

## **BAB V**

### **KESIMPULAN DAN SARAN**

#### **A. KESIMPULAN**

Berdasarkan hasil penelitian dapat disimpulkan :

Pertama, imipenem 100 ppm merupakan antibiotik paling sensitiv dibanding antibiotik seftriakson, siprofloksasin, sefotaksim dan amikasin terhadap daya hambat bakteri *Klebsiella pneumoniae* ATCC 10031.

Kedua, kombinasi simvastatin 15 ppm dan 150 ppm dengan antibiotik seftriakson, siprofloksasin, imipenem, dan amikasin tidak memberikan peningkatan efek terhadap diameter zona hambat bakteri *Klebsiella pneumoniae* ATCC 10031, hanya kombinasi sefotaksim 100 ppm dan simvastatin 150 ppm yang memberikan hasil diameter daya hambat beda signifikan.

Ketiga, kombinasi simvastatin 150 ppm dengan sefotaksim 100 ppm memberikan hasil diameter daya hambat berbeda signifikan terhadap pertumbuhan bakteri *Klebsiella pneumoniae* ATCC 10031.

#### **B. SARAN**

Saran yang dapat diberikan untuk penelitian lebih lanjut :

Pertama, perlu dilakukan penelitian lebih lanjut efek kombinasi simvastatin dengan antibiotik yang berbeda dengan bakteri Gram negatif lain untuk mengetahui kemungkinan peningkatan efek antibakteri.

Kedua, perlu dilakukan penelitian efek antibakteri simvastatin pada konsentrasi dibawah 150 ppm untuk kemungkinan mendapatkan konsentrasi lebih kecil yang dapat memberikan aktivitas terhadap bakteri Gram negatif lain.

Ketiga, perlu dilakukan penelitian lanjutan untuk mengetahui secara pasti mekanisme kerja kombinasi sefotaksim 100 ppm dengan simvastatin 150 ppm agar dapat digunakan untuk pengobatan.

Keempat, perlu dilakukan penelitian lebih lanjut untuk mengetahui jenis kombinasi simvastatin 150 ppm dengan sefotaksim 100 ppm termasuk dalam kombinasi sinergisme adisi atau potensiasi.

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## Lampiran 1. Certificate of Analysis simvastatin


 TA : B-14/12/2012  
 TO : 28-11-2012  
 SHANGYU JINGXIN PHARMACEUTICAL CO., LTD.  
 CERTIFICATE OF ANALYSIS  
 Simvastatin

Aa Sample  
12/12

D-QA542-F05-R03 Analysis serial No.:DK40-1204281-01

Batch No.: DK40-1204281	Quantity: 25.00Kg	
Package Size: 25 Kg/Drum	Manufacturing Date: 28 Apr. 2012	
Issuing Date: 30 Apr. 2012	Expiry Date: 27 Apr. 2015	
Source: 516 Workshop	Quality Specification: USP34	
Items	Specification	Results
<b>CHARACTERS</b>		
Appearance	White to off-white powder	white powder
Solubility	Practically insoluble in water, Freely soluble in chloroform, in methanol, and in ethanol. Sparingly soluble in propylene glycol. Very slightly soluble in Hexane.	Complies
<b>IDENTIFICATION</b>		
IR	The spectrum obtained from sample consists with that obtained from Simvastatin RS	Complies
HPLC	The retention time of the major peak in the chromatogram of the standard preparation, as obtained in the Assay	Complies
Specific rotation	+285°~+298°	+291.0°
Loss on drying	Not more than 0.5%	0.02%
Residue on ignition	Not more than 0.1%	0.04%
Heavy metals	Not more than 0.002%	Less than 0.002%
<b>Chromatographic purity</b>		
Simvastatin hydroxyacid	Not more than 0.4%	0.04%
Epilovastatin and Lovastatin	Not more than 1.0%	0.44%
Methylene simvastatin	Not more than 0.4%	0.11%
Acetyl simvastatin	Not more than 0.4%	0.09%
Anhydro simvastatin	Not more than 0.4%	0.02%
Simvastatin dimer	Not more than 0.4%	0.17%
Any other individual impurity	Not more than 0.1%	0.06%
Total impurities other than lovastatin and epilovastatin	Not more than 1.0%	0.55%
<b>Residual solvents</b>		
Ethanol	Not more than 5000ppm	724ppm
Dichloromethane	Not more than 600ppm	Not more than 600ppm
ASSAY (on the dried basis)	98.0% to 102.0% of C <sub>25</sub> H <sub>38</sub> O <sub>5</sub>	99.4%
<b>Conclusion: The results conform with and do not conform with the specifications</b>		
Analyst: Wu Xiaofei 吴晓飞	Checker: Geng Ruifeng 耿瑞峰	QA Manager: [Signature]

Address: No. 31 Weisan Road, Zhejiang Hangzhou Bay Shangyu Industrial Area, Shangyu City Zhejiang Province, P.R. China, 312369  
 Tel.: +86-575-82728559 Fax: +86-575-82728551

## Lampiran 2. Certificate of Analysis siprofloksasin

As Sample  
02/6  
27/8

浙江国邦药业有限公司  
ZHEJIANG GUOBANG PHARMACEUTICAL CO., LTD  
地址: 中国浙江宁波保税工业园区五路 邮编: 315169 电话: 086-575-82735575 电传: 086-575-82735575  
110 Wu Road, Free Chemical Zone, Shanghai, Zhejiang, China 315169 Fax: 086-575-82735575 Tel: 086-575-82735575

质量检验报告书  
CERTIFICATE OF ANALYSIS

检验项目 (Tests)	标准规定 (Acceptance Criteria)	结果 (Results)	
样品名称 Product	盐酸环丙沙星 Ciprofloxacin HCL	批号 Batch No 101-130225-1 ✓	
包装 Packaging Size	25Kg/桶 (drum)	数量 Quantity 400Kg	
生产日期 MFG Date	25/02/2013 (daily)	检测日期 Testing Date 01/03/2013 (daily)	
执行标准 According to	美国药典 (USP35)	失效日期 Expiry Date 24/02/2016 (daily)	
外观 Description	微黄色至淡黄色结晶性粉末 Faintly yellowish to light yellow crystalline powder	符合 Conforms	
溶解性 Solubility	在水中略溶, 难溶于醋酸和甲醇, 在乙醇中微溶, 几乎不溶于丙酮、乙醇、乙酸乙酯、正己烷和二氯甲烷。Sparingly soluble in water, slightly soluble in acetic acid and methanol, very slightly soluble in dehydrated alcohol, practically insoluble in acetone, in acetonitrile, in ethyl acetate, in hexane, and in methylene chloride		
鉴别 Identification	(1) IR: 红外光谱图特征与对照品的图谱一致 IR: Conforms to the spectrum of Ciprofloxacin Hydrochloride RS (2) HPLC: 在含量测定项下, 供试品溶液主峰保留时间应与对照品溶液主峰保留时间一致 HPLC: The retention time of the major peak of the Sample solution corresponds to that of the Standard solution, as obtained in the Assay (3) 应呈氯化物的鉴别反应 Responds to the tests for chloride	符合 Conforms	
酸度 pH	3.0-4.5 (1g/10ml water)	3.6	
水分 Water	4.7-6.7%	5.7%	
炽灼残渣 Residue on ignition	≤ 0.1%	0.05%	
硫酸盐 Sulphate	≤ 0.04%	< 0.04%	
重金属 Heavy metals	≤ 0.002%	< 0.002%	
荧光杂质 (TLC) Limit of fluoroquinolonic acid	≤ 0.2%	< 0.2%	
色谱纯度 (HPLC) Chromatographic purity	(1) 乙二胺类环丙沙星 Ciprofloxacin ethylenediamine analog	≤ 0.2%	0.10%
	(2) 其它单个杂质 Any other single impurity	≤ 0.2%	0.06%
	(3) 所有杂质 The sum of all impurities	≤ 0.5%	0.21%
含量 (HPLC) Assay	按无水物计算, 含 C <sub>17</sub> H <sub>14</sub> F <sub>3</sub> N <sub>3</sub> O <sub>3</sub> · HCl 应为 98.0%-102.0% 98.0%-102.0% (On the anhydrous substance)	99.9%	
残留溶剂 Residual solvents	(1) 乙醇 Ethanol	≤ 5000ppm	453ppm
	(2) 甲苯 Toluene	≤ 890ppm	未检出 Not detected

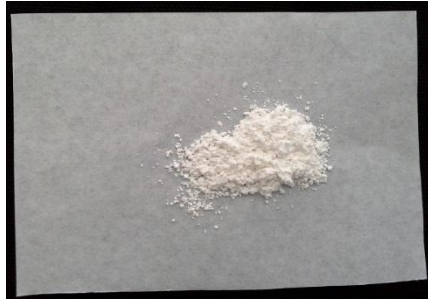
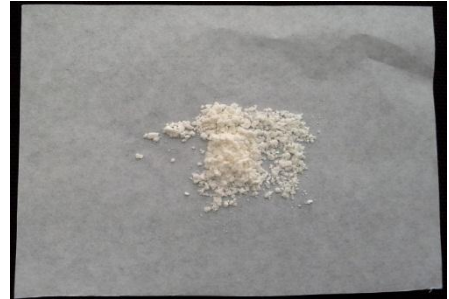
结论: 本品按美国药典 35 版标准检验, 结果符合规定  
Conclusion: Conforms to USP 35 specification for ciprofloxacin hydrochloride

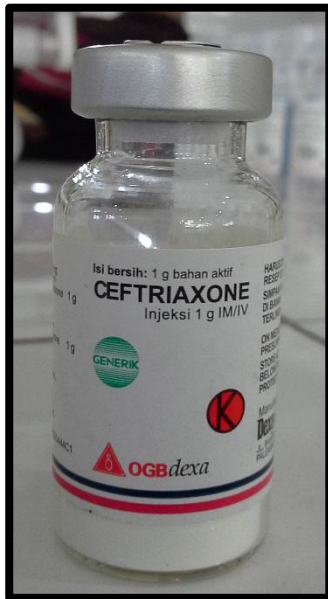
备注 (note): 松密度 (bulk density) 0.26g/ml

Reported by: Li Na  
Reviewed by: Pang Yanhua  
Approved by: Wu Qinghua

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0150 09:01 01/03/2013



**Lampiran 3. Foto bahan penelitian****3a. Foto simvastatin serbuk****3b. Foto siprofloksasin serbuk****3c. Foto injeksi imipenem****3d. Foto injeksi amikasin**



3e. Foto injeksi seftriakson



3f. Foto injeksi sefotaksim



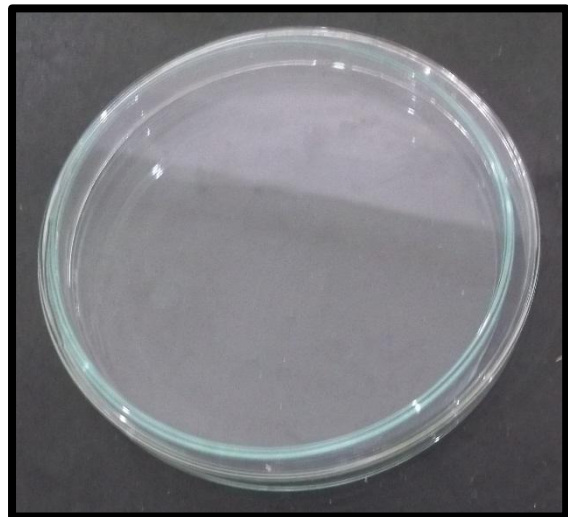
3g. Foto Sodium chloride 0,9%



3h. Foto ringer laktat

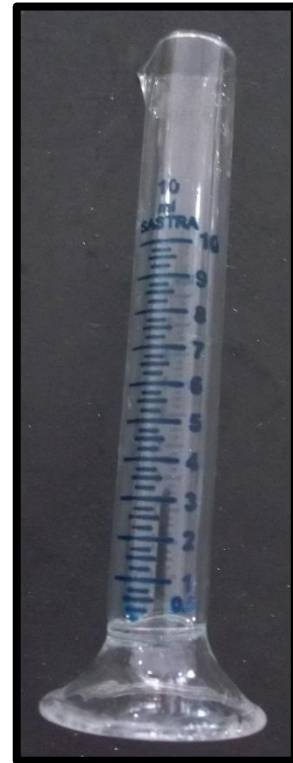


3i. Foto *sterille water for injection*    3j. Foto aqudest steril

**Lampiran 4. Foto alat penelitian.****4a. Foto mikropipet dan tip****4b. Fo****4c. Foto jarum ose****4d. Foto cawan petri**



4e. Foto inkas



4f. Foto gelas ukur



4g. Foto labu takar



4h. Foto bunsen



4i. vortex



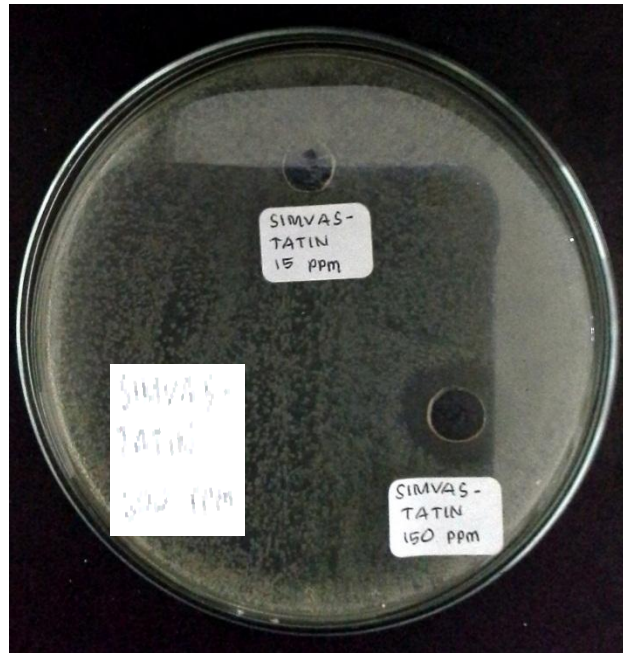
4j. foto timbangan analitik



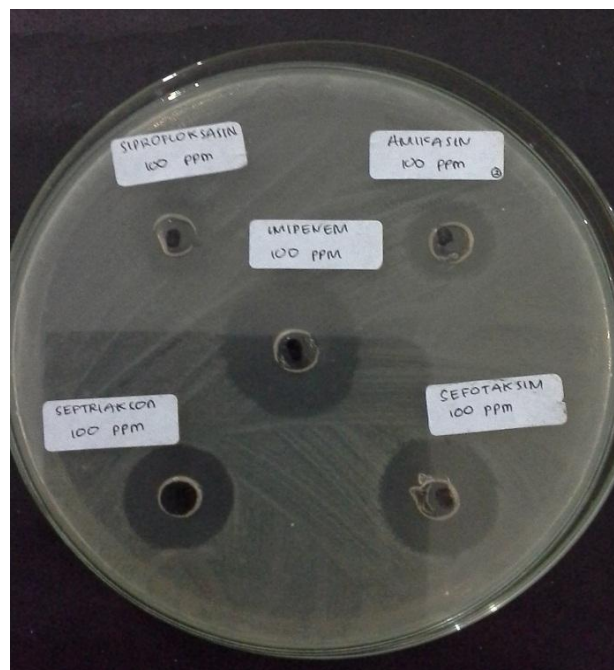
4k. Foto autoklav



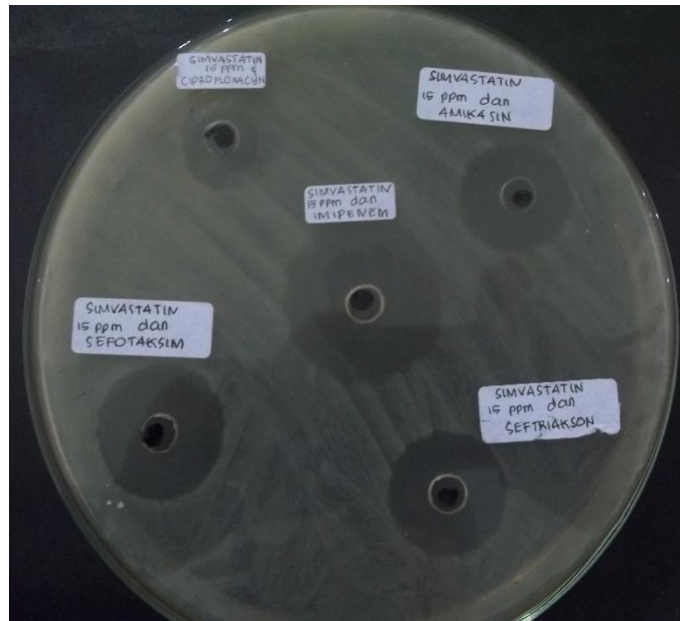
4l. Foto beaker glass

**Lampiran 5. Foto hasil percobaan**

**5a. foto hasil efek simvastatin 15 dan 150 ppm terhadap bakteri *Klebsiella pneumoniae***



**5b. foto hasil efek antibiotik seftriakson, siprofloksasin, sefotaksim, imipenem, dan amikasin 100 ppm terhadap bakteri *Klebsiella pneumoniae*.**

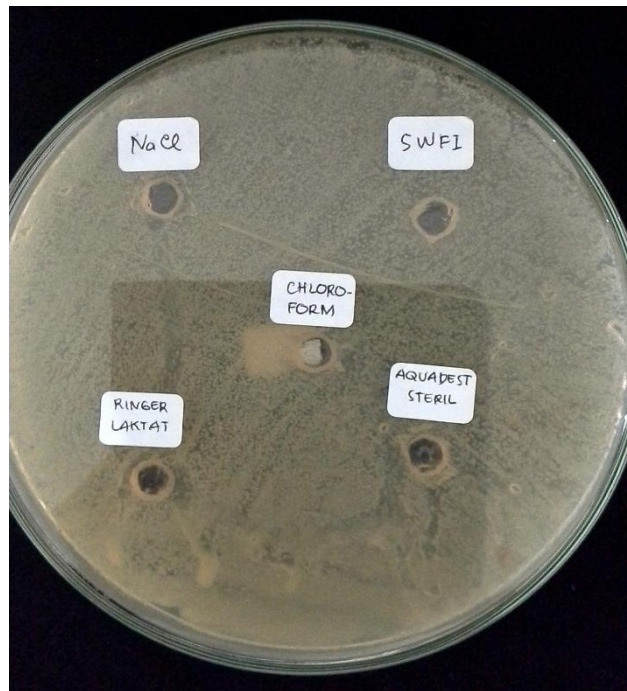


5c. foto hasil efek kombinasi simvastatin 15 ppm dengan kelima antibiotik terhadap bakteri *Klebsiella pneumoniae*



5d. foto hasil efek kombinasi simvastatin 150 ppm dengan kelima antibiotik terhadap bakteri *Klebsiella pneumoniae*.





**5f. foto kontrol pelarut.**

**Lampiran 6. Tabel hasil uji statistik.**

**6a. Hasil uji statistik perbandingan diameter daya hambat seftriakson dan kombinasi seftriakson dengan simvastatin 15 dan 150ppm.**

**Npar Tests**

**Descriptive Statistics**

	N	Mean	Std. Deviation	Minimum	Maximum
diameter daya hambat	9	25.22	2.108	23	29

**One-Sample Kolmogorov-Smirnov Test**

		diameter daya hambat
N		9
Normal Parameters <sup>a,b</sup>	Mean	25.22
	Std. Deviation	2.108
Most Extreme Differences	Absolute	.209
	Positive	.209
	Negative	-.146
Kolmogorov-Smirnov Z		.626
Asymp. Sig. (2-tailed)		.828

a. Test distribution is Normal.

b. Calculated from data.

**Oneway**

**Test of Homogeneity of Variances**

diameter daya hambat

Levene Statistic	df1	df2	Sig.
1.968	2	6	.220

**ANOVA**

diameter daya hambat

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	13.556	2	6.778	1.848	.237
Within Groups	22.000	6	3.667		
Total	35.556	8			

**6b. Hasil uji statistik perbandingan diameter daya hambat sefotaksim dan kombinasi sefotaksim dengan simvastatin 15 dan 150 ppm.**

**NPar Tests**

**Descriptive Statistics**

	N	Mean	Std. Deviation	Minimum	Maximum
diameter daya hambat	9	25.67	4.000	18	30

**One-Sample Kolmogorov-Smirnov Test**

		diameter daya hambat
N		9
Normal Parameters <sup>a,b</sup>	Mean	25.67
	Std. Deviation	4.000
Most Extreme Differences	Absolute	.311
	Positive	.169
	Negative	-.311
Kolmogorov-Smirnov Z		.933
Asymp. Sig. (2-tailed)		.349

a. Test distribution is Normal.

b. Calculated from data.

**Oneway**

**Test of Homogeneity of Variances**

diameter daya hambat

Levene Statistic	df1	df2	Sig.
4.989	2	6	.053

**ANOVA**

diameter daya hambat

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	88.667	2	44.333	6.763	.029
Within Groups	39.333	6	6.556		
Total	128.000	8			

## Post Hoc Tests

## Multiple Comparisons

Dependent Variable: diameter daya hambat

	(I) sampel	(J) sampel	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Tukey HSD	sefotaksim	sefotaksim + simvastatin 15 ppm	-5.667	2.091	.078	-12.08	.75
		sefotaksim + simvastatin 150 ppm	-7.333*	2.091	.029	-13.75	-.92
	sefotaksim + simvastatin 15 ppm	sefotaksim	5.667	2.091	.078	-.75	12.08
		sefotaksim + simvastatin 150 ppm	-1.667	2.091	.718	-8.08	4.75
	sefotaksim + simvastatin 150 ppm	sefotaksim	7.333*	2.091	.029	.92	13.75
		sefotaksim + simvastatin 15 ppm	1.667	2.091	.718	-4.75	8.08
Bonferroni	sefotaksim	sefotaksim + simvastatin 15 ppm	-5.667	2.091	.105	-12.54	1.21
		sefotaksim + simvastatin 150 ppm	-7.333*	2.091	.038	-14.21	-.46
	sefotaksim + simvastatin 15 ppm	sefotaksim	5.667	2.091	.105	-1.21	12.54
		sefotaksim + simvastatin 150 ppm	-1.667	2.091	1.000	-8.54	5.21
	sefotaksim + simvastatin 150 ppm	sefotaksim	7.333*	2.091	.038	.46	14.21
		sefotaksim + simvastatin 15 ppm	1.667	2.091	1.000	-5.21	8.54

\*. The mean difference is significant at the 0.05 level.

## Homogeneous Subsets

### diameter daya hambat

sampel	N	Subset for alpha = 0.05	
		1	2
Tukey HSD <sup>a</sup> sefotaksim	3	21.33	
sefotaksim + simvastatin 15 ppm	3	27.00	27.00
sefotaksim + simvastatin 150 ppm	3		28.67
Sig.		.078	.718

Means for groups in homogeneous subsets are displayed.

a. Uses Harmonic Mean Sample Size = 3,000.

**6c. Hasil uji statistik perbandingan diameter daya hambat siprofloksasin dan kombinasi siprofloksasin dengan simvastatin 15 dan 150 ppm.**

**NPar Tests**

**Descriptive Statistics**

	N	Mean	Std. Deviation	Minimum	Maximum
diameter daya hambat	9	21.00	3.428	17	28

**One-Sample Kolmogorov-Smirnov Test**

		diameter daya hambat
N		9
Normal Parameters <sup>a,b</sup>	Mean	21.00
	Std. Deviation	3.428
Most Extreme Differences	Absolute	.170
	Positive	.170
	Negative	-.122
Kolmogorov-Smirnov Z		.511
Asymp. Sig. (2-tailed)		.957

a. Test distribution is Normal.

b. Calculated from data.

**Oneway**

**Test of Homogeneity of Variances**

diameter daya hambat

Levene Statistic	df1	df2	Sig.
.630	2	6	.564

**ANOVA**

diameter daya hambat

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	18.667	2	9.333	.743	.515
Within Groups	75.333	6	12.556		
Total	94.000	8			

**6d. Hasil uji statistik perbandingan diameter daya hambat imipenem dan kombinasi imipenem dengan simvastatin 15 dan 150 ppm.**

**NPar Tests**

**Descriptive Statistics**

	N	Mean	Std. Deviation	Minimum	Maximum
diameter daya hambat	9	32.11	2.472	29	37

**One-Sample Kolmogorov-Smirnov Test**

		diameter daya hambat
N		9
Normal Parameters <sup>a,b</sup>	Mean	32.11
	Std. Deviation	2.472
Most Extreme Differences	Absolute	.185
	Positive	.185
	Negative	-.149
Kolmogorov-Smirnov Z		.554
Asymp. Sig. (2-tailed)		.919

a. Test distribution is Normal.

b. Calculated from data.

**Oneway**

**Test of Homogeneity of Variances**

diameter daya hambat

Levene Statistic	df1	df2	Sig.
3.564	2	6	.095

**ANOVA**

diameter daya hambat

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	20.222	2	10.111	2.116	.202
Within Groups	28.667	6	4.778		
Total	48.889	8			

**6e. Hasil uji statistik perbandingan diameter daya hambat amikasin dan kombinasi amikasin dengan simvastatin 15 dan 150ppm.**

**NPar Tests**

**Descriptive Statistics**

	N	Mean	Std. Deviation	Minimum	Maximum
diameter daya hambat	9	19.11	1.364	17	22

**One-Sample Kolmogorov-Smirnov Test**

		diameter daya hambat
N		9
Normal Parameters <sup>a,b</sup>	Mean	19.11
	Std. Deviation	1.364
Most Extreme Differences	Absolute	.310
	Positive	.310
	Negative	-.245
Kolmogorov-Smirnov Z		.931
Asymp. Sig. (2-tailed)		.352

a. Test distribution is Normal.

b. Calculated from data.

**Oneway**

**Test of Homogeneity of Variances**

diameter daya hambat

Levene Statistic	df1	df2	Sig.
2.261	2	6	.185

**ANOVA**

diameter daya hambat

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	3.556	2	1.778	.941	.441
Within Groups	11.333	6	1.889		
Total	14.889	8			



## Lampiran 7. Perhitungan pembuatan larutan uji

### 7a. Perhitungan pembuatan simvastatin 15 dan 150ppm.

- Pembuatan larutan stock simvastatin 600 ppm dengan cara melarutkan simvastatin 60 mg, masukkan labu takar 100 ml, larutkan dengan kloroform ad 100 mL.
- Pengenceran simvastatin 600 ppm menjadi 150 ppm.

$$\begin{aligned}
 V_1 \cdot C_1 &= V_2 \cdot C_2 \\
 100 \cdot 150 &= V_2 \cdot 600 \\
 V_2 &= \frac{15000}{600} \\
 &= 25
 \end{aligned}$$

Pipet 25 ml dari larutan stock 600 ppm, masukkan dalam labu takar 100 ml, tambahkan kloroform ad 100 ml.

- Pengenceran simvastatin 150 ppm menjadi 15 ppm

$$\begin{aligned}
 V_1 \cdot C_1 &= V_2 \cdot C_2 \\
 100 \cdot 15 &= V_2 \cdot 150 \\
 V_2 &= \frac{1500}{150} \\
 &= 10
 \end{aligned}$$

Pipet 10 ml dari larutan simvastatin 150 ppm, masukkan labu takar 100 ml, tambahkan kloroform ad 100 ml.

### 7b. Perhitungan pembuatan antibiotik siprofloksasin 100 ppm

- Membuat larutan stock dengan menimbang siprofloksasin 100 mg, masukkan labu takar 100 ml, larutkan dengan aquadest steril ad 100 ml.
- Pengenceran siprofloksasin 1000 ppm menjadi 100 ppm

$$C1 \cdot V1 = C2 \cdot V2$$

$$1000 \cdot 10 = C2 \cdot 100$$

$$C2 = \frac{10000}{100}$$

$$= 100 \text{ ppm}$$

Pipet 10 ml larutan siprofloksain 1000 ppm, masukkan labu takar 100 ml, tambahkan aquadest steril ad 100 ml.

### 7c. Perhitungan pembuatan antibiotik seftriakson 100 ppm

- Tersedia injeksi seftriakson  $1\frac{g}{10 \text{ ml}}$  pelarut, dibuat konsentrasi 100 ppm.
- Seftriakson  $1\frac{g}{10 \text{ ml}} = 100000 \frac{\text{mg}}{1000 \text{ ml}} = 100000 \text{ ppm}$  larutan stock diencerkan menjadi 100 ppm

$$C1 \cdot V1 = C2 \cdot V2$$

$$100000 \cdot 0,1 = C2 \cdot 100$$

$$C2 = \frac{10000}{100}$$

$$= 100 \text{ ppm}$$

Pipet 0,1 ml injeksi seftriakson, masukkan labu takar 100 ml, tambahkan dengan *Sterile Water for Injection* ad 100 ml.

#### 7d. Perhitungan pembuatan antibiotik sefotaksim 100 ppm

- Tersedia injeksi sefotaksim  $1\frac{g}{4\text{ ml}}$  pelarut, dibuat konsentrasi 100 ppm.
- Sefotaksim  $1\frac{g}{4\text{ ml}} = 250000\frac{\text{mg}}{1000\text{ ml}} = 250000\text{ ppm}$  diencerkan menjadi 5000 ppm

$$C1 \cdot V1 = C2 \cdot V2$$

$$250000 \cdot 1 = C2 \cdot 50$$

$$C2 = \frac{250000}{50}$$

$$= 5000\text{ ppm}$$

Pipet 1 ml injeksi sefotaksim dari larutan stock 250000 ppm, masukkan labu takar 50 ml, tambahkan dengan *Sterille Water for Injection* ad 50 ml.

- Pengenceran sefotaksim 5000 ppm menjadi 100 ppm

$$C1 \cdot V1 = C2 \cdot V2$$

$$5000 \cdot 1 = C2 \cdot 50$$

$$C2 = \frac{5000}{50}$$

$$= 100\text{ ppm}$$

Pipet larutan injeksi sefotaksim 5000 ppm, masukkan labu takar 50 ml, tambahkan *Sterille Water for Injection* ad 50 ml.

#### 7e. Perhitungan pembuatan antibiotik imipenem 100 ppm.

- Tersedia injeksi imipenem  $500\frac{\text{mg}}{100\text{ ml}}$  pelarut, dibuat konsentrasi 100 ppm.
- Imipenem  $5000\frac{\text{mg}}{1000\text{ ml}} = 5000\text{ ppm}$  diencerkan menjadi 100 ppm

$$C1 \cdot V1 = C2 \cdot V2$$

$$5000 \cdot 1 = C2 \cdot 50$$

$$C2 = \frac{5000}{50}$$

$$50$$

$$= 100 \text{ ppm}$$

Pipet 1 ml larutan injeksi imipenem dari larutan stock 5000 ppm, masukkan labu takar 50 ml, tambahkan pelarut NaCl ad 50 ml.

#### **Lampiran 16. Perhitungan pembuatan antibiotik amikasin 100 ppm**

- Tersedia injeksi amikasin 250  $\text{mg}/2 \text{ ml}$  pelarut, dibuat konsentrasi 100 ppm
- Amikasin 250  $\text{mg}/2 \text{ ml} = 125000 \text{ mg}/1000 \text{ ml} = 125000 \text{ ppm}$  dijadikan 500 ppm

$$C1 \cdot V1 = C2 \cdot V2$$

$$125000 \cdot 0,1 = C2 \cdot 25$$

$$C2 = \frac{12500}{25}$$

$$25$$

$$= 500 \text{ ppm}$$

Pipet 0,1 ml larutan injeksi amikasin dari larutan stock 125000 ppm, masukkan labu takar 25 ml, tambahkan ringer laktat ad 25 ml.

- Pengenceran amikasin 500 ppm menjadi 100 ppm

$$C1 \cdot V1 = C2 \cdot V2$$

$$500 \cdot 5 = C2 \cdot 25$$

$$C2 = \frac{2500}{25}$$

$$25$$

$$= 100 \text{ ppm}$$

Pipet 5 ml larutan injeksi amikasin dari 500 ppm, masukkan labu takar 25 ml, tambahkan ringer laktat ad 25 ml.