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.

Petersen SB, Gluud C. *BMJ EBM* 2021; 26:285–289. doi: 10.1136/bmjebm-2020-111419

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

Petersen SB, Gluud C. *BMJ EBM* 2021; 26:285–289. doi: 10.1136/bmjebm-2020-111419

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

Petersen SB, Gluud C. *BMJ EBM* 2021; 26:285–289. doi: 10.1136/bmjebm-2020-111419

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

Petersen SB, Gluud C. *BMJ EBM* 2021; 26:285–289. doi: 10.1136/bmjebm-2020-111419

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

Petersen SB, Gluud C. *BMJ EBM* 2021; 26:285–289. doi: 10.1136/bmjebm-2020-111419

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

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Kind regards

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