OPKO CHILE S.A.

ESTUDIO DE ESTABILIDAD

Bencilpenicilina benzatina polvo para suspensión inyectable
1.200.000 U.I.

I. Protocolo

Se realizará una evaluación de la estabilidad de tres lotes de Bencilpenicilina benzatina 1.200.000 U.I. polvo para suspensión inyectable fabricado por Reyoung Pharmaceutical Co. Ltd. El estudio es realizado a dos tiempos y condiciones ambientales, por el fabricante del producto terminado Reyoung Pharmaceutical Co., Ltd.

A continuación se detallan los lotes a analizar, con sus fechas de inicio y termino de estudio.

Tabla 1: Detalle de los lotes a analizar y tiempo de estudio.

Lote	Fecha de Fabricación	Tamaño de lote (vial)	Tiempo de estudio		
			Inicio	Final (Tiempo real)	Final (Acelerado)
10051201	Mayo 2010	100.000	27 Mayo 2010	27 Mayo 2013	27 Nov. 2010
10051202	Mayo 2010	100.000	27 Mayo 2010	27 Mayo 2013	27 Nov. 2010
10051203	Mayo 2010	100.000	27 Mayo 2010	27 Mayo 2013	27 Nov. 2010

1- Condiciones

El estudio se realizó almacenando muestras en las siguientes condiciones de temperatura y humedad relativa.

Tabla 2: Condiciones de almacenamiento durante el estudio.

	Estudio Acelerado	Estudio a tiempo real
Temperatura	40 ± 2°C	30 ± 2°C
Humedad	75 ± 5%	65 ± 5%

2- Tipo de envase

. **Primario**: Frasco ampolla de vidrio tipo II con tapón de butilo y casquete de aluminio.
. **Secundario**: Estuche de cartulina impresa, más folleto de información al paciente, todo debidamente rotulado y sellado.

3- Análisis realizados y frecuencia de testeo

a) Estudio acelerado

Tabla 3: Análisis realizados y frecuencia de testeo en Estudio acelerado.

Parámetro medido	**Test en intervalos de meses**				
	0	1	2	3	6
Descripción	•	•	•	•	•
Agua	•	•	•	•	•
Identificación	•	•	•	•	•
Material Particulado	•	•	•	•	•
Uniformidad de dosis	•	•	•	•	•
Material extraño visible	•	•	•	•	•
pH	•	•	•	•	•
Sustancia relacionadas	•	•	•	•	•
Esterilidad	•	•	•	•	•
Endotoxinas bacterianas	•	•	•	•	•
Valoración	•	•	•	•	•

b) Estudio a tiempo real

Tabla 4: Análisis realizados y frecuencia de testeo a Estudio en tiempo real.

Parámetro medido	**Test en intervalos**								
	0	1	3	6	9	12	18	24	36
Descripción	•	•	•	•	•	•	•	•	•
Agua	•	•	•	•	•	•	•	•	•
Identificación	•	•	•	•	•	•	•	•	•
Material Particulado	•	•	•	•	•	•	•	•	•
Uniformidad de dosis	•	•	•	•	•	•	•	•	•
Material extraño visible	•	•	•	•	•	•	•	•	•
pH	•	•	•	•	•	•	•	•	•
Sustancia relacionadas	•	•	•	•	•	•	•	•	•
Esterilidad	•	•	•	•	•	•	•	•	•
Endotoxinas bacterianas	•	•	•	•	•	•	•	•	•
Valoración	•	•	•	•	•	•	•	•	•

4- Especificaciones de producto terminado

Tabla 5: Especificaciones de producto terminado.

TEST	**SPECIFICATION**	**REMARKS-APPENDIX**
Description	White or almost white powder	VISUAL METHOD, BP
Identification	A. Infrared absorption spectrophotometry	APPENDIX II A, BP
	B. Thin-layer chromatography	APPENDIX III A, BP
	C. a reddish-brown color develops	BP
	D. The crystals melt (2.2.14) at about 214 °C	BP
Acidity or alkalinity	Not more than 0.2 ml of 0.02 M sodium hydroxide is required to change the color of the indicator to blue.	BP
Water	5.0 per cent to 8.0 per cent	APPENDIX IX C, BP
Bacterial endotoxins	less than 0.13 IU/ml	APPENDIX XIV C, BP
Sterility	Sterile	APPENDIX XVI A BP
Related substances	Impurity C(benzylpeniciloic acids benzathide): not more than 2 per cent Any other impurity: not more than 1per cent	HPLC, APPENDIX III D, BP
Assay	95%-105%	HPLC, APPENDIX III D, BP
Particulate matter	≥ 10um NMT 6000/vial ≥25um NMT 600/vial	Appendix XIII A, BP
Visible foreign matter	Absent	Appendix XIII B, BP
Uniformity of dosage units	AV≤L1%,L1=15.0	Appendix XII N, BP

II. Fórmula cuali- cuantitativa

瑞 阳 制 药 有 限 公 司

Reyoung Pharmaceutical Co., Ltd.

Cada frasco ampolla con polvo para suspensión inyectable contiene:

Ingredientes	Especificación	Cantidad/ ampolla	Función
Bencilpenicilina Benzatina (Equivalente a 1.200.000 U.I. de Bencilpenicilina)	BP	0.991 g	Principio activo
Lecithin	USP	0.01 g	Excipiente

*Basado en una potencia de 1.211 U.I./mg

REYOUNG PHARMACEUTICAL CO., LTD 瑞阳制药有限公司

III. Resultados

1- Estudio de estabilidad acelerado

Accelerated stability test charts
Product name: Benzathine benzylpenicillin for injection 1.2mega
Batch Number: 10051201
Date the study started: 27-05-2010
Date the study ended: 27-11-2010
Primary packaging: Packed in 7 mL USP mould glass vials type II, butyl rubber stopper, non flip-off cap adhesive label

Test items	*Requirement of BP*	T=0 *May 27,2010*	1 months *Jun 27,2010*	2 months *Jul 27,2010*	3 months *Aug 27,2010*	6months *Nov 27,2010*
Description	A white or almost white powder	White powder	White powder	White powder	White powder	White powder
Water	5.0%-8.0%	6.86	7.04	7.06	7.08	7.1
Identification	As per BP	Complies	Complies	Complies	Complies	Complies
Particulate matter	Particles≥ 10μm: ≤6000 Particles ≥ 25μm: ≤ 600	114 13	119 15	121 18	127 21	138 27
Uniformity of dosage units	AV≤15%	6.4%	6.5%	6.5%	6.7%	6.5%
Visible foreign matter	Absent	Absent	Absent	Absent	Absent	Absent
pH	Not more than 0.2 ml	0.08	0.10	0.11	0.12	0.12
Related substances	Impurity C ≤2.0% Any other impurity ≤ 1.0%	0 0.26	0 0.30	0 0.31	0 0.29	0 0.31
Sterility	Sterile	Sterile	Sterile	Sterile	Sterile	Sterile
Bacterial endotoxins	Less than 0.13 IU/ml	Less than 0.13 IU/ml	Less than 0.13 IU/ml	Less than 0.13 IU/ml	Less than 0.13 IU/ml	Less than 0.13 IU/ml
Assay	95.0 %-105.0%	100.3%	98.67%	98.22%	97.36%	97.3%

Results: the results show that the batch under the condition-40℃75% has no obvious change regarding the physic-chemical and microbiological items as per BP during 6 months

Product name: Benzathine benzylpenicillin for injection 1.2mega
Batch Number: 10051202
Date the study started: 27-05-2010
Date the study ended: 27-11-2010
Primary packaging: Packed in 7 mL USP mould glass vials type II, butyl rubber stopper, non flip-off cap, adhesive label

Test items	*Requirement of BP*	T=0 *May 27,2010*	1 months *Jun 27,2010*	2 months *Jul 27,2010*	3 months *Aug 27,2010*	6months *Nov 27,2010*
Description	A white or almost white powder	White powder	White powder	White powder	White powder	White powder
Water	5.0%-8.0%	6.97	6.98	7.00	7.04	7.03
Identification	As per BP	Complies	Complies	Complies	Complies	Complies
Particulate matter	Particles≥ 10μm: ≤6000 Particles ≥ 25μm: ≤ 600	115 13	119 15	121 18	127 22	138 28
Uniformity of dosage units	AV≤15%	6.5%	6.7%	6.6%	6.7%	6.5%
Visible foreign matter	Absent	Absent	Absent	Absent	Absent	Absent
pH	Not more than 0.2 ml	0.08	0.11	0.10	0.09	0.12
Related substances	Impurity C ≤2.0% Any other impurity ≤ 1.0%	0 0.28	0 0.43	0 0.30	0 0.30	0 0.42
Sterility	Sterile	Sterile	Sterile	Sterile	Sterile	Sterile
Bacterial endotoxins	Less than 0.13 IU/ml	Less than 0.13 IU/ml	Less than 0.13 IU/ml	Less than 0.13 IU/ml	Less than 0.13 IU/ml	Less than 0.13 IU/ml
Assay	95.0 %-105.0%	99.96%	98.42%	97.72%	96.69%	96.57%

Results: the results show that the batch under the condition-40℃75% has no obvious change regarding the physic-chemical and microbiological items as per BP during 6 months

Product name: Benzathine benzylpenicillin for injection 1.2mega
Batch Number: 10051203
Date the study started: 27-05-2010
Date the study ended: 27-11-2010
Primary packaging: Packed in 7 mL USP mould glass vials type II, butyl rubber stopper, non flip-off cap, adhesive label

Test items	*Requirement of BP*	T=0 *May 27,2010*	1 months *Jun 27,2010*	2 months *Jul 27,2010*	3 months *Aug 27,2010*	6months *Nov 27,2010*
Description	A white or almost white powder	White powder	White powder	White powder	White powder	White powder
Water	5.0%-8.0%	6.74	6.82	6.9	7.00	7.13
Identification	As per BP	Complies	Complies	Complies	Complies	Complies
Particulate matter	Particles≥ 10μm: ≤6000 Particles ≥ 25μm: ≤ 600	116 13	119 17	121 18	127 21	144 28
Uniformity of dosage units	AV≤15%	6.6%	6.6%	6.5%	6.7%	6.5%
Visible foreign matter	Absent	Absent	Absent	Absent	Absent	Absent
pH	Not more than 0.2 ml	0.09	0.11	0.10	0.09	0.12
Related substances	Impurity C ≤2.0% Any other impurity ≤ 1.0%	0.09 0.12	0.19 0.12	0.30 0.13	0.50 0.37	0 0.27
Sterility	Sterile	Sterile	Sterile	Sterile	Sterile	Sterile
Bacterial endotoxins	Less than 0.13 IU/ml	Less than 0.13 IU/ml	Less than 0.13 IU/ml	Less than 0.13 IU/ml	Less than 0.13 IU/ml	Less than 0.13 IU/ml
Assay	95.0 %-105.0%	99.95%	99.85%	98.78%	98.54%	97.68%

Results: the results show that the batch under the condition-40°C75% has no obvious change regarding the physic-chemical and microbiological items as per BP during 6 months

2- Estudio a tiempo real.

Long term stability test charts
Product name: Benzathine benzylpenicillin for injection 1.2mega
Batch Number: 10051201
Date the study started: 27-05-2010
Date the study ended: 27-05-2013
Primary packaging: Packed in 7 mL USP mould glass vials type II, butyl rubber stopper, non flip-off cap, adhesive label

Test items	*Requirement of BP*	T=0 *May 27,2010*	3 months *Aug 27,2010*	6 months *Nov 27,2010*	9 months *Feb 27,2011*	12 months *Feb 27,2011*	18 months *May 27,2011*	24 months *Nov 27,2011*	36 months *May 27,2013*
Description	A white or almost white powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder
Water	5.0%-8.0%	6.86	7.03	7.05	7.07	7.08	7.12	7.12	7.14
Identification	As per BP	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies
Particulate matter	Particles≥ 10μm: ≤6000 Particles ≥ 25μm: ≤ 600	114 13	119 15	121 18	125 20	128 23	135 26	138 30	144 39
Uniformity of dosage units	AV≤15%	6.4%	6.4%	6.5%	6.7%	6.5%	6.5%	6.3%	6.4%
Visible foreign matter	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent
pH	Not more than 0.2 ml	0.08	0.09	0.08	0.10	0.11	0.10	0.12	0.11
Related substances	Impurity C ≤2.0% Any other impurity ≤ 1.0%	0 0.26	0 0.30	0 0.31	0 0.31	0 0.31	0 0.32	0 0.50	0 0.52
Sterility	Sterile	Sterile	Sterile	Sterile	Sterile	Sterile	Sterile	Sterile	Sterile
Bacterial endotoxins	Less than 0.13 IU/ml	Less than 0.13 IU/ml	Less than 0.13 IU/ml	Less than 0.13 IU/ml	Less than 0.13 IU/ml	Less than 0.13 IU/ml	Less than 0.13 IU/ml	Less than 0.13 IU/ml	Less than 0.13 IU/ml
Assay	95.0 %-105.0%	100.3%	98.84%	98.78%	98.64%	98.3%	98.21%	97.54%	97.76%

Results: the results show that the batch under the condition-30°C65% has no obvious change regarding the physic-chemical and microbiological items as per BP during 36 months

Product name: Benzathine benzylpenicillin for injection 1.2mega
Batch Number: 10051202
Date the study started: 27-05-2010
Date the study ended: 27-05-2013
Primary packaging: Packed in 7 mL USP mould glass vials type II, butyl rubber stopper, non flip-off cap, adhesive label

Test items	*Requirement of BP*	T=0 *May 27,2010*	3 months *Aug 27,2010*	6 months *Nov 27,2010*	9 months *Feb 27,2011*	12 months *Feb 27,2011*	18 months *May 27,2011*	24 months *Nov 27,2011*	36 months *May 27,2013*
Description	A white or almost white powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder
Water	5.0%-8.0%	6.97	7.02	6.98	7.06	7.06	7.07	7.09	7.1
Identification	As per BP	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies
Particulate matter	Particles≥ 10μm: ≤6000 Particles ≥ 25μm: ≤ 600	115 13	119 15	121 18	125 21	129 23	135 26	138 30	144 42
Uniformity of dosage units	AV≤15%	6.5%	6.6%	6.4%	6.7%	6.5%	6.6%	6.3%	6.4%
Visible foreign matter	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent
pH	Not more than 0.2 ml	0.08	0.10	0.08	0.09	0.11	0.10	0.10	0.11
Related substances	Impurity C ≤2.0% Any other impurity ≤ 1.0%	0 0.28	0 0.42	0 0.42	0 0.43	0 0.30	0 0.46	0 0.70	0 0.97
Sterility	Sterile	Sterile	Sterile	Sterile	Sterile	Sterile	Sterile	Sterile	Sterile
Bacterial endotoxins	Less than 0.13 IU/ml	Less than 0.13 IU/ml	Less than 0.13 IU/ml	Less than 0.13 IU/ml	Less than 0.13 IU/ml	Less than 0.13 IU/ml	Less than 0.13 IU/ml	Less than 0.13 IU/ml	Less than 0.13 IU/ml
Assay	95.0 %-105.0%	99.96%	98.51%	98.42%	98.32%	98.11%	97.86%	97.35%	97.31%

Results: the results show that the batch under the condition-30°C65% has no obvious change regarding the physic-chemical and microbiological items as per BP during 36 months

Product name: Benzathine benzylpenicillin for injection 1.2mega
Batch Number: 10051203
Date the study started: 27-05-2010
Date the study ended: 27-05-2013
Primary packaging: Packed in 7 mL USP mould glass vials type II, butyl rubber stopper, non flip-off cap, adhesive label

Test items	*Requirement of BP*	T=0 *May 27,2010*	3 months *Aug 27,2010*	6 months *Nov 27,2010*	9 months *Feb 27,2011*	12 months *Feb 27,2011*	18 months *May 27,2011*	24 months *Nov 27,2011*	36 months *May 27,2013*
Description	A white or almost white powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder	White powder
Water	5.0%-8.0%	6.74	6.96	7.08	7.18	7.24	7.36	7.4	7.5
Identification	As per BP	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies
Particulate matter	Particles≥ 10μm: ≤6000 Particles ≥ 25μm: ≤ 600	116 13	119 15	121 18	127 21	129 23	135 26	138 30	141 43
Uniformity of dosage units	AV≤15%	6.6%	6.6%	6.5%	6.7%	6.5%	6.6%	6.3%	6.4%
Visible foreign matter	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent
pH	Not more than 0.2 ml	0.09	0.08	0.10	0.09	0.10	0.10	0.09	0.11
Related substances	Impurity C ≤2.0% Any other impurity ≤ 1.0%	0.09 0.12	0.22 0.12	0 0.17	0 0.18	0 0.56	0 0.61	0 0.70	0.38 0.85
Sterility	Sterile	Sterile	Sterile	Sterile	Sterile	Sterile	Sterile	Sterile	Sterile
Bacterial endotoxins	Less than 0.13 IU/ml	Less than 0.13 IU/ml	Less than 0.13 IU/ml	Less than 0.13 IU/ml	Less than 0.13 IU/ml	Less than 0.13 IU/ml	Less than 0.13 IU/ml	Less than 0.13 IU/ml	Less than 0.13 IU/ml
Assay	95.0 %-105.0%	99.95%	99.56%	99.04%	98.83%	98.80%	98.14%	97.91%	96.11%

Results: the results show that the batch under the condition-30°C65% has no obvious change regarding the physic-chemical and microbiological items as per BP during 36 months

IV. Discusión

De acuerdo a los resultados obtenidos en el Estudio de Estabilidad de estantería, tanto acelerado como a tiempo real de los lotes 10051201, 10051202 y 10051203, se puede verificar que los lotes estudiados no muestran deterioro físico o químico en el envase utilizado, frasco ampolla de vidrio tipo II con tapón de butilo y casquete de aluminio, no se evidencia una disminución significativa en la valoración del activo, y los parámetros analizados se mantuvieron dentro de los límites especificados, durante 36 meses en el estudio a tiempo real y durante 6 meses en el estudio acelerado.

V. Conclusión

Basado en los datos adquiridos de los estudios de estabilidad a tiempo real y acelerado, se concluye que el producto analizado es estable por un periodo de 36 meses si se almacena cerrado a una temperatura no mayor a 30°C y a una humedad ambiental máxima de 65% ± 5%.

VI. Especificación de la vida útil

Se propone un periodo de eficacia para Bencilpenicilina benzatina 1.200.000 U.I. de 36 meses a partir de su fecha de fabricación, almacenándolo cerrado a una temperatura ambiente no mayor a 30°C, protegido de la humedad.

DECLARACIÓN DE ORIGEN.

REYOUNG 瑞 阳 制 药 有 限 公 司

Reyoung Pharmaceutical Co., Ltd

Date: 17-05-2018

To,
Instituto de Salud Pública de Chile
Santiago, Chile.

Subject- API's manufacturer for batch of stability study of Benzathine Benzylpenicillin 1.200.000 U.I.

Dear Sir;

We, Reyoung Pharmaceutical Co. Ltd. No. 1, address: Ruiyang Road, Yiyuan County, Shandong Province, China, hereby declare that the manufacturer of API, used in the batch of the stability study of Benzathine Benzylpenicillin 1.200.000 U.I. is Jiangxi Dongfeng Pharmaceutical Co. Ltd., address: No. 1 Dongfend Road, Leping Industrial Park, Leping City, Jiangxi Province.

Signature:

QA Manager
Reyoung Pharmaceutical Co., Ltd.

REYOUNG PHARMACEUTICAL CO., LTD. 瑞阳制药有限公司