RAPORT ASUPRA STUDIULUI COLABORATIV PENTRU STABILIREA POTENTEI STANDARDULUI DE REFERINTA: COLISTIMETHAT SODIC

REPORT CONCERNING THE COLABORATIVE STUDY FOR ESTABLISH OF REFERENCE STANDARD EFICACITY OF COLISTIMETHAT SODIUM

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Rezumat

Institutul pentru Controlul Produselor Biologice si Medicamentelor de uz Veterinar a participat la studiul colaborativ pentru determinarea potentei colistimethatului sodic CRS, lotul 2, conform protocolului trimis de EDQM (Directoratul European pentru Calitatea Medicamentelor) - coordonatorul studiului.

Scopul studiului a fost de a stabili potenta lotului 2 de colistimethat sodic, in vederea caracterizarii cat mai exacte a substantei de referinta.

Potenta a fost determinata prin metoda microbiologica, bazata pe compararea zonelor de inhibare a creşterii unui microorganism sensibil, cu cele ale unui standard de referinţă, conform prevederilor din Farmacopeea Europeana «Colistimethate sodic», capitolul 2.7.2. – testarea microbiologica a antibioticelor.

In urma analizei si coroborarii rezultaleor primite de la participanti si a prelucrarii statistice a acestora de catre EDQM, valoarea potentei lotului 2 de colistimethate sodic – substanta de referinta, a fost stabilita la 285000UI/fiola.

Cuvinte cheie: *studiu colaborativ, colistimethat sodic, metoda difuzimetrica, patrate latine*

Abstract

Institute for the Control of Veterinary Biological Products and Medicines participated at the collaborative study for determine the potency of colistimethate sodium CRS, Lot 2, according to the protocol sent by the EDQM (European Directorate for the Quality of Medicines) - coordinator of the study.

The purpose of the study was to determine the potency of the batch 2 colistimethate sodium in the characterization of the substance as reference standard.

Potency was determined by microbiological method, based on comparing the inhibition zones of growth of micro-organisms sensitive to those of a reference standard, as specified in European Pharmacopoeia "Colistimethate sodium", Chapter 2.7.2. - Microbiological testing of antibiotics.

After analysis of received data from participants and their statistical processing by the EDQM, the potency of the batch 2, colistimethate sodium - reference materials, was established in 285000UI/fiola.

Keyword: *collaborative study, sodium colistimethat method difuzimetrica, Latin squares*

În ultimii ani, comparările interlaboratoare au căpătat o importantă deosebită atât ca instrument de verificare a trasabilitătii în procesul de asigurare a calitatii, cât si ca instrument de validare a procedurilor de lucru aferente activitătilor desfăsurate în cadrul laboratoare de încercări, acreditate sau în curs de acreditare. Participarea la comparari interlaboratoare se poate face prin inscrierea laboratoarelor candidate la scheme de comparări interlaboratoare sau studii colaborative in scopul unei verificari independente a competentei privind analizele pe care acesta le desfăsoară.

Institutul pentru Controlul Produselor Biologice si Medicamentelor de uz Veterinar a participat la studiul colaborativ pentru determinarea potentei colistimethatului sodic CRS, lotul 2, conform protocolului trimis de EDQM (Directoratul European pentru Calitatea Medicamentelor) - coordonatorul studiului.

MATERIAL SI METODA

Probele si Protocolul de lucru au fost transmise de catre EDQM si au fost primite la ICBMV in buna stare.

Metoda de lucru a fost aplicata in cadrul Serviciului Control Microbiologic si Evaluare Biologica Medicamente, Laboratorul Control Microbiologic, cu respectarea conditiilor impuse de Protocolul de lucru al studiului.

Fiecare laborator participant la studiu a primit:

- 3 fiole cu colistimethat sodic, substanta de referinta standardizata WHO (12700 UI/mg)
- 8 filole de colistimethat sodic, lot 2, pentru determinarea potentei (potenta estimata la 260000UI/fiola)

Estimarea potentei s-a efectuat pe 6 probe prin metoda difuzimetrica, utilizand ca microorganism test *Bordetella bronchiseptica ATCC 4617*, prin cultivare pe mediul B,

preparat conform cerintelor Farmacopeei Europene, iar temperatura de incubare a fost de 37°C, timp de 18 ore. Diametrele zonelor de inhibitie au fost masurate vizual utilizand rigla.

REZULTATE SI DISCUTII

Raportarea rezultatelor s-a facut pe e-mail conform specificatiilor din protocolul de testare, utilizand un fisier Excel separat pentru fiecare din cele 6 teste individuale, prin metoda de calcul a patratului latin.

Rezultatele obtinute pentru cele 6 probe lucrate, trimise de Laboratorul Control Microbiologic din cadrul ICBMV, sunt prezentate in figurile 1-6. Initial s-au inscris la studiu 9 laboratoare dar numai 5 laboratoare (Danemarca, Portugalia, Polonia, Rusia si Romania) au trimis rezultatele in timp util pentru prelucrare.

Dintre cele 5 laboratoare participante un laborator a fost exclus de la inregistrarea rezultatelor datorita valoarilor mult prea mari obtinute, valori care se situeaza in afara potentei combinate estimate. Laboratorul Control Microbiologic din Institutul pentru Controlul Produselor Biologice si Medicamentelor de uz Veterinar a avut codul de participant nr. 4.

Din cele 6 rezultate trimise, 3 au fost acceptate ca fiind bune și 3 au fost respinse datorita deviatiei de la liniaritate.

Pentru celelalte 3 rezultate acceptate din punct de verdere al omogenitatii (P a avut valori sub 0,883), valoarea medie a potentei a fost de 273953 UI / fiola (cu o abatere de ± 2,6%). Rezultatele obtinute de laboratoarele participante au fost analizate comparativ cu cele obtinute in cadrul laboratoarelor EDQM si sunt prezentate in figurile 7, 8 și 9.

Raportul EDQM in care sunt prezentate rezultatele obtinute de participanti, insotite de comentariile organizatorilor studiului legate de intervalul de confidenta, valoarea potentei, deviatia de la liniaritate, omogenitatea citirilor, media rezultatelor, deviatia standard, deviatia standard relativa, etc. a fost inaintat fiecarui laborator participant.

Evaluarea rezultatelor s-a facut utilizand calculul statistic pentru modelul liniilor paralele utilizand programul System SAS si CombiStats.

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Date of assay:	07/04/2009

REFERENCE STANDARD				TEST SAMPLE			
Batch number	First IWHO IS EDQM code :18113			Batch number	Proposed CRS bath 2 (EDQM code 360+1)		
Potency	12700 IU/mg			Potency	about 260000 IU/fial		
Ampoule number	1			Vial number	1		
Weight taken	10,2+			Weight taken	21 mg		
Total volume	5 ml			Total volume	10 ml		
Primary dilution	26000 IU/ml			Primary dilution	26000 IU/ml		
Dilution s lep	1,5			Dilution s lep	1,5		
Dose	S1	S2	S3	Dose	T1	T2	T3
Final dilutions	17333 IU/ml	17333 IU/ml	26000 IU/ml	Final dilutions	17333 IU/ml	17333 IU/ml	26000 IU/ml

Number of doses per preparation (max. 5)			3			Number of replicates per dose (max. 20)			6	
	MEASURED RESPONSES OF REFERENCE (S) AND TEST (T) SOLUTIONS									
Dose replicates	S1	S2	S3			Dose replicates	T1	T2	T3	
	1	2	3	4	5		1	2	3	4	5
1	130,0	145,0	155,0			1	125,0	145,0	155,0		
2	120,0	145,0	155,0			2	125,0	145,0	160,0		
3	120,0	140,0	150,0			3	125,0	140,0	155,0		
4	125,0	140,0	155,0			4	125,0	140,0	155,0		
5	120,0	140,0	155,0			5	120,0	140,0	155,0		
6	120,0	140,0	155,0			6	125,0	145,0	155,0		

Experimental design	
Completely randomized	
Randomized blocks	
Latin Square	
Size of plate (max. 8 x 8)	
Nbr of rows	6
Nbr of columns	6

Plate lay-out (Use the notation S1, S2, S3, T1,T2, T3 to indicate the position of the doses)

	1	2	3	4	5	6
1	S1	T1	T2	S3	S2	T3
2	T1	T3	S1	S2	T2	S3
3	T2	S3	S2	S1	T3	T1
4	S3	S2	T3	T1	S1	T2
5	S2	T2	S3	T3	T1	S1
6	T3	S1	T1	T2	S3	S2

Inhibition zones in mm as positioned on the plate

	1	2	3	4	5	6
1	130,0	125,0	140,0	155,0	140,0	155,0
2	125,0	160,0	120,0	140,0	140,0	155,0
3	145,0	155,0	140,0	125,0	155,0	125,0
4	155,0	145,0	155,0	125,0	120,0	145,0
5	145,0	145,0	150,0	155,0	120,0	120,0
6	155,0	120,0	125,0	140,0	155,0	140,0

Estimated potency:	12833,96883	Lower 95% confidence limit:	12300,03196	Upper 95% confidence limit:	13396,02337

Fig. 1. Rezultate proba 1

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Date of assay:	07/04/2009

REFERENCE STANDARD		TEST SAMPLE	
Batch number	First I.W.H.O. IS EDQM code :18113	Batch number	Proposed CRS bath 2 (EDQM code 3604-1)
Potency	12700 IU/mg	Potency	about 260000 IU/Vial
Ampoule number	1	Vial number	2
Weight taken	10,24	Weight taken	21,3 mg
Total volume	5 ml	Total volume	10 ml
Primary dilution	26000 IU/ml	Primary dilution	26000 IU/ml
Dilution s tep	1,5	Dilution s tep	1,5
Dose	S1 S2 S3	Dose	T1 T2 T3
Final dilutions	17000 IU/ml 17000 IU/ml 26000 IU/ml	Final dilutions	17000 IU/ml 17000 IU/ml 26000 IU/ml

Number of doses per preparation (max. 5)	3	Number of replicates per dose (max. 20)	6

MEASURED RESPONSES OF REFERENCE (S) AND TEST (T) SOLUTIONS

Dose replicates	S1	S2	S3			Dose replicates	T1	T2	T3		
	1	2	3	4	5		1	2	3	4	5
1	120,0	140,0	150,0			1	125,0	145,0	150,0		
2	120,0	130,0	155,0			2	125,0	140,0	160,0		
3	120,0	140,0	150,0			3	120,0	145,0	150,0		
4	120,0	140,0	150,0			4	125,0	135,0	155,0		
5	120,0	135,0	150,0			5	120,0	135,0	150,0		
6	120,0	135,0	150,0			6	120,0	135,0	150,0		

Experimental design
- Completely randomised
- Randomised blocks
- Latin Square

Plate lay-out (Use the notation S1, S2, S3, T1,T2, T3 to indicate the position of the doses)

	1	2	3	4	5	6
1	S1	T1	T2	S3	S2	T3
2	T1	T3	S1	S2	T2	S3
3	T2	S3	S2	S1	T3	T1
4	S3	S2	T3	T1	S1	T2
5	S2	T2	S3	T3	T1	S1
6	T3	S1	T1	T2	S3	S2

Size of plate (max. 8 x 8)	
Nbr of rows	6
Nbr of columns	6

Inhibition zones in mm as positioned on the plate

	1	2	3	4	5	6
1	120,0	125,0	145,0	150,0	135,0	150,0
2	125,0	160,0	120,0	140,0	135,0	150,0
3	145,0	155,0	140,0	120,0	150,0	120,0
4	150,0	130,0	150,0	125,0	120,0	135,0
5	140,0	140,0	150,0	155,0	120,0	120,0
6	150,0	120,0	120,0	135,0	150,0	135,0

Estimated potency:	12956,39857	Lower 95% confidence limit:	12208,81898	Upper 95% confidence limit:	13762,99365

Fig. 2. Rezultate proba 2

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Date of assay:	07/04/2009

REFERENCE STANDARD		TEST SAMPLE	
Batch number	First I.W.H.O. IS EDQM code :18113	Batch number	Proposed CRS bath 2 (EDQM code 3604-1)
Potency	12700 IU/mg	Potency	about 260000 IU/Vial
Ampoule number	2	Vial number	3
Weight taken	10,24	Weight taken	21,2 mg
Total volume	5 ml	Total volume	10 ml
Primary dilution	26000 IU/ml	Primary dilution	26000 IU/ml
Dilution s tep	1,5	Dilution s tep	1,5
Dose	S1 S2 S3	Dose	T1 T2 T3
Final dilutions	17000 IU/ml 17000 IU/ml 26000 IU/ml	Final dilutions	17000 IU/ml 17000 IU/ml 26000 IU/ml

Number of doses per preparation (max. 5)	3	Number of replicates per dose (max. 20)	6

MEASURED RESPONSES OF REFERENCE (S) AND TEST (T) SOLUTIONS

Dose replicates	S1	S2	S3			Dose replicates	T1	T2	T3		
	1	2	3	4	5		1	2	3	4	5
1	125,0	135,0	150,0			1	125,0	135,0	150,0		
2	120,0	135,0	145,0			2	125,0	140,0	150,0		
3	120,0	135,0	150,0			3	120,0	135,0	150,0		
4	120,0	135,0	150,0			4	120,0	135,0	155,0		
5	120,0	135,0	150,0			5	125,0	140,0	155,0		
6	125,0	140,0	150,0			6	125,0	135,0	155,0		

Experimental design
- Completely randomised
- Randomised blocks
- Latin Square

Plate lay-out (Use the notation S1, S2, S3, T1,T2, T3 to indicate the position of the doses)

	1	2	3	4	5	6
1	S1	T1	T2	S3	S2	T3
2	T1	T3	S1	S2	T2	S3
3	T2	S3	S2	S1	T3	T1
4	S3	S2	T3	T1	S1	T2
5	S2	T2	S3	T3	T1	S1
6	T3	S1	T1	T2	S3	S2

Size of plate (max. 8 x 8)	
Nbr of rows	6
Nbr of columns	6

Inhibition zones in mm as positioned on the plate

	1	2	3	4	5	6
1	125,0	125,0	135,0	150,0	135,0	155,0
2	125,0	150,0	120,0	135,0	140,0	150,0
3	135,0	145,0	135,0	120,0	155,0	125,0
4	150,0	135,0	150,0	120,0	120,0	135,0
5	135,0	140,0	150,0	155,0	125,0	125,0
6	150,0	120,0	120,0	135,0	150,0	140,0

Estimated potency:	12870,81308	Lower 95% confidence limit:	12487,76423	Upper 95% confidence limit:	13282,77778

Fig. 3. Rezultate proba 3

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Date of assay:	08/04/2009

REFERENCE STANDARD		TEST SAMPLE	
Batch number	Firs t WHO IS 66/254 (EDQM code :18113)	Batch number	Proposed CRS bath 2 (EDQM code 3604 f)
Potency	12700 IU/mg	Potency	about 260000 IU/fial
Ampoule number	2	Vial number	4
Weight taken	10,24	Weight taken	21,28 mg
Total volume	5 ml	Total volume	10 ml
Primary dilution	26000 IU/ml	Primary dilution	26000 IU/ml
Dilution s tep	1,5	Dilution s tep	1,5
Dose	S1 S2 S3	Dose	T1 T2 T3
Final dilutions	17333 IU/ml 11556 IU/ml 7704 IU/ml	Final dilutions	17333 IU/ml 11556 IU/ml 7704 IU/ml

Number of doses per preparation (max. 5)	3	Number of replicates per dose (max. 20)	6

MEASURED RESPONSES OF REFERENCE (S) AND TEST (T) SOLUTIONS

Dose replicates	S1	S2	S3			Dose replicates	T1	T2	T3		
	1	2	3	4	5		1	2	3	4	5
1	125,0	130,0	145,0			1	125,0	130,0	150,0		
2	120,0	130,0	145,0			2	120,0	130,0	150,0		
3	120,0	125,0	145,0			3	120,0	135,0	145,0		
4	120,0	130,0	140,0			4	120,0	130,0	145,0		
5	120,0	130,0	145,0			5	120,0	130,0	145,0		
6	125,0	130,0	145,0			6	125,0	130,0	145,0		

Experimental design
- Completely randomised
- Randomised blocks
- Latin Square

Size of plate (max. 8 x 8)

Nbr of rows	6
Nbr of columns	6

Plate lay-out (Use the notation S1, S2, S3, T1,T2, T3 to indicate the position of the doses)

	1	2	3	4	5	6
1	S1	T1	T2	S3	S2	T3
2	T1	T3	S1	S2	T2	S3
3	T2	S3	S2	S1	T3	T1
4	S3	S2	T3	T1	S1	T2
5	S2	T2	S3	T3	T1	S1
6	T3	S1	T1	T2	S3	S2

Inhibition zones in mm as positioned on the plate

	1	2	3	4	5	6
1	125,0	120,0	135,0	140,0	130,0	145,0
2	125,0	150,0	120,0	130,0	130,0	145,0
3	130,0	145,0	125,0	120,0	145,0	125,0
4	145,0	130,0	145,0	120,0	120,0	130,0
5	130,0	130,0	145,0	145,0	120,0	125,0
6	150,0	120,0	120,0	130,0	145,0	130,0

Estimated potency:	128 16, 148 13	Lower 95% confidence limit:	12 136,80 12 1	Upper 95% confidence limit:	13643,40938

Fig. 4. Rezultate proba 4

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Date of assay:	08/04/2009

REFERENCE STANDARD		TEST SAMPLE	
Batch number	Firs t WHO IS 66/254 (EDQM code :18113)	Batch number	Proposed CRS bath 2 (EDQM code 3604 f)
Potency	12700 IU/mg	Potency	about 260000 IU/fial
Ampoule number	3	Vial number	5
Weight taken	10,24	Weight taken	21 mg
Total volume	5 ml	Total volume	10 ml
Primary dilution	26000 IU/ml	Primary dilution	26000 IU/ml
Dilution s tep	1,5	Dilution s tep	1,5
Dose	S1 S2 S3	Dose	T1 T2 T3
Final dilutions	17333 IU/ml 11556 IU/ml 7704 IU/ml	Final dilutions	17333 IU/ml 11556 IU/ml 7704 IU/ml

Number of doses per preparation (max. 5)	3	Number of replicates per dose (max. 20)	6

MEASURED RESPONSES OF REFERENCE (S) AND TEST (T) SOLUTIONS

Dose replicates	S1	S2	S3			Dose replicates	T1	T2	T3		
	1	2	3	4	5		1	2	3	4	5
1	120,0	130,0	145,0			1	125,0	130,0	150,0		
2	120,0	130,0	145,0			2	120,0	130,0	150,0		
3	120,0	135,0	145,0			3	120,0	130,0	145,0		
4	120,0	130,0	145,0			4	125,0	130,0	145,0		
5	120,0	130,0	145,0			5	120,0	130,0	145,0		
6	115,0	130,0	145,0			6	120,0	130,0	145,0		

Experimental design
- Completely randomised
- Randomised blocks
- Latin Square

Size of plate (max. 8 x 8)

Nbr of rows	6
Nbr of columns	6

Plate lay-out (Use the notation S1, S2, S3, T1,T2, T3 to indicate the position of the doses)

	1	2	3	4	5	6
1	S1	T1	T2	S3	S2	T3
2	T1	T3	S1	S2	T2	S3
3	T2	S3	S2	S1	T3	T1
4	S3	S2	T3	T1	S1	T2
5	S2	T2	S3	T3	T1	S1
6	T3	S1	T1	T2	S3	S2

Inhibition zones in mm as positioned on the plate

	1	2	3	4	5	6
1	120,0	120,0	130,0	145,0	130,0	145,0
2	125,0	150,0	120,0	130,0	130,0	145,0
3	130,0	145,0	135,0	120,0	145,0	120,0
4	145,0	130,0	145,0	125,0	120,0	130,0
5	130,0	130,0	145,0	145,0	120,0	115,0
6	150,0	120,0	120,0	130,0	145,0	130,0

Estimated potency:	12832,4723	Lower 95% confidence limit:	12333,69605	Upper 95% confidence limit:	13354,93487

Fig. 5. Rezultate proba 5

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Date of assay:	08/04/2009

REFERENCE STANDARD				TEST SAMPLE			
Batch number	First IWHO IS 66/254 (EDQM code :18113)			Batch number	Proposed CRS bath 2 (EDQM code 36041)		
Potency	12700 IU/mg			Potency	about 260000 IU/Vial		
Ampoule number	5			Vial number	5		
Weight taken	10,24			Weight taken	21,3 mg		
Total volume	5 ml			Total volume	10 ml		
Primary dilution	26000 IU/ml			Primary dilution	26000 IU/ml		
Dilution s lep	1,5			Dilution s lep	1,5		
Dose	S1	S2	S3	Dose	T1	T2	T3
Final dilutions	17333 IU/ml	17333 IU/ml	26000 IU/ml	Final dilutions	17333 IU/ml	17333 IU/ml	26000 IU/ml

Number of doses per preparation (max. 5)			3			Number of replicates per dose (max. 20)				6
MEASURED RESPONSES OF REFERENCE (S) AND TEST (T) SOLUTIONS										
Dose replicates	S1	S2	S3			Dose replicates	T1	T2	T3	
	1	2	3	4	5		1	2	3	4	5
1	120,0	130,0	145,0			1	125,0	135,0	150,0		
2	120,0	130,0	145,0			2	120,0	135,0	150,0		
3	120,0	135,0	145,0			3	120,0	135,0	145,0		
4	120,0	135,0	145,0			4	120,0	130,0	145,0		
5	120,0	130,0	145,0			5	120,0	130,0	145,0		
6	120,0	130,0	145,0			6	120,0	130,0	150,0		

Experimental design
Completely randomized
Randomized blocks
Latin Square

Size of plate (max. 8 x 8)	
Nbr of rows:	6
Nbr of columns:	6

Plate lay-out (Use the notation S1, S2, S3, T1,T2, T3 to indicate the position of the doses)

	1	2	3	4	5	6
1	S1	T1	T2	S3	S2	T3
2	T1	T3	S1	S2	T2	S3
3	T2	S3	S2	S1	T3	T1
4	S3	S2	T3	T1	S1	T2
5	S2	T2	S3	T3	T1	S1
6	T3	S1	T1	T2	S3	S2

Inhibition zones in mm as positioned on the plate

	1	2	3	4	5	6
1	120,0	120,0	135,0	145,0	130,0	150,0
2	125,0	150,0	120,0	135,0	130,0	145,0
3	135,0	145,0	135,0	120,0	145,0	120,0
4	145,0	130,0	145,0	120,0	120,0	130,0
5	130,0	135,0	145,0	145,0	120,0	120,0
6	150,0	120,0	120,0	130,0	145,0	130,0

Estimated potency:	12756,28939	Lower 95% confidence limit:	12199,41119	Upper 95% confidence limit:	13341,68

Fig. 6. Rezultate proba 6

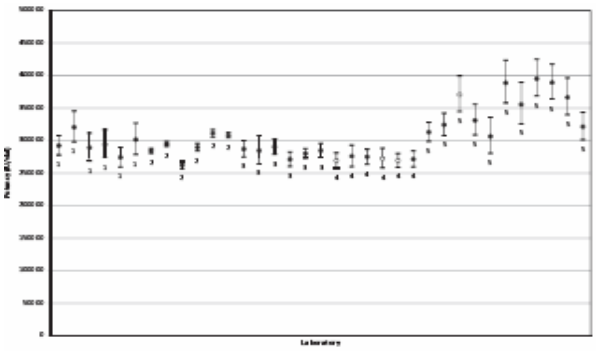

Fig. 7. Rezultatele obtinute pentru estimarea potentei colostimethate sodic in urma raportarilor laboratoarelor participante

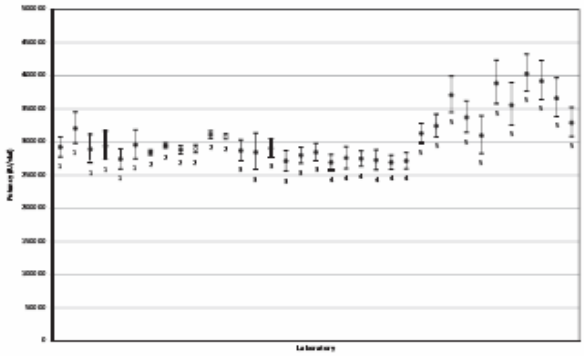

Fig. 7. Rezultatele obtinute pentru estimarea potentei colostimethate sodic in urma prelucrarii statistice de catre EDQM

CONCLUZII

In urma analizei si coroborarii rezultaleor primite de la participanti si a prelucrarii statistice a acestora de catre EDQM, valoarea potentei lotului 2 de colistimethate sodic – substanta de referinta, a fost stabilita la 285000UI/fiola.

BIBLOGRAFIE

1. **Farmacopeea Europeana** editia a 3 a: Capitolul 2.7. Teste biologice – testarea microbiologica a antibioticelor
2. **Protocol de lucru** pentru determinarea potentei colistimethatului sodic CRS, lotul 2 elaborat de EDQ