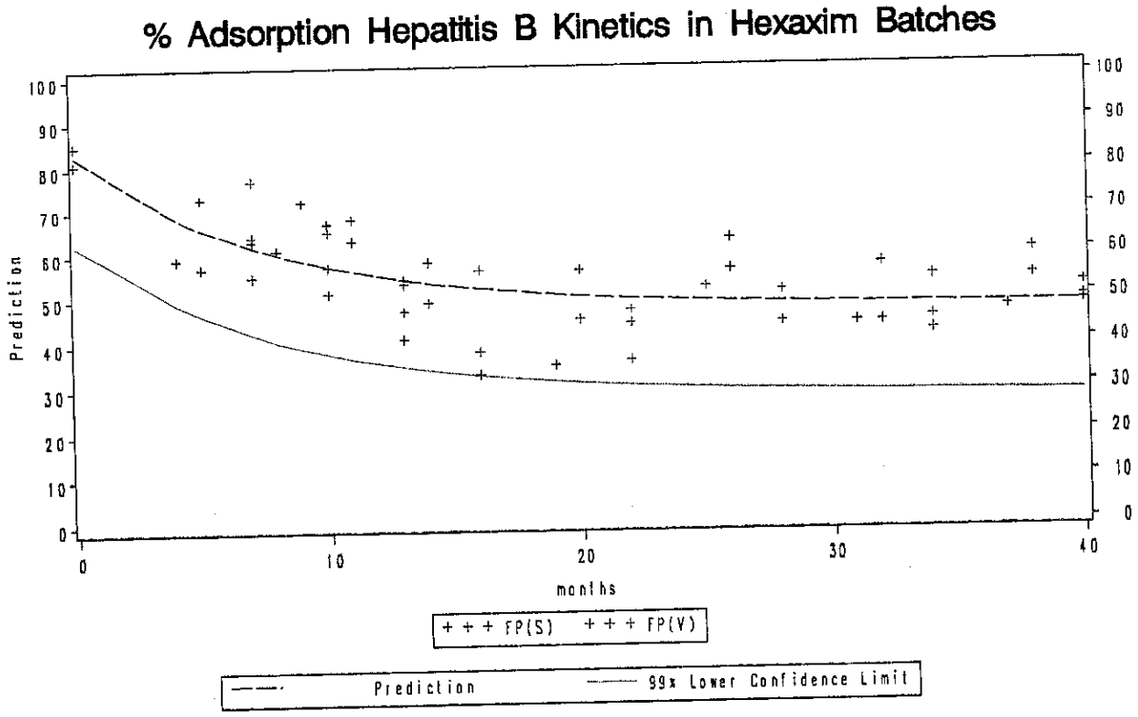
Figura 2: Porcentaje de adsorción de la hepatitis B, datos con la formulación inicial junto con la línea de cinética y el límite inferior unilateral del 99 %



a

Los datos farmacéuticos y clínicos disponibles demuestran que el producto es seguro e inmunogénico y cumple con los estándares de calidad requeridos durante la vida útil de 36 meses.

Utilizando el modelo de curva cinética de mejor ajuste y el límite de confianza unilateral inferior del 99 %, se justifica un criterio de aceptación para la vida útil del porcentaje de hepatitis B a los 36 meses mayor o igual que 28 % para los estudios de estabilidad futuros.

[a] FP(S): lotes de producto llenado en jeringas monodosis con la formulación inicial
FP(V): lotes de producto llenado en viales monodosis con la formulación inicial

JOXANA MONTENEGRO
DIRECTORA TECNICA
SANOFI PASTEUR S.A

CHRISTIAN DOMINGUEZ
APODERADO
SANOFI PASTEUR S.A

5 Conclusión general

Los datos de estabilidad de respaldo se resumen en la Tabla 14.

Tabla 14: Resumen de los datos de estabilidad de respaldo

Estudio	Producto almacenado	Formulación	Envase y sellos de cierre	Condiciones de almacenamiento
Estudio 1	PFAG de MLE	Formulación optimizada	Tanques de acero inoxidable	+5°C ± 3°C
Estudio 2	PF de MLE	Formulación inicial	Jeringas monodosis	+5°C ± 3°C
Estudio 3	PF de MLE	Formulación optimizada	Jeringas monodosis	+5°C ± 3°C +25°C ± 2°C
Estudio 4	PF de Anagni	Formulación inicial	Viales monodosis	+5°C ± 3°C
Estudio 5	PF de VDR	Formulación optimizada	Viales monodosis	+5°C ± 3°C +25°C ± 2°C

Basándose en los resultados obtenidos en condiciones a largo plazo, se declara una vida útil de 9 meses para el producto final a granel.

Basándonos en los resultados obtenidos en condiciones a largo plazo y en el estudio de comparabilidad (vea la sección 3.2.P.2.3 Desarrollo del proceso de elaboración), se declara una vida útil de 36 meses para el producto llenado almacenado en viales y jeringas monodosis.

Además, estos estudios permiten definir pruebas indicadoras de estabilidad monitoreadas para los estudios de estabilidad futuros durante el programa de estabilidad anual, como se describe en la sección 3.2.P.5.1 Especificaciones.

OXANA BUNTEMILUNE
DIRECTORA TÉCNICA
SANOFI PASTEUR S.A.

CHRISTIAN DOMINGUEZ
APODERADO
SANOFI PASTEUR S.A.

Section 3.2.P.8.3 - Stability Data

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ROXANA MONTEMILONE
DIRECTORA TECNICA
SANOFI PASTEUR S.A.

CHRISTIAN DOMINGUEZ
APODERADO
SANOFI PASTEUR S.A.

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ROXANA MONTEMILONE
DIRECTORA TECNICA
SANOFI PASTEUR S.A.

CHRISTIAN DOMINGUEZ
APODERADO
SANOFI PASTEUR S.A.

ROXANA MONTEMILONE
DIRECTORA TÉCNICA
SANOFI PASTEUR S.A.

CHRISTIAN DOMINGUEZ
APODERADO
SANOFI PASTEUR S.A.

List of abbreviations: see 2.3 Quality Overall Summary, Introduction

1 Stability Results

This chapter provides the stability data results for the studies presented in 3.2.P.8.1 Stability Summary and Conclusions. The tests not planned in the stability protocol are abbreviated as follow: NP.

1.1 Study 1: Marcy l'Etoile Final Bulk Product – Optimized Formulation – Stability Data on Long-Term Storage Conditions at +5°C ± 3°C

9 months stability data with the optimized formulation on 3 batches of MLE FBP are presented in Table 1 to Table 3.

ROXANA MONTEMILONE
DIRECTORA TÉCNICA
SANOFI PASTEUR S.A.

CHRISTIAN DOMINGUEZ
APODERADO
SANOFI PASTEUR S.A

Table 1: Stability Study Results for Marcy l'Etoile Final Bulk Product Batch FDV01398 at +5°C ± 3°C

Tests	Acceptance criteria	T0	1 month	2 months	3 months	4 months	5 months	6 months	9 months
Appearence	Whitish and cloudy suspension	Conforms	NP*	NP	Conforms	NP	NP	Conforms	Conforms
pH measurement	6.5 – 7.5	7.21	NP	NP	7.28	NP	NP	7.31	7.31
Free formaldehyde content	≤ 30 µg/mL	3.23	NP	NP	0.50	NP	NP	< 0.36	< 0.36
Aluminium content	0.80 – 1.60 mg/mL	1.15	NP	NP	1.22	NP	NP	1.20	1.22
Osmolality measurement	300 - 400 mosmol/kg	338	NP	NP	338	NP	NP	337	335
Non-adsorbed PRP	≥ 16 µg/mL	22.6	23.1	23.3	24.9	24.2	22.2	27.7	27.0
Depolymerized PRP	For information (%)	9.1	7.1	10.7	12.3	12.0	12.9	17.4	22.9
Diphtheria potency: **Activity** **Lower limit** **Upper limit**	Activity ≥ 60 IU/mL Lower confidence limit (*P = 0.95*) of the estimated potency ≥ 40 IU/mL	 84 68 104	NP	NP	 154 110 222	NP	NP	 138 100 194	 92 66 126
Tetanus potency: **Activity** **Lower limit** **Upper limit**	Lower confidence limit (*P = 0.95*) of the estimated potency ≥ 80 IU/mL	 1112 560 1706	NP	NP	 1970 1448 2740	NP	NP	 1152 800 1830	 1426 1042 1942 at 11 months
Histamine-sensitizing activity	≥ 95% survival (%)	100	NP	NP	100	NP	NP	100	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	NP	Conforms	NP	NP	Conforms	Conforms

Tests	Acceptance criteria	T0	1 month	2 months	3 months	4 months	5 months	6 months	9 months
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	NP	Conforms	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	NP	Conforms	NP	NP	Conforms at 8 months	Conforms
Non-adsorbed PT	For information (µg/mL)†	< 2.5	NP	NP	< 2.5	NP	NP	< 2.5 at 8 months	< 2.5
Non-adsorbed FHA	For information (µg/mL)†	< 2.5	NP	NP	< 2.5	NP	NP	< 2.5 at 7 months	< 2.5
Percent adsorption – tetanus toxoid	For information (%)	23	NP	NP	33	NP	NP	35	28
Percent adsorption – diphtheria toxoid	For information (%)	46	NP	NP	54	NP	NP	53	54
Rat immunogenicity assay for IPV	For information (relative potency)								
Type 1		0.7	NP	NP	NP	NP	NP	1.3	1.0
Type 2		0.6	NP	NP	NP	NP	NP	0.8	2.1
Type 3		1.9	NP	NP	NP	NP	NP	0.6	1.1
D-antigen content	Type 1: 40 – 86 DU‡/mL	53.8	NP	NP	60.1	NP	NP	53.6	52.5
	Type 2: 10 – 18 DU/mL	11.0	NP	NP	12.1	NP	NP	11.4	10.8
	Type 3: 34 – 72 DU/mL	52.6	NP	NP	52.0	NP	NP	47.9	49.7 at 10 months
Percent adsorption – hepatitis B (ELISA)	For information (%)	95	92	92	91	89	85	89	88

Tests	Acceptance criteria	T0	1 month	2 months	3 months	4 months	5 months	6 months	9 months
Hepatitis B *in-vitro* relative potency (IVRP)	For information (relative potency)	1.22	NP	NP	1.34	NP	NP	1.51	1.45
Hepatitis B immunogenicity	Upper confidence limit (P = 0.95) of the estimated relative potency is not less than 1.0	1.21	NP	NP	1.23	NP	NP	1.00	1.05
Lower limit		0.628	NP	NP	0.703	NP	NP	0.576	0.619
Upper limit		2.561	NP	NP	2.293 at 4 months	NP	NP	1.736	1.813
Bacterial and fungal sterility test	No microbial growth	Conforms	NP	NP	NP	NP	NP	Conforms	Conforms

* Not Planned as per protocol

† Expected value: ≤ 2.5 µg/mL

‡ DU: D-antigen Unit

Table 2: Stability Study Results for Marcy l'Etoile Final Bulk Product Batch FDV01416 at +5°C ± 3°C

Tests	Acceptance criteria	T0	1 month	2 months	3 months	4 months	5 months	6 months	9 months
Appearence	Whitish and cloudy suspension	Conforms	NP*	NP	Conforms	NP	NP	Conforms	Conforms
pH measurement	6.5 – 7.5	7.11	NP	NP	7.18	NP	NP	7.22	7.20
Free formaldehyde content	≤ 30 µg/mL	3.34	NP	NP	0.47	NP	NP	0.41	< 0.36
Aluminium content	0.80 – 1.60 mg/mL	1.21	NP	NP	1.21	NP	NP	1.20	1.23
Osmolality measurement	300 - 400 mosmol/kg	338	NP	NP	335	NP	NP	336	335
Non-adsorbed PRP	≥ 16 µg/mL	20.0	19.5	21.6	22.6	22.0	22.7	22.9	24.8
Depolymerized PRP	For information (%)	3.7	5.7	6.3	16.1	10.6	11.5	18.4	18.4
Diphtheria potency : **Activity** **Lower limit** **Upper limit**	Activity ≥ 60 IU/mL Lower confidence limit ($P = 0.95$) of the estimated potency ≥ 40 IU/mL	 114 86 164	NP	NP	 102 72 144	NP	NP	 116 76 182	 148 102 218
Tetanus Potency : **Activity** **Lower limit** **Upper limit**	Lower confidence limit ($P = 0.95$) of the estimated potency ≥ 80 IU/mL	 1168 826 1590	NP	NP	 1724 1162 3106	NP	NP	 1568 1168 2110	 1652 1042 2332
Histamine-sensitizing activity	≥ 95% survival (%)	100	NP	NP	100	NP	NP	100	100

Tests	Acceptance criteria	T0	1 month	2 months	3 months	4 months	5 months	6 months	9 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	NP	Conforms	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	NP	Conforms	NP	NP	Conforms	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	NP	Conforms at 4 months	NP	NP	Conforms at 7.5 months	Conforms
Non-adsorbed PT	For information (µg/mL)†	< 2.5	NP	NP	< 2.5	NP	NP	< 2.5	< 2.5
Non-adsorbed FHA	For information (µg/mL)†	< 2.5	NP	NP	< 2.5	NP	NP	< 2.5	< 2.5
Percent adsorption – tetanus toxoid	For information (%)	33	NP	NP	27	NP	NP	39	41
Percent adsorption – diphtheria toxoid	For information (%)	54	NP	NP	55	NP	NP	55	63
Rat immunogenicity assay for IPV	For information (relative potency)								
Type 1		0.5	NP	NP	NP	NP	NP	Invalid test‡	0.9
Type 2		0.5	NP	NP	NP	NP	NP	Invalid test‡	1.3
Type 3		1.6	NP	NP	NP	NP	NP	0.4	0.7
D-antigen content	Type 1: 40 – 86 DU/mL	57.5	NP	NP	57.4	NP	NP	53.9	54.7
	Type 2: 10 – 18 DU/mL	12.0	NP	NP	12.0	NP	NP	11.8	11.2
	Type 3: 34 – 72 DU/mL	51.3	NP	NP	51.3	NP	NP	50.4	53.3

ROXANA MONTEMILONE
DIRECTORA TECNICA
SANOFI PASTEUR S.A.

CHRISTIAN DOMINGUEZ
APODERADO
SANOFI PASTEUR S.A.

Tests	Acceptance criteria	T0	1 month	2 months	3 months	4 months	5 months	6 months	9 months
Percent adsorption – hepatitis B (ELISA)	For information (%)	97	93	92	90	90	88	88	86
Hepatiti B *in-vitro* relative potency (IVRP)	For information (relative potency)	1.18	NP	NP	1.15	NP	NP	1.32	1.53
Hepatitis B Immunogenicity	Upper confidence limit (P = 0.95) of the estimated relative potency is not less than 1.0	1.16	NP	NP	1.05	NP	NP	1.09	1.47
Lower limit		0.658	NP	NP	0.570	NP	NP	0.631	0.901
Upper limit		2.041	NP	NP	2.087 at 3.5 months	NP	NP	1.983	2.793
Bacterial and fungal sterility test	No microbial growth	Conforms	NP	NP	NP	NP	NP	Conforms	Conforms

* Not Planned as per protocol

† Expected value: ≤ 2.5 µg/mL

‡ No retest because of proximity of next time point

ROXANA MONTEMILONE
APODERADO
SANOFI PASTEUR S.A.

CHRISTIAN DOMINGUEZ
APODERADO
SANOFI PASTEUR S.A.

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Table 3: Stability Study Results for Marcy l'Etoile Final Bulk Product Batch FDV01420 at +5°C ± 3°C

Tests	Acceptance criteria	T0	1 month	2 months	3 months	4 months	5 months	6 months	9 months
Appearence	Whitish and cloudy suspension	Conforms	NP*	NP	Conforms	NP	NP	Conforms	Conforms
pH measurement	6.5 – 7.5	7.13	NP	NP	7.21	NP	NP	7.26	7.24
Free formaldehyde content	≤ 30 µg/mL	1.36	NP	NP	< 0.36	NP	NP	< 0.36	< 0.36
Aluminium content	0.80 – 1.60 mg/mL	1.17	NP	NP	1.21	NP	NP	1.19	1.21
Osmolality measurement	300 - 400 mosmol/kg	336	NP	NP	334	NP	NP	332	333
Non-adsorbed PRP	≥ 16 µg/mL	21.0	20.4	22.9	23.1	20.7	24.5	21.6	23.9
Depolymerized PRP	For information (%)	7.3	11.0	9.5	9.3	12.0	16.2	18.0	22.9
Diphtheria potency : **Activity** **Lower limit** **Upper limit**	Activity ≥ 60 IU/mL Lower confidence limit ($P = 0.95$) of the estimated potency ≥ 40 IU/mL	 152 114 226	NP	NP	 176 132 240	NP	NP	 140 102 196	 190 116 296
Tetanus Potency : **Activity** **Lower limit** **Upper limit**	Lower confidence limit ($P = 0.95$) of the estimated potency ≥ 80 IU/mL	 1112 560 1706	NP	NP	Invalid test†	NP	NP	 1646 1116 2330	 1058 714 1470
Histamine-sensitizing activity	≥ 95% survival (%)	100	NP	NP	100	NP	NP	100	100

ROXANA MONTENEGRO
DIRECTORA TECNICA
SANOFI PASTEUR S.A.

CHRISTIAN DOMINGUEZ
APODERADO
SANOFI PASTEUR S.A.

Tests	Acceptance criteria	T0	1 month	2 months	3 months	4 months	5 months	6 months	9 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	NP	Invalid test†	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	NP	Conforms	NP	NP	Invalid test†	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	NP	Conforms	NP	NP	Conforms	Conforms
Non-adsorbed PT	For information (µg/mL)‡	< 2.5	NP	NP	< 2.5	NP	NP	< 2.5	< 2.5
Non-adsorbed FHA	For information (µg/mL)‡	< 2.5	NP	NP	< 2.5	NP	NP	< 2.5	< 2.5
Percent adsorption – tetanus toxoid	For information (%)	18	NP	NP	16	NP	NP	31	32
Percent adsorption – diphtheria toxoid	For information	49	NP	NP	52	NP	NP	60	60.5
Rat immunogenicity assay for IPV	For information (relative potency)								
Type 1		0.6	NP	NP	NP	NP	NP	1.3	1.0
Type 2		1.2	NP	NP	NP	NP	NP	1.1	3.2
Type 3		3.1	NP	NP	NP	NP	NP	0.4	0.7

ROXANA MONTEMILONE
DIRECTORA TECNICA
SANOFI PASTEUR S.A.

CHRISTIAN DOMINGUEZ
APODERADO
SANOFI PASTEUR S.A.

Tests	Acceptance criteria	T0	1 month	2 months	3 months	4 months	5 months	6 months	9 months
D-antigen content	Type 1: 40 – 86 DU§/mL	56.2	NP	NP	52.0	NP	NP	52.1	48.4
	Type 2: 10 – 18 DU/mL	11.6	NP	NP	12.0	NP	NP	10.8	10.6
	Type 3: 34 – 72 DU/mL	49.2	NP	NP	47.5 at 4 months	NP	NP	45.4 at 7 months	46.2
Percent adsorption – hepatitis B (ELISA)	For information (%)	98	95	93	91	92	91	89	91
Hepatitis B in-vitro relative potency (IVRP)	For information (relative potency)	1.27	NP	NP	1.25	NP	NP	1.51	1.34
Hepatitis B immunogenicity	Upper confidence limit (P = 0.95) of the estimated relative potency is not less than 1.0	1.17	NP	NP	1.48	NP	NP	1.26	1.13
Lower limit		0.644	NP	NP	0.885	NP	NP	0.748	0.61
Upper limit		2.268	NP	NP	2.655	NP	NP	2.235	2.147
Bacterial and fungal sterility test	No microbial growth	Conforms	NP	NP	NP	NP	NP	Conforms	Conforms

* Not Planned as per protocol

† No retest because of proximity of next time point

‡ Expected value : ≤ 2.5 µg/mL

§ DU: D-antigen Unit

ROXANA MONTEMILONE
DIRECTORA TECNICA
SANOFI PASTEUR S.A.

CHRISTIAN DOMINGUEZ
APODERADO
SANOFI PASTEUR S.A.

1.2 Study 2: Marcy l'Etoile 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 MLE FP are presented in Table 4 to Table 6.

ROXANA MONTEMILONE
DIRECTORA TÉCNICA
SANOFI PASTEUR S.A.

CHRISTIAN DOMINGUEZ
APODERADO
SANOFI PASTEUR S.A.

Table 4: Stability Study Results for Marcy l'Etoile Filled Product Batch S4009 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	7.11	7.47	7.18	7.28	7.36	7.28	7.32	7.23
Free formaldehyde content	≤ 30 µg/mL	Not Performed†	Not Performed†	Not Performed†	11.68	11.64	12.46	6.24	6.67	12.86
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†	Not Performed†	337	338	337	336	334	339
Non-adsorbed PRP	≥ 16 µg/mL	20.4	22.6	21.3	24.1	21.9	23.1	23.9	26.2	24.7
Depolymerized PRP	For information (%)	8.7	14.9 at 4 months	16.5	21.1	24.6	30.7	39.2 at 27 months	38.7	40.9
Diphtheria potency :	Activity ≥ 30 IU/mL									
Activity	Lower confidence limit ($P = 0.95$) of the estimated potency ≥ 20 IU/mL	41	NP	47	NP	55	33	122	49	59
Lower limit		27	NP	32	NP	39	22	77	35	44
Upper limit		58	NP	68	NP	79	48	230	69	81
Tetanus potency :	Lower confidence limit ($P = 0.95$) of the estimated potency ≥ 40 IU/mL									
Activity		555	NP	443	NP	595	669	327	Not Performed†	629
Lower limit		407	NP	322	NP	432	499	194	Not Performed†	416
Upper limit		781	NP	619 at 7 months	NP	804 at 13 months	891 at 19 months	491	Not Performed†	911
Histamine-sensitizing activity	≥ 95% survival (%)	100	NP	NP	NP	100	NP	100	NP	100

ROXANA MONTEMILLONE
DIRECTORA TECNICA
SANOFI PASTEUR S.A.

CHRISTIAN DOMINGUEZ
APODERADO
SANOFI PASTEUR S.A.