We hope you find this information useful. We would be grateful if you could take part in a short survey on our service, which you can access through the following link: https://ec.europa.eu/eusurvey/runner/AskEMA

Kind regards,
R. Gonzalez
Stakeholders and Communication Division

Dear Sir/Madam

Re: ASK-55497 Amorphous aluminum hydroxyphosphate sulfate (AAHS) received on **20 May 2019**

Thank you for your message and your interest in the European Medicines Agency. Your request has been given the reference number **ASK-55497**.

We will reply to you on all information enquiries (RFI) as soon as we can. For complex queries, it may take longer to answer. In any case we will write back to you within 2 months from the date of receipt.

Concerning requests for access to documents (ATD), your enquiry will be processed according to Regulation (EC) No 1049/2001.
For more information on ATD please refer to our guide on access to unpublished documents: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/11/news_detail_002224.jsp&mid=WC0b01ac058004d5c1

This automated response is not an acknowledgement of receipt or registration for the purpose of the ATD process. Such acknowledgment/registration will be issued separately following validation.

Please do not reply to this email, this is an automated response to confirm that we have received your request. If you need to contact us again about the same matter, please use the form on our website and mention the reference number.

Kind regards

European Medicines Agency
Official Address: Domenico Scarlattilaan 6, 1083 HS Amsterdam, The Netherlands