

RESULTADOS ESTUDIO DE ESTABILIDAD

Las siguientes tablas, indican los resultados obtenidos en el Estudio de Estabilidad del producto **Bleomicina Liofilizado para solución inyectable 15 U**
Temperatura Ambiente = 30 °C ± 2 °C Humedad Relativa = 75 % ± 5 % HR

Lote: 1174402

Parámetros	Especificación	0 meses	3 meses	6 meses	9 meses	12 meses	18 meses	24 meses
Aspecto Físico	Taco liofilizado blanco.	Cumple	Cumple	Cumple	Cumple	Cumple	Cumple	Cumple
Solución reconstituida	Cumple requerimientos de claridad de la solución,	Cumple	Cumple	Cumple	Cumple	Cumple	Cumple	Cumple
	No debe presentar partículas y/o pelusas en suspensión.	No detectado	No detectado	No detectado	No detectado	No detectado	No detectado	No detectado
pH	Límites: 4,5 - 6,0	4,7	4,7	4,8	4,8	4,7	4,8	4,8
Contenido de Agua	Límites: No más de 6,0 %	2,7	2,6	2,9	2,2	2,5	2,4	2,9
Cobre	Límites: No más de 0,1 %	No más de 0,1 %	No más de 0,1 %	No más de 0,1 %	No más de 0,1 %	No más de 0,1 %	No más de 0,1 %	No más de 0,1 %
Contenido de Bleomicina	A2: 55% - 70%	68	64	68	68	69	62	65
	B2: 25% - 32%	29	32	30	30	30	31	31
	B4: No más de 1 %	0,5	0,1	0	0	0	0,3	0
	A2 + B2: No menos de 90%	98	96	98	98	99	94	96
Endotoxinas Bacterianas	Límites: No más de 10,0 UE/ Unidad de Bleomicina.	Menos de 10,0 UE/ unidad	-	-	-	-	-	Menos de 10,0 UE/ unidad
Esterilidad	Esteril	Cumple	-	-	-	-	-	Cumple
Identidad	IR: Cumple Test de Sulfato: Cumple	Cumple	Cumple	Cumple	Cumple	Cumple	Cumple	Cumple
Valoración	Límites: 90,0-120,0 % (13,5 - 18,0 UI/frasco ampolla)	15,21 UI (101,4%)	15,26 UI (101,7%)	15,03 UI (100,2%)	15,08 UI (100,5%)	14,73 UI (98,2%)	14,97 UI (99,8%)	15,03 UI (100,2%)

Lote: 1174403

Parámetros	Especificación	0 meses	3 meses	6 meses	9 meses	12 meses	18 meses	24 meses
Aspecto Físico	Taco liofilizado blanco.	Cumple	Cumple	Cumple	Cumple	Cumple	Cumple	Cumple
Solución reconstituida	Cumple requerimientos de claridad de la solución,	Cumple	Cumple	Cumple	Cumple	Cumple	Cumple	Cumple
	No debe presentar partículas y/o pelusas en suspensión.	No detectado	No detectado	No detectado	No detectado	No detectado	No detectado	No detectado
pH	Límites: 4,5 - 6,0	4,7	4,7	4,8	4,8	4,7	4,7	4,7
Contenido de Agua	Límites: No más de 6,0 %	2,6	2,9	2,5	2,8	2,6	2,4	2,5
Cobre	Límites: No más de 0,1 %	No más de 0,1 %	No más de 0,1 %	No más de 0,1 %	No más de 0,1 %	No más de 0,1 %	No más de 0,1 %	No más de 0,1 %
Contenido de Bleomicina	A ₂ : 55% - 70%	68	65	68	68	69	62	66
	B ₂ : 25% - 32%	29	31	29	29	30	31	32
	B ₄ : No más de 1 %	0,5	0,2	0	0	0	0,2	0,3
	A ₂ + B ₂ : No menos de 90%	98	96	98	98	99	94	95
Endotoxinas Bacterianas	Límites: No más de 10,0 UE/ Unidad de Bleomicina.	Menos de 10,0 UE/ unidad	-	-	-	-	-	Menos de 10,0 UE/ unidad
Esterilidad	Esteril	Cumple	-	-	-	-	-	Cumple
Identidad	IR: Cumple Test de Sulfato: Cumple	Cumple	Cumple	Cumple	Cumple	Cumple	Cumple	Cumple
Valoración	Límites: 90,0-120,0 % (13,5 - 18,0 UI/frasco ampolla)	15,15 UI (101,0%)	15,23 UI (101,5%)	15,26 UI (101,7%)	15,02 UI (100,1%)	14,81 UI (98,7%)	14,87 UI (99,1%)	14,72 UI (98,1%)

Lote: 1174404

Parámetros	Especificación	0 meses	3 meses	6 meses	9 meses	12 meses	18 meses	24 meses
Aspecto Físico	Taco liofilizado blanco.	Cumple	Cumple	Cumple	Cumple	Cumple	Cumple	Cumple
Solución reconstituida	Cumple requerimientos de claridad de la solución,	Cumple	Cumple	Cumple	Cumple	Cumple	Cumple	Cumple
	No debe presentar partículas y/o pelusas en suspensión.	No detectado	No detectado	No detectado	No detectado	No detectado	No detectado	No detectado
pH	Límites: 4,5 - 6,0	4,9	4,9	4,9	4,9	4,9	4,9	4,9
Contenido de Agua	Límites: No más de 6,0 %	3,6	2,7	3,6	3,7	3,0	3,6	3,3
Cobre	Límites: No más de 0,1 %	No más de 0,1 %	No más de 0,1 %	No más de 0,1 %	No más de 0,1 %	No más de 0,1 %	No más de 0,1 %	No más de 0,1 %
Contenido de Bleomicina	A2: 55% - 70%	65	64	64	68	62	61	63
	B2: 25% - 32%	31	31	31	30	31	31	30
	B4: No más de 1 %	0,3	0	0,3	0	0,2	0,5	0,3
	A2 + B2: No menos de 90%	96	96	95	98	93	93	94
Endotoxinas Bacterianas	Límites: No más de 10,0 UE/ Unidad de Bleomicina.	Menos de 10,0 UE/ unidad	-	-	-	-	-	Menos de 10,0 UE/ unidad
Esterilidad	Esteril	Cumple	-	-	-	-	-	Cumple
Identidad	IR: Cumple Test de Sulfato: Cumple	Cumple	Cumple	Cumple	Cumple	Cumple	Cumple	Cumple
Valoración	Límites: 90,0-120,0 % (13,5 - 18,0 UI/frasco ampolla)	15,50 UI (103,3%)	15,21 UI (101,4%)	15,41 UI (102,7%)	15,17 UI (101,1%)	15,08 UI (100,5%)	15,09 UI (100,6%)	15,03 UI (100,2%)

LONG TERM STABILITY STUDY REPORT

Product Name	BLEOMYCIN SULFATE for Injection 15 units	Mfg. Date	June 11, 2014
Active Ingredient	Bleomycin Sulfate	Exp. Date	June 10, 2016
Batch No.	1174402	Packaging	Colorless Vial
Storage Condition	30 ± 2°C/75 ± 5% RH	Reference	USP

		Months						
Test	Specification	0	3	6	9	12	18	24
Description	White freeze-dried cake in a colorless vial	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
Identification	By IR : The IR absorption spectrum of the Test specimen and the Standard specimen exhibit maxima at the same wavelengths.	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
	By Test for Sulfate : It responds to the test for sulfate	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
pH	Between 4.5 and 6.0	4.7	4.7	4.8	4.8	4.7	4.8	4.8
Water	NMT* 6.0%	2.7	2.6	2.9	2.2	2.5	2.4	2.9
Copper	NMT 0.1%	NMT 0.1%	NMT 0.1%	NMT 0.1%	NMT 0.1%	NMT 0.1%	NMT 0.1%	NMT 0.1%
Constituted Solution	Completeness and Clarity of solution : Meet the requirement	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
	Foreign matter : Not detected	Not detected	Not detected	Not detected	Not detected	Not detected	Not detected	Not detected
Content of Bleomycin	A ₁ : 55% ~ 70%	68	64	68	68	69	62	65
	B ₂ : 25% ~ 32%	29	32	30	30	30	31	31
	B ₄ : NMT 1%	0.5	0.1	0	0	0	0.3	0
	A ₁ + B ₂ : NLT 90%	98	96	98	98	99	94	96
Bacterial Endotoxins	NMT 10.0 EU/Unit	Less than 10.0 EU/Unit	-	-	-	-	-	Less than 10.0 EU/Unit
Sterility	Sterile	Sterile	-	-	-	-	-	Sterile
Particulate Matter	≥ 10 μm NMT 6000	25	55	9	5	1	5	45
	≥ 25 μm NMT 600	1	5	3	1	1	4	2
Weight Variation	Acceptance Value : NMT 15.0%	3.5	3.6	3.3	3.5	5.9	3.3	3.2
Airtightness	No leak	No leak	No leak	No leak	No leak	No leak	No leak	No leak
Assay	90.0% to 120.0%	101.4	101.7	100.2	100.5	98.2	99.8	100.2

*NMT : Not more than, **ND : Not detected



KOREA UNITED PHARM. INC.
107, Gongsan-ro, Yuseong-gu, Sejong-si, Korea

LONG TERM STABILITY STUDY REPORT

Product Name	BLEOMYCIN SULFATE for Injection 15 units	Mfg. Date	June 20, 2014
Active Ingredient	Bleomycin Sulfate	Exp. Date	June 19, 2016
Batch No.	1174403	Packaging	Colorless Vial
Storage Condition	30 ± 2°C/75 ± 5% RH	Reference	USP

Test	Specification	Months						
		0	3	6	9	12	18	24
Description	White freeze-dried cake in a colorless vial	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
Identification	By IR : The IR absorption spectrum of the <i>Test specimen</i> and the <i>Standard specimen</i> exhibit maxima at the same wavelengths.	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
	By Test for Sulfate : It responds to the test for sulfate	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
pH	Between 4.5 and 6.0	4.7	4.7	4.8	4.8	4.7	4.7	4.7
Water	NMT* 6.0%	2.6	2.9	2.5	2.8	2.6	2.4	2.5
Copper	NMT* 0.1%	NMT 0.1%	NMT 0.1%	NMT 0.1%	NMT 0.1%	NMT 0.1%	NMT 0.1%	NMT 0.1%
Constituted Solution	Completeness and Clarity of solution : Meet the requirement	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
	Foreign matter : Not detected	Not detected	Not detected	Not detected	Not detected	Not detected	Not detected	Not detected
Content of Bleomycin	A ₃ : 55% ~ 70%	68	65	68	68	69	62	66
	B ₂ : 25% ~ 32%	29	31	29	29	30	31	32
	B ₄ : NMT 1%	0.5	0.2	0	0	0	0.2	0.3
	A ₃ + B ₂ : NLT 90%	98	96	98	98	99	94	95
Bacterial Endotoxins	NMT 10.0 EU/Unit	Less than 10.0 EU/Unit	-	-	-	-	-	Less than 10.0 EU/Unit
Sterility	Sterile	Sterile	-	-	-	-	-	Sterile
Particulate Matter	≥ 10 μm NMT 6000	14	23	9	4	1	3	5
	≥ 25 μm NMT 600	0	3	1	0	0	1	2
Weight Variation	Acceptance Value : NMT 15.0%	3.6	3.7	4.1	4.4	5.5	4.2	5.6
Airtightness	No leak	No leak	No leak	No leak	No leak	No leak	No leak	No leak
Assay	90.0% to 120.0%	101.0	101.5	101.7	100.1	98.7	99.1	98.1

*NMT : Not more than, **ND : Not detected



KOREA UNITED PHARM. INC.

107, Bongdam-ro, Yeosu-si, Jeon-si, Korea

LONG TERM STABILITY STUDY REPORT

Product Name	BLEOMYCIN SULFATE for Injection 15 units	Mfg. Date	July 25, 2014
Active Ingredient	Bleomycin Sulfate	Exp. Date	July 24, 2016
Batch No.	1174404	Packaging	Colorless Vial
Storage Condition	30 ± 2°C/75 ± 5% RH	Reference	USP

		Months						
Test	Specification	0	3	6	9	12	18	24
Description	White freeze-dried cake in a colorless vial	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
Identification	By IR : The IR absorption spectrum of the <i>Test specimen</i> and the <i>Standard specimen</i> exhibit maxima at the same wavelengths.	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
	By Test for Sulfate : It responds to the test for sulfate	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
pH	Between 4.5 and 6.0	4.9	4.9	4.9	4.9	4.9	4.9	4.9
Water	NMT* 6.0%	3.6	2.7	3.6	3.7	3.0	3.6	3.3
Copper	NMT* 0.1%	NMT 0.1%	NMT 0.1%	NMT 0.1%	NMT 0.1%	NMT 0.1%	NMT 0.1%	NMT 0.1%
Constituted Solution	Completeness and Clarity of solution : Meet the requirement	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
	Foreign matter : Not detected	Not detected	Not detected	Not detected	Not detected	Not detected	Not detected	Not detected
Content of Bleomycin	A ₃ : 55% ~ 70%	65	64	64	68	62	61	63
	B ₂ : 25% ~ 32%	31	31	31	30	31	31	30
	B ₄ : NMT 1%	0.3	0	0.3	0	0.2	0.5	0.3
	A ₃ + B ₂ : NLT 90%	96	96	95	98	93	93	94
Bacterial Endotoxins	NMT 10.0 EU/Unit	Less than 10.0 EU/Unit	-	-	-	-	-	Less than 10.0 EU/Unit
Sterility	Sterile	Sterile	-	-	-	-	-	Sterile
Particulate Matter	≥ 10 μm NMT 6000	35	35	22	29	9	39	42
	≥ 25 μm NMT 600	3	1	3	2	0	1	2
Weight Variation	Acceptance Value : NMT 15.0%	6.4	6.5	5.9	4.9	6.2	3.3	3.6
Airtightness	No leak	No leak	No leak	No leak	No leak	No leak	No leak	No leak
Assay	90.0% to 120.0%	103.3	101.4	102.7	101.1	100.5	100.6	100.2

*NMT : Not more than, **ND : Not detected



KOREA UNITED PHARM. INC.

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Estudio de estabilidad del reconstituido y diluido.

IN-USE STABILITY STUDIES

BLEOMYCIN SULFATE for Injection 15 units



KOREA UNITED PHARM. INC.

1. PROTOCOL

- 1.1. Product Name : BLEOMYCIN SULFATE for Injection 15 units
- 1.2. Active Ingredient : Bleomycin Sulfate
- 1.3. Analysis Date : June 04, 2018 ~ June 07, 2018
- 1.4. Conc. of Reconstitution : 3 units/mL, 1.2 units/mL
- 1.5. Method of Reconstitution : The BLEOMYCIN SULFATE 15 units vial should be reconstituted with 5 mL of sterile water for injection and sterile bacteriostatic water for injection. 60 units of BLEOMYCIN SULFATE are dissolved in 50 mL of sodium chloride for injection 0.9%.
- 1.6. Storage Condition : The reconstituted solution is stored at room temperature (30°C) for up to 24 hours.
- 1.7. Test Products

Batch No.	Mfg. Date	Exp. Date	Batch Size
1174604	June 19, 2016	June 18, 2018	5,000 Vials
1174801	February 14, 2018	February 13, 2020	5,000 Vials
1174802	February 18, 2018	February 17, 2020	5,000 Vials

1.8. Test Parameters

Test	Requirements
Description	Visual Inspection
pH	Between 4.5 and 6.0
Assay	Between 90.0% and 120.0%
Content of Bleomycins	A ₂ : Between 55% and 70%
	B ₂ : Between 25% and 32%
	B ₄ : Not more than 1%
	A ₂ & B ₂ : Not less than 90%

1.9. Test Conditions

Diluents	Conditions	Concentration
Sterile water for injection	For 24 hours at room temperature (30°C)	3 units/mL
Sterile bacteriostatic water for injection	For 24 hours at room temperature (30°C)	3 units/mL
Sodium chloride for injection 0.9%	For 24 hours at room temperature (30°C)	1.2 units/mL

1.10. Test Plans

Conditions	Sampling Intervals (hours)
Sterile water for injection for 24 hours at room temperature (30°C)	Initial, 12, 24
Sterile bacteriostatic water for injection for 24 hours at room temperature (30°C)	Initial, 12, 24
Sodium chloride for injection 0.9% for 24 hours at room temperature (30°C)	Initial, 12, 24

2. RESULT

2.1. Sterile water for injection for 24 hours at room temperature (30°C)

1) Batch No. 1174604

Test	Specification	Initial	12 hours	24 hours
Description	Clear, colorless solution	Conforms	Conforms	Conforms
pH	Between 4.5 and 6.0	5.2	5.2	5.3
Assay	Between 90.0% and 120.0%	102.5	100.9	98.5
Content of Bleomycins	A ₂ : Between 55% and 70%	67.5	67.8	67.5
	B ₂ : Between 25% and 32%	31.5	31.2	30.8
	B ₄ : Not more than 1%	0.2	0.4	0.5
	A ₂ & B ₂ : Not less than 90%	98.1	97.5	97.3

2) Batch No. 1174801

Test	Specification	Initial	12 hours	24 hours
Description	Clear, colorless solution	Conforms	Conforms	Conforms
pH	Between 4.5 and 6.0	5.1	5.2	5.2
Assay	Between 90.0% and 120.0%	104.8	102.4	98.1
Content of Bleomycins	A ₂ : Between 55% and 70%	68.7	68.0	67.5
	B ₂ : Between 25% and 32%	30.5	30.3	29.8
	B ₄ : Not more than 1%	0.2	0.4	0.5
	A ₂ & B ₂ : Not less than 90%	98.5	98.0	97.5

3) Batch No. 1174802

Test	Specification	Initial	12 hours	24 hours
Description	Clear, colorless solution	Conforms	Conforms	Conforms
pH	Between 4.5 and 6.0	5.1	5.2	5.3
Assay	Between 90.0% and 120.0%	103.5	100.4	98.1
Content of Bleomycins	A ₂ : Between 55% and 70%	68.8	68.3	68.5
	B ₂ : Between 25% and 32%	30.2	29.7	29.9
	B ₄ : Not more than 1%	0.2	0.5	0.5
	A ₂ & B ₂ : Not less than 90%	98.7	98.1	97.9

2.2. Sterile bacteriostatic water for injection for 24 hours at room temperature (30°C)

1) Batch No. 1174604

Test	Specification	Initial	12 hours	24 hours
Description	Clear, colorless solution	Conforms	Conforms	Conforms
pH	Between 4.5 and 6.0	5.1	5.2	5.3
Assay	Between 90.0% and 120.0%	100.5	100.9	97.9
Content of Bleomycins	A ₂ : Between 55% and 70%	66.9	67.8	67.0
	B ₂ : Between 25% and 32%	30.5	31.2	31.0
	B ₄ : Not more than 1%	0.3	0.4	0.5
	A ₂ & B ₂ : Not less than 90%	97.4	97.5	96.3

2) Batch No. 1174801

Test	Specification	Initial	12 hours	24 hours
Description	Clear, colorless solution	Conforms	Conforms	Conforms
pH	Between 4.5 and 6.0	5.2	5.2	5.2
Assay	Between 90.0% and 120.0%	103.5	101.0	98.5
Content of Bleomycins	A ₂ : Between 55% and 70%	69.2	68.7	67.9
	B ₂ : Between 25% and 32%	30.1	29.9	29.1
	B ₄ : Not more than 1%	0.2	0.2	0.4
	A ₂ & B ₂ : Not less than 90%	98.7	98.3	97.8

3) Batch No. 1174802

Test	Specification	Initial	12 hours	24 hours
Description	Clear, colorless solution	Conforms	Conforms	Conforms
pH	Between 4.5 and 6.0	5.1	5.2	5.2
Assay	Between 90.0% and 120.0%	104.2	102.5	100.8
Content of Bleomycins	A ₂ : Between 55% and 70%	68.4	68.3	68.1
	B ₂ : Between 25% and 32%	29.9	29.5	29.7
	B ₄ : Not more than 1%	0.2	0.3	0.3
	A ₂ & B ₂ : Not less than 90%	98.3	97.8	97.5

2.3. Sodium chloride for injection 0.9% for 24 hours at room temperature (30°C)

1) Batch No. 1174604

Test	Specification	Initial	12 hours	24 hours
Description	Clear, colorless solution	Conforms	Conforms	Conforms
pH	Between 4.5 and 6.0	5.2	5.3	5.3
Assay	Between 90.0% and 120.0%	99.8	98.1	95.9
Content of Bleomycins	A ₂ : Between 55% and 70%	67.3	67.0	66.7
	B ₂ : Between 25% and 32%	30.2	29.5	29.3
	B ₄ : Not more than 1%	0.4	0.6	0.7
	A ₂ & B ₂ : Not less than 90%	97.1	95.9	94.2

2) Batch No. 1174801

Test	Specification	Initial	12 hours	24 hours
Description	Clear, colorless solution	Conforms	Conforms	Conforms
pH	Between 4.5 and 6.0	5.3	5.3	5.3
Assay	Between 90.0% and 120.0%	101.8	99.9	98.3
Content of Bleomycins	A ₂ : Between 55% and 70%	69.0	68.4	68.1
	B ₂ : Between 25% and 32%	30.0	29.3	29.5
	B ₄ : Not more than 1%	0.3	0.4	0.5
	A ₂ & B ₂ : Not less than 90%	98.1	97.6	97.1

3) Batch No. 1174802

Test	Specification	Initial	12 hours	24 hours
Description	Clear, colorless solution	Conforms	Conforms	Conforms
pH	Between 4.5 and 6.0	5.2	5.2	5.3
Assay	Between 90.0% and 120.0%	103.4	100.3	98.9
Content of Bleomycins	A ₂ : Between 55% and 70%	68.5	68.1	68.0
	B ₂ : Between 25% and 32%	29.7	29.5	29.3
	B ₄ : Not more than 1%	0.2	0.2	0.3
	A ₂ & B ₂ : Not less than 90%	98.7	98.0	97.8

3. CONCLUSION

The stability test of the reconstituted solution performed for 24 hours at room temperature (30°C). The satisfactory result was found in the stability test, conforming to the required specifications. Therefore, the stability test of this product is guaranteed for a period of 24 hours at room temperature (30°C).

김기영

Mr. Ki-Young Do
QC/QA Director



KOREA UNITED PHARM. INC.