OPKO CHILE S.A.

ESTUDIO DE ESTABILIDAD DEL PRODUCTO TERMINADO

PARACETAMOL COMPRIMIDOS 500 mg

ESTUDIO DE ESTABILIDAD

Objetivo:
Proveer y establecer evidencia documentada de la estabilidad del producto Paracetamol comprimidos 500 mg, elaborado por Hebei Jiheng (Group) Pharmaceutical Co., Ltd.

Fórmula Cualicuantitativa de Paracetamol comprimidos 500 mg:

Cada comprimido contiene:

Ingrediente	Función	Cantidad (mg)	Especificaciones
Paracetamol	Principio Activo	500,00	BPv
Almidón de maíz	Adhesivo/ Diluyente	45,00	BPv
Almidón glicolato de sodio	Desintegrante	16,65	BPv
Hidroxipropilcelulosa de baja sustitución	Desintegrante	9,00	USPv
Estearato de Magnesio	Lubricante	5,00	BPv

***** Agua purificada: Solvente utilizado y posteriormente eliminado durante el proceso de fabricación.

Declaración de fórmula (Origen):

HEBEI JIHENG (GROUP) PHARMACEUTICAL CO., LTD.
368 Jianshe Street Hengshui City Hebei, P.R.China 053000
Tel: +86 318-2133598 fax: +86 318-2182958 web: www.jihengpharmaceutical.com

Appendix 1

UNIT DOSE FORMULATION

PRODUCT NAME: Paracetamol tablet 500mg
GENERIC NAME: Paracetamol tablet

Ingredients	Quantity (mg)	Purpose
Paracetamol	500,00*	Active substance
Maize Starch	45,00	Adhesive/filling
Sodium Starch Glycolate	16,65	Disintegrant
Low-substituted Hydroxypropyl Cellulose	9,00	Disintegrant
Magnesium Stearate	5,00	Lubricant

Each Tablet contains:

*Purified Water is a solvent used and then eliminated during the manufacturing process.

ESTABILIDAD ACELERADA

Condiciones del estudio:

Temperatura y Humedad Relativa	**:**	40ºC ± 2ºC y 75% ± 5% H.R.
Lotes analizados	**:**	100914; 100915 y 100916
Fechas de Fabricación	**:**	Septiembre 2010
Tipo y Tamaño de lotes	**:**	Lotes industriales de 5.003.600 comprimidos
Tipo de material de envase	**:**	Blíster ALU/PVC

Los parámetros testeados por el fabricante del producto terminado son:
Descripción, Identidad, Friabilidad, Uniformidad de peso, Disolución, Sustancias relacionadas, Valoración y límites microbiológicos.

Fabricante de API empleado en el Estudio:
Hebei Jiheng (Group) Pharmaceutical co., Ltd.
Dirección:
No 368 Jianshe Street, Hengshui city, Hebei Province, China

Fabricante del producto terminado empleado en el Estudio:
Hebei Jiheng (Group) Pharmaceutical Co., Ltd.
Dirección:
No 368 Jianshe Street, Hengshui City, Hebei Province, China

Laboratorio que desarrolla el Estudio de Estabilidad:
Hebei Jiheng (Group) Pharmaceutical Co., Ltd.
Dirección:
No 368 Jianshe Street, Hengshui City, Hebei Province, China

ESTABILIDAD A TIEMPO REAL

Temperatura y Humedad Relativa	**:**	30ºC ± 2ºC y 70% ± 5% H.R.
Lotes analizados	**:**	100914; 100915 y 100916
Fechas de Fabricación	**:**	Septiembre 2010
Tipo y Tamaño de lotes	**:**	Lotes industriales de 5.003.600 comprimidos
Tipo de material de envase	**:**	Blíster ALU/PVC

Los parámetros testeados por el fabricante del producto terminado son:
Descripción, Identidad, Friabilidad, Uniformidad de peso, Disolución, Sustancias relacionadas, Valoración y límites microbiológicos.

Fabricante de API empleado en el Estudio:
Hebei Jiheng (Group) Pharmaceutical co., Ltd.
Dirección:
No 368 Jianshe Street, Hengshui city, Hebei Province

Fabricante del producto terminado empleado en el Estudio:
Hebei Jiheng (Group) Pharmaceutical Co., Ltd.
Dirección:
No368 Jianshe Street, Hengshui City, Hebei Province, China

Laboratorio que desarrolla el Estudio de Estabilidad:
Hebei Jiheng (Group) Pharmaceutical Co., Ltd.
Dirección:
No 368 Jianshe Street, Hengshui City, Hebei Province, China

Método de análisis del Producto Terminado:

El método de análisis de producto terminado empleado en este Estudio de Estabilidad, responde a la metodología de producto terminado utilizada por el fabricante del producto terminado.

Evaluación y análisis de los resultados:

De acuerdo a los resultados obtenidos en el Estudio de Estabilidad Acelerado (40ºC ± 2ºC; 75 ± 5% HR) y en el Estudio de Estabilidad a Tiempo Real (30°C ± 2° C; 70% ± 5% HR) para los Lotes 100914; 100915 y 100916, se puede verificar que los lotes estudiados no muestran deterioro físico o químico en el material de envase utilizado. No se evidencia una disminución significativa en la valoración del activo y los parámetros analizados se mantuvieron dentro de los límites especificados.

Conclusiones:

Los resultados obtenidos nos permiten proponer para el producto Paracetamol comprimidos 500 mg, un período de eficacia de 36 meses, almacenado en su envase original a una temperatura no mayor a 30ºC.

En las páginas siguientes se adjunta el Protocolo del Estudio de Estabilidad de origen y las tablas de resultados de los Estudios de Estabilidad realizados por el fabricante del producto a los Lotes 100914; 100915 y 100916 en las condiciones de temperatura y humedad anteriormente señaladas.

18. Stability Study (Protocol & Report)

In order to test the stability of export production Paracetamol tablets(0.5g/ tablet). We plan to continue with the product stability testing in 2010. That can ensure the patients with a safe and effective medication also provide a scientific basis for the revision of quality standards, product quality improvement and the determination of the validity period.

1. Accelerated testing

Take three batches of paracetamol tablets (0.5g / tablet) of this year. Adopt the market final product packaging (Blister packing, ALU-PVC), and placed in constant temperature and humidity control box. The storage condition of temperature is 40℃±2℃, relative humidity is 75 %±5%, testing for six months. Take the sample for testing respectively in the end of the first month, the second month, the third month and the sixth month .

Testing items: Identification, friability, uniformity of weight, dissolution, related substances, assay and microbial limit.

Testing basis: B.P current (Test according to new edition of pharmacopoeia when that has been executed)

Product batch number, observation dates and the others please see the Schedule.

2. Real time testing

Take three batches of paracetamol tablets (0.5g / tablet) of this year. Adopt the market final product packaging (Blister packing, ALU-PVC), and placed in constant temperature and humidity control box. The storage condition of temperature is 30℃±2℃, relative humidity is 70 %±5% (Basis on international climate zone IV with region B to set), testing for forty-eighth months. Take the sample for testing respectively in the end of the third month, the sixth month, the ninth month, the twelfth month, the eighteenth month, the twenty-fourth month, the thirty-sixth month.

Testing items: Identification, friability, uniformity of weight, dissolution, related substances, assay and microbial limit.

Testing basis: B.P current (Test according to new edition of pharmacopoeia when that has been executed)

Product batch number, observation dates and the others please see the Schedule.

Prepared by: Liu Licun Date: 2010/08/18

Approved by: Feng Xiangli Date:2010/08/18

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TABLAS RESUMEN DE RESULTADOS

Chart 1

Stability test on Medicine

Schedule:

Product Name:Paracetamol tablets Specifications: 0.5g/ tablet Batch no.:100914 Reference specification: BP current
Mfg. Date: 2010/09/18 Exp. Date: 2013/08 Batch Size: 5.003.600 tablets
Packge: Blister packaging(ALU-PVC) Sampling date: 2010/09/18 Person of retaining sample: Chen Yan
Manufacture workshop: 11st workshop Testing type: Accelerated testing Testing conditions: 40 ± 2 ℃ & RH 75 ± 5%

Items		Detecting Time (months)					
		Standard	Initial (2010/09/18)	1 month (2010/10/18)	2 month (2010/11/18)	3 month (2010/12/18)	6 month (2011/03/18)
Appearance		White, circular, flat beveled tablets having P/500 monogram on one side and plain on the other side.	Comply	Comply	Comply	Comply	Comply
Identification		(1)(2)shall be positive (3)about169℃	Comply	Comply	Comply	Comply	Comply
Uniformity of weight		± 4.5%	Comply	Comply	Comply	Comply	Comply
Friability		≤1%	Comply 0.3%	Comply 0.3%	Comply 0.3%	Comply 0.2%	Comply 0.3%
Dissolution		≥75%	93%	92%	92%	92%	92%
Related substances	4-Aminophenol	≤0.1%	0.0008%	0.0001%	0.0001%	0.0001%	0.0001%
	4 - Chloro-acetanilide	≤10ppm	2.5ppm	1.9ppm	1.6ppm	1.8ppm	1.9ppm
	The largest single impurity	≤0.25%	0.13%	0.11%	0.11%	0.11%	0.11%
Assay		96.0%-104.0%	99.2%	99.2%	99.0%	99.0%	99.2%
Microbial limit		Total amount of bacteria ≤1000/g Total amount of mold and yeast ≤100/g E.coli,acariens and its egg None	Comply	Comply	Comply	Comply	Comply

Chart 2 **Stability test on Medicine**

Schedule:

Product Name:Paracetamol tablets Specifications: 0.5g/ tablet Batch no.:100915 Reference specification:BP current

Mfg. Date: 2010/09/20 Exp. Date: 2013/08 Batch Size: 5.003.600 tablets

Packge: Blister packaging(ALU-PVC) Sampling date: 2010/09/20 Person of retaining sample: Chen Yan

Manufacture workshop: 11st workshop Testing type: Accelerated testing Testing conditions: 40 ± 2 ℃ & RH 75 ± 5%

Items		Detecting Time (months)					
		Standard	Initial (2010/09/20)	1 month (2010/10/20)	2 month (2010/11/20)	3 month (2010/12/20)	6 month (2011/03/20)
Appearance	White, circular, flat beveled tablets having P/500 monogram on one side and plain on the other side.		Comply	Comply	Comply	Comply	Comply
Identification		(1)(2)shall be positive (3)about169℃	Comply	Comply	Comply	Comply	Comply
Uniformity of weight		± 4.5%	Comply	Comply	Comply	Comply	Comply
Friability		≤1%	Comply 0.3%	Comply 0.2%	Comply 0.2%	Comply 0.3%	Comply 0.3%
Dissolution		≥75%	92%	92%	92%	91%	93%
Related substances	4-Aminophenol	≤0.1%	0.0003%	0.0001%	0.0001%	0.0001%	0.0001%
	4 - Chloro-acetanilide	≤10ppm	2.3ppm	1.6ppm	1.4ppm	1.6ppm	1.7ppm
	The largest single impurity	≤0.25%	0.12%	0.12%	0.11%	0.12%	0.12%
Assay		96.0%-104.0%	99.5%	99.5%	99.1%	99.2%	99.1%
Microbial limit	Total amount of bacteria ≤1000/g Total amount of mold and yeast ≤100/g E.coli,acariens and its egg None		Comply	Comply	Comply	Comply	Comply

Chart 3

Stability test on Medicine

Schedule:

Product Name:Paracetamol tablets Specifications: 0.5g/ tablet Batch no.: 100916 Reference specification:BP current
Mfg. Date:2010/09/22 Exp. Date: 2013/08 Batch Size: 5.003.600 tablets
Packge: Blister packaging(ALU-PVC) Sampling date: 2010/09/22 Person of retaining sample: Chen Yan
Manufacture workshop: 11st workshop Testing type: Accelerated testing Testing conditions: 40 ± 2 ℃ & RH 75 ± 5%

Items		Detecting Time (months)					
		Standard	Initial (2010/09/22)	1 month (2010/10/22)	2 month (2010/11/22)	3 month (2010/12/22)	6 month (2011/03/22)
Appearance		White, circular, flat beveled tablets having P/500 monogram on one side and plain on the other side.	Comply	Comply	Comply	Comply	Comply
Identification		(1)(2)shall be positive (3)about169℃	Comply	Comply	omply	Comply	Comply
Uniformity of weight		± 4.5%	Comply	Comply	Comply	Comply	Comply
Friability		≤1%	Comply 0.3%	Comply 0.2%	Comply 0.2%	Comply 0.2%	Comply 0.3%
Dissolution		≥75%	92%	92%	91%	91%	93%
Related substances	4-Aminophenol	≤0.1%	0.0002%	0.0001%	0.0001%	0.0001%	0.0001%
	4 - Chloro-acetanilide	≤10ppm	2.6ppm	1.7ppm	1.5ppm	1.4ppm	1.9ppm
	The largest single impurity	≤0.25%	0.16%	0.11%	0.12%	0.12%	0.11%
Assay		96.0%-104.0%	99.3%	99.2%	99.0%	99.2%	99.0%
Microbial limit		Total amount of bacteria ≤1000/g Total amount of mold and yeast ≤100/g E.coli, acariens and its egg None	Comply	Comply	Comply	Comply	Comply

Conclusion:

The accelerated testing for 6 month indicate that: The quality indicator without obvious change.

The product quality is stability store for 6 month （temperature is 40℃±2℃, relative humidity is 75 %±5%）

Chart 1 **Stability test on Medicine**

Schedule:

Product Name: Paracetamol tablets Specifications: 0.5g/ tablet Batch no.:100914 Mfg. Date: 2010/09/18

Exp. Date: 2013/08 Batch Size: 5.003.600 tablets Packge: Blister packaging(ALU-PVC) Sampling date: 2010/09/18

Reference specification: BP current Manufacture workshop: 11st workshop Person of retaining sample: Chen Yan

Testing type: Real time testing Testing conditions: 30 ± 2 ℃ & RH 70 ± 5%

Items		Standard	Detecting Time (months)							
			Inicial (2010/09/18)	3 month (2010/12/18)	6 month (2011/03/18)	9 month (2011/06/18)	12 month (2011/09/18)	18 month (2012/03/18)	24 month (2012/09/18)	36 month (2013/09/18)
Appearance		White, circular, flat beveled tablets having P/500 monogram on one side and plain on the other side	Comply	Comply	Comply	Comply	Comply	Comply	Comply	Comply
Identification		(1)(2)shall be positive (3)about169℃	Comply	Comply	Comply	Comply	Comply	Comply	Comply	Comply
Uniformity of weight		± 4.5%	Comply	Comply	Comply	Comply	Comply	Comply	Comply	Comply
Friability		≤1%	Comply 0.3%	Comply 0.2%	Comply 0.3%	Comply 0.2%	Comply 0.2%	Comply 0.2%	Comply 0.3%	Comply 0.2%
Dissolution		≥75%	93%	91%	92%	93%	92%	93%	93%	93%
Related substances	4-Aminophenol	≤0.1%	0.0008%	0.0001%	0.0001%	0.0002%	0.0004%	0.0002%	0.0001%	0.0004%
	4-Chloro-acetanilide	≤10ppm	2.5ppm	1.8ppm	1.9ppm	Not detected	3.4ppm	2.3ppm	1.4ppm	2.0ppm
	The largest single impurity	≤0.25%	0.13%	0.11%	0.11%	0.14%	0.099%	0.088%	0.10%	0.14%
Assay		96.0%-104.0%	99.2%	99.2%	99.0%	99.2%	98.9%	99.2%	99.1%	99.2%
Microbial limit		Total amount of bacteria ≤1000/g Total amount of mold and yeast ≤100/g E.coli, acariens and its egg None	Comply	Comply	Comply	Comply	Comply	Comply	Comply	Comply

Chart 2 **Stability test on Medicine**

Schedule:

Product Name**:** Paracetamol tablets Specifications: 0.5g/ tablet Batch no.: 100915 Mfg. Date: 2010/09/20

Exp. Date:2013/08 Batch Size: 5.003.600 tablets Packge: Blister packaging(ALU-PVC) Sampling date: 2010/09/20

Reference specification: BP current Manufacture workshop: 11st workshop Person of retaining sample: Chen Yan

Testing type: Real time testing Testing conditions: 30 ± 2 ℃ & RH 70 ± 5%

Items		Standard	Detecting Time (months)							
			Inicial (2010/09/20)	3month (2010/12/20)	6month (2011/03/20)	9month (2011/06/20)	12month (2011/09/20)	18month (2012/03/20)	24 month (2012/09/20)	36monh (2013/09/20)
Appearance		White, circular, flat beveled tablets having P/500 monogram on one side and plain on the other side	Comply	Comply	Comply	Comply	Comply	Comply	Comply	Comply
Identification		(1)(2)shall be positive (3)about169℃	Comply	Comply	Comply	Comply	Comply	Comply	Comply	Comply
Uniformity of weight		± 4.5%	Comply	Comply	Comply	Comply	Comply	Comply	Comply	Comply
Friability		≤1%	Comply 0.3%	Comply 0.2%	Comply 0.2%	Comply 0.2%	Comply 0.3%	Comply 0.2%	Comply 0.2%	Comply 0.2%
Dissolution		≥75%	92%	92%	92%	93%	92%	93%	93%	93%
Related substances	4-Aminophenol	≤0.1%	0.0003%	0.0001%	0.0001%	0.0002%	0.0001%	0.0003%	0.0002%	0.0001%
	4- Chloro-acetanilide	≤10ppm	2.3ppm	1.5ppm	1.4ppm	Not detected	3.6ppm	2.6ppm	2.9ppm	0.4ppm
	The largest single impurity	≤0.25%	0.12%	0.11%	0.12%	0.13%	0.090%	0.095%	0.10%	0.15%
Assay		96.0%-104.0%	99.5%	99.3%	99.4%	99.2%	99.4%	99.6%	99.4%	99.5%
Microbial limit	Total amount of Bacteria ≤1000/g Total amount of mold and yeast ≤100/g E.coli, acariens and its egg None		Comply	Comply	Comply	Comply	Comply	Comply	Comply	Comply

Chart 3 **Stability test on Medicine**

Schedule:

Product Name: Paracetamol tablets Specifications: 0.5g/ tablet Batch no.: 100916 Mfg. Date: 2010/09/22
Exp. Date:2013/08 Batch Size: 5.003.600tablets Packge: Blister packaging(ALU-PVC) Sampling date: 2010/09/22
Reference specification: BP current Manufacture workshop: 11st workshop Person of retaining sample: Chen Yan
Testing type: Real time testing Testing conditions: 30 ± 2 ℃ & RH 70 ± 5%

Items		Standard	Detecting Time (months)							
			Inicial (2010/09/22)	3month (2010/12/22)	6month (2011/03/22)	9month (2011/06/22)	12month (2011/09/22)	18month (2012/03/22)	24 month (2012/09/22)	36monh (2013/09/22)
Appearance		White, circular, flat beveled tablets having P/500 monogram on one side and plain on the other side	Comply	Comply	Comply	Comply	Comply	Comply	Comply	Comply
Identification		(1)(2)shall be positive (3)about169℃	Comply	Comply	Comply	Comply	Comply	Comply	Comply	Comply
Uniformity of weight		± 4.5%	Comply	Comply	Comply	Comply	Comply	Comply	Comply	Comply
Friability		≤1%	Comply 0.3%	Comply 0.3%	Comply 0.3%	Comply 0.2	Comply 0.2%	Comply 0.2	Comply 0.2	Comply 0.2
Dissolution		≥75%	92%	92%	92%	93%	92%	93%	93%	93%
Related substances	4-Aminophenol	≤0.1%	0.0002%	0.0001%	0.0001%	0.0002%	0.03%	0.0002%	0.0001%	0.0003%
	4 - Chloro-acetanilide	≤10ppm	2.6ppm	1.4ppm	2.0ppm	Not detected	6.0ppm	Not detected	1.3ppm	0.4ppm
	The largest single impurity	≤0.25%	0.16%	0.12%	0.11%	0.17%	0.094%	0.092%	0.094%	0.15%
Assay		96.0%-104.0%	99.3%	99.0%	99.0%	99.1%	99.2%	99.4%	99.3%	99.4%
Microbial limit		Total amount of Bacteria ≤1000/g Total amount of mold and yeast ≤100/g E.coli, acariens and its egg None	Comply	Comply	Comply	Comply	Comply	Comply	Comply	Comply

Conclusion:

The real time study is for 36 month, and up to now it has been tested for 36 month. The quality indicator without obvious change within 36month（Temperature 30℃±2℃, relative humidity is 70 %±5%）. So the quality standard is stable within the expiry date.

Prepared by: Liu Licun Date: 2010/08/18

Approved by: Feng Xiangli Date:2010/08/18