Table 8: Stability Study Results for Marcy l'Etoile Filled Product Batch FDNC0504 at +5°C ± 3°C

Tests	Acceptance criteria	T0*	1 month	3 months	6 months	9 months	12 months	18 months	24 months	30 months	36 months
Appearence	Whitish and cloudy suspension	Conforms	NP†	Conforms	Conforms	Conforms	Conforms	Conforms	On-going	On-going	On-going
pH measurement	6.5 – 7.5	7.17	NP	7.20	7.21	7.22	7.24	7.24	On-going	On-going	On-going
Free formaldehyde Content	≤ 30 µg/mL	3.34	NP	NP	NP	NP	< 0.36	NP	On-going	NP	On-going
Extractable volume	At least the nominal volume	Conforms	NP	NP	NP	NP	NP	NP	NP	NP	On-going
Aluminium content	0.40 – 0.80 mg/dose	0.61	NP	NP	NP	NP	NP	NP	NP	NP	On-going
Osmolality measurement	300 - 400 mosmol/kg	338	NP	NP	NP	NP	NP	NP	NP	NP	On-going
Non-adsorbed PRP	≥ 16 µg/mL	23.8	20.3	24.0	22.6	21.8	21.7	21.9	On-going	On-going	On-going
Depolymerized PRP	For information (%)	17.1	18.0	19.8	20.8	28.0	29.7	34.4	On-going	On-going	On-going
Diphtheria potency :	Activity ≥ 30 IU/mL										
Activity	Lower confidence limit ($P = 0.95$) of the estimated potency ≥ 20 IU/mL	57	NP	NP	67	NP	53	47	On-going	On-going	On-going
Lower limit		43	NP	NP	49	NP	40	35	On-going	On-going	On-going
Upper limit		82	NP	NP	95 at 7.5 months	NP	70	62	On-going	On-going	On-going
Tetanus potency :	Lower confidence limit ($P = 0.95$) of the estimated potency ≥ 40 IU/mL										
Activity		584	NP	NP	806	NP	659	674	On-going	On-going	On-going
Lower limit		413	NP	NP	589	NP	488	469	On-going	On-going	On-going
Upper limit		795	NP	NP	1108	NP	881	949	On-going	On-going	On-going
Histamine-sensitizing activity	≥ 95% survival (%)	100	NP	NP	NP	NP	100	NP	On-going	NP	On-going

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Tests	Acceptance criteria	T0*	1 month	3 months	6 months	9 months	12 months	18 months	24 months	30 months	36 months
Pertussis immunogenicity anti-FHA	Anti-Filamentous Hemagglutinin (FHA) antibody titer obtained for the vaccine is not significantly *(P = 0.95)* less than that of the reference vaccine	Conforms	NP	NP	Conforms	NP	Conforms	In-progress‡	On-going	On-going	On-going
Pertussis immunogenicity anti-PT	Anti-Pertussis Toxoid (PTxd) and antibody titer obtained for the vaccine is not significantly *(P = 0.95)* less than that of the reference vaccine	Conforms	NP	NP	Conforms	NP	Conforms	In-progress‡	On-going	On-going	On-going
Haemophilus immunogenicity	For information§	Conforms	NP	NP	Conforms	NP	Conforms	Conforms	On-going	On-going	On-going
Non-adsorbed PT	For information (µg/mL)**	< 2.5	NP	NP	< 2.5 at 9 months	NP	< 2.5	NP	On-going	NP	On-going
Non-adsorbed FHA	For information (µg/mL)**	< 2.5	NP	NP	< 2.5 at 8 months	NP	< 2.5	NP	On-going	NP	On-going
Percent adsorption – tetanus toxoid	For information (%)	42	NP	39	44	NP	41	38	On-going	On-going	On-going
Percent Adsorption – diphtheria toxoid	For information (%)	54	NP	59	63	NP	71	66	On-going	On-going	On-going
Rat immunogenicity assay for IPV	For information (relative potency)										
Type 1		0.5	NP	NP	NP	NP	0.9	NP	On-going	NP	On-going
Type 2		0.5	NP	NP	NP	NP	1.6	NP	On-going	NP	On-going
Type 3		1.6	NP	NP	NP	NP	1.1	NP	On-going	NP	On-going

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Tests	Acceptance criteria	T0*	1 month	3 months	6 months	9 months	12 months	18 months	24 months	30 months	36 months
D-antigen content	Type 1: 20 – 43 DU/dose	Not Performed††	NP	26.8	26.3	NP	27.4	27.2	On-going	On-going	On-going
	Type 2: 5 – 9 DU/dose		NP	6.7	6.3	NP	6.9	6.8	On-going	On-going	On-going
	Type 3: 17 – 36 DU/dose		NP	24.6	23.8	NP	25.5	25.8	On-going	On-going	On-going
Non-adsorbed D-antigen content	For information										
Type 1		28.8	NP	26.1	25.5	NP	27.2	28.0	On-going	On-going	On-going
Type 2		6.0	NP	5.7	4.8	NP	5.3	5.1	On-going	On-going	On-going
Type 3		25.7	NP	25.7	24.3	NP	25.7	25.9	On-going	On-going	On-going
Percent adsorption – hepatitis B (ELISA)	For information (%)	90	87	90	88	87	86	86	On-going	On-going	On-going
Hepatitis B *in-vitro* relative potency (IVRP)	For information (relative potency)	1.47	NP	1.36	1.33	1.44	1.42	1.24	On-going	On-going	On-going
Hepatitis B immunogenicity	Upper confidence limit (P = 0.95) of the estimated relative potency is not less than 1.0	1.16	NP	NP	1.50	NP	1.21	1.45	On-going	On-going	On-going
Lower limit		0.568	NP	NP	0.797	NP	0.680	0.799	On-going	On-going	On-going
Upper limit		2.041	NP	NP	3.062	NP	2.256	2.933	On-going	On-going	On-going
Bacterial and fungal sterility test	No microbial growth	Conforms	NP	NP	NP	NP	NP	NP	NP	NP	On-going
Pyrogen test	Conforms to Ph. Eur. criterion	0.23 (0.00 - 0.23 - 0.00)	NP	NP	NP	NP	NP	NP	NP	NP	On-going
Specific toxicity for diphtheria and tetanus components	There must be no toxic reactions or deaths. All animals must maintain a healthy appearance during the period of observation and weigh no less at the end of the test than at the time of injection	Conforms	NP	NP	NP	NP	NP	NP	NP	NP	On-going

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Tests	Acceptance criteria	T0*	1 month	3 months	6 months	9 months	12 months	18 months	24 months	30 months	36 months
Integrity test	The CCIT‡‡ is acceptable if no presence of dye is detected in the contents of any of the tested syringes	Conforms	NP	NP	NP	NP	Conforms	NP	On-going	NP	On-going

* All the results are obtained from the T0 of the Filled Product excepted for the following tests: free formaldehyde content, osmolality measurement, diphtheria and tetanus potency, histamine-sensitizing activity, pertussis immunogenicity anti-FHA and anti-PT, haemophilus immunogenicity, non-adsorbed PT and FHA, rat immunogenicity assay for IPV, non-adsorbed D-antigen content, hepatitis B immunogenicity and specific toxicity for diphtheria and tetanus components. For these tests, the results are release results of the Final Bulk Product.

† Not Planned as per protocol

‡ The reference vaccine for pertussis immunogenicity test was changed at T18 months. The qualification of this reference standard was performed by a statistical comparison to the previous one

§ Expected results: Not less than 50% of the vaccinated mice are seroconverted. Their titer is not less than 4 times that of the pooled control serum

** Expected value: ≤ 2.5 µg/mL

†† Not Performed due to industrial constraints

‡‡ CCIT: Container Closure Integrity Test

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Table 9: Stability Study Results for Marcy l'Etoile Filled Product Batch FDNC0505 at +5°C ± 3°C

Tests	Acceptance criteria	T0*	1 month	3 months	6 months	9 months	12 months	18 months	24 months	30 months	36 months
Appearence	Whitish and cloudy suspension	Conforms	NP†	Conforms	Conforms	Conforms	Conforms	Conforms	On-going	On-going	On-going
pH measurement	6.5 – 7.5	7.19	NP	7.23	7.24	7.25	7.28	7.28	On-going	On-going	On-going
Free formaldehyde content	≤ 30 µg/mL	1.36	NP	NP	NP	NP	< 0.36	NP	On-going	NP	On-going
Extractable volume	At least the nominal volume	Conforms	NP	NP	NP	NP	NP	NP	NP	NP	On-going
Aluminium content	0.40 – 0.80 mg/dose	0.59	NP	NP	NP	NP	NP	NP	NP	NP	On-going
Osmolality measurement	300 - 400 mosmol/kg	336	NP	NP	NP	NP	NP	NP	NP	NP	On-going
Non-adsorbed PRP	≥ 16 µg/mL	22.4	19.2	23.5	21.2	20.9	20.5	21.4	On-going	On-going	On-going
Depolymerized PRP	For information (%)	18.2	19.0	19.4	22.3	27.4	29.9	34.0	On-going	On-going	On-going
Diphtheria potency :	Activity ≥ 30 IU/mL										
Activity	Lower confidence limit ($P = 0.95$) of the estimated potency ≥ 20 IU/mL	76	NP	NP	48	NP	65	61	On-going	On-going	On-going
Lower limit		57	NP	NP	30	NP	47	48	On-going	On-going	On-going
Upper limit		113	NP	NP	76 at 8 months	NP	92	77	On-going	On-going	On-going
Tetanus potency :	Lower confidence limit ($P = 0.95$) of the estimated potency ≥ 40 IU/mL										
Activity		705	NP	NP	773	NP	710	1082	On-going	On-going	On-going
Lower limit		485	NP	NP	579	NP	527	712	On-going	On-going	On-going
Upper limit		1017	NP	NP	1035	NP	948	1850	On-going	On-going	On-going
Histamine-sensitizing activity	≥ 95% survival (%)	100	NP	NP	NP	NP	100	NP	On-going	NP	On-going

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Tests	Acceptance criteria	T0*	1 month	3 months	6 months	9 months	12 months	18 months	24 months	30 months	36 months
Pertussis immunogenicity anti-FHA	Anti-Filamentous Hemagglutinin (FHA) antibody titer obtained for the vaccine is not significantly *(P = 0.95)* less than that of the reference vaccine	Conforms	NP	NP	Conforms	NP	Conforms	Conforms‡	On-going	On-going	On-going
Pertussis immunogenicity anti-PT	Anti-Pertussis Toxoid (PTxd) and antibody titer obtained for the vaccine is not significantly *(P = 0.95)* less than that of the reference vaccine	Conforms	NP	NP	Conforms	NP	Conforms	Conforms‡	On-going	On-going	On-going
Haemophilus immunogenicity	For information§	Conforms	NP	NP	Conforms	NP	Conforms	Conforms	On-going	On-going	On-going
Non-adsorbed PT	For information (µg/mL)**	< 2.5	NP	NP	< 2.5 at 9 months	NP	< 2.5	NP	On-going	NP	On-going
Non-adsorbed FHA	For information (µg/mL)**	< 2.5	NP	NP	< 2.5 at 8 months	NP	< 2.5	NP	On-going	NP	On-going
Percent adsorption – tetanus toxoid	For information (%)	24	NP	29	31	NP	40	38	On-going	On-going	On-going
Percent adsorption – diphtheria toxoid	For information (%)	52	NP	57	62	NP	65	65	On-going	On-going	On-going
Rat immunogenicity assay for IPV	For information (relative potency)										
Type 1		0.6	NP	NP	NP	NP	0.8	NP	On-going	NP	On-going
Type 2		1.2	NP	NP	NP	NP	2.0	NP	On-going	NP	On-going
Type 3		3.1	NP	NP	NP	NP	/††	NP	On-going	NP	On-going

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Tests	Acceptance criteria	T0*	1 month	3 months	6 months	9 months	12 months	18 months	24 months	30 months	36 months
D-antigen content	Type 1: 20 – 43 DU/dose	Not Performed‡‡	NP	25.4	27.3	NP	28.4	24.8	On-going	On-going	On-going
	Type 2: 5 – 9 DU/dose		NP	6.6	7.1	NP	7.3	6.7	On-going	On-going	On-going
	Type 3: 17 – 36 DU/dose		NP	23.8	24.4	NP	22.6	22.9	On-going	On-going	On-going
Non-adsorbed D-antigen content	For information										
Type 1		28.1	NP	25.1	25.1	NP	25.7	24.5	On-going	On-going	On-going
Type 2		5.8	NP	5.5	5.1	NP	4.9	4.4	On-going	On-going	On-going
Type 3		24.6	NP	24.1	23.8	NP	22.5	23.1	On-going	On-going	On-going
Percent adsorption – hepatitis B (ELISA)	For information (%)	92	88	88	90	90	87	90	On-going	On-going	On-going
Hepatitis B *in- vitro* relative potency (IVRP)	For information (relative potency)	1.43	NP	1.43	1.44	1.38	1.30	1.33	On-going	On-going	On-going
Hepatitis B immunogenicity	Upper confidence limit (P = 0.95) of the estimated relative potency is not less than 1.0	1.17	NP	NP	1.51	NP	1.35	1.40	On-going	On-going	On-going
Lower limit		0.644	NP	NP	0.821	NP	0.740	0.88	On-going	On-going	On-going
Upper limit		2.268	NP	NP	2.972	NP	3.134	2.31	On-going	On-going	On-going
Bacterial and fungal sterility test	No microbial growth	Conforms	NP	NP	NP	NP	NP	NP	NP	NP	On-going
Pyrogen test	Conforms to Ph. Eur. criterion	0.68 (0.25 - 0.31 - 0.12)	NP	NP	NP	NP	NP	NP	NP	NP	On-going
Specific toxicity for diphtheria and tetanus components	There must be no toxic reactions or deaths. All animals must maintain a healthy appearance during the period of observation and weigh no less at the end of the test than at the time of injection	Conforms	NP	NP	NP	NP	NP	NP	NP	NP	On-going

Tests	Acceptance criteria	T0*	1 month	3 months	6 months	9 months	12 months	18 months	24 months	30 months	36 months
Integrity test	The CCIT§§ is acceptable if no presence of dye is detected in the contents of any of the tested syringes	Conforms	NP	NP	NP	NP	Conforms	NP	On-going	NP	On-going

* All the results are obtained from the T0 of the Filled Product excepted for the following tests: free formaldehyde content, osmolality measurement, diphtheria and tetanus potency, histamine sensitizing activity, pertussis immunogenicity anti-FHA and anti-PT, haemophilus immunogenicity, non-adsorbed PT and FHA, rat immunogenicity assay for IPV, non-adsorbed D-antigen content, hepatitis B immunogenicity and specific toxicity for diphtheria and tetanus components. For these tests, the results are release results of the Final Bulk Product.

† Not Planned as per protocol

‡ The reference vaccine for pertussis immunogenicity test was changed at T18 months. The qualification of this reference standard was performed by a statistical comparison to the previous one

§ Expected results: Not less than 50% of the vaccinated mice are seroconverted. Their titer is not less than 4 times that of the pooled control serum

** Expected value: ≤ 2.5 µg/mL

†† Test invalid. A complementary test is in-progress

‡‡ Not Performed due to industrial constraints

§§ CCIT: Container Closure Integrity Test

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1.4 Study 3: Marcy l'Etoile Filled Product – Optimized Formulation – Stability Data on Accelerated Storage Conditions at +25°C ± 2°C

6 months stability data with the optimized formulation on 3 batches of MLE FP are presented in Table 10 to Table 12.

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Table 10: Stability Study Results for Marcy l'Etoile Filled Product Batch FDNC0491 at +25°C ± 2°C

Tests	Acceptance criteria	T0*	1 month	3 months	6 months
Appearence	Whitish and cloudy suspension	Conforms	Conforms	Conforms	Whitish and cloudy suspension with one white particle
pH measurement	6.5 – 7.5	7.27	7.35	7.38	7.43
Non-adsorbed PRP	≥ 16 µg/mL	25.4	25.8	31.4	29.1
Depolymerized PRP	For information (%)	17.9	42.5	66.2	78.6
Diphtheria potency : **Activity** **Lower limit** **Upper limit**	Activity ≥ 30 IU/mL Lower confidence limit (*P = 0.95*) of the estimated potency ≥ 20 IU/mL	 42 34 52	 NP† NP NP	 58 44 78	 42 29 60 at 7.5 months
Tetanus potency : **Activity** **Lower limit** **Upper limit**	Lower confidence limit (*P = 0.95*) of the estimated potency ≥ 40 IU/mL	 556 280 853	 NP NP NP	 307 230 405 *at 4 months*	 261 190 361 at 7.5 months
Pertussis immunogenicity anti-FHA	Anti-Filamentous Hemagglutinin (FHA) antibody titer obtained for the vaccine is not significantly *(P = 0.95)* less than that of the reference vaccine	Conforms	NP	Conforms	On-going
Pertussis immunogenicity anti-PT	Anti-Pertussis Toxoid (PTxd) and antibody titer obtained for the vaccine is not significantly *(P = 0.95)* less than that of the reference vaccine	Conforms	NP	Conforms	On-going
Haemophilus immunogenicity	For information‡	Conforms	NP	Conforms	Fails

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Tests	Acceptance criteria	T0*	1 month	3 months	6 months
Non-adsorbed PT	For information (µg/mL)§	< 2.5	NP	< 2.5	< 2.5 at 9 months
Non-adsorbed FHA	For information (µg/mL)§	< 2.5	NP	< 2.5	< 2.5 at 8 months
Percent adsorption – tetanus toxoid	For information (%)	31	41	46	44
Percent adsorption – diphtheria toxoid	For information (%)	53	63	71	75
D-antigen content	Type 1: 20 – 43 DU/dose Type 2: 5 – 9 DU/dose Type 3: 17 – 36 DU/dose	Not performed**	25.6 5.9 22.4 at 1.5 months	24.9 6.2 25.1	22.2 5.8 22.8
Percent adsorption – hepatitis B (ELISA)	For information (%)	89	76	71	80
Hepatitis B *in- vitro* relative potency (IVRP)	For information (relative potency)	1.43	1.41	0.95	0.88
Hepatitis B immunogenicity	Upper confidence limit (P = 0.95) of the estimated relative potency is not less than 1.0	1.21	NP	1.31	1.28
Lower limit		0.628	NP	0.823	0.767
Upper limit		2.561	NP	1.986	2.286
Bacterial and fungal sterility test	No microbial growth	Conforms	NP	NP	Conforms
Integrity test	The CCIT is acceptable if no presence of dye is detected in the contents of any of the tested syringes	Conforms	NP	NP	Conforms

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* All the results are obtained from the T0 of the Filled Product excepted for the following tests: diphtheria and tetanus potency, pertussis immunogenicity anti-FHA and anti-PT, haemophilus immunogenicity, non-adsorbed PT and FHA and hepatitis B immunogenicity. For these tests, the results are release results of the Final Bulk Product.

Not Planned as per protocol

‡ Expected results: Not less than 50% of the vaccinated mice are seroconverted. Their titer is not less than 4 times that of the pooled control serum

§ Expected value: ≤ 2.5 µg/mL

** Not Performed due to industrial constraints

Table 11: Stability Study Results for Marcy l'Etoile Filled Product Batch FDNC0504 at +25°C ± 2°C

Tests	Acceptance criteria	T0*	1 month	3 months	6 months
Appearence	Whitish and cloudy suspension	Conforms	Conforms	Conforms	Conforms
pH measurement	6.5 – 7.5	7.17	7.25	7.26	7.28
Non-adsorbed PRP	≥ 16 µg/mL	23.8	24.8	32.0	27.7
Depolymerized PRP	For information (%)	17.1	39.4	61.7	76.0
Diphtheria potency **Activity** **Lower limit** **Upper limit**	Activity ≥ 30 IU/mL Lower confidence limit (*P = 0.95*) of the estimated potency ≥ 20 IU/mL	 57 43 82	 NP† NP NP	 76 50 120	 48 32 74 at 7.5 months
Tetanus potency **Activity** **Lower limit** **Upper limit**	Lower confidence limit (*P = 0.95*) of the estimated potency ≥ 40 IU/mL	 584 413 795	 NP NP NP	 232 149 328 at 4 months	 177 113 256
Pertussis immunogenicity anti-FHA	Anti-Filamentous Hemagglutinin (FHA) antibody titer obtained for the vaccine is not significantly *(P = 0.95)* less than that of the reference vaccine	Conforms	NP	Invalid test	On-going
Pertussis immunogenicity anti-PT	Anti-Pertussis Toxoid (PTxd) and antibody titer obtained for the vaccine is not significantly *(P = 0.95)* less than that of the reference vaccine	Conforms	NP	Invalid test	On-going
Haemophilus immunogenicity	For information‡	Conforms	NP	Conforms	Fails
Non-adsorbed PT	For information (µg/mL)§	< 2.5	NP	< 2.5	< 2.5 at 9 months

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Tests	Acceptance criteria	T0*	1 month	3 months	6 months
Non-adsorbed FHA	For information (µg/mL)§	< 2.5	NP	< 2.5	< 2.5 at 8 months
Percent adsorption – tetanus toxoid	For information (%)	42	49	55	50
Percent adsorption – diphtheria toxoid	For information (%)	54	68	75	75
D-antigen content	Type 1: 20 – 43 DU/dose Type 2: 5 – 9 DU/dose Type 3: 17 – 36 DU/dose	Not Performed**	26.8 7.1 26.3 at 1.5 months	24.9 6.5 25.1	22.8 6.3 24.2
Percent adsorption – hepatitis B (ELISA)	For information (%)	90	76	75	76
Hepatitis B *in-vitro* relative potency (IVRP)	For information (relative potency)	1.47	1.46	1.11	0.86
Hepatitis B immunogenicity	Upper confidence limit (P = 0.95) of the estimated relative potency is not less than 1.0	1.16	NP	1.17	1.06
Lower limit		0.568	NP	0.709	0.661
Upper limit		2.041	NP	1.981	1.703
Bacterial and fungal sterility test	No microbial growth	Conforms	NP	NP	Conforms
Integrity test	The CCIT is acceptable if no presence of dye is detected in the contents of any of the tested syringes	Conforms	NP	NP	Conforms

* All the results are obtained from the T0 of the Filled Product excepted for the following tests: diphtheria and tetanus potency, pertussis immunogenicity anti-FHA and anti-PT, haemophilus immunogenicity, non-adsorbed PT and FHA and hepatitis B immunogenicity. For these tests, the results are release results of the Final Bulk Product.

† Not Planned as per protocol

‡ Expected results: Not less than 50% of the vaccinated mice are seroconverted. Their titer is not less than 4 times that of the pooled control serum

§ Expected value: ≤ 2.5 µg/mL

** Not Performed due to industrial constraints

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Table 12: Stability Study Results for Marcy l'Etoile Filled Product Batch FDNC0505 at +25°C ± 2°C

Tests	Acceptance criteria	T0*	1 month	3 months	6 months
Appearence	Whitish and cloudy suspension	Conforms	Conforms	Conforms	Conforms
pH measurement	6.5 – 7.5	7.19	7.28	7.30	7.34
Non-adsorbed PRP	≥ 16 µg/mL	22.4	24.4	30.0	27.7
Depolymerized PRP	For information (%)	18.2	42.1	61.3	76.0
Diphtheria potency : **Activity** **Lower limit** **Upper limit**	Activity ≥ 30 IU/mL Lower confidence limit (*P = 0.95*) of the estimated potency ≥ 20 IU/mL	 76 57 113	 NP† NP NP	 90 61 152	 45 28 67 at 7.5 months
Tetanus potency : **Activity** **Lower limit** **Upper limit**	Lower confidence limit (*P = 0.95*) of the estimated potency ≥ 40 IU/mL	 705 485 1017	 NP NP NP	 344 256 459 at 4 months	 188 125 264
Pertussis immunogenicity anti-FHA	Anti-Filamentous Hemagglutinin (FHA) antibody titer obtained for the vaccine is not significantly *(P = 0.95)* less than that of the reference vaccine	Conforms	NP	Conforms	On-going
Pertussis immunogenicity anti-PT	Anti-Pertussis Toxoid (PTxd) and antibody titer obtained for the vaccine is not significantly *(P = 0.95)* less than that of the reference vaccine	Conforms	NP	Conforms	On-going
Haemophilus immunogenicity	For information‡	Conforms	NP	Conforms	Fails
Non-adsorbed PT	For information (µg/mL)§	< 2.5	NP	< 2.5	< 2.5 at 9 months

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Tests	Acceptance criteria	T0*	1 month	3 months	6 months
Non-adsorbed FHA	For information (µg/mL)§	< 2.5	NP	< 2.5	< 2.5 at 8 months
Percent adsorption – tetanus toxoid	For information (%)	24	37	41	46
Percent adsorption – diphtheria toxoid	For information (%)	52	63	72	73
D-antigen content	Type 1: 20 – 43 DU/dose Type 2: 5 – 9 DU/dose Type 3: 17 – 36 DU/dose	Not performed**	26.8 6.6 23.8 at 1.5 months	23.2 6.4 21.0	20.3 5.9 19.0
Percent adsorption – hepatitis B (ELISA)	For information (%)	92	80	61	84
Hepatitis B *in- vitro* relative potency (IVRP)	For information (relative potency)	1.43	1.54	0.99	0.87
Hepatitis B immunogenicity	Upper confidence limit (P = 0.95) of the estimated relative potency is not less than 1.0	1.17	NP	0.96	2.07
Lower limit		0.644	NP	0.632	1.281
Upper limit		2.268	NP	1.440	3.519
Bacterial and fungal sterility test	No microbial growth	Conforms	NP	NP	Conforms
Integrity test	The CCIT is acceptable if no presence of dye is detected in the contents of any of the tested syringes	Conforms	NP	NP	Conforms

* All the results are obtained from the T0 of the Filled Product excepted for the following tests: diphtheria and tetanus potency, pertussis immunogenicity anti-FHA and anti-PT, haemophilus immunogenicity, non-adsorbed PT and FHA and hepatitis B immunogenicity. For these tests, the results are release results of the Final Bulk Product.

† Not Planned as per protocol

‡ Expected results: Not less than 50% of the vaccinated mice are seroconverted. Their titer is not less than 4 times that of the pooled control serum

§ Expected value: ≤ 2.5 µg/mL

** Not Performed due to industrial constraints

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1.5 Study 4: Anagni Filled Product – Initial Formulation – Stability Data on Long-Term Storage Conditions at +5°C ± 3°C

36 months stability data with the initial formulation on 3 batches of Anagni FP are presented in Table 13 to Table 15.

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Table 13: Stability Study Results for Anagni Filled Product Batch S4114 at +5°C ± 3°C

Tests	Acceptance criteria	T0*	3 months	6 months	9 months	12 months	18 months	24 months	30 months	36 months
Appearence	Whitish and cloudy suspension	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
pH measurement	6.5 – 8.0	7.03	7.27	7.24	7.27	7.53	7.30	7.24	7.28	7.27
Free formaldehyde content	≤ 30 µg/mL	Not Performed†	Not Performed†	11.70	11.97	10.18	12.58	12.94	6.41	13.25
Extractable volume	At least the nominal volume	Conforms	NP‡	NP	NP	NP	NP	NP	NP	Conforms
Osmolality measurement	250 - 450 mosmol/kg	Not Performed†	Not Performed†	338	337	333	342	327	338	337
Non-adsorbed PRP	≥ 16 µg/mL	20.4	22.3	22.3	22.8	23.0	24.7	24.7	24.5	28.2
Depolymerized PRP	For information (%)	8.7	18.2 at 5 months	18.8	24.7§	29.2 at 13 months	34.5 at 20 months	40.6 at 26 months	40.4	43.0
Diphtheria potency	Activity ≥ 30 IU/mL									
Activity	Lower confidence limit ($P = 0.95$) of the estimated potency ≥ 20 IU/mL	41	NP	51	NP	43	52	34	52	52
Lower limit		27	NP	32	NP	25	35	21	31	34
Upper limit		58	NP	85 at 7 months	NP	72	77	53	87	78
Tetanus potency	Lower confidence limit ($P = 0.95$) of the estimated potency ≥ 40 IU/mL									
Activity		555	NP	750	NP	509	659	502	Not Performed†	571
Lower limit		407	NP	406	NP	330	493	276	Not Performed†	352
Upper limit		781	NP	1133 at 7 months	NP	724	873	789	Not Performed†	855

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Tests	Acceptance criteria	T0*	3 months	6 months	9 months	12 months	18 months	24 months	30 months	36 months
Histamine-sensitizing activity	≥ 95% survival (%)	100	NP	NP	NP	95	NP	100	NP	100
Pertussis immunogenicity anti-FHA	Anti-Filamentous Hemagglutinin (FHA) antibody titer obtained for the vaccine is not significantly *(P = 0.95)* less than that of the reference vaccine	Conforms	NP	Conforms	NP	Conforms	Conforms	Conforms	Not Performed†	Conforms
Pertussis immunogenicity anti-PT	Anti-Pertussis Toxoid (PTxd) and antibody titer obtained for the vaccine is not significantly *(P = 0.95)* less than that of the reference vaccine	Conforms	NP	Conforms	NP	Conforms	Conforms	Conforms	Not Performed†	Conforms
Haemophilus immunogenicity	Not less than 50% of the vaccinated mice are seroconverted. Their titer is not less than 4 times that of the pooled control serum	Conforms	NP	Conforms	NP	Conforms	Conforms	Conforms	Not Performed†	Conforms
Non-adsorbed PT	For information (µg/mL)**	< 2.5	NP	NP	NP	< 2.5 at 13 months	NP	< 2.5	NP	< 2.5
Non-adsorbed FHA	For information (µg/mL)**	< 2.5	NP	NP	NP	< 2.5 at 15 months	NP	< 2.5	NP	< 2.5
Percent adsorption – tetanus toxoid	For information (%)	31	NP	27	NP	38	36	35	33	41
Percent adsorption – diphtheria toxoid	For information (%)	44	NP	47	NP	52	46	51	52	51

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Tests	Acceptance criteria	T0*	3 months	6 months	9 months	12 months	18 months	24 months	30 months	36 months
Poliomyelitis potency on chicken	Type 1 ≥ 2 Type 2 ≥ 2 Type 3 ≥ 2	3.51 4.05 3.77	NP NP NP	2.96 2.87 3.22	NP NP NP	2.46 2.39 3.10	2.63 2.50 3.35	2.82 2.35 2.78	3.19 3.30 3.71	2.59 2.26 3.32
D-antigen content	Type 1: 20 – 43 DU/mL Type 2: 5 – 9 DU/mL Type 3: 17 – 36 DU/mL	27.6 6.0 22.6	NP NP NP	27.8 6.1 22.5	NP NP NP	27.8 5.8 24.6	26.9 5.7 25.6	30.9 5.7 21.9	27.2 6.1 24.4	28.4 6.0 24.5
Percent adsorption – hepatitis B (ELISA)	For information (%)	81	63	57	47	33	44	44	45	49
Hepatitis B *in-vitro* relative potency (IVRP)	For information (relative potency)	1.07	1.00	1.09	1.04	0.91	1.44	0.99	1.21	1.16
Hepatitis B immunogenicity **Lower limit** **Upper limit**	Upper confidence limit (P = 0.95) of the estimated relative potency is not less than 1.0	0.71 0.37 1.38	NP NP NP	NP NP NP	NP NP NP	1.06 0.56 2.40	NP NP NP	1.19 0.74 2.01	NP NP NP	1.03 0.67 1.66
Bacterial and fungal sterility test	No microbial growth	Conforms	NP	NP	NP	NP	NP	NP	NP	Conforms
Pyrogen test	Conforms to Ph. Eur. criterion	0.35 (0.20 - 0.10 - 0.05)	NP	NP	NP	NP	NP	NP	NP	0.54 (0.13 - 0.32 - 0.10)

* All the results are release results obtained from the Final Bulk Product excepted for the following tests: appearance, extractable volume, non-adsorbed PT and FHA, D-antigen content, bacterial and fungal sterility test and pyrogen test. For these tests, the results are release results of the T0 of the Filled Product.

† Not Performed due to industrial constraints

‡ Not Planned as per protocol

§ First determination at 9.5 months and second determination at 12 months

** Expected value: ≤ 2.5 µg/mL

Table 14: Stability Study Results for Anagni Filled Product Batch S4115 at +5°C ± 3°C

Tests	Acceptance criteria	T0*	3 months	6 months	9 months	12 months	18 months	24 months	30 months	36 months
Appearence	Whitish and cloudy suspension	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
pH measurement	6.5 – 8.0	7.03	7.19	7.20	7.21	7.44	7.19	7.18	7.18	7.19
Free formaldehyde content	≤ 30 µg/mL	Not Performed†	Not Performed†	10.32	10.88	11.58	11.18	11.18	5.76	11.82
Extractable volume	At least the nominal volume	Conforms	NP‡	NP	NP	NP	NP	NP	NP	Conforms
Osmolality measurement	250 - 450 mosmol/kg	Not Performed†	Not Performed†	332	335	333	342	325	335	334
Non-adsorbed PRP	≥ 16 µg/mL	19.6	21.5	20.8	21.0	22.7	24.3	25.1	23.9	27.0
Depolymerized PRP	For information (%)	8.7	18.8 at 5 months	20.1	24.0§	27.0	32.3	36.5	38.9	43.5
Diphtheria potency	Activity ≥ 30 IU/mL									
Activity	Lower confidence limit ($P = 0.95$) of the estimated potency ≥ 20 IU/mL	77	NP	85	NP	62	38	66	53	66
Lower limit		47	NP	53	NP	43	23	41	36	45
Upper limit		138	NP	153 at 7 months	NP	91	59	111	77	101
Tetanus potency	Lower confidence limit ($P = 0.95$) of the estimated potency ≥ 40 IU/mL									
Activity		516	NP	586	NP	538	662	615	Not Performed†	512
Lower limit		294	NP	407	NP	362	492	405	Not Performed†	326
Upper limit		796	NP	937 at 7 months	NP	842	883	892	Not Performed†	737

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Tests	Acceptance criteria	T0*	3 months	6 months	9 months	12 months	18 months	24 months	30 months	36 months
Histamine-sensitizing activity	≥ 95% survival (%)	98	NP	NP	NP	92.5	NP	100	NP	100
Pertussis immunogenicity anti-FHA	Anti-Filamentous Hemagglutinin (FHA) antibody titer obtained for the vaccine is not significantly *(P = 0.95)* less than that of the reference vaccine	Conforms	NP	Conforms	NP	Conforms	Conforms	Conforms	Not Performed†	Conforms
Pertussis immunogenicity anti-PT	Anti-Pertussis Toxoid (PTxd) and antibody titer obtained for the vaccine is not significantly *(P = 0.95)* less than that of the reference vaccine	Conforms	NP	Conforms	NP	Conforms	Conforms	Conforms	Not Performed†	Conforms
Haemophilus immunogenicity	Not less than 50% of the vaccinated mice are seroconverted. Their titer is not less than 4 times that of the pooled control serum	Conforms	NP	Conforms	NP	Conforms at 14 months	Conforms	Conforms	Not Performed†	Conforms
Non-adsorbed PT	For information (µg/mL)**	< 2.5	NP	NP	NP	< 2.5 at 13 months	NP	< 2.5	NP	< 2.5
Non-adsorbed FHA	For information (µg/mL)**	< 2.5	NP	NP	NP	< 2.5 at 15 months	NP	< 2.5	NP	< 2.5
Percent adsorption – tetanus toxoid	For information (%)	24	NP	34	NP	37	36	31	40	49
Percent adsorption – diphtheria toxoid	For information (%)	35	NP	36	NP	42	39	38	32	40

Tests	Acceptance criteria	T0*	3 months	6 months	9 months	12 months	18 months	24 months	30 months	36 months
Poliomyelitis potency on chicken	Type 1 ≥ 2	3.00	NP	2.75	NP	2.90	2.51	3.01	2.66	2.52
	Type 2 ≥ 2	3.21	NP	2.84	NP	2.86	2.35	2.63	2.60	2.98
	Type 3 ≥ 2	3.01	NP	2.97	NP	3.04	2.95	3.18	3.42	3.06
D-antigen content	Type 1: 20 – 43 DU/dose	28.2	NP	27.0	NP	27.5	26.1	26.3	27.0	27.2
	Type 2: 5 – 9 DU/dose	5.5	NP	5.7	NP	5.8	5.8	5.5	6.3	5.9
	Type 3: 17 – 36 DU/dose	20.0	NP	21.2	NP	24.0	21.3	21.6	23.7	22.7
Percent adsorption – hepatitis B (ELISA)	For information (%)	85	64	65	54	56	47	51	54	52
Hepatitis B *in-vitro* relative potency (IVRP)	For information (relative potency)	0.87	1.05	0.94	0.93	1.03	1.24	1.00	1.13	1.04
Hepatitis B immunogenicity	Upper confidence limit (P = 0.95) of the estimated relative potency is not less than 1.0	1.09	NP	NP	NP	0.88	NP	1.26	NP	1.10
Lower limit		0.69	NP	NP	NP	0.50	NP	0.74	NP	0.66
Upper limit		1.72	NP	NP	NP	1.47	NP	2.16	NP	1.97
Bacterial and fungal sterility test	No microbial growth	Conforms	NP	NP	NP	NP	NP	NP	NP	Conforms
Pyrogen test	Conforms to Ph. Eur. criterion	0.43 (0.17 - 0.08 - 0.19)	NP	NP	NP	NP	NP	NP	NP	0.15 (0.00 - 0.00 - 0.15)

* All the results are release results obtained from the Final Bulk Product excepted for the following tests: appearance, extractable volume, non-adsorbed PT and FHA, D-antigen content, bacterial and fungal sterility test and pyrogen test. For these tests, the results are release results of the T0 of the Filled Product.

† Not Performed due to industrial constraints

‡ Not Planned as per protocol

§ First determination at 9.5 months and second determination at 12 months

** Expected value: ≤ 2.5 µg/mL

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