Public Assessment Report
for paediatric studies submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended

Avaxim 80U Pediatric
hepatitis A inactivated vaccine (whole virus)

HU/W/0007/pdWS/002

Marketing Authorisation Holder: Sanofi Pasteur

Rapporteur:	Hungary
Finalisation procedure (day 120):	21 November 2015
Date of finalisation of PAR	21 January 2016

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Avaxim 80U Pediatric
INN (or common name) of the active substance:	hepatitis A inactivated vaccine (whole virus)
MAH:	Sanofi Pasteur
Currently approved Indication	active immunisation against infection caused by hepatits A virus in children aged from 12 months to 15 years inclusive, who are at risk either of contaminating or spreading infection or of a life-threatening diseases if infected
Pharmaco-therapeutic group (ATC Code):	hepatitis A inactivated vaccine (whole virus) J07BC02
Pharmaceutical form and strength:	Liquid suspension. Each 0.5 mL individual dose contains: - Inactivated hepatitis A virus..... 80 antigen units* - Aluminum hydroxide (expressed as aluminum)..... 0.15 mg - 2-phenoxyethanol..... 2.5 µL - Formaldehyde..... 12.5 µg - Medium 199, water for injections ..... up to 0.5 mL * antigen units expressed as enzyme-linked immunosorbent assay (ELISA) units using in-house reagents and in-house reference
Rapporteur's contact person:	**Name:** Istvan NAGY Tel: +36 1 886 9318 Email: paediatric@ogyei.gov.hu
Name of the Assessor:	**Name: Katalin Rapi, MD,MS**

I. EXECUTIVE SUMMARY

The result of this work-sharing procedure (HU/W/007/pdWS/002):
No SmPC and PL changes are proposed.
No further action required.

II. RECOMMENDATION

The Rapporteur's conclusion:

1. In the current (Hungarian) SmPC AEs and theirs frequencies are listed based on administration of 7000 doses in clinical trials.
   In present study after 600 doses some AE were observed with higher frequency than that, some of them were not observed at all and some new AEs were observed. (see tables under „Discussion on clinical aspects")
   The MAH proposed to change the frequency of AEs observed with higher frequency from "common" to be listed as "Very common" in the SmPC based on the frequencies reported in JEC01 study.

2. The MAH was requested to reconsider the change of frequency categories as the frequency category in SmPC should be based on cumulative data and not on the latest study's result only. Pooled safety data from several studies increases the precision of adverse event's rate and provide a more clinically useful representation of a vaccine's adverse event profile.

3. The rapporteur agrees with the inclusion of the suggested new AEs (malaise, drowsiness and crying abnormal), they seem to be a reasonable possibility.

4. The very common frequency category observed in this study seems to be unlikely to occur in general. The MAH is requested to reconsider the frequency categories in SmPC taking into account the previous studies' data by making pooled analysis across suitable studies.

The MAH's commitment:
Sanofi Pasteur agrees to perform a pooled safety analysis taking into account the more pertinent clinical studies results generated with Avaxim 80U paediatric vaccine to reconsider the frequency of adverse events in SmPCs and CCDS.

The timing estimated to achieve this pooled safety analysis and prepare a proposal of CCDS/SmPC update is 10 to 12 months (around 20 studies concerned, some studies quite old with data not managed in recent software).

Moreover in the meantime, a request for work-sharing (HU/W/007/pdWS/003) for Phase IV study HAF87 has been received from EMA, with Hungary as Rapporteur. This study will also be taken into consideration in the pooled analysis.

So Sanofi Pasteur proposes to submit the pooled safety analysis and a proposition of SmPC/CCDS update as part of paediatric work-sharing for study HAF87 (HU/W/007/pdWS/003)

by September 2016. A Type IB variation will be submitted after this paediatric work-sharing procedure on the basis of wording approved during the procedure.

The MAH's proposal is accepted. The assessment of the pooled safety analysis and a proposition of SmPC/CCDS update will be the part of next paediatric work-sharing procedure (study HAF87, HU/W/007/pdWS/003).

III. INTRODUCTION

Following the request of worksharing, the MAH submitted a completed paediatric study for Avaxim 80U Paediatric, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use:

"A Controlled Study of the Safety and Immunogenicity of ChimeriVax® Japanese Encephalitis Vaccine in Thai Toddlers and Children"

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric study does not influence the benefit risk for Avaxim 80U Paediatric and the MAH proposed the following regulatory action:

The JEC01 study revealed new information regarding adverse events among children and toddlers receiving Avaxim 80U Paediatric that are not already listed in the SmPCs and CCDS: 1 in children (malaise) and 2 in toddlers (drowsiness and crying abnormal). It is recommended that the Product Information and CCDS be updated to include these additional solicited systemic reactions.

• Three ARs are proposed to be added with the frequency "Very common": malaise under General disorders and administration site condition, drowsiness under Nervous system disorders and crying abnormal under Psychiatric disorders

• The solicited AR in JEC01 (decreased appetite, irritability, headache, vomiting, myalgia, injection site pain, pyrexia, injection site erythema) already listed in CCDS and SmPC as "common" are proposed to be listed as "Very common" based on the frequencies reported in JEC01.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the study

Avaxim 80U Paediatric was approved in France in July 2001.

Hepatitis A paediatric vaccine is indicated for active immunization against infection caused by Hepatitis A virus in children aged 12 months to 15 years inclusive and can be used for primary immunization or booster. The current primary vaccination consists of one dose of vaccine

followed by a booster dose 6 to 18 months apart in order to confer long-term protection. This vaccine is currently approved in approximately 80 countries, including 5 countries belonging to the European Union (Bulgaria, Cyprus, France, Hungary and Romania).

Batch Number: A0543.

IV.2 Clinical aspects

1. Introduction

The MAH submitted a final report for a phase 2 study conducted in Thailand from 02 March 2008 to 28 May 2013:

Study Number: **JEC01**
"A Controlled Study of the Safety and Immunogenicity of ChimeriVax® Japanese Encephalitis Vaccine in Thai Toddlers and Children"

2. Clinical study

- **Description**

Investigational Product: Japanese encephalitis chimeric virus vaccine (JE-CV)
Control Product: **Hepatitis A vaccine manufactured by Sanofi Pasteur**

- **Methods**

- Objectives

safety objective:
to describe the **safety** of a single dose of JE-CV vaccine **compared with Avaxim 80U Paediatric** in

- children (aged 2 to 5 years) previously vaccinated (according to national immunization schedule) with 2 doses of mouse-brain-derived inactivated JE vaccine, and
- in toddlers (aged 12 to 24 months) with no history of previous JE vaccination.

immunogenicity objectives:

- to describe the immunogenicity and yearly persistence of immunogenicity of a
  - single dose of JE-CV vaccine in children (aged 2 to 5 years) previously vaccinated with 2 doses of mouse-brain-derived inactivated JE vaccine, and
  - in toddlers (aged 12 to 24 months) with no history of previous JE vaccination.
- **No immunogenicity data were collected for Avaxim 80U Paediatric in this study.**

For the purposes of the current report, only safety data related to Avaxim 80U Paediatric will be presented.

- Study design

Randomized, cross-over, open, active controlled (hepatitis A vaccine), multi-center trial.
The study included a 5-year follow-up period.

- Study population /Sample size

100 children (2 to 5 years of age) and 200 toddlers (12 to 24 months of age) in Thailand.

- Treatments

single dose of Japanese encephalitis chimeric virus vaccine (JE-CV, also referred to as ChimeriVax™-JE)

followed by

1 dose of Avaxim 80U Pediatric at 1 month and a second dose of Avaxim 80U Pediatric at 7 months.

- Outcomes/endpoints

Only safety endpoints are presented:

- Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term and grouped term), duration, and intensity of any unsolicited systemic adverse events (AEs) reported in the 30 minutes after each vaccination
- Occurrence, time to onset, number of days of occurrence, and intensity of solicited (pre-listed in the subject's diary and electronic Case Report Form) injection site reactions up to 7 days after each vaccination
- Occurrence, time to onset, number of days of occurrence, and intensity of solicited systemic reactions up to 14 days after each vaccination
- Occurrence, nature (MedDRA preferred term), time to onset, duration, intensity, and relationship to vaccination (for systemic AEs only) of unsolicited (spontaneously reported) AEs up to 28 days after each vaccination
- Occurrence of any SAEs up to 6 months after the last vaccination
- Occurrence of out-of-normal-range biological test results 4 days and 28 days after vaccination with JE-CV in Groups 1 and 3
- Occurrence and level of JE-CV viruses in sera collected 4 days after vaccination with JE-CV in Groups 1 and 3 measured by JE plaque assay
- Occurrence of JE-CV and flavivirus viremia and out-of-normal-range biological test results in the event of severe fever, or suspicion of neurotropic disease or acute viscerotropic diseases within 14 days after any vaccination

- Statistical Methods

All the main analyses were descriptive. For the main parameters, 95% confidence intervals (CI) of point estimates were calculated using normal approximation for quantitative data and exact binomial distribution (Clopper-Pearson method) for proportions.

Six interim statistical analyses were performed:
• 28 days after the last injection on safety data collected up to 28 days after any vaccination, and immunogenicity data collected 28 days after JE-CV vaccination

• 6 months after the last injection on the safety and immunogenicity data collected at the 6-month follow-up visit

• 1 year, 2 years, 3 years, and 4 years after the first injection on immunogenicity data

and confirmed JE cases reported at the Year 1, Year 2, Year 3, and Year 4 follow-up visits, respectively

The final analysis of safety and immunogenicity data was performed at the end of the 5-year follow-up.

Sample size
The objective of the trial was to provide safety and immunogenicity data. The sample size was arbitrarily set to 50 subjects in Groups 1 and 2 and 100 subjects in Groups 3 and
4, so that there was a 95% probability of observing an event that had a true incidence of 5.9% in Groups 1 and 2 and 3% in Groups 3 and 4.

- **Results**

- Recruitment/ Number analysed

Enrollment was sequential in two age cohorts.

STEP 1		**D0** **2 to 5 years of age**	**D28** **2 to 5 years of age + 28 days**
Group 1	(n=50)	JE-CV	Hepatitis A
Group 2	(n=50)	Hepatitis A	JE-CV

STEP 2: flavivirus naïve toddlers aged 12 to 24 months received:

STEP 2		**D0** **≥12 months of age**	**D28** **≥12 months of age + 28 days**
Group 3	(n=100)	JE-CV	Hepatitis A
Group 4	(n=100)	Hepatitis A	JE-CV

Sample Size:

	Children aged 2 to 5 years		Toddlers aged 12 to 24 months		
	JE-CV / Hep. A Group 1	Hep. A / JE-CV Group 2	JE-CV / Hep. A Group 3	Hep. A / JE-CV Group 4	All
Planned sample sized	50	50	100	100	300
Randomized	50	51	101	99	301
Safety Set	50	50	101	99	300
Full Analysis Set	50	50	101	99	300
Per Protol Set*	49	48	87	95	279
Subject attendance					
28 days after the second vaccination	49	50	100	98	297
6 months after the second vaccination	49	50	100	98	297
1 year after the first vaccination	48	45	91	90	274
2 years after the first vaccination	43	41	85	79	248
3 years after the first vaccination	40	39	73	63	215
4 years after the first vaccination	41	36	66	58	201
5 years after the first vaccination	40	38	60	50	188

*** Per protocol Set was used fort all analyses on immunogenicity performed 28 days after vaccination with JE-CV**

- Baseline data

At screening, the mean age of randomized toddlers was 16.2 months (in the FAS) and all subjects were Asian. There were similar proportions of male and female subjects in Group 3 and Group 4.

- Efficacy results

  No immunogenicity data were collected for Avaxim 80U Pediatric in this study.

- Safety results

Safety Results in Subjects in the Safety Set

	Children				Toddlers				All			
	JE-CV		Hepatitis A		JE-CV		Hepatitis A		JE-CV		Hepatitis A	
Subjects experiencing at least one:	n/M	%	n/M	%	n/M	%	n/M	%	n/M	%	n/M	%
Solicited reaction	53/100	53.0	55/98	56.1	136/199	68.3	130/199	65.3	189/299	63.2	185/297	62.3
Grade 3 Solicited reaction	1/100	1.0	1/98	1.0	5/199	2.5	6/199	3.0	6/299	2.0	7/297	2.4
Solicited injection site reaction	32/100	32.0	35/98	35.7	81/199	40.7	72/199	36.2	113/299	37.8	107/297	36.0
Solicited systemic reaction	44/100	44.0	35/98	35.7	97/199	48.7	101/199	50.8	141/299	47.2	136/297	45.8
Unsolicited AE	49/100	49.0	49/98	50.0	120/199	60.3	123/200	61.5	169/299	56.5	172/298	57.7
Unsolicited AR	4/100	4.0	0/98	0.0	3/199	1.5	1/200	0.5	7/299	2.3	1/298	0.3
AE leading to study discontinuation	0/100	0.0	0/98	0.0	0/199	0.0	0/200	0.0	0/299	0.0	0/298	0.0
SAE (within 28 days)	1/100	1.0	1/98	1.0	0/199	0.0	7/200	3.5	1/299	0.3	8/298	2.7
SAE (within 6 months*)	4/100	4.0	2/98	2.0	7/199	3.5	14/200	7.0	11/299	3.7	16/298	5.4
Death (within 6 months*)	0/100	0.0	0/98	0.0	0/199	0.0	0/200	0.0	0/299	0.0	0/298	0.0

* *Events reported from D0 up to 6 months after the last vaccination*

Solicited Reactions After Vaccine Injections - All Subjects - Safety Analysis Set

	Children						Toddlers					
	JE-CV			Hepatitis A			JE-CV			Hepatitis A		
Subjects experiencing at least one:	n/M	%	(95% CI)	n/M	%	(95% CI)	n/M	%	(95% CI)	n/M	%	(95% CI)
Solicited reaction	53/100	53.0	(42.8; 63.1)	55/98	56.1	(45.7; 66.1)	136/199	68.3	(61.4; 74.7)	130/199	65.3	(58.3; 71.9)
Injection site reaction	32/100	32.0	(23.0; 42.1)	35/98	35.7	(26.3; 46.0)	81/199	40.7	(33.8; 47.9)	72/199	36.2	(29.5; 43.3)
Injection site pain/tenderness	24/100	24.0	(16.0; 33.6)	28/98	28.6	(19.9; 38.6)	63/199	31.7	(25.3; 38.6)	54/199	27.1	(21.1; 33.9)
Injection site erythema	14/100	14.0	(7.9; 22.4)	17/98	17.3	(10.4; 26.3)	45/199	22.6	(17.0; 29.1)	39/199	19.6	(14.3; 25.8)
Injection site swelling	8/100	8.0	(3.5; 15.2)	13/98	13.3	(7.3; 21.6)	17/199	8.5	(5.1; 13.3)	14/199	7.0	(3.9; 11.5)
Systemic reaction	44/100	44.0	(34.1; 54.3)	35/98	35.7	(26.3; 46.0)	97/199	48.7	(41.6; 55.9)	101/199	50.8	(43.6; 57.9)
Fever	22/100	22.0	(14.3; 31.4)	13/98	13.3	(7.3; 21.6)	42/199	21.1	(15.7; 27.4)	41/199	20.6	(15.2; 26.9)
Headache	21/100	21.0	(13.5; 30.3)	14/98	14.3	(8.0; 22.8)						
Malaise	33/100	33.0	(23.9; 43.1)	26/98	26.5	(18.1; 36.4)						
Myalgia	24/100	24.0	(16.0; 33.6)	15/98	15.3	(8.8; 24.0)						
Vomiting							40/199	20.1	(14.8; 26.3)	44/199	22.1	(16.5; 28.5)
Crying abnormal							45/199	22.6	(17.0; 29.1)	39/199	19.6	(14.3; 25.8)
Drowsiness							36/199	18.1	(13.0; 24.2)	30/199	15.1	(10.4; 20.8)
Appetite lost							52/199	26.1	(20.2; 32.8)	58/199	29.1	(22.9; 36.0)
Irritability							56/199	28.1	(22.0; 34.9)	46/199	23.1	(17.4; 29.6)

Subjects experiencing at least one:	All					
	JE-CV			Hepatitis A		
	n/M	%	(95% CI)	n/M	%	(95% CI)
Solicited reaction	189/299	63.2	(57.5; 68.7)	185/297	62.3	(56.5; 67.8)
Injection site reaction	113/299	37.8	(32.3; 43.6)	107/297	36.0	(30.6; 41.8)
Injection site pain/tenderness	87/299	29.1	(24.0; 34.6)	82/297	27.6	(22.6; 33.1)
Injection site erythema	59/299	19.7	(15.4; 24.7)	56/297	18.9	(14.6; 23.8)
Injection site swelling	25/299	8.4	(5.5; 12.1)	27/297	9.1	(6.1; 13.0)
Systemic reaction	141/299	47.2	(41.4; 53.0)	136/297	45.8	(40.0; 51.6)
Fever	64/299	21.4	(16.9; 26.5)	54/297	18.2	(14.0; 23.0)
Headache	21/100	21.0	(13.5; 30.3)	14/98	14.3	(8.0; 22.8)
Malaise	33/100	33.0	(23.9; 43.1)	26/98	26.5	(18.1; 36.4)
Myalgia	24/100	24.0	(16.0; 33.6)	15/98	15.3	(8.8; 24.0)
Vomiting	40/199	20.1	(14.8; 26.3)	44/199	22.1	(16.5; 28.5)
Crying abnormal	45/199	22.6	(17.0; 29.1)	39/199	19.6	(14.3; 25.8)
Drowsiness	36/199	18.1	(13.0; 24.2)	30/199	15.1	(10.4; 20.8)
Appetite lost	52/199	26.1	(20.2; 32.8)	58/199	29.1	(22.9; 36.0)
Irritability	56/199	28.1	(22.0; 34.9)	46/199	23.1	(17.4; 29.6)

n: number of subjects experiencing the endpoint listed in the first column
M: number of subjects with available data for the relevant endpoint
JE-CV: JE-CV as first or second injection
Hepatitis A: Hepatitis A as first or second injection
Subject 003-00027, aged 2-5 years, received 2 injections of JE-CV (D0 and D28) in error. This table includes solicited reactions occurring after both JE-CV
injections for this subject
Source: Study JEC01 CSR Table 9.49.

No immediate AEs were reported. No subject was withdrawn from the study for an AE.

The most frequently reported solicited injection site reaction in children (2 to 5 years) after both JE-CV and hepatitis A vaccination was injection site pain, followed by injection site erythema and injection site swelling (the incidence is shown in the table below).

In toddlers (12 to 24 months), the most frequently reported injection site reaction after both JE-CV and hepatitis A vaccination was injection site tenderness, followed by injection site erythema and injection site swelling.

The majority of the solicited injection site reactions were of grade 1 intensity, occurred within 3 days after vaccination, and had between 1 and 3 days of occurrence.

In children, the most frequently reported solicited systemic reaction after both JE-CV and hepatitis A vaccination was malaise. Fever was slightly more frequent after JE-CV (22.0%) than hepatitis A (13.3%) vaccination.

In toddlers, the most frequently reported solicited systemic reactions after both JE-CV and hepatitis A vaccination were irritability and appetite lost. Fever was reported as frequently after JE-CV (21.1%) as after hepatitis A (20.6%) vaccination.

The majority of the solicited systemic reactions were of grade 1 or grade 2 intensity, occurred within 7 days after vaccination, and had between 1 and 3 days of occurrence.

Solicited Injection Site Within 7 Days and Systemic Reactions Within 14 Days After Vaccination in the Safety Set

	Children				Toddlers			
	JE-CV		Hepatitis A		JE-CV		Hepatitis A	
Subjects experiencing at least one:	n/M	%	n/M	%	n/M	%	n/M	%
Solicited reaction	53/100	53.0	55/98	56.1	136/199	68.3	130/199	65.3
Injection site reaction	32/100	32.0	35/98	35.7	81/199	40.7	72/199	36.2
Injection site pain/tenderness	24/100	24.0	28/98	28.6	63/199	31.7	54/199	27.1
Injection site erythema	14/100	14.0	17/98	17.3	45/199	22.6	39/199	19.6
Injection site swelling	8/100	8.0	13/98	13.3	17/199	8.5	14/199	7.0
Systemic reaction*	44/100	44.0	35/98	35.7	97/199	48.7	101/199	50.8
Fever	22/100	22.0	13/98	13.3	42/199	21.1	41/199	20.6
Headache	21/100	21.0	14/98	14.3				
Malaise	33/100	33.0	26/98	26.5				
Myalgia	24/100	24.0	15/98	15.3				
Vomiting					40/199	20.1	44/199	22.1
Crying abnormal					45/199	22.6	39/199	19.6
Drowsiness					36/199	18.1	30/199	15.1
Appetite lost					52/199	26.1	58/199	29.1
Irritability					56/199	28.1	46/199	23.1

A grade 3 solicited injection site reaction was reported in one toddler (injection site tenderness) after hepatitis A vaccination. Grade 3 solicited systemic reactions were reported in two children after JE-CV vaccination (fever) and after hepatitis A vaccination (fever), and in five toddlers after JE-CV vaccination and six toddlers after hepatitis A vaccination (appetite lost, fever, vomiting, crying abnormal and/or irritability).

The incidences of unsolicited AEs 28 days after vaccination were comparable after JE-CV and hepatitis A vaccination overall and in each age group. The most frequent events were upper respiratory tract infection, rhinorrhea, and nasopharyngitis. Unsolicited reactions were reported by few subjects (seven subjects after JE-CV and one subject after hepatitis A vaccination) and were mainly injection site reactions; no reaction was of grade 3 intensity. Two subjects reported grade 3 unsolicited AEs not related to vaccination according to the Investigator after hepatitis A vaccination (acute bronchitis and joint dislocation).

A total of 27 subjects reported 32 SAEs up to 6 months after the last vaccination: 6 children experienced 7 SAEs and 21 toddlers experienced 25 SAEs. None of the SAEs were considered related to vaccination by the Investigator. All subjects recovered. No death was reported.

In the period up to 28 days after vaccination, 9 subjects reported 9 SAEs; 2 were reported by children aged 2 to 5 years and 7 were reported by toddlers aged 12 to 24 months. Eight of these nine SAEs were reported after hepatitis A vaccination. During the follow-up period (from 28 days to 6 months after the last vaccination) 20 subjects reported 23 SAEs: 4 children experienced 5 SAEs and 16 toddlers experienced 18 SAEs.

No subject experienced any SAE considered as related to vaccination by the Investigator in the period from the 6 months follow-up visit after the last vaccination and up to the Year 5 follow-up

visit after vaccination. The most frequent reported system organ class was “Infections and infestations” whatever the group and study period.

Biological parameters were measured at screening, D4 and D28. The majority of subjects had values within normal ranges throughout the study, although some subjects with normal biological parameters at baseline reported a switch outside the normal ranges after JE-CV vaccination. However, no change was judged clinically significant by the Investigators, and the observed abnormalities (e.g., ALT, AST) could be considered as minor.

Hypersensitivity/allergic reactions, neurological events, and vaccine failure reported up to 28 days after vaccination were considered events of specific interest in the present study. One case of febrile convulsion was reported after hepatitis A vaccination, while no hypersensitivity reaction, vaccine failure or other neurological event were observed up to 28 days after any vaccination.

During the entire study, 5 subjects reported 6 episodes of febrile convulsion: one toddler within 28 days after hepatitis A vaccination, and one child and three toddlers during the 6-month follow-up period (53 to 117 days after the last of two vaccinations with JE-CV and hepatitis A, respectively). Moreover, two other subjects (one child and one toddler) presented with febrile convulsions (which were considered as SAEs) during the screening period; these subjects were not eligible for vaccination.

Six subjects came to unscheduled visits within 14 days after vaccination due to severe fever related to infectious diseases. Two children aged 2 to 5 years presented at the study center after hepatitis A vaccination, and four toddlers aged 12 to 24 months came for unscheduled visits: two subjects in Group 3 after hepatitis A vaccination and two subjects in Group 4 after JE-CV vaccination. No subject had confirmed neurotropic or acute viscerotropic disease. No subject presented with confirmed JE during the long-term follow-up period after the 6-month follow-up visit.

No subject presented with confirmed JE during the long-term follow-up period after the 6-month follow-up visit.

Conclusions regarding Avaxim 80U Pediatric:

The safety profile of JE-CV is similar to that of hepatitis A vaccine.

3. Discussion on clinical aspects

The present document provides information from Phase 2 study JEC01 for Avaxim 80U Pediatric. Three solicited systemic reactions reported during the study are currently not listed in the SmPCs and CCDS for Avaxim 80U Pediatric: 1 in children (malaise) and 2 in toddlers (drowsiness and crying abnormal). Overall, solicited AR are reported more frequently than the frequency indicated in the Avaxim 80U Pediatric CCDS or SmPCs.

Rapporteur's comment on proposed frequency change

SmPC HUNGARY In clinical studies study population: 3500, 12 mo -15 years 7000 doses		The **JEC01 study** 200 toddlers (12 to 24 mo) 100 children (2 to 5 years) 600 doses	**Proposed changes by the MAH** based on the frequences reported in the JEC01 study
AE	**frequency**	**AEs frequency (%)**	**SmPC frequency category**
decreased appetite	common	29,1	very common
irritability	common	23,1	very common
insomnia	common		
headache	common	14,3	very common
abdominal pain	common	-	
diarrhoea	common	-	
nausea	common	-	
womiting	common	22,1	very common
itching	uncommon	-	
urticaria	uncommon	-	
arthralgia	common	-	
myalgia	common	15,3	very common
fever	common	18,2	very common
asthenia	common		
injection site pain, erythema, nodule or induration	common	36	pain and erythema: very common

Rapporteur's comment:

In the current (Hungarian) SmPC AEs and theirs frequencies are listed based on administration of 7000 doses in previous clinical trials.
In present study after 600 doses some AE were observed with higher frequency than that, some of them were not observed at all and some new AEs were observed.

The MAH proposed to change the frequency of AEs observed with higher frequency from "common" to be listed as "Very common" in the SmPC based on the frequencies reported in JEC01 study.

The MAH is requested to reconsider the change of frequency categories as the frequency category in SmPC should be based on cumulative data and not on the latest study's result only. Pooled safety data from several studies increases the precision of adverse event's rate and provide a more clinically useful representation of a vaccine's adverse event profile.

Rapporteur's comment on inclusion new AE and it's frequency		
New AE proposed by the MAH to include in the SmPC	**Frequency (%) reported in the JEC01 study**	**suggested frequency category in SmPC**
malaise*	26,5	very common
drowsiness**	15,1	very common
crying abnormal**	19,6	very common
Rapporteur's comment		
The rapporteur agrees with the inclusion of the suggested new AEs (malaise, drowsiness and crying abnormal), they seem to be a reasonable possibility. **The very common frequency category observed in this study (e.g. crying abnormal) seems to be unlikely to occur.** **The MAH is requested to reconsider the frequency categories proposed in SmPC taking into account the previous studies' data by making pooled analysis across suitable studies.**		

* malaise was observed among children only

** crying abnormal and drowsiness was observed among toddlers only

Analysis of the literature

The original research publications of the results of clinical trials conducted with hepatitis A inactivated vaccine Avaxim 80U Pediatric, which have been identified through the literature search, revealed no new information regarding immunogenicity or safety profile not already included in the respective national Summary of Product Characteristics (SmPCs) and in the Company Core Data Sheet (CCDS). The search for literature was performed using multiple databases. Four literature databases were searched: the PubMed database (http://www.ncbi.nlm.nih.gov/pubmed) from the National Center for Biotechnology Information at the United States National Library of Medicine, Embase (www.embase.com) from Elsevier B.V., and Chemical Abstracts Plus and Biosis via the STN database platform from Chemical Abstracts Service. Trial results for Avaxim were also extracted from the TrialTrove clinical trial database (https://sanofi.citeline.com/default.asp) from Citeline and compared with the results from the literature database searches. Additional conference abstracts were added to the results based on this review. As of 04 February 2015, a total of 32 articles and conference abstracts were identified using the keyword "Avaxim" or "Hepabest" and additional keywords for clinical studies. The search was further extended using keywords for hepatitis A vaccine and Sanofi Pasteur (or "Pasteur Mérieux" or "Aventis Pasteur") as the vaccine manufacturer or article author. A total of 16 original research publications have been identified manually using the following inclusion criteria: "Pediatric formulation of Sanofi Pasteur" (or "Pasteur Mérieux" or "Aventis Pasteur") produced inactivated hepatitis A vaccine - Avaxim 80U." Thirteen of the 16 identified studies were sponsored by Sanofi Pasteur (formerly named "Pasteur Mérieux" and then "Aventis Pasteur"). The 3 remaining studies were based on clinical trials with Avaxim 80U Pediatric conducted by a sponsor other than Sanofi Pasteur.

V. MEMBER STATES' OVEALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

The result of this work-sharing procedure (HU/W/007/pdWS/002):
No SmPC and PL changes are proposed.
No further action required.

- **Recommendation**

The assessment of the pooled safety analysis and a proposition of SmPC/CCDS update will be the part of next paediatric work-sharing procedure (study HAF87, HU/W/007/pdWS/003).