SAYANA PRESS
Suspensión Inyectable 104 mg/0,65 mL

Estudio de Estabilidad del Producto Terminado

El presente archivo contiene la siguiente información:

- Formula declaration
- 3.2.S.7.1 Stability Summary and Conclusions
- 3.2.S.7.3 Stability - Stability Data
- 3.2.P.7 Container closure system
- 3.2.P.2.6 Compatibility
- 3.2.P.8.1 Stability Summary and Conclusion
- 3.2.P.8.2 Post approval stability commitment
- 3.2.P.8.3 Stability Data

[Logotipo Pfizer]

Pfizer Manufacturing Belgium NV
Rijksweg 12
2870 Puurs
tel +32 3 890 92 11
fax +32 3 889 65 32

FÓRMULA CUALITATIVA Y CUANTITATIVA
SAYANA PRESS 104 MG/0,65 ML EN UN SISTEMA DE INYECCIÓN PRECARGADO

Declaro que la información presentada en la tabla que figura a continuación indica la fórmula para Sayana Press (Acetato de medroxiprogesterona) 104 MG/0,65 ML en un sistema de inyección precargado, fabricada por Pfizer Manufacturing Belgium NV, Rijksweg 12, 2870 Puurs, Bélgica. Esta fórmula se relaciona con los siguientes lotes presentados para los estudios de estabilidad: Z03940, Z03941 y Z03942.

Principio Activo	**Cantidad (Porcentaje p/v)**	**Cantidad por Unidad de Dosis**	**Referencias[1]**
Acetato de Medroxiprogesterona			Farm. Eur.
Otros ingredientes			
Parahidroxibenzoato de metilo			Farm. Eur./NF
Parahidroxibenzoato de propilo			Farm. Eur./NF
Cloruro de sodio			Farm. Eur./USP
Macrogol 3350			Farm. Eur./NF
Polisorbato 80			Farm. Eur./NF
Fosfato de sodio monobásico 1 H_2O			USP
Fosfato Disódico Dodecahidrato			Farm. Eur./USP
Metionina			Farm. Eur./USP
Povidona, K17 PF			Farm. Eur./USP
Hidróxido de sodio (ajuste de pH)			Farm. Eur./NF
Ácido clorhídrico (ajuste de pH)			Farm. Eur./NF
Agua para inyección			Farm. Eur./USP

[1] Farm. Eur.: edición actual de la Farmacopea Europea; USP: edición vigente de la Farmacopea de los Estados Unidos; NF: Formulario Nacional

[2] c.s.p.: cantidad suficiente

2017/03/24

[Firma Ilegible]
Isabel Uyttendaele
Miembro de la Red de Cumplimiento del Centro
Pfizer Manufacturing Belgium NV

[Traducción del inglés – Original disponible a pedido]

Pfizer Manufacturing Belgium NV
Rijksweg 12
2870 Puurs
tel +32 3 890 92 11
fax +32 3 889 65 32

QUALITATIVE – QUANTITATIVE FORMULA
SAYANA PRESS 104 MG/0.65 ML IN A PRE-FILLED INJECTION SYSTEM

I declare that the information presented in the table below indicates the formula for Sayana Press (Medroxyprogesterone acetate) 104 MG/0.65 ML in a pre-filled injection system, manufactured by Pfizer Manufacturing Belgium NV, Rijksweg 12, 2870 Puurs, Belgium. This formula is related to the following lots submitted for stability studies: Z03940, Z03941 and Z03942.

Active Ingredient	**Quantity (Percentage w/v)**	**Quantity per Unit Dose**	**References [1]**
Medroxyprogesterone Acetate			Ph.Eur.
Other Ingredients			
Methyl Parahydroxybenzoate			Ph.Eur./NF
Propyl Parahydroxybenzoate			Ph.Eur./NF
Sodium Chloride			Ph.Eur./USP
Macrogol 3350			Ph.Eur./NF
Polysorbate 80			Ph.Eur./NF
Monobasic Sodium Phosphate. 1 H_2O			USP
Disodium Phosphate Dodecahydrate			Ph.Eur./USP
Methionine			Ph.Eur./USP
Povidone, K17 PF			Ph.Eur./USP
Sodium Hydroxide (pH adjustment)			Ph.Eur./NF
Hydrochloric Acid (pH adjustement)			Ph.Eur./NF
Water for Injections			Ph.Eur./USP

[1] Ph. Eur.: current edition of European Pharmacopoeia – USP: Current edition of United States Pharmacopeia – NF: National Formulary

[2] q.s. – quantity, sufficient

March 24, 2017

Isabel Uyttendaele
Site Compliance Network Member
Pfizer Manufacturing Belgium NV

3.2.S.7. ESTABILIDAD

Esta sección del informe presenta información sobre la estabilidad en las siguientes vías del proceso del principio activo acetato de medroxiprogesterona:

Acetato de Medroxiprogesterona - AC Estéril Micronizado: Proceso A en Kalamazoo

Acetato de Medroxiprogesterona - AC Estéril Micronizado: Proceso B en Kalamazoo

3.2.S.7.1. Resumen de Estabilidad y Conclusiones

General

El principio activo acetato medroxiprogesterona se fabrica desde hace varios años en Pharmacia & Upjohn, 7000 Portage Road, Kalamazoo, MI 49000, EE. UU., y se esteriliza en Sterigenics, 7775 Quincy Road, Willowbrook, IL 60521, EE. UU. Este principio activo está reconocido como una sustancia bien conocida descrita en todas las farmacopeas importantes.

Las muestras de estabilidad se almacenan en una bolsa permeable a los gases con un tapón de polipropileno dentro de dos bolsas Tyvek®. Se dispone de datos de hasta 60 meses para las muestras almacenadas a 25 °C/60% de humedad relativa. Las muestras de estabilidad se almacenan en un entorno controlado termostáticamente en el cual las condiciones pueden variar entre estaciones dentro del rango de la temperatura ambiente controlada como lo define la Farmacopea de los Estados Unidos (USP), es decir, la temperatura media es de 20 °C a 25 °C, con desviaciones entre los 15 °C y 30 °C. Los datos de estabilidad siguen respaldando un periodo de reanálisis de 24 meses para acetato de medroxiprogesterona estéril envasado en una bolsa permeable a los gases con un tapón de polipropileno dentro de 2 bolsas Tyvek® cuando se almacena a 25 °C/60% de humedad relativa.

Información del Lote del Proceso A en Kalamazoo

Los detalles de los lotes utilizados en los estudios de estabilidad primaria se enumeran en la Tabla 3.2.S.7.1-1. Se incluyen en la presentación 7 lotes de acetato de medroxiprogesterona-AC estéril micronizado. Los lotes de estabilidad se fabricaron, se almacenaron y analizaron en el centro Kalamazoo.

Tabla 3.2.S.7.1-1. Detalles de los Lotes del Principio Activo empleado en los Estudios de Estabilidad Primaria

Número de Lote	Condición de Almacenamiento	Propósito del Estudio	Datos Disponibles
08KPY	25 °C/60% HR/40 °C/75% HR	Lote Comercial 2004	60 meses
15KYT	25 °C/60% HR/40 °C/75% HR	Lote Comercial 2004	60 meses
16KPY	25 °C/60% HR/40 °C/75% HR	Lote Comercial 2004	60 meses
MPBAMS06004	25 °C/60% HR	Lote Anual 2006 [a]	60 meses
MPBAMS09001	25 °C/60% HR	Lote Anual 2009 [a]	60 meses
MPBAMS010001-2	25 °C/60% HR	Lote Anual 2010 [a]	48 meses
MPBAMS11002K	25 °C/60% HR	Lote Anual 2011 [a]	24 meses

[(1)] Estos lotes son parte de los controles de estabilidad de rutina de acuerdo con las buenas prácticas de fabricación para los cuales se coloca un lote al año en estabilidad.

Descripción del Envase Cierre para el Principio Activo del Proceso A

Las muestras de estabilidad del principio activo se empaquetan en una bolsa permeable a los gases con un tapón de polipropileno dentro de 2 bolsas Tyvek®. La bolsa permeable a los gases es de aproximadamente 19" x 13", con un accesorio de polietileno de 89 mm en una esquina de la bolsa. La bolsa está compuesta por dos materiales diferentes. El lado de la bolsa que tiene el accesorio es una estructura laminada de poliéster metalizado con una superficie de contacto con el producto de polietileno. La parte exterior de la bolsa es una hoja Tyvek® no recubierta. Las 2 bolsas externas idénticas Tyvek® (Grado 1422) se utilizan para proteger la esterilidad de la bolsa permeable a los gases. El sistema de envase cierre para estudios de estabilidad es el mismo sistema de envase cierre para el medicamento a granel.

Condiciones de Almacenamiento y Frecuencia de los Análisis para el Principio Activo del Proceso A

Los parámetros de prueba, los métodos de ensayo y las especificaciones para los lotes estudiados bajo las condiciones de la ICH se detallan a continuación en la Tabla 3.2.S.7.1-2.

Tabla 3.2.S.7.1-2. Parámetros, Métodos de Prueba y Especificaciones Utilizados en los Estudios de Estabilidad bajo Condiciones de la ICH de Acetato de Medroxiprogesterona - AC Estéril Micronizado

Identificador de Prueba	Método de Prueba	Criterios de Aceptación
Descripción		
Aspecto	Inspección visual	Polvo cristalino blanco a blancuzco
Impurezas		
Sustancias Relacionadas[1]	Farm. Eur. Actual	Farm. Eur.
Impureza F[2]	Farm. Eur. Actual	Farm. Eur.
17a-α- CH_3D-homólogo	TA5102	≤0,2%
Potencia		
Ensayo (base seca)	TA5114	97,0%-103,0%
Otro		
Pérdida por Secado	Farm. Eur. Actual	Farm. Eur.

[1]Los lotes anuales muestran los resultados de la prueba individual para todas las sustancias relacionadas con la Ph. Eur.
[2]Prueba retirada del protocolo de estabilidad en el 2008 ya que este es un proceso relacionado con la impureza (no es un producto de degradación).

Se analizaron los primeros tres lotes configurados bajo las condiciones de la ICH de 25 ºC ± 2 ºC/60% ± 5% HR en los siguientes plazos: Inicial, 3 meses, 6 meses, 9 meses, 12 meses, 18 meses, 24 meses, 36 meses, 48 meses y 60 meses. Estos lotes también se analizaron en condiciones aceleradas de 40 ºC ± 2 ºC y 75% ± 5% de humedad relativa al inicio, a los 3 meses y a los 6 meses.

El Lote MPBAMS06004 se analizó de conformidad con el mismo protocolo que los tres primeros lotes. Por lo tanto, se informan los intervalos de análisis a los 6 meses y a los 18 meses. Sin embargo, la frecuencia de los análisis establecida en el protocolo se modificó en el año 2007 y todos los lotes posteriores estudiados bajo condiciones ICH de 25 ºC ± 2 ºC/60% ± 5% de humedad relativa se analizarán anualmente hasta el periodo de reanálisis.

Resultados de la Especificación para el Principio Activo del Proceso A

Todos los parámetros evaluados durante los estudios de estabilidad bajo las condiciones de la ICH se mantuvieron prácticamente sin cambios. No se observaron tendencias que mostraran una disminución de los valores de ensayo o un aumento de las impurezas (tanto en valores individuales como totales). El aspecto y los valores de pérdida por secado también se mantuvieron inalterados en el tiempo.

Dos resultados para las Sustancias Relacionadas no cumplieron con la especificación para el lote 08KPY y tres resultados para las Sustancias Relacionadas no cumplieron con la especificación para el lote 16KPY. La Farmacopea Europea ajustó los límites para las sustancias relacionadas en enero de 2006, de no más de 1,5% a no más de 1,0%. El límite se restableció en enero de 2008 según los criterios de aceptación anteriores de no más de 1,5%. Los resultados que no cumplían con la especificación se obtuvieron durante el periodo en el cual los criterios de aceptación para las sustancias relacionadas se ajustaron a no más de 1,0%. Los datos disponibles después de restablecer los límites de no más de 1,5% cumplieron con las especificaciones. No hubo problemas para estos lotes analizados durante 6 meses en condiciones aceleradas. Los resultados anuales de estabilidad del lote posteriores cumplen con los criterios de aceptación para todos los lotes en todos los plazos sin tendencias aparentes observadas.

Procedimientos Analíticos para el Principio Activo del Proceso A

En la actualidad, el centro de fabricación Kalamazoo analiza el acetato de medroxiprogesterona utilizando métodos descritos en la versión actual de la monografía de la Farmacopea Europea para el acetato de medroxiprogesterona para todas las pruebas, a excepción de las pruebas para el ensayo y 17a-α-CH_3D-homólogo.

Los métodos analíticos utilizados en el programa de estabilidad para el ensayo y la evaluación de impurezas (17a-α- CH_3D-homólogo) se describen en la Sección 3.2.S.4.2 Procedimientos Analíticos y completamente validados como se presentan en la Sección 3.2.S.4.3 Validación de los Procedimientos Analíticos.

Conclusiones sobre el Periodo de Reanálisis, Almacenamiento y Etiquetado para el Principio Activo del Proceso A

Los datos de estabilidad respaldan la conclusión de que Acetato de Medroxiprogesterona AC Micronizado y Estéril es estable con respecto a la descripción, la potencia, las impurezas y la degradación en el plazo del periodo de reanálisis de 24 meses cuando se almacena a temperatura ambiente controlada, se empaqueta en una bolsa permeable al gas con una tapa de polipropileno (PP) dentro de 2 bolsas Tyvek®.

No se requiere una instrucción de almacenamiento “protegido de la luz” para el principio activo debido a las capas de empaque utilizadas. El Acetato de Medroxiprogesterona estéril se almacena en un empaque primario que es una bolsa estratificada compuesta por una lámina de poliéster/aluminio/PE con tapas de PP. Esta bolsa primaria cuenta con un sellado

externo con dos capas adicionales de poliéster. El empaque secundario adicional es una caja de cartón o un cubo de plástico con tapa.

Estabilidad del Principio Activo del Proceso B en Kalamazoo

Las muestras de estabilidad se almacenan en el mismo envase cierre que las muestras de estabilidad del Proceso A en Kalamazoo. Están disponibles los datos de 12 meses para las muestras almacenadas a 25 °C/60% HR.

Información del Lote del Proceso B en Kalamazoo

Los detalles de los lotes utilizados en los estudios de estabilidad se enumeran en la Tabla 3.2.S.7.1-3. Se incluyen en la presentación tres lotes de Acetato de Medroxiprogesterona-AC micronizado estéril. Los lotes de estabilidad se fabricaron, se almacenaron y analizaron en el centro Kalamazoo.

Tabla 3.2.S.7.1-3. Detalles de los Lotes del Principio Activo Acetato de Medroxiprogesterona Micronizado Estéril de la USP

Número de Lote del Principio Activo	MPAAMS10001K	MPAAMS10002K	MPAAMS10003K
Tamaño del lote (kg)	171,0	194,0	166,5
Escala de Producción	Industrial	Industrial	Industrial
Fecha de Fabricación	2010-11-01	2010-11-01	2010-11-01
Inicio del estudio de estabilidad	2011-07-20	2011-07-20	2011-07-20
Condiciones de almacenamiento (temperatura/humedad)	25 °C/60% de HR	25 °C/60% de HR	25 °C/60% de HR

Descripción del Envase Cierre para el Principio Activo del Proceso B en Kalamazoo

El sistema de envase cierre para los estudios de estabilidad es el mismo sistema de envase cierre para el medicamento comercial a granel que se utiliza para Acetato de Medroxiprogesterona micronizado estéril, producido mediante el Proceso A de fabricación. Es decir, empaqueto en una bolsa permeable al gas con una tapa de polipropileno dentro de 2 bolsas Tyvek®.

Condiciones de Almacenamiento y Frecuencia de Análisis para el Principio Activo del Proceso B en Kalamazoo

Los parámetros de prueba, los métodos de prueba y las especificaciones para los lotes estudiados bajo las condiciones de la ICH se detallan a continuación en la Tabla 3.2.S.7.1-2.

El protocolo de estabilidad para los tres primeros lotes comerciales establece un análisis a los 0, 3, 6, 9, 12 y 18 meses; luego, anualmente durante todo el periodo de reanálisis. Los lotes de producción anual continuarán seleccionándose a un índice de uno lote por año (suponiendo una producción adecuada) y se evaluarán en el tiempo cero y anualmente durante todo el periodo de reanálisis.

Resultados de Especificación para el Principio Activo del Proceso B en Kalamazoo

Todos los resultados cumplen con los criterios de aceptación indicados en la Tabla 3.2.S.7.1-2 anterior para los tres lotes.

Procedimientos Analíticos para el Principio Activo del Proceso B en Kalamazoo

Iguales que los procedimientos analíticos utilizados para Acetato de Medroxiprogesterona micronizado estéril producido mediante el Proceso A de fabricación.

Conclusiones para el Periodo de Reanálisis, Almacenamiento y Etiquetado para el Principio Activo del Proceso B en Kalamazoo

Los datos de estabilidad para Acetato de Medroxiprogesterona micronizado estéril respaldan el intervalo de reevaluación actual de 24 meses cuando se almacena a condiciones de temperatura ambiente controlada, igual que el intervalo de reanálisis para Acetato de Medroxiprogesterona micronizado estéril producido con el Proceso A de fabricación.

3.2.S.7.3. STABILITY DATA

Stability Data – Kalamazoo Process A Drug Substance

Data from stability studies for Medroxyprogesterone Acetate – AC Sterile Micronized lots 08KPY, 15KYT and 16KPY stored under ICH conditions of 25°C/60% RH and 40°C/75% RH are provided in Table 3.2.S.7.3-1 throughTable 3.2.S.7.3-6. Data from stability studies for Medroxyprogesterone Acetate – AC Sterile Micronized lots MPBAMS06004, MPBAMS09001 and MPBAMS10001-2 stored under ICH conditions of 25°C/60% RH are provided in Tables Table 3.2.S.7.3-7 through Table 3.2.S.7.3-10.

Stability Data – Kalamazoo Process B Drug Substance

Data from stability studies for Medroxyprogesterone Acetate – AC Sterile Micronized lots MPAAMS10001K, MPAAMS10002K & MPAAMS10003K stored under ICH condition of 25°C/60% RH are provided in Table 3.2.S.7.3-11 through Table 3.2.S.7.3-13.

The following tests are performed:

- Appearance
- Assay
- Impurities determination
- Loss on drying
- Imp F (test removed from the stability protocol in 2008)

3.2.S.7.3.1. Analytical Procedures

The analytical methods used in the stability program are the same as those described in Section 3.2.S.4.2 Analytical Procedures and validated as described in Section 3.2.S.4.3 Validation of Analytical Procedures of the registration dossier.

Table 3.2.S.7.3-1. Stability Data for Medroxyprogesterone Acetate, Ph Eur - AC Sterile Micronized Process A Batch 08KPY (25°C/60%RH)

Package Description: TYVEK OUTER BAG / TYVEK OUTER BAG
GAS PERMEABLE BAG / CAP LINLSS PP WHT

Start Date: 06 May 2004

Test	Specifications	Method	Time 0	3 months	6 months	9 months	12 months	18 months	24 months	36 months	48 months	60 months
Appearance	White to off white crystalline powder	Visual inspection	Meets test	Meets test	Meets test	Meets test	Meets test	Meets test	Meets test	Meets test	Meets test	Meets test
Assay (dried basis)	97.0-103.0%	TA5114	100.1% 99.3%	98.8% 99.2%	98.8% 98.7%	99.5% 99.2%	98.9% 98.8%	99.7% 99.1%	99.1% 99.6%	99.2% 99.0%	99.1% 99.1%	100.1% 100.1%
Impurity F	Current Ph Eur	Ph Eur	Meets test	Meets test	Meets test	Meets test	Meets test	Meets test	Meets test	NT	NT	NT
Related Substances	Current Ph Eur	Ph Eur	Meets test	Meets test	Meets test	Meets test	Meets test	Meets test	Does not meet test [a]	Does not meet test [a]	Meets test	Meets test
17a-α- CH_3 D-homolog	NMT 0.2%	TA5102	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%
Loss on Drying	Current Ph Eur	Ph Eur	< 0.1%	0.1%	< 0.1%	0.1%	< 0.1%	0.1%	0.1%	< 0.1%	< 0.1%	< 0.1%

NT – Testing discontinued as process related impurity (not a degradation product)

[a] The EP monograph specification for Related Substances was changed in January 2006 from Not More Than 1.5% to Not More Than 1.0% . The Does Not Meet Test results were obtained in 2006 and 2007, during the time that the limit was tightened in the EP monograph. The specification was revised in January 2008 to Not More Than 1.5%. The results at the 48 month interval met specification.

Table 3.2.S.7.3-2. Stability Data for Medroxyprogesterone Acetate, Ph Eur - AC Sterile Micronized Process A Batch 08KPY (40°C/75%RH)

Package Description:	TYVEK OUTER BAG / TYVEK OUTER BAG GAS PERMEABLE BAG / CAP LINLSS PP WHT				
Start Date:	06 May 2004				
Test	**Specifications**	**Method**	**Time 0**	**3 months**	**6 months**
Appearance	White to off white crystalline powder	Visual inspection	Meets test	Meets test	Meets Test
Assay (dried basis)	97.0 – 103.0%	TA5114	100.1% 99.3%	99.6% 99.5%	98.5% 98.6%
Impurity F	Current Ph Eur	Ph Eur	Meets test	Meets test	Meets test
Related Substances	Current Ph Eur	Ph Eur	Meets test	Meets test	Meets test
17a-α- CH_3 D-homolog	NMT 0.2%	TA5102	< 0.1%	LT 0.1%	LT 0.1%
Loss on Drying	Current Ph Eur	Ph Eur	LT 0.1%	0.1%	0.1%

Table 3.2.S.7.3-3. Stability Data for Medroxyprogesterone Acetate, Ph Eur - AC Sterile Micronized Process A Batch 15KYT (25°C/60%RH)

Package Description: TYVEK OUTER BAG / TYVEK OUTER BAG
GAS PERMEABLE BAG / CAP LINLSS PP WHT

Start Date: 26 Oct 2004

Test	Specifications	Method	Time 0	3 months	6 months	9 months	12 months	18 months	24 months	36 months	48 months	60 months
Appearance	White to off white crystalline powder	Visual inspection	Meets test	Meets test	Meets test	Meets test	Meets test	Meets test	Meets test	Meets test	Meets test	Meets test
Assay (dried basis)	97.0-103.0%	TA5114	98.8% 98.9%	99.1% 99.8%	98.8% 98.9%	99.0% 99.1%	99.1% 99.4%	99.5% 100.1%	99.4% 99.2%	99.2% 99.1%	99.5% 98.9%	99.7% 99.7%
Impurity F	Current Ph Eur	Ph Eur	Meets test	Meets test	Meets test	Meets test	Meets test	Meets test	Meets test	NT	NT	NT
Related Substances	Current Ph Eur	Ph Eur	Meets test	Meets test	Meets test	Meets test	Meets test	Meets test	Meets test	Meets test	Meets test	Meets test
17a-α- CH_3 D-homolog	NMT 0.2%	TA5102	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	< 0.1%
Loss on Drying	Current Ph Eur	Ph Eur	< 0.1%	0.1%	0.1%	0.1%	0.2%	0.1%	0.2%	< 0.1%	< 0.1%	0.1%

NT – Testing discontinued as process related impurity (not a degradation product)

Table 3.2.S.7.3-4. Stability Data for Medroxyprogesterone Acetate, Ph Eur - AC Sterile Micronized Process A Batch 15KYT (40°C/75%RH)

Package Description:	TYVEK OUTER BAG / TYVEK OUTER BAG GAS PERMEABLE BAG / CAP LINLSS PP WHT				
Start Date:	26 Oct 2004				
Test	**Specifications**	**Method**	**Time 0**	**3 months**	**6 months**
Appearance	White to off white crystalline powder	Visual inspection	Meets test	Meets test	Meets test
Assay (dried basis)	97.0-103.0%	TA5114.	98.8% 98.9%	99.5% 98.6%	98.8% 98.6%
Impurity F	Current Ph Eur	Ph Eur	Meets test	Meets test	Meets test
Related Substances	Current Ph Eur	Ph Eur	Meets test	Meets test	Meets test
17a-α- CH_3 D-homolog	NMT 0.2%	TA5102	0.1%	0.1%	0.1%
Loss on Drying	Current Ph Eur	Ph Eur	< 0.1%	0.1%	0.2%

Table 3.2.S.7.3-5. Stability Data for Medroxyprogesterone Acetate, Ph Eur - AC Sterile Micronized Process A Batch 16KPY (25°C/60%RH)

Package Description: TYVEK OUTER BAG / TYVEK OUTER BAG
GAS PERMEABLE BAG / CAP LINLSS PP WHT

Start Date: 26 Oct 2004

Test	Specifications	Method	Time 0	3 months	6 months	9 months	12 months	18 months	24 months	36 months	48 months	60 months
Appearance	White to off white crystalline powder	Visual inspection	Meets test	Meets test	Meets test	Meets test	Meets test	Meets test	Meets test	Meets test	Meets test	Meets test
Assay (dried basis)	97.0-103.0%	TA5114	99.1% 99.3%	98.8% 99.1%	98.9% 98.8%	99.9% 99.6%	98.9% 98.9%	99.5% 100.4%	99.5% 99.9%	98.8% 99.3%	99.5% 99.3%	99.1% 99.3%
Impurity F	Current Ph Eur	Ph Eur	Meets test	Meets test	Meets test	Meets test	Meets test	Meets test	Meets test	NT	NT	NT
Related Substances	Current Ph Eur	Ph Eur	Meets test	Meets test	Meets test	Meets test	Meets test	Does not meet test [a]	Does not meet test [a]	Does not meet test [a]	Meets test	Meets test
17a-α- CH_3 D-homolog	NMT 0.2%	TA5102	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%
Loss on Drying	Current Ph Eur	Ph Eur	< 0.1%	0.1%	< 0.1%	0.1%	0.1%	0.2%	0.1%	0.2%	< 0.1%	< 0.1%

NT – Testing discontinued as process related impurity (not a degradation product)

[a] The EP monograph specification for Related Substances was changed in January 2006 from Not More Than 1.5% to Not More Than 1.0% . The Does Not Meet Test results were obtained in 2006 and 2007, during the time that the limit was tightened in the EP monograph. The specification was revised in January 2008 to Not More Than 1.5%. The results at the 48 month interval met specification.

Table 3.2.S.7.3-6. Stability Data for Medroxyprogesterone Acetate, Ph Eur - AC Sterile Micronized Process A Batch 16KPY (40°C/75%RH)

Package Description:	TYVEK OUTER BAG / TYVEK OUTER BAG GAS PERMEABLE BAG / CAP LINLSS PP WHT				
Start Date:	26 Oct 2004				
Test	**Specifications**	**Method**	**Time 0**	**3 months**	**6 months**
Appearance	White to off white crystalline powder	Visual inspection	Meets test	Meets test	Meets test
Assay (dried basis)	97.0-103.0%	TA5114	99.1% 99.3%	99.1% 99.3%	98.8% 98.9%
Impurity F	Current Ph Eur	Ph Eur	Meets test	Meets test	Meets test
Related Substances	Current Ph. Eur.	Ph. Eur.	Meets test	Meets test	Meets test
17a-α- CH_3 D-homolog	NMT 0.2%	TA5102	< 0.1%	< 0.1%	< 0.1%
Loss on Drying	Current Ph Eur	Ph Eur	< 0.1%	< 0.1%	< 0.1%

Table 3.2.S.7.3-7. Stability Data for Medroxyprogesterone Acetate, Ph Eur - AC Sterile Micronized Process A Batch MPBAMS06004 (25°C/60%RH)

Package Description: TYVEK OUTER BAG / TYVEK OUTER BAG
GAS PERMEABLE BAG / CAP LINLSS PP WHT

Start Date: 06 September 2006

Test	Specifications	Method	Time 0	6 months	12 months	18 months	24 months	36 months	48 months	60 months
Appearance	White to off white crystalline powder	Visual inspection	Meets test	Meets test	Meets test	Meets test	Meets test	Meets test	Meets test	Meets test
Assay (dried basis)	97.0-103.0%	TA5114	99.8% 99.6%	99.1% 98.7%	99.6% 100.1%	98.7% 99.8%	99.7% 99.0%	98.9% 99.1%	99.1% 99.4%	99.6% 99.4%
Impurity F	Current Ph Eur	Ph Eur	Meets test	Meets test	Meets test	Meets test	NT	NT	NT	NT
Related Substances	Current Ph Eur	Ph Eur	Meets test	Meets test	Meets test	Meets test	Meets test	Meets test	Meets test	Meets test
Related Substance A	Current Ph Eur	Ph Eur	NR	NR	NR	NR	NR	NR	< 0.1%	< 0.1%
Related Substance B	Current Ph Eur	Ph Eur	NR	NR	NR	NR	NR	NR	0.1%	0.1%
Related Substance C	Current Ph Eur	Ph Eur	NR	NR	NR	NR	NR	NR	LT 0.1%	< 0.1%
Related Substance D	Current Ph Eur	Ph Eur	NR	NR	NR	NR	NR	NR	0.3%	0.3%
Related Substance E	Current Ph Eur	Ph Eur	NR	NR	NR	NR	NR	NR	< 0.1%	< 0.1%
Related Substance G	Current Ph Eur	Ph Eur	NR	NR	NR	NR	NR	NR	< 0.1%	< 0.1%
Related Substance I	Current Ph Eur	Ph Eur	NR	NR	NR	NR	NR	NR	< 0.1%	0.1%
Any unspecified impurity	Current Ph Eur	Ph Eur	NR	NR	NR	NR	NR	NR	< 0.1%	< 0.05%
Total Impurities	Current Ph Eur	Ph Eur	NR	NR	NR	NR	NR	NR	0.5%	0.5%
Loss on Drying	Current Ph Eur	Ph Eur	0.6%	0.2%	< 0.1%	0.2%	< 0.1%	< 0.1%	< 0.1%	< 0.1%

NR = Individual results not reported until 2009
NT = Testing discontinued as process related impurity (not a degradation product)

Table 3.2.S.7.3-8. Stability Data for Medroxyprogesterone Acetate, Ph Eur - AC Sterile Micronized Process A Batch MPBAMS09001 (25°C/60%RH)

Package Description:	TYVEK OUTER BAG / TYVEK OUTER BAG GAS PERMEABLE BAG / CAP LINLSS PP WHT							
Manufacture Date:	31 March 2009							
Start Date:	18 August 2009							
Test	**Specifications**	**Method**	**Time 0**	**12 months**	**24 months**	**36months**	**48 months**	**60 months**
Appearance	White to off white crystalline powder	Visual inspection	Meets test	Meets test	Meets test	Meets test	Meets test	Meets test
Assay (dried basis)	97.0-103.0%	TA5114	99.0% 98.7%	98.8% 99.1%	100.2%	99.9%	100.8%	99.8%
Impurity F	Current Ph Eur	Ph Eur	NT	NT	NT	NT	NT	NT
Related Substances								
- Related Substance A	Current Ph Eur	Ph Eur	NR	< 0.1%	< 0.1%	< 0.1%	< 0.1%	0.1%
- Related Substance B	Current Ph Eur	Ph Eur	NR	0.1%	0.1%	0.1%	0.2% 0.2% 0.1% 0.2%	0.1%
- Related Substance C	Current Ph Eur	Ph Eur	NR	< 0.1%	< 0.1%	< 0.1%	< 0.1% < 0.1% < 0.1% < 0.1%	< 0.1%
- Related Substance D	Current Ph Eur	Ph Eur	NR	0.4%	0.4%	0.4%	0.4% 0.4% 0.4% 0.4%	0.4%
- Related Substance E	Current Ph Eur	Ph Eur	NR	< 0.1%	< 0.1%	< 0.1%	< 0.1% < 0.1% < 0.1% < 0.1%	< 0.1%
- Related Substance G	Current Ph Eur	Ph Eur	NR	< 0.1%	< 0.1%	< 0.1%	< 0.1% < 0.1% < 0.1% < 0.1%	< 0.1%

Package Description:	TYVEK OUTER BAG / TYVEK OUTER BAG GAS PERMEABLE BAG / CAP LINLSS PP WHT							
Manufacture Date:	31 March 2009							
Start Date:	18 August 2009							
Test	**Specifications**	**Method**	**Time 0**	**12 months**	**24 months**	**36months**	**48 months**	**60 months**
- Related Substance I	Current Ph Eur	Ph Eur	NR	0.1%	0.1%	0.1%	0.1% 0.1% 0.1% 0.1%	0.1%
Any unspecified impurity	Current Ph Eur	Ph Eur	NR	< 0.05%	< 0.05%	< 0.05%	< 0.0.5% < 0.05% < 0.05% < 0.05%	< 0.05%
Total Impurities	Current Ph Eur	Ph Eur	NR	0.7%	0.7%	0.7%	0.7% 0.7% 0.7% 0.7%	0.7%
Loss on Drying	Current Ph Eur	Ph Eur	0.2%	0.1%	0.1%	0.2%	0.2%	0.1%

NR = Individual results not reported until 2009
NT = Testing discontinued as process related impurity (not a degradation product)

Table 3.2.S.7.3-9. Stability Data for Medroxyprogesterone Acetate, Ph Eur - AC Sterile Micronized Process A Batch MPBAMS10001-2 (25°C/60%RH)

Package Description:	TYVEK OUTER BAG / TYVEK OUTER BAG GAS PERMEABLE BAG / CAP LINLSS PP WHT						
Manufacture Date:	16 February 2010						
Start Date:	21 May 2010						
Test	**Specifications**	**Method**	**Time 0**	**12 months**	**24 months**	**36 months**	**48 months**
Appearance	White to off white crystalline powder	Visual inspection	Meets test	Meets test	Meets test	Meets test	Meets test
Assay (dried basis)	97.0-103.0%	TA5114	101.6% 101.9%	99.4%	101.3%	99.6%	99.3%
Impurity F	Current Ph Eur	Ph Eur	NT	NT	NT	NT	NT
Related Substances							
- Related Substance A	Current Ph Eur	Ph Eur	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%
- Related Substance B	Current Ph Eur	Ph Eur	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%
- Related Substance C	Current Ph Eur	Ph Eur	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%
- Related Substance D	Current Ph Eur	Ph Eur	0.4%	0.4%	0.4%	0.4%	0.4%
- Related Substance E	Current Ph Eur	Ph Eur	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%
- Related Substance G	Current Ph Eur	Ph Eur	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%
- Related Substance I	Current Ph Eur	Ph Eur	0.1%	0.1%	0.1%	0.1%	0.1%
Any unspecified impurity	Current Ph Eur	Ph Eur	< 0.05%	< 0.05%	< 0.05%	< 0.05%	< 0.05%
Total Impurities	Current Ph Eur	Ph Eur	0.6%	0.6%	0.6%	0.6%	0.6%
Loss on Drying	Current Ph Eur	Ph Eur	0.5%	0.1%	0.3%	<0.1%	0.1%

NT = Testing discontinued as process related impurity (not a degradation product)

Table 3.2.S.7.3-10. Stability Data for Medroxyprogesterone Acetate, Ph Eur - AC Sterile Micronized Process A Batch MPBAMS10002K (25°C/60%RH)

Package Description:	TYVEK OUTER BAG / TYVEK OUTER BAG GAS PERMEABLE BAG / CAP LINLSS PP WHT				
Manufacture Date:	24 February 2011				
Start Date:	16 August 2011				
Test	**Specifications**	**Method**	**Time 0**	**12 months**	**24 months**
Appearance	White to off white crystalline powder	Visual inspection	Meets test	Meets test	Meets test
Assay (dried basis)	97.0-103.0%	TA5114	100.0%	100.3%	99.8%
Impurity F	Current Ph Eur	Ph Eur	NT	NT	NT
Related Substances					
- Related Substance A	Current Ph Eur	Ph Eur	< 0.1%	< 0.1%	< 0.1%
- Related Substance B	Current Ph Eur	Ph Eur	0.1%	< 0.1%	< 0.1%
- Related Substance C	Current Ph Eur	Ph Eur	< 0.1%	< 0.1%	< 0.1%
- Related Substance D	Current Ph Eur	Ph Eur	0.4%	0.4%	0.4%
- Related Substance E	Current Ph Eur	Ph Eur	< 0.1%	< 0.1%	< 0.1%
- Related Substance G	Current Ph Eur	Ph Eur	< 0.1%	< 0.1%	< 0.1%
- Related Substance I	Current Ph Eur	Ph Eur	< 0.1%	< 0.1%	< 0.1%
Any unspecified impurity	Current Ph Eur	Ph Eur	< 0.05%	< 0.05%	< 0.05%
Total Impurities	Current Ph Eur	Ph Eur	0.5%	0.5%	0.5%
Loss on Drying	Current Ph Eur	Ph Eur	< 0.1%	0.2%	0.2%

NT = Testing discontinued as process related impurity (not a degradation product)

Table 3.2.S.7.3-11. Stability Data for Medroxyprogesterone Acetate, Ph Eur - AC Sterile Micronized Process B Batch MPAAMS10001K (25°C/60%RH)

Package description:	Gas permeable bag inside Tyvek® bags.										
Manufacture Date:	01 November 2010										
Start Date:	20 July 2011										
Test	**Specifications**	**Method**	**Units**	**Time 0**	**3 Months**	**6 Months**	**9 Months**	**12 Months**	**18 Months**	**24 Months**	**36 Months**
Appearance	White to off white crystalline powder	Visual inspection	--	Meets Test	Meets Test	Meets Test	Meets Test	Meets Test	Meets Test	Meets Test	--
Assay (dried basis)	97.0-103.0%	TA5114	%	98.5	100.5	101.4	101.8	99.6	102.1	99.9	--
Impurities											
- Related Substance A	Current Ph Eur	Ph Eur	%	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	--
- Related Substance B	Current Ph Eur	Ph Eur	%	0.1	0.1	0.1	0.1	0.1	0.1	0.1	--
- Related Substance C	Current Ph Eur	Ph Eur	%	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	--
- Related Substance D	Current Ph Eur	Ph Eur	%	0.3	0.3	0.3	0.3	0.3	0.3	0.3	--
- Related Substance E	Current Ph Eur	Ph Eur	%	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	--
- Related Substance G	Current Ph Eur	Ph Eur	%	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	--
- Related Substance I	Current Ph Eur	Ph Eur	%	0.1	0.1	0.1	0.1	0.1	0.1	0.1	--
Any unspecified impurity	Current Ph Eur	Ph Eur	%	< 0.05	< 0.05	< 0.05	0.05	< 0.05	< 0.05	< 0.05	--
Total Impurities	Current Ph Eur	Ph Eur	%	0.5	0.5	0.5	0.5	0.5	0.5	0.5	--
Loss on Drying	Current Ph Eur	Ph Eur	%	0.2	< 0.1	0.1	0.3	< 0.1	0.2	< 0.1	--

Table 3.2.S.7.3-12. Stability Data for Medroxyprogesterone Acetate, Ph Eur - AC Sterile Micronized Process B Batch MPAAMS10002K (25°C/60%RH)

Package description:	Gas permeable bag inside Tyvek® bags.										
Manufacture Date:	01 November 2010										
Start Date:	20 July 2011										
Test	**Specifications**	**Method**	**Units**	**Time 0**	**3 Months**	**6 Months**	**9 Months**	**12 Months**	**18 Months**	**24 Months**	**36 Months**
Appearance	White to off white crystalline powder	Visual inspection	--	Meets Test	Meets Test	Meets Test	Meets Test	Meets Test	Meets Test	Meets Test	--
Assay (dried basis)	97.0-103.0%	TA5114	%	98.2	100.6	101.0	101.2	98.0	101.9	100.4	--
Impurities											
- Related Substance A	Current Ph Eur	Ph Eur	%	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	--
- Related Substance B	Current Ph Eur	Ph Eur	%	0.1	0.1	0.1	0.1	0.1	0.1	0.1	--
- Related Substance C	Current Ph Eur	Ph Eur	%	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	--
- Related Substance D	Current Ph Eur	Ph Eur	%	0.3	0.3	0.3	0.3	0.3	0.3	0.3	--
- Related Substance E	Current Ph Eur	Ph Eur	%	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	--
- Related Substance G	Current Ph Eur	Ph Eur	%	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	--
- Related Substance I	Current Ph Eur	Ph Eur	%	< 0.1	< 0.1	0.1	0.1	< 0.1	0.1	0.1	--
Any unspecified impurity	Current Ph Eur	Ph Eur	%	< 0.05	< 0.05	< 0.05	<0.05	< 0.05	< 0.05	< 0.05	--
Total Impurities	Current Ph Eur	Ph Eur	%	0.5	0.5	0.5	0.5	0.5	0.5	0.5	--
Loss on Drying	Current Ph Eur	Ph Eur	%	0.1	< 0.1	0.1	0.2	0.1	0.1	< 0.1	--

Table 3.2.S.7.3-13. Stability Data for Medroxyprogesterone Acetate, Ph Eur - AC Sterile Micronized Process B Batch MPAAMS10003K (25°C/60%RH)

Package description:	Gas permeable bag inside Tyvek® bags.									
Manufacture Date:	01 November 2010									
Start Date:	20 July 2011									
Test	**Specifications**	**Method**	**Units**	**Time 0**	**3 Months**	**6 Months**	**9 Months**	**12 Months**	**24 Months**	**36 Months**
Appearance	White to off white crystalline powder	Visual inspection	--	Meets Test	Meets Test	Meets Test	Meets Test	Meets Test	Meets Test	--
Assay (dried basis)	97.0-103.0%	TA5114	%	98.3	100.4	101.1	100.9	97.5	100.0	--
Impurities										
- Related Substance A	Current Ph. Eur.	Ph. Eur.	%	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	--
- Related Substance B	Current Ph. Eur.	Ph. Eur.	%	0.1	0.1	0.1	0.1	0.1	0.1	--
- Related Substance C	Current Ph. Eur.	Ph. Eur.	%	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	--
- Related Substance D	Current Ph. Eur.	Ph. Eur.	%	0.2	0.2	0.2	0.2	0.2	0.2	--
- Related Substance E	Current Ph. Eur.	Ph. Eur.	%	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	--
- Related Substance G	Current Ph. Eur.	Ph. Eur.	%	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	--
- Related Substance I	Current Ph. Eur.	Ph. Eur.	%	< 0.1	0.1	0.1	< 0.1	0.1	0.1	--
Any unspecified impurity	Current Ph. Eur.	Ph. Eur.	%	< 0.05	< 0.05	< 0.05	<0.05	< 0.05	< 0.05	--
Total Impurities	Current Ph. Eur.	Ph. Eur.	%	0.4	0.4	0.4	0.4	0.4	0.4	--
Loss on Drying	Current Ph. Eur.	Ph. Eur.	%	0.1	< 0.1	< 0.1	0.2	0.2	< 0.1	--

3.2.P.7. CONTAINER CLOSURE SYSTEM(S)

3.2.P.7.1. Description(s) of Container Closure System(s)

DMPA-SC-Pre-Filled Injection System

Depot-Medroxyprogesterone Acetate-SC (DMPA-SC) 104 mg/ 0.65 mL is packaged in an all in one, pre-fillable single use drug delivery system (manufactured and sterilized by Becton Dickinson) designed for subcutaneous injections. This delivery system features with a 1 mL multilayered thermoformed plastic film reservoir with linear low-density polyethylene (LLDPE) product contact layer. Each DMPA-SC 104 mg/ 0.65 mL pre-filled single use injection system is packaged in a foil laminate pouch.

Prior to use the injection system is activated by the piercing of the membrane barrier by the double pointed cannula. The dose is then delivered by depressing the unit reservoir. After the dose is expressed, the collapsed reservoir and a one-way valve inhibit refill, preventing reuse.

Table 3.2.P.7-1. Container Closure System Description: Single Use Injection System

Component Description: Injection System	
SIZE	1 mL (reservoir)
COLOR	Natural (clear to translucent)
MATERIALS OF CONSTRUCTION	Reservoir: multilayered thermoformed plastic film with a linear low density polyethylene innermost layer Port: low density polyethylene Needle hub: polystyrene Needle shield: polypropylene Cannula: stainless steel grade 304 (siliconized)
SIZE (NEEDLE)	23-gauge thin walled
DRAWING	Provided for illustrative purposes only

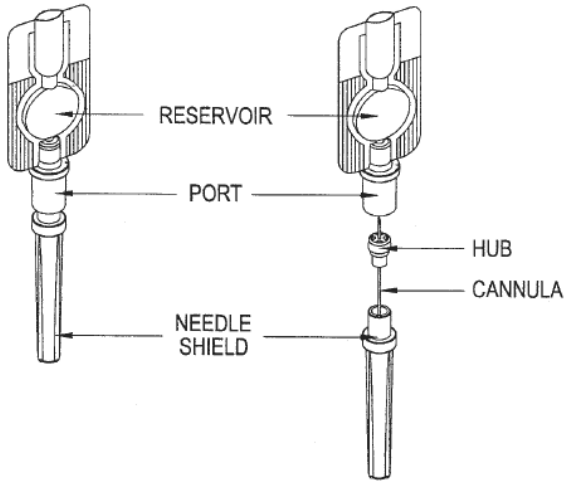
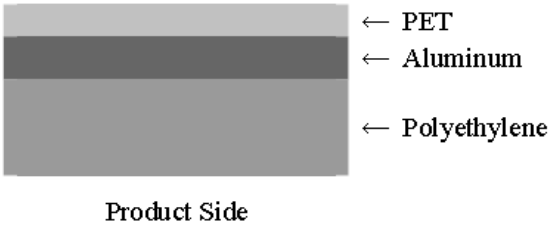


Table 3.2.P.7-2. Critical Secondary Packaging Description: Pouch

Component Description: Foil Pouch	
MATERIALS OF CONSTRUCTION	PET / adhesive / aluminum / PE (product contact side)
COLOR	Silver, printed overall white
DRAWING	Provided for illustrative purposes only



3.2.P.7.2. Specifications

Each packaging component is identified with a unique code number. This number is used to order and track components and corresponds to a descriptive document that provides all relevant information pertaining to the component, such as materials of construction, dimensions, and supplier's drawings.

Each incoming shipment of packaging materials is assigned a unique receiving number and is withheld from use until it has been sampled, tested, and examined for conformance using internal plant standard operating procedures (SOPs) and standard test procedures.

Pre-fillable injection system components are visually inspected. Their physical dimensions and style are verified against supplier drawings or approved packaging specifications.

3.2.P.7.3. Analytical Procedures for Packaging Components

Test methods that comprise the Incoming Testing Specifications and are not described in a compendium are listed in this section. Method summaries are provided below.

Identity Check

Pre-fillable injection system components are visually inspected. Their physical dimensions and style are verified against supplier drawings or approved packaging specifications.

Appearance and Cleanliness

Inspect for the presence of biological foreign material, loose particulate matter or fibers within the fluid path of the device, wrinkles or cuts in the filling channel (compared to limit samples; causing leakage), foreign material on the needle, curved or bent needle or needle shield, and loose needle shield.

Sterility Check

Confirm sterilization of components indicated on Certificate of Compliance received from manufacturer.

Particles per Container

Particulate matter is determined by the supplier and conformance to the criteria is stated on the Certificate of Compliance for each batch.

Acceptance Criteria: max. 5 particles/unit > 25 µm; max. 35 particles/unit > 10µm.

Standard IR Spectra, Representative Certificates of Compliance

Standard IR spectra and certificates of compliance are used during incoming inspection of primary packaging components. The standard IR spectra are used for comparative purposes to identify the material of construction (Figure 3.2.P.7-1). A certificate of compliance (Figure 3.2.P.7-2) is used to ensure each lot of packaging components meets or exceeds specifications.

Figure 3.2.P.7-1. Representative IR Spectrum for Product Contact Surface of Injection System Cavity

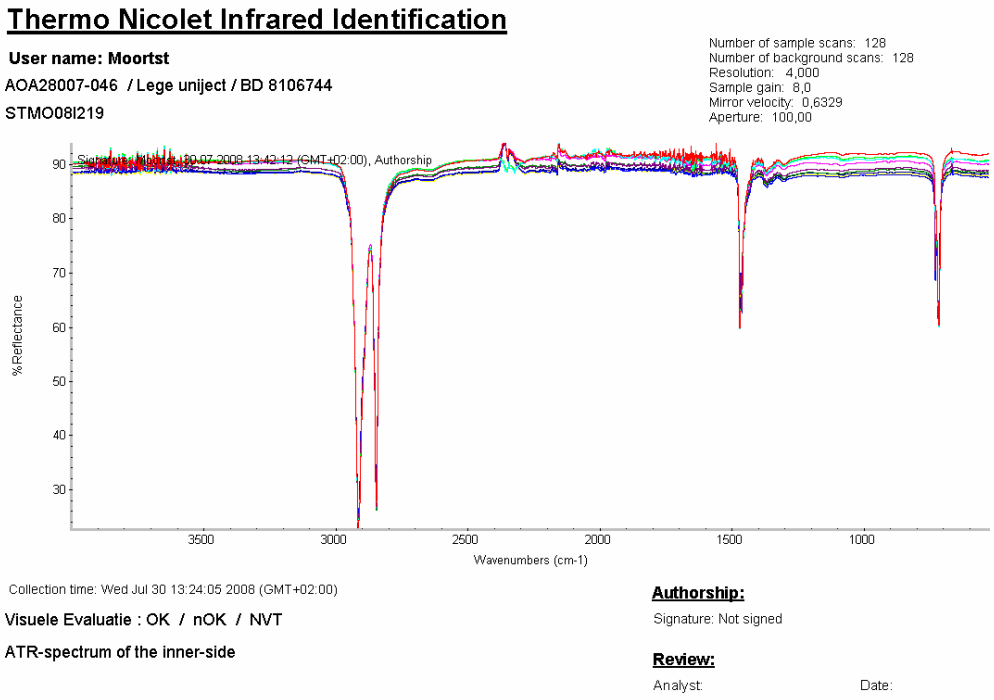


Figure 3.2.P.7-2. Representative Supplier Certificate of Compliance for Pre-Fillable Drug Delivery System

30 Tuas Avenue 2
Singapore 639461
tel: 68610633
fax: 68601592
www.bd.com

BD
Helping all people live healthy lives

CERTIFICATE OF COMPLIANCE

CUSTOMER : **Pfizer Manufacturing Belgium N.V.**

B.D. REF NO. : **8010334934**

This is to certify that the Uniject Injection Device were manufactured in accordance with Becton Dickinson Medical (Singapore) Pte Ltd Customer Specification No. SC47.

PURCHASE ORDER NO.	PRODUCT CATALOG NO. DESCRIPTION	PRODUCT LOT NO.	PRODUCT LOT QTY
4502371210	UNIJECT 1 ML 23G X 3/8IN TW 47290187	2017957	199,266

Quality control steps were carried out accordingly to established quality system at the manufacturing site. All products which are labeled as sterile and released for sale by Becton Dickinson are certified to be sterile as long as the package is unopened and undamaged.
All products which are labeled as non-pyrogenic and released for sale by Becton Dickinson have been originally tested and found to be non-pyrogenic. All materials which are labeled non-toxic and released for sale by Becton Dickinson have passed animal toxicity and/or cytotoxicity tests.

All products meet the foreign matter flush test specification defined as >10µm of 35 particles and >25µm of 5 particles as tested per BD test procedure 80005644.

Date : 09 April 2012

Name : Florence Kuan

Sign : 9 Apr 12

BECTON DICKINSON MEDICAL
(SINGAPORE) PTE LTD
QA Engineer/~~QA Manager~~

Becton Dickinson Medical (S) Pte Ltd

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3.2.P.8. ESTABILIDAD

3.2.P.8.1. RESUMEN DE ESTABILIDAD Y CONCLUSIÓN

Resumen General

Las pruebas de estabilidad para los lotes comerciales de Acetato de Medroxiprogesterona de Depósito-Subcutáneo (DMPA-SC) 104 mg/0,65 mL Suspensión para Inyección empaquetados en un sistema de inyección precargada de un solo uso se han llevado a cabo según las condiciones de la Conferencia Internacional sobre Armonización (ICH, por sus siglas en inglés) de Zona IVb (30 °C ± 2 °C/75% ± 5% de humedad relativa [HR]) y aceleradas (40 °C ± 2 °C/75% ± 5% de HR). Los estudios de estabilidad se han completado con datos a largo plazo disponibles e informados a lo largo de la vida útil (36 meses) y los datos acelerados a lo largo de 6 meses.

En la Tabla 3.2.P.8.1-1 se proporcionan los resúmenes de los lotes del medicamento que se utilizaron para los estudios de estabilidad formales.

Tabla 3.2.P.8.1-1. Resúmenes de Información de Lotes de DMPA-SC 104 mg/0,65 mL Sistema de Inyección precargada, Lotes Comerciales Usados en Estudios de Estabilidad

Número de Lote	Condiciones de Almacenamiento	Periodo de Almacenamiento	Datos Disponibles	Fecha de Fab.	Fecha de Inicio del Estudio	Tamaño del Lote (Unidades)	Lugar de Fab.
Z03940	30 °C/75% de HR	36 meses	36 meses	2012-06	2012-08	102482	Pfizer Manufacturing Belgium, Puurs, Bélgica
	40 °C/75% de HR	6 meses	6 meses				
Z03941	30 °C/75% de HR	36 meses	36 meses	2012-06	2012-09	101795	Pfizer Manufacturing Belgium, Puurs, Bélgica
	40 °C/75% de HR	6 meses	6 meses				
Z03942	30 °C/75% de HR	36 meses	36 meses	2012-06	2012-09	102960	Pfizer Manufacturing Belgium, Puurs, Bélgica
	40 °C/75% de HR	6 meses	6 meses				

HR = humedad relativa.

Sistema de Envase Cierre

El sistema de inyección precargada de un solo uso de DMPA-SC 104 mg/0,65 mL se empaca en una bolsa laminada (empaque secundario).

Características Estudiadas y Especificaciones de Calidad

Las muestras de estabilidad de Acetato de Medroxiprogesterona de Depósito-Subcutáneo (DMPA-SC) 104 mg/0,65 mL Suspensión para Inyección empaquetadas en un sistema de inyección precargada de un solo uso se han probado de acuerdo con las especificaciones de vida útil propuestas que se presentan en la Sección 3.2.P.5.1 Especificaciones.

Evaluación de los Métodos

Los métodos utilizados para el análisis de las muestras de estabilidad son los mismos métodos que aquellos utilizados para el análisis del producto terminado y se describen en la Sección 3.2.P.5.2 Procedimientos Analíticos.

Condiciones de Almacenamiento y Frecuencia de Análisis

Los diseños del protocolo de estabilidad para los estudios de estabilidad, incluidas las condiciones de almacenamiento y los puntos de control, se describen en la Tabla 3.2.P.8.1-2.

Tabla 3.2.P.8.1-2. Protocolo de Estabilidad para los Lotes Z03940, Z03941 y Z03942

Condición de Almacenamiento	Punto de Control (Meses)							
	Inicial	3	6	9	12	18	24	36
30 °C/75% de HR	A	B	B	B	B	B	B	A
40 °C/75% de HR	B	B	B	---	---	---	---	---

Las pruebas programadas aplicadas de acuerdo con los protocolos mencionados incluyen:

A: Descripción, ensayo, productos de degradación, contenido de metionina, distribución del tamaño de partícula y esterilidad.

B: Descripción, ensayo, productos de degradación, contenido de metionina y distribución de tamaño de partícula.

Categorías

DMPA-SC solamente se proporcionará a una concentración comercial, volumen de llenado y tipo de empaque; por lo tanto, un diseño de estabilidad de extremos no fue aplicable para el programa de estabilidad para registro.

Resultados del Análisis

Todos los resultados se encuentran dentro de las especificaciones. Los resultados de estabilidad se muestran en la Sección 3.2.P.8.3 Datos de Estabilidad.

Conclusiones

Todos los datos permanecen dentro de los criterios de aceptación por hasta 36 meses para las muestras almacenadas a 30 °C/75% de HR y por hasta 6 meses para las muestras almacenadas a 40 °C/75% de HR. No se han observado tendencias negativas.

Los datos de estabilidad respaldan una vida útil de 36 meses para la suspensión acuosa estéril de DMPA-SC 104 mg/0,65 mL, empacada en un sistema de inyección precargada de un solo uso y almacenada en una bolsa laminada. Como los resultados (tanto a largo plazo como acelerados) están dentro de los criterios de aceptación sin cambios significativos, no se requieren condiciones especiales de almacenamiento.

Condiciones de Almacenamiento

No se requiere de ninguna condición especial de almacenamiento debido al buen perfil de estabilidad demostrado por el sistema de inyección precargada de DMPA-SC, tanto en condiciones a largo plazo como aceleradas. Sin embargo, la declaración recomendada de condición de almacenamiento se determinará de acuerdo con los lineamientos locales de etiquetado. Ya que este producto es una suspensión acuosa, se recomienda la advertencia de "no refrigerar o congelar".

3.2.P.8.2. PROTOCOLO DE ESTABILIDAD Y COMPROMISO DE ESTABILIDAD POSTERIORES A LA APROBACIÓN

3.2.P.8.2.1. Protocolo de Estabilidad Posterior a la Aprobación y Compromiso

De acuerdo con CPMP/QWP/122/02 “Nota orientadora sobre los análisis de estabilidad: análisis de estabilidad de los principios activos y productos finales relacionados existentes”, no se considera necesario un compromiso de estabilidad posterior a la aprobación. Pfizer continuará monitoreando los lotes colocados en estabilidad bajo la condición de almacenamiento a largo plazo para asegurar que el producto cumpla con las especificaciones registradas hasta el vencimiento.

Stability Test report of

SAYANA PRESS 160 mg/mL 0.65 mL Injection System

ISSUED BY: Britt Deckers	Site Compliance Support Technician, Pfizer Puurs, Belgium	16 / MAR / 2017
VERIFIED BY: Bert CHRISTIAEN	Site Compliance Support Technician, Pfizer Puurs, Belgium	16 / MAR / 2017
Name	Job title	Signature and date

Contents

1. Study information

Study Number	Man Lotnumber	Storage Condition	Storage Period	Container	Closure	Lot Quantity	Start Date	Manufacturing Date	Manufacturing Place
ST12233XF	Z03940	30°C ± 2°C – 75% RH ± 5% RH	36 MONTHS	PLASTIC INJECTION SYSTEM	NA	102482	21/08/2012	05/06/2012	PFIZER BELGIUM
ST12245XF	Z03941	30°C ± 2°C – 75% RH ± 5% RH	36 MONTHS	PLASTIC INJECTION SYSTEM	NA	101795	07/09/2012	08/06/2012	PFIZER BELGIUM
ST12257XF	Z03942	30°C ± 2°C – 75% RH ± 5% RH	36 MONTHS	PLASTIC INJECTION SYSTEM	NA	102960	10/09/2012	15/06/2012	PFIZER BELGIUM

2. Schedule

		DEGRADATON PRODUCT INDIVIDUAL UNSPECIFIED	DESCRIPTION	MEDROXYPROGESTERONE (DEGRADATION PRODUCT)	MEDROXYPROGESTERONE ACETATE	METHIONINE	PARTICLE SIZE LESS THAN 10MCM	PARTICLE SIZE LESS THAN 20MCM	STERILITY	TOTAL DEGRADATION PRODUCTS
ST12233XF	00 MONTHS	X	X	X	X	X	X	X	X	X
	03 MONTHS	X	X	X	X	X	X	X		X
	06 MONTHS	X	X	X	X	X	X	X		X
	09 MONTHS	X	X	X	X	X	X	X		X
	12 MONTHS	X	X	X	X	X	X	X		X
	18 MONTHS	X	X	X	X	X	X	X		X
	24 MONTHS	X	X	X	X	X	X	X		X
	36 MONTHS	X	X	X	X	X	X	X	X	X
ST12245XF	00 MONTHS	X	X	X	X	X	X	X	X	X
	03 MONTHS	X	X	X	X	X	X	X		X
	06 MONTHS	X	X	X	X	X	X	X		X
	09 MONTHS	X	X	X	X	X	X	X		X
	12 MONTHS	X	X	X	X	X	X	X		X
	18 MONTHS	X	X	X	X	X	X	X		X
	24 MONTHS	X	X	X	X	X	X	X		X
	36 MONTHS	X	X	X	X	X	X	X	X	X
ST12257XF	00 MONTHS	X	X	X	X	X	X	X	X	X
	03 MONTHS	X	X	X	X	X	X	X		X
	06 MONTHS	X	X	X	X	X	X	X		X
	09 MONTHS	X	X	X	X	X	X	X		X
	12 MONTHS	X	X	X	X	X	X	X		X
	18 MONTHS	X	X	X	X	X	X	X		X
	24 MONTHS	X	X	X	X	X	X	X		X
	36 MONTHS	X	X	X	X	X	X	X	X	X

3. Currently registered procedures and limits on stability

Test	Test Method	Limits
Degradation Product Individual Unspecified	TMC0003	Not More Than 0.2 %
Description	Visual	White to off-white homogeneous suspension when mixed
Medroxyprogesterone (Degradation Product)	TMC0003	Not More Than 0.6 %
Medroxyprogesterone Acetate	TMC0003	95.0 to 105.0 % of label
Methionine	TMC0002	90.0 to 110.0 % of label at time of release; 85.0 to 110.0 % of label during shelf life
Particle size less than 10 MCM	004NPD01	Not Less Than 75 %
Particle size less than 20 MCM	004NPD01	Not Less Than 99 %
Sterility	Ph Eur	Meets Ph Eur requirements
Total Degradation Products	TMC0003	Not More Than 0.6 %

4. Stability Test results at 30°C ± 2°C – 75% RH ± 5% RH

DEGRADATION PRODUCT INDIVIDUAL UNSPECIFIED

	ST12233XF	ST12245XF	ST12257XF
00 MONTHS	NOT DETECTED	NOT DETECTED	NOT DETECTED
03 MONTHS	NOT DETECTED	NOT DETECTED	0.1
06 MONTHS	NOT DETECTED	NOT DETECTED	NOT DETECTED
09 MONTHS	NOT DETECTED	NOT DETECTED	NOT DETECTED
12 MONTHS	NOT DETECTED	0.1	0.1
18 MONTHS	NOT DETECTED	NOT DETECTED	NOT DETECTED
24 MONTHS	NOT DETECTED	NOT DETECTED	NOT DETECTED
36 MONTHS	NOT DETECTED	NOT DETECTED	NOT DETECTED

All results within limits up to testing period: no problems reported.

DESCRIPTION

	ST12233XF	ST12245XF	ST12257XF
00 MONTHS	MEETS TEST	MEETS TEST	MEETS TEST
03 MONTHS	MEETS TEST	MEETS TEST	MEETS TEST
06 MONTHS	MEETS TEST	MEETS TEST	MEETS TEST
09 MONTHS	MEETS TEST	MEETS TEST	MEETS TEST
12 MONTHS	MEETS TEST	MEETS TEST	MEETS TEST
18 MONTHS	MEETS TEST	MEETS TEST	MEETS TEST
24 MONTHS	MEETS TEST	MEETS TEST	MEETS TEST
36 MONTHS	MEETS TEST	MEETS TEST	MEETS TEST

All results within limits up to testing period: no problems reported.

MEDROXYPROGESTERONE (DEGRADATION PRODUCT)

	ST12233XF	ST12245XF	ST12257XF
00 MONTHS	0.2	0.1	0.1
03 MONTHS	0.2	0.1	0.1
06 MONTHS	0.2	NOT DETECTED	0.1
09 MONTHS	0.2	0.1	0.2
12 MONTHS	0.2	0.1	0.1
18 MONTHS	0.2	0.1	0.1
24 MONTHS	0.2	0.1	0.1
36 MONTHS	0.2	0.1	0.1

All results within limits up to testing period: no problems reported.

MEDROXYPROGESTERONE ACETATE

	ST12233XF	ST12245XF	ST12257XF
00 MONTHS	101.2	100.3	100.8
03 MONTHS	102.4	100.6	102.1
06 MONTHS	102.9	101.6	102.2
09 MONTHS	102.5	102.0	103.2
12 MONTHS	101.5	101.0	101.4
18 MONTHS	102.2	103.0	103.1
24 MONTHS	103.4	101.5	102.9
36 MONTHS	104.2	102.0	103.3

All results within limits up to testing period: no problems reported.

METHIONINE

	ST12233XF	ST12245XF	ST12257XF
00 MONTHS	99.1	99.4	98.1
03 MONTHS	99.0	99.2	97.8
06 MONTHS	99.2	98.8	97.5
09 MONTHS	98.1	98.3	98.0
12 MONTHS	97.7	97.8	98.3
18 MONTHS	97.0	97.4	97.2
24 MONTHS	96.3	97.1	96.4
36 MONTHS	95.3	96.0	95.5

All results within limits up to testing period: no problems reported.

PARTICLE SIZE LESS THAN 10 MCM

	ST12233XF	ST12245XF	ST12257XF
00 MONTHS	MEETS TEST	MEETS TEST	MEETS TEST
03 MONTHS	MEETS TEST	MEETS TEST	MEETS TEST
06 MONTHS	MEETS TEST	MEETS TEST	MEETS TEST
09 MONTHS	MEETS TEST	MEETS TEST	MEETS TEST
12 MONTHS	MEETS TEST	MEETS TEST	MEETS TEST
18 MONTHS	MEETS TEST	MEETS TEST	MEETS TEST
24 MONTHS	MEETS TEST	MEETS TEST	MEETS TEST
36 MONTHS	MEETS TEST	MEETS TEST	MEETS TEST

All results within limits up to testing period: no problems reported.

PARTICLE SIZE LESS THAN 20 MCM

	ST12233XF	ST12245XF	ST12257XF
00 MONTHS	MEETS TEST	MEETS TEST	MEETS TEST
03 MONTHS	MEETS TEST	MEETS TEST	MEETS TEST
06 MONTHS	MEETS TEST	MEETS TEST	MEETS TEST
09 MONTHS	MEETS TEST	MEETS TEST	MEETS TEST
12 MONTHS	MEETS TEST	MEETS TEST	MEETS TEST
18 MONTHS	MEETS TEST	MEETS TEST	MEETS TEST
24 MONTHS	MEETS TEST	MEETS TEST	MEETS TEST
36 MONTHS	MEETS TEST	MEETS TEST	MEETS TEST

All results within limits up to testing period: no problems reported.

STERILITY

	ST12233XF	ST12245XF	ST12257XF
00 MONTHS	MEETS TEST	MEETS TEST	MEETS TEST
36 MONTHS	MEETS TEST	MEETS TEST	MEETS TEST

All results within limits up to testing period: no problems reported.

TOTAL DEGRADATION PRODUCTS

	ST12233XF	ST12245XF	ST12257XF
00 MONTHS	0.2	0.1	0.1
03 MONTHS	0.2	0.1	0.3
06 MONTHS	0.2	0.1	0.1
09 MONTHS	0.2	0.1	0.2
12 MONTHS	0.2	0.2	0.2
18 MONTHS	0.2	0.1	0.1
24 MONTHS	0.2	0.1	0.1
36 MONTHS	0.2	0.1	0.1

All results within limits up to testing period: no problems reported.

5. Conclusion

The results show that Sayana Press 160 mg/mL 0.65 mL Injection System is stable up to testing period when stored at 30°C ± 2°C – 75% RH ± 5% RH.

3.2.P.8.3. STABILITY DATA

Stability Data

Detailed stability data tables for 3 batches of DMPA-SC 104 mg/0.65 mL sterile aqueous suspension, packaged in a pre-filled single use injection system stored within a foil pouch at International Conference on Harmonisation (ICH) accelerated (40°C ± 2°C /75% ± 5% RH) conditions. Stability studies have been completed with accelerated data through 6 months in Table 3.2.P.8.3-2 through Table 3.2.P.8.3-4.

Stability Data Tables

Table 3.2.P.8.3-1. Index for Stability Data Tables

Batch Number	Manufacture Date	Storage Condition	Table Number
Z03940	05 Jun 2012	40°C/75% RH	Table 3.2.P.8.3-2
Z03941	08 Jun 2012	40°C/75% RH	Table 3.2.P.8.3-3
Z03942	15 Jun 2012	40°C/75% RH	Table 3.2.P.8.3-4

RH = relative humidity.

Table 3.2.P.8.3-2. DMPA-SC 104 mg/0.65 mL Pre-Filled Injection System in Foil Pouch, 40°C/75% RH, Lot Z03940

Lot Number:	**Z03940**		**Date of Manufacture:**	June 2012		
Strength:	104 mg/0.65 mL		**Manufacturing Site:**	Pfizer Manufacturing Belgium NV		
Study Start Date:	21 August 2012		**Packaging:**	Pre-filled injection system in a foil pouch		
Storage Conditions:	**40°C/75% RH**		**Units:**	1 unit/pouch		
Test	**Test Procedure**	**Acceptance Criteria**	**Checkpoint (Months)**			
			Initial	**2**	**4**	**6**
Description	I 2.02 (Visual inspection)	White to off-white homogenous suspension when mixed	Meets test	Meets test	Meets test	Meets test
Assay (% of LC)	M 160.1 (TM-01-C0003)	95.0% to 105.0%	101.2	102.4	102.5	102.8
Impurities (Degradation Products)						
Medroxyprogesterone	M 160.1 (TM-01-C0003)	NMT 0.6%	0.2	0.2	0.2	0.2
Individual Unspecified		NMT 0.2%	ND	<0.1	0.1	ND
Total Degradation		NMT 0.6%	0.2	0.2	0.3	0.2
Methionine Assay (% of LC)	D 211.1 (TM-01-C0002)	85.0% to 110.0%	99.1	97.7	96.8	97.7
Particle Size Distribution						
<20 µm	004NPD01	NLT 99%	Meets test	Meets test	Meets test	Meets test
<10 µm		NLT 75%	Meets test	Meets test	Meets test	Meets test

LC = label claim; ND = none detected; NLT = not less than; NMT = not more than; NS = test not scheduled; Ph Eur = current edition of the European Pharmacopoeia; RH = relative humidity.

Table 3.2.P.8.3-3. DMPA-SC 104 mg/0.65 mL Pre-Filled Injection System in Foil Pouch, 40°C/75% RH, Lot Z03941

Lot Number:	**Z03941**		**Date of Manufacture:**	June 2012		
Strength:	104 mg/0.65 mL		**Manufacturing Site:**	Pfizer Manufacturing Belgium NV		
Study Start Date:	7 September 2012		**Packaging:**	Pre-filled injection system in a foil pouch		
Storage Conditions:	40°C/75% RH		**Units:**	1 unit/pouch		
Test	**Test Procedure**	**Acceptance Criteria**	**Checkpoint (Months)**			
			Initial	**2**	**4**	**6**
Description	I 2.02 (Visual inspection)	White to off-white homogenous suspension when mixed	Meets test	Meets test	Meets test	Meets test
Assay (% of LC)	M 160.1 (TM-01-C0003)	95.0% to 105.0%	100.3	101.6	101.5	102.0
Impurities (Degradation Products)						
Medroxyprogesterone	M 160.1 (TM-01-C0003)	NMT 0.6%	0.1	0.1	0.1	0.1
Individual Unspecified		NMT 0.2%	ND	ND	0.1	ND
Total Degradation		NMT 0.6%	0.1	0.1	0.3	0.1
Methionine Assay (% of LC)	D 211.1 (TM-01-C0002)	85.0% to 110.0%	99.4	97.8	97.7	96.7
Particle Size Distribution						
<20 µm	004NPD01	NLT 99%	Meets test	Meets test	Meets test	Meets test
<10 µm		NLT 75%	Meets test	Meets test	Meets test	Meets test

LC = label claim; ND = none detected; NLT = not less than; NMT = not more than; NS = test not scheduled; Ph Eur = current edition of the European Pharmacopoeia; RH = relative humidity.

Table 3.2.P.8.3-4. DMPA-SC 104 mg/0.65 mL Pre-Filled Injection System in Foil Pouch, 40°C/75% RH, Lot Z03942

Lot Number:	**Z03942**		**Date of Manufacture:**	June 2012		
Strength:	104 mg/0.65 mL		**Manufacturing Site:**	Pfizer Manufacturing Belgium NV		
Study Start Date:	10 September 2012		**Packaging:**	Pre-filled injection system in a foil pouch		
Storage Conditions:	40°C/75% RH		**Units:**	1 unit/pouch		
Test	**Test Procedure**	**Acceptance Criteria**	**Checkpoint (Months)**			
			Initial	**2**	**4**	**6**
Description	I 2.02 (Visual inspection)	White to off-white homogenous suspension when mixed	Meets test	Meets test	Meets test	Meets test
Assay (% of LC)	M 160.1 (TM-01-C0003)	95.0% to 105.0%	100.8	103.2	102.8	103.0
Impurities (Degradation Products)						
Medroxyprogesterone	M 160.1 (TM-01-C0003)	NMT 0.6%	0.1	0.1	0.1	0.1
Individual Unspecified		NMT 0.2%	ND	ND	0.1	ND
Total Degradation		NMT 0.6%	0.1	0.1	0.3	0.1
Methionine Assay (% of LC)	D 211.1 (TM-01-C0002)	85.0% to 110.0%	98.1	97.1	96.9	96.3
Particle Size Distribution						
<20 µm	004NPD01	NLT 99%	Meets test	Meets test	Meets test	Meets test
<10 µm		NLT 75%	Meets test	Meets test	Meets test	Meets test

LC = label claim; ND = none detected; NLT = not less than; NMT = not more than; NS = test not scheduled; Ph Eur = current edition of the European Pharmacopoeia; RH = relative humidity.

3.2.P.2.6. Compatibilidad

Esta sección no es aplicable ya que se relaciona con la compatibilidad del medicamento con el/los diluyente(s) de reconstitución o los dispositivos de posología (p. ej., precipitación del principio activo en solución, sorción en recipientes de inyección, estabilidad) ninguno de las cuales es aplicable al DMPA-SC en el sistema de inyección precargada de una sola administración.

3.2.P.7. CONTAINER CLOSURE SYSTEM(S)

3.2.P.7.1. Description(s) of Container Closure System(s)

DMPA-SC-Pre-Filled Injection System

Depot-Medroxyprogesterone Acetate-SC (DMPA-SC) 104 mg/ 0.65 mL is packaged in an all in one, pre-fillable single use drug delivery system (manufactured and sterilized by Becton Dickinson) designed for subcutaneous injections. This delivery system features with a 1 mL multilayered thermoformed plastic film reservoir with linear low-density polyethylene (LLDPE) product contact layer. Each DMPA-SC 104 mg/ 0.65 mL pre-filled single use injection system is packaged in a foil laminate pouch.

Prior to use the injection system is activated by the piercing of the membrane barrier by the double pointed cannula. The dose is then delivered by depressing the unit reservoir. After the dose is expressed, the collapsed reservoir and a one-way valve inhibit refill, preventing reuse.

Table 3.2.P.7-1. Container Closure System Description: Single Use Injection System

Component Description: Injection System	
SIZE	1 mL (reservoir)
COLOR	Natural (clear to translucent)
MATERIALS OF CONSTRUCTION	Reservoir: multilayered thermoformed plastic film with a linear low density polyethylene innermost layer Port: low density polyethylene Needle hub: polystyrene Needle shield: polypropylene Cannula: stainless steel grade 304 (siliconized)
SIZE (NEEDLE)	23-gauge thin walled
DRAWING	Provided for illustrative purposes only

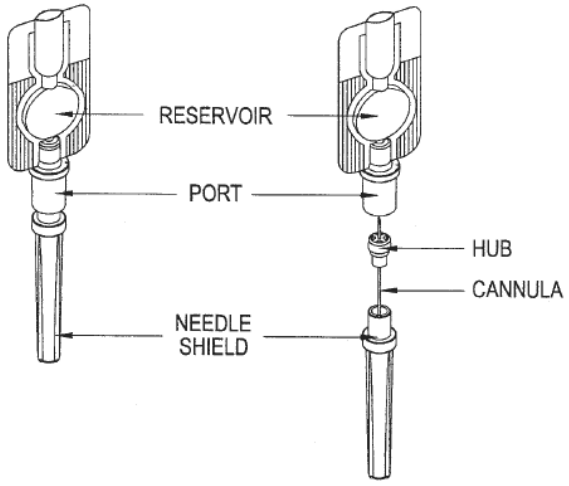

Table 3.2.P.7-2. Critical Secondary Packaging Description: Pouch

Component Description: Foil Pouch	
MATERIALS OF CONSTRUCTION	PET / adhesive / aluminum / PE (product contact side)
COLOR	Silver, printed overall white
DRAWING	Provided for illustrative purposes only

Product Side

3.2.P.7.2. Specifications

Each packaging component is identified with a unique code number. This number is used to order and track components and corresponds to a descriptive document that provides all relevant information pertaining to the component, such as materials of construction, dimensions, and supplier's drawings.

Each incoming shipment of packaging materials is assigned a unique receiving number and is withheld from use until it has been sampled, tested, and examined for conformance using internal plant standard operating procedures (SOPs) and standard test procedures.

Pre-fillable injection system components are visually inspected. Their physical dimensions and style are verified against supplier drawings or approved packaging specifications.

3.2.P.7.3. Analytical Procedures for Packaging Components

Test methods that comprise the Incoming Testing Specifications and are not described in a compendium are listed in this section. Method summaries are provided below.

Identity Check

Pre-fillable injection system components are visually inspected. Their physical dimensions and style are verified against supplier drawings or approved packaging specifications.

Appearance and Cleanliness

Inspect for the presence of biological foreign material, loose particulate matter or fibers within the fluid path of the device, wrinkles or cuts in the filling channel (compared to limit samples; causing leakage), foreign material on the needle, curved or bent needle or needle shield, and loose needle shield.

Sterility Check

Confirm sterilization of components indicated on Certificate of Compliance received from manufacturer.

Particles per Container

Particulate matter is determined by the supplier and conformance to the criteria is stated on the Certificate of Compliance for each batch.

Acceptance Criteria: max. 5 particles/unit > 25 µm; max. 35 particles/unit > 10µm.

Standard IR Spectra, Representative Certificates of Compliance

Standard IR spectra and certificates of compliance are used during incoming inspection of primary packaging components. The standard IR spectra are used for comparative purposes to identify the material of construction (Figure 3.2.P.7-1). A certificate of compliance (Figure 3.2.P.7-2) is used to ensure each lot of packaging components meets or exceeds specifications.

Figure 3.2.P.7-1. Representative IR Spectrum for Product Contact Surface of Injection System Cavity

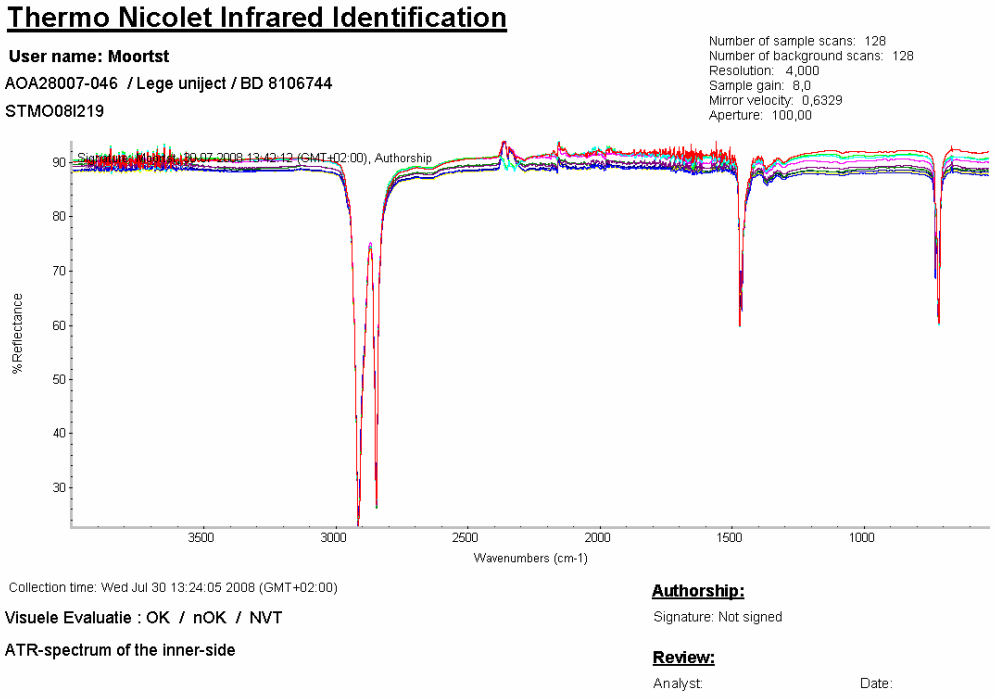

Figure 3.2.P.7-2. Representative Supplier Certificate of Compliance for Pre-Fillable Drug Delivery System

30 Tuas Avenue 2
Singapore 639461
tel: 68610633
fax: 68601592
www.bd.com

BD
Helping all people live healthy lives

CERTIFICATE OF COMPLIANCE

CUSTOMER : **Pfizer Manufacturing Belgium N.V.**

B.D. REF NO. : **8010334934**

This is to certify that the Uniject Injection Device were manufactured in accordance with Becton Dickinson Medical (Singapore) Pte Ltd Customer Specification No. SC47.

PURCHASE ORDER NO.	PRODUCT CATALOG NO. DESCRIPTION	PRODUCT LOT NO.	PRODUCT LOT QTY
4502371210	UNIJECT 1 ML 23G X 3/8IN TW 47290187	2017957	199,266

Quality control steps were carried out accordingly to established quality system at the manufacturing site. All products which are labeled as sterile and released for sale by Becton Dickinson are certified to be sterile as long as the package is unopened and undamaged.
All products which are labeled as non-pyrogenic and released for sale by Becton Dickinson have been originally tested and found to be non-pyrogenic. All materials which are labeled non-toxic and released for sale by Becton Dickinson have passed animal toxicity and/or cytotoxicity tests.

All products meet the foreign matter flush test specification defined as >10µm of 35 particles and >25µm of 5 particles as tested per BD test procedure 80005644.

Date : 09 April 2012

Name : Florence Kuan

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BECTON DICKINSON MEDICAL
(SINGAPORE) PTE LTD
QA Engineer/~~QA Manager~~

Becton Dickinson Medical (S) Pte Ltd

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3.2.P.8. STABILITY

3.2.P.8.1. STABILITY SUMMARY AND CONCLUSION

Overall Summary

Stability tests for Depot Medroxyprogesterone Acetate-Sub Cutaneous (DMPA-SC) 104 mg/0.65 mL Suspension for Injection commercial batches packaged in pre-filled single use injection system have been carried out under International Conference on Harmonisation (ICH) Zone IVb (30°C ± 2°C/75% ± 5% relative humidity [RH]) and accelerated (40°C ± 2°C /75% ± 5% RH) conditions. Stability studies have been completed with long-term data available and reported through the shelf life (36 months) and accelerated data through 6 months.

Summaries of the drug product batches that were used for formal stability studies are provided in Table 3.2.P.8.1-1.

Table 3.2.P.8.1-1. Summaries of DMPA-SC 104 mg/0.65 mL Pre-Filled Injection System Batch Information Commercial Batches Used in Stability Studies

Lot Number	Storage Conditions	Storage Period	Available Data	Mfg Date	Study Start Date	Lot Size (Units)	Mfg Place
Z03940	30°C/75%RH	36 months	36 months	06/2012	08/2012	102482	Pfizer Manufacturing Belgium, Puurs, Belgium
	40°C/75% RH	6 months	6 months				
Z03941	30°C/75%RH	36 months	36 months	06/2012	09/2012	101795	Pfizer Manufacturing Belgium, Puurs, Belgium
	40°C/75% RH	6 months	6 months				
Z03942	30°C/75%RH	36 months	36 months	06/2012	09/2012	102960	Pfizer Manufacturing Belgium, Puurs, Belgium
	40°C/75% RH	6 months	6 months				

RH = relative humidity.

Container Closure System

The DMPA-SC 104 mg/0.65 mL pre-filled single use injection system is packaged in a foil pouch (secondary packaging).

Characteristics Studied and Quality Specifications

Depot Medroxyprogesterone Acetate-Sub Cutaneous (DMPA-SC) 104 mg/0.65 mL Suspension for Injection packaged in pre-filled single use injection system stability samples have been tested according to the proposed shelf-life specifications presented in Section 3.2.P.5.1 Specifications.

Evaluation of Methods

The methods used for testing the stability samples are the same methods used for testing finished product and are described in Section 3.2.P.5.2 Analytical Procedures.

Storage Conditions and Testing Frequency

The stability protocol designs for the stability studies, including storage conditions and checkpoints, are described in Table 3.2.P.8.1-2.

Table 3.2.P.8.1-2. Stability Protocol for Batches Z03940, Z03941, and Z03942

Storage Condition	Checkpoint (Months)							
	Initial	3	6	9	12	18	24	36
30°C/75% RH	A	B	B	B	B	B	B	A
40°C/75% RH	B	B	B	---	---	---	---	---

Scheduled tests applied in accordance with the above protocols include:

A: Description, assay, degradation products, methionine content, particle size distribution, and sterility.

B: Description, assay, degradation products, methionine content and particle size distribution.

Bracketing

DMPA-SC will only be provided at one commercial strength, fill volume, and packaging type; therefore, a bracketing design was not applicable to the registration stability program.

Results of Testing

All results are within specifications. The stability results are presented in Section 3.2.P.8.3 Stability Data.

Conclusions

All data remain within the acceptance criteria up to 36 months for samples stored at 30°C/75% RH and up to 6 months for samples stored at 40°C/75% RH. No negative trends have been observed.

The stability data support a shelf life of 36 months for DMPA-SC 104 mg/0.65 mL sterile aqueous suspension, packaged in a pre-filled single use injection system and stored in a foil pouch. As the results (both long-term and accelerated) are all within the acceptance criteria with no significant changes, no particular storage conditions are required.

Storage Conditions

No special condition for storage is required due to the good stability profile displayed by DMPA-SC pre-filled injection system at both long-term and accelerated conditions. However, the recommended storage condition statement will be determined by local labeling guidelines. As this product is an aqueous suspension, the advice “do not refrigerate or freeze” is recommended.

3.2.P.8.2. POST-APPROVAL STABILITY PROTOCOL AND STABILITY COMMITMENT

3.2.P.8.2.1. Post-Approval Stability Protocol and Commitment

According to CPMP/QWP/122/02 "Note for Guidance on Stability Testing: Stability Testing of Existing Active Substances and Related Finished Products", a post-approval stability commitment is considered unnecessary. Pfizer will continue to monitor batches on stability under long term condition to provide assurance that the product continues to meet the registered specifications through expiry.