Tribunal del proceso selectivo para ingreso, por el sistema general de acceso libre, en la Escala Técnica de Gestión de OOAA, especialidad Sanidad y Consumo, Resolución de 24 de mayo de 2018, de la Subsecretaria.

ESCALA TÉCNICA DE GESTIÓN DE OO.AA. ESP. SANIDAD Y CONSUMO, ACCESO LIBRE

AREA DE ANÁLISIS QUÍMICO DE MEDICAMENTOS

CUARTO EJERCICIO

18 de marzo de 2019

Se presenta una solicitud de autorización de ensayo clínico titulado "Estudio en fase III, aleatorizado, doble ciego, sobre 325BZC más capecitabina en comparación con placebo más capecitabina en sujetos con cáncer de páncreas avanzado o metastásico que no respondieron o no toleran la quimioterapia en primera línea".
De acuerdo con el formulario de solicitud 325BZC, ha sido designado medicamento huérfano por el Comité de Medicamentos Huérfanos de la EMA.
En el dossier de medicamento para investigación de 325BZC, polvo para solución para perfusión se presentan los siguientes datos de estabilidad de la sustancia activa:

2.1.S.7 Stability
2.1.S.7.1 Stability summary and conclusions
After 36 months of storage at 25 ºC / 60% relative humidity, and 6 months at 40 °C / 75% relative humidity, no changes in the physical or chemical characteristics of 325BZC drug substance have been observed. Therefore, a retest period of 48 months is fully acceptable.
2.1.S.7.2 Stability protocol and stability commitment
A clinical batch (Batch 60593) manufactured by the proposed manufacturer and following current synthetic process has been put on stability. Samples were tested according to the following schedule:

Table 24 Stability protocol

Conditions	Months of storage								
	3	6	9	12	18	24	36	48	60
30 °C / 65% relative humidity	X	X	X	X	X	X	X	X	X
40 °C / 75% relative humidity	X	X	–	–	–	–	–		

To date, 36 months' stability data are available and presented in Section 2.1.S.7.3.2. The stability study is still on-going
2.1.S.7.3 Stability protocol and stability commitment
2.1.S.7.3.1 Stress tests
Results of the stress testing are provided, showing the main degradations pathways and the stability indicating power of the analytical methods.
2.1.S.7.3.2 Long term results
To date, 36 months stability data are available and presented in Section 2.1.S.7.3.2.
Table 25 Physical characteristics of Clinical Batch 60593

	Appearance Colour	Water content (%)	Assay (w/w %)	Enantiomeric ratio
Acceptance criteria	White to light yellow powder	Max. 0.5%	98.0–102.0%	Min. 99.5% : Max. 0.5%
Initial analysis	White to light	0.1	99.4	<99.8: <0.2

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	yellow powder			
1 month				
25 °C / 60% relative humidity	White to light yellow powder	0.2	100.3	100.0:<0.2
40 °C / 75% relative humidity	White to light yellow powder	0.2	100.5	100.0:<0.2
3 months				
25 °C / 60% relative humidity	White to light yellow powder	0.1	99.7	100.0:<0.2
40 °C / 75% relative humidity	White to light yellow powder	0.1	99.6	100.0:<0.2
6 months				
25 °C / 60% relative humidity	White to light yellow powder	0.1	100.2	100.0:<0.2
40 °C / 75% relative humidity	White to light yellow powder	0.1	100.6	100.0:<0.2
9 months 25 °C / 60% relative humidity	White to light yellow powder	< 0.1	99.2	100.0:<0.2
12 months 25 °C / 60% relative humidity	White to light yellow powder	0.1	99.8	100.0:<0.2
18 months 25 °C / 60% relative humidity	White to light yellow powder	0.2	100.1	100.0:<0.2
24 months 25 °C / 60% relative humidity	White to light yellow powder	0.1	99.7	100.0:<0.2
36 months 25 °C / 60% relative humidity	White to light yellow powder	0.1	99.3	100.0:<0.2

Table 26 Related substance Clinical Batch 60593

	Related substances (%)				
	RS-1	RS-2	RS-3	Any other impurity	Total
Acceptance criteria	0.40	0.15	0.15	0.10	NMT 2.0
Initial analysis	<0.05	0.05	0.05	0.07	0.22
1 month					
25 °C / 60% relative humidity	<0.05	0.05	0.05	0.07	0.22
40 °C / 75% relative humidity	0.05	0.05	0.05	0.06	0.27
3 months					
25 °C / 60% relative	0.05	<0.05	0.06	0.07	0.23

humidity 40 °C / 75% relative humidity	<0.05	<0.05	0.06	0.07	0.19
6 months					
25 °C / 60% relative humidity 40 °C / 75% relative humidity	0.05 0.05	0.05 0.05	0.07 0.07	0.07 0.07	0.30 0.30
9 months 25 °C / 60% relative humidity	0.06	0.05	0.06	0.08	0.31
12 months 25 °C / 60% relative humidity	0.05	0.05	0.07	0.07	0.31
18 months 25 °C / 60% relative humidity	0.05	0.06	0.07	0.08	0.33
24 months 25 °C / 60% relative humidity	0.05	0.05	0.07	0.08	0.32
36 months 25 °C / 60% relative humidity	0.05	0.05	0.07	0.07	0.33

PREGUNTA 1.

a) ¿Considera aceptable el periodo de re-test solicitado? Justifique su respuesta. Si el sponsor quisiera aumentar el periodo de recontrol a 60 meses ¿tendría que presentar una modificación sustancial?
b) ¿Serían estos datos de estabilidad suficientes para avalar el periodo de recontrol cuando se solicite una autorización de comercialización?

PREGUNTA 2.

Una vez finalizado el ensayo clínico se decide presentar la solicitud de autorización de comercialización para el medicamento 325BZC, polvo para solución para perfusión. Explique detalladamente el procedimiento de autorización de comercialización que debe seguir esta solicitud.

PREGUNTA 3.

De acuerdo con la solicitud de autorización del medicamento arriba indicado, los productos de degradación de 325BZC, polvo para solución para perfusión, se controlan por HPLC. La especificación propuesta para este parámetro es:

Impurity A ≤1.0%
Any other impurity ≤0.20%
Total impurities ≤2.0%

Se presentan los siguientes resultados de la validación de dicho método. ¿Se consideran adecuados? Justifique su respuesta

VALIDATION OF THE ANALYTICAL METHOD BY HPLC TO DETERMINE RELATED SUBSTANCES OF 325BZC 2.5 MG and 5 MG POWDER FOR SOLUTION FOR INFUSION

VARIABLE	ACCEPTANCE CRITERIA	RESULTS
SPECIFICITY		
Identification	RT and UV spectra of the known degradation products in the impurities standard solution and test solution spiked with known degradation product must be similar	CONFORMS
	Known degradation product peak must be pure in test solution spiked with known degradation product	CONFORMS
	Resolution of known degradation products peak with any other peak must be ≥ 1.5 in test solution spiked with known degradation product	CONFORMS
	Interference of known degradation product ≤ 5.0% in test solution spiked with known degradation product	CONFORMS
Stress at Heat and Heat-Humidity conditions	Known degradation product peaks must be pure in test solution	CONFORMS
	Resolution of known degradation product with any other peak is ≥ 1.5 in test solution	CONFORMS
	Identification of known degradation product (RT and spectra)	CONFORMS
	Mass balance 90-110%	CONFORMS
Stress Strong conditions	Identification of known degradation product (RT and spectra)	
	Stability indicative technique	
	Mass balance 90-110%	
SYSTEM SUITABILITY		
Related substances	RSD areas of active ≤ 2.7	

standard solution	%	0.5 %
System Suitability Solution	Theoretical plates for known degradation product ≥ 2000	Impurity A = 14337
	Tailing factor for known degradation product ≤ 2.0	Impurity A = 1.2
	Resolution for known degradation product ≥ 1.5	Impurity A = 2.2
DETECTION AND QUANTIFICATION LIMITS		
Detection limit	LOD must be verified	325BZC= 0.0086
		Impurity A = 0.0066
Quantification limit	LOQ reporting limit (0.05%) and must comply with linearity, precision and accuracy	325BZC= 0.0259
		Impurity A = 0.0199
	PRECISION	
Method repeatability	RSDMR ≤ 5.3 %	2.7
Intermediate precision of the method	RSDMIP ≤ 10.0% (< 2 X RSDMR)	Day: 3.6 Operator: 3.6
	RSDFACTOR ≤ 7.4% (1.4 X RSDMR)	Day 1: 4.5 Day 2: 2.1 Operator 1: 2.3 Operator 2: 4.4
	ACCURACY	
LOQ level	RSD ≤ 10.0%	325BZC= 0.8 Impurity A=1.0
	Recovery between 80.0% - 110.0%	325BZC= 107.9, 107.0, 106.3 Impurity A= 104.5, 106.2, 104.4
Level 2 and Level 3	RSD ≤ 5.3%	325BZC: Level 2: 3.0 Level 3: 2.1 Impurity A: Level 2: 1.1 Level 3: 1.5
	Recovery between 90.0-107.0%	325BZC: Level 2: 101.8, 107.0, 107.4 Level 3: 105.4, 104.1, 101.0 Impurity A: Level 2: 102.8, 103.8, 104.9 Level 3: 102.8, 104.1, 101.1
	ROBUSTNESS	
Robustness	It will be considered robust if each experiment complies with specificity and system suitability criteria	Method robustness to determine 325BZC related substances is proven. This method is established under the

		described conditions for 325BZC 2.5 and 5 mg powder for solution for infusion, changes in column batch, column temperature and watery phase pH variation.
SOLUTION STABILITY		
Stability	**Related substances standard solution** It is considered stable if % variation of response of active and known degradations ≤ 10.0% if %analyte ≤ 0.5%	CONFORMS 48 hours
	Test solution It is considered stable if: - % variation of response of the impurities is: - ≤ 20.0% if %analyte ≤ 0.1% - ≤ 10.0% if %analyte ≤0.5% - ≤ 5.0% if %analyte > 0.5% - New degradation products ≤ Reporting limit	325BZC 2.5 mg powder for solution for infusion: Conforms 48 hours for fridge and room temperature and 24 hours for light exposure 325BZC 5 mg powder for solution for infusion: Conforms 48 hours for the three conditions

PREGUNTA 4.

El medicamento 325BZC, polvo para solución para perfusión, debe ser almacenado en nevera.
a) Indique los datos que se deben incluir en el dossier de registro de este medicamento con respecto a estabilidad en uso y compatibilidad.
b) ¿Cómo debe reflejarse esta información en ficha técnica? ¿En qué secciones?

PREGUNTA 5.

Durante la campaña de control de mercado se recoge y analiza el medicamento 325BZC, polvo para solución para perfusión. Tras la realización de estos análisis se detecta en el laboratorio un resultado fuera de especificaciones para el parámetro valoración. Se procede a analizar las causas de este resultado fuera de especificaciones analizando todos los pasos seguidos durante el análisis. Se detecta que hubo un error durante la pesada del patrón, tratándose, por tanto de un trabajo no conforme del laboratorio.
Indique como debe gestionarse este trabajo no conforme y las oportunas acciones correctivas en el laboratorio de acuerdo a lo establecido en la norma UNE-EN ISO/IEC 1025:2017.