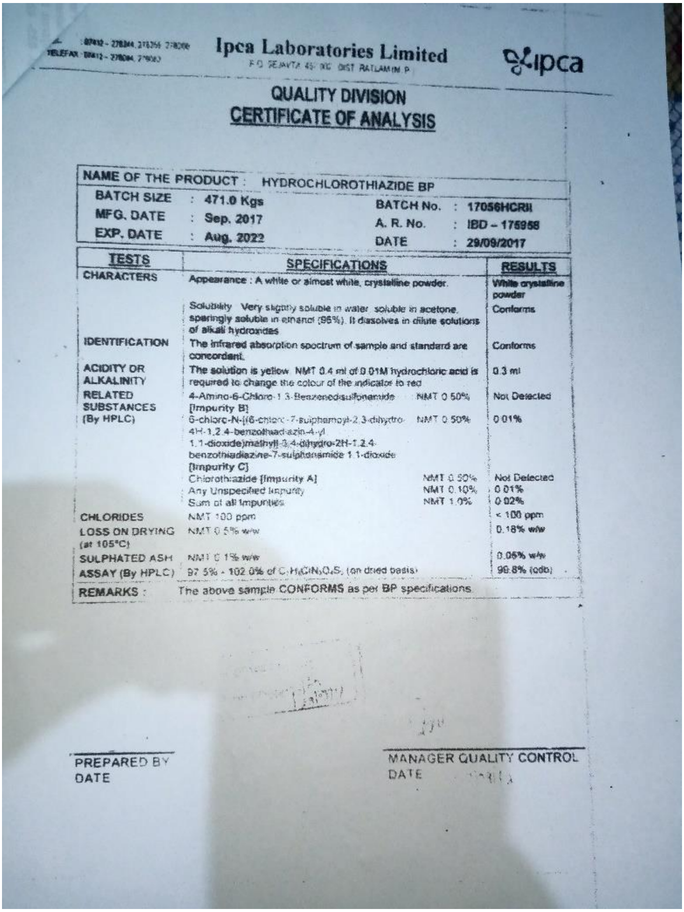
LAMPIRAN

Lampiran 1. COA Hidroklorotiazide



Ipca Laboratories Limited

QUALITY DIVISION

CERTIFICATE OF ANALYSIS

NAME OF THE PRODUCT :	HYDROCHLOROTHIAZIDE BP		
BATCH SIZE	: 471.0 Kgs	BATCH No.	: 17056HCRII
MFG. DATE	: Sep. 2017	A. R. No.	: IBD – 175958
EXP. DATE	: Aug. 2022	DATE	: 29/09/2017

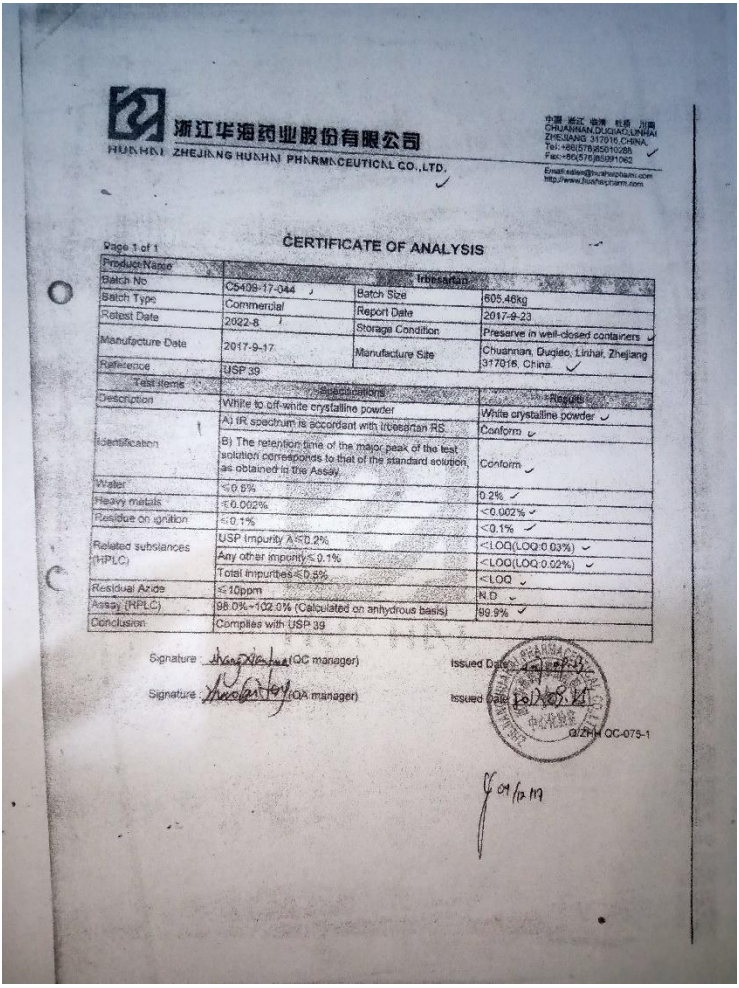
TESTS	SPECIFICATIONS		RESULTS
CHARACTERS	Appearance : A white or almost white, crystalline powder.		White crystalline powder
	Solubility : Very slightly soluble in water, soluble in acetone, sparingly soluble in ethanol (96%). It dissolves in dilute solutions of alkali hydroxides		Conforms
IDENTIFICATION	The infrared absorption spectrum of sample and standard are concordant.		Conforms
ACIDITY OR ALKALINITY	The solution is yellow. NMT 0.4 ml of 0.01M hydrochloric acid is required to change the colour of the indicator to red		0.3 ml
RELATED SUBSTANCES (By HPLC)	4-Amino-6-Chloro-1,3-Benzenedisulfonamide [Impurity B]	NMT 0.50%	Not Detected
	6-chloro-N-[(6-chloro-7-sulphamoyl-2,3-dihydro-4H-1,2,4-benzothiadiazin-4-yl 1,1-dioxide)methyl]-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide [Impurity C]	NMT 0.50%	0.01%
	Chlorothiazide [Impurity A]	NMT 0.50%	Not Detected
	Any Unspecified Impurity	NMT 0.10%	0.01%
	Sum of all Impurities	NMT 1.0%	0.02%
CHLORIDES	NMT 100 ppm		< 100 ppm
LOSS ON DRYING (at 105°C)	NMT 0.5% w/w		0.18% w/w
SULPHATED ASH	NMT 0.1% w/w		0.06% w/w
ASSAY (By HPLC)	97.5% - 102.0% of $C_7H_8ClN_3O_4S_2$ (on dried basis)		99.8% (odb)

REMARKS : The above sample CONFORMS as per BP specifications.

PREPARED BY
DATE

MANAGER QUALITY CONTROL
DATE

Lampiran 2. COA Irbesartan



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Page 1 of 1

CERTIFICATE OF ANALYSIS

Product Name	Irbesartan		
Batch No	C5409-17-044	Batch Size	605.46kg
Batch Type	Commercial	Report Date	2017-9-23
Retest Date	2022-8	Storage Condition	Preserve in well-closed containers
Manufacture Date	2017-9-17	Manufacture Site	Chuannan, Duqiao, Linhai, Zhejiang 317016, China.
Reference	USP 39		

Test Items	Specifications	Results
Description	White to off-white crystalline powder	White crystalline powder
Identification	A) IR spectrum is accordant with Irbesartan RS	Conform
	B) The retention time of the major peak of the test solution corresponds to that of the standard solution, as obtained in the Assay	Conform
Water	≤0.5%	0.2%
Heavy metals	≤0.002%	<0.002%
Residue on ignition	≤0.1%	<0.1%
Related substances (HPLC)	USP Impurity A≤0.2%	<LOQ(LOQ:0.03%)
	Any other impurity ≤ 0.1%	<LOQ(LOQ:0.02%)
	Total impurities ≤0.3%	<LOQ
Residual Azide	≤10ppm	N.D
Assay (RPLC)	98.0%~102.0% (Calculated on anhydrous basis)	99.9%
Conclusion	Complies with USP 39	

Signature: (QC manager) Issued Date:

Signature: (QA manager) Issued Date:

Q/ZHH QC-075-1

Lampiran 3. Hasil Batas Deteksi dan Batas Kuantisasi Irbesartan

No	c (bpj)	A	selisih	$(x_i - x)$	$(x_i - x)^2$	$(y_i - y)$	$(y_i - y)^2$
1	700	49000,62		-250	62500	-17172,4	294890680,7
2	800	56403,295	7402,675	-150	22500	-9769,71	95447161,84
3	900	63610,759	7207,464	-50	2500	-2562,24	6565085,775
4	1000	70510,78	6900,021	50	2500	4337,78	18816323,76
5	1100	75000,41	4489,63	150	22500	8827,41	77923143,77
6	1200	82512,144	7511,734	250	62500	16339,1	266967583,1
Σ	5700	397038,008		Σ	175000	Σ	760609978,9
rata-rata	950	66173,0013					

Sy/x	902,5815511
LoD	**41,160252**
LoQ	**137,20084**
Vx0	**1,44%**
r	0,997855595
b(slope)	65,78542457
a(intercep	3676,84799

$$Sxx = \Sigma(xi - x)2 \quad ; \quad Syy = \Sigma(yi - y)2$$

$$Sy/x = \sqrt{\frac{Syy - b2\ Sxx}{n - 2}}$$

$$LoD = \frac{3\ Sy/x}{b} \qquad LoQ = \frac{10\ Sy/x}{b}$$

Lampiran 4. Hasil Batas Deteksi dan Batas Kuantisasi Hidroklorotiazide

No	c (bpj)	A	selisih	$(x_i - x)$	$(x_i - x)^2$	$(y_i - y)$	$(y_i - y)^2$
1	70	4071,8		-25	625	-1226,29	1503789,6
2	80	4474,05	402,242	-15	225	-824,049	679056,75
3	90	5011,8	537,758	-5	25	-286,291	81962,537
4	100	5455,41	443,606	5	25	157,315	24748,009
5	110	6058,05	602,636	15	225	759,951	577525,52
6	120	6717,46	659,414	25	625	1419,37	2014597
Σ		31788,6		Σ	1750	Σ	4881679,4
rata-rata	95	5298,09					

r	0,99666129
b(slope)	52,6396743
a(intercep	297,324943
Sxx	1750
Syy	4881679,44
Sy/x	90,1979102
LoD	**5,14049022**
LoQ	**17,1349674**
Vx0	**1,80%**

$$Sxx = \Sigma(xi - x)2 \quad ; \quad Syy = \Sigma(yi - y)2$$

$$Sy/x = \sqrt{\frac{Syy - b2\ Sxx}{n - 2}}$$

$$LoD = \frac{3\ Sy/x}{b} \qquad LoQ = \frac{10\ Sy/x}{b}$$

Lampiran 5. Uji Presisi Hasil Presisi Hidroklorotiazide

	AUC	Cs	Ci	Massa	%rec	RSD
1	4795,093	85,44445	122,0635	3,051588	97,65%	1,63%
2	4684,295	83,33961	119,0566	2,976415	95,25%	
3	4666,884	83,00885	118,5841	2,964602	94,87%	
4	4742,864	84,45226	120,6461	3,016152	96,52%	
5	4643,932	82,57284	117,9612	2,94903	94,37%	
6	4584,581	81,44534	116,3505	2,908762	93,08%	
7	4818,371	85,88667	122,6952	3,067381	98,16%	
8	4761,273	84,80198	121,1457	3,028642	96,92%	
9	4713,377	83,89208	119,8458	2,996146	95,88%	
Rata-rata					**95,85%**	

Lampiran 6. Uji Presisi Hasil Presisi Irbesartan

Hari ke-1	AUC	Cs	Ci	Massa	%rec	RSD
1	61482,24	878,6961	1255,28	31,38200	83,69%	1,39%
2	60333,22	861,2299	1230,328	30,75821	82,02%	
3	61598,24	880,4593	1257,799	31,44498	83,85%	
4	62433,27	893,1526	1275,932	31,89831	85,06%	
5	60197,31	859,1640	1227,377	30,68443	81,83%	
6	61864,51	884,5069	1263,581	31,58953	84,24%	
7	60316,24	860,9717	1229,960	30,74899	82,00%	
8	59912,36	854,8323	1221,189	30,52973	81,41%	
9	59854,56	853,9538	1219,934	30,49835	81,33%	
Rata-rata					82,83%	

Lampiran 7. Hasil Perhitungan Akurasi untuk Sampel Hidroklorotiazide dan Irbesartan

Sampel	Massa teoritis (mg)	Massa pengukuran (µg / mL)	*% recovery*
Hidriklorotiazide	3,13	3,051588	97,65%
		2,976415	95,25%
		2,964602	94,87%
	Rata-rata	2,997535	95,92%
	3,13	3,016152	96,52%
		2,94903	94,37%
		2,908762	93,08%
	Rata-rata	2,957981	94,66%
	3,13	3,067381	98,16%
		3,028642	96,92%
		2,996146	95,88%
	Rata-rata	3,030723	96,98%
Irbesartan		31,382	83,69%
	37,5	30,75821	82,02%
		31,44498	83,85%

	Rata-rata	31,19506	83,19%
	37,5	31,89831	85,06%
		30,68443	81,83%
		31,58953	84,24%
	Rata-rata	31,39076	83,71%
	37,5	30,74899	82,00%
		30,52973	81,41%
		30,49835	81,33%
	Rata-rata	30,59236	81,58%

Contoh perhitungan :

Persamaan regresi linear :

$y = bx + a$

$y = 52,64\ Cs - 297,3249$

$4795,093 = 52,64\ Cs - 297,3249$

$Cs = \frac{4795,093 - 297,3249}{52,64}$

$Cs = 85,44445\ \mu g / mL$

$Ci = Cs \times F$

$Ci = 85,44445\ \mu g / mL \times 1, 43$

$Ci = 122,0635\ \mu g / mL$

$Massa = \frac{Ci\ x\ Vi}{1000}$

$Massa = \frac{122,0635\ \mu g — mL\ X\ 25\ mL}{1000}$

$Massa = 3,051588\ mg$

$$\% \text{ recovery} = \frac{bobot\ terukur}{bobot\ teoritis} \text{ x } 100\ \%$$

$$= \frac{3{,}051588}{3{,}13} \text{x } 100\%$$

$$= 97{,}65\ \%$$

Lampiran 8. Penetapan Kadar Hidroklorotiazide

AUC	Cs (ug/mL)	Ci (ug/mL)	Massa per tablet (mg)	Masa tablet (mg)	Kadar (%)
5128,4	91,77630984	131,109	11,92	3,277725351	95,20
5004,1	89,41497304	127,7357	11,61	3,193391894	92,90
5008,7	89,5023596	127,8605	11,62	3,196512843	92,99
				Rata-rata	**93,7**

Lampiran 9. Penetapan Kadar Irbesartan

AUC	Cs (ug/mL)	Ci (ug/mL)	Massa per tablet (mg)	Massa Tablet (mg)	Kadar (%)
71128,3	1025,325176	1464,75	154,10	36,61875628	102,73
70224,7	1011,58961	1445,128	152,04	36,12820037	101,36
70029,3	1008,619348	1440,885	151,59	36,02211956	101,06
				Rata2	**101,72**

Contoh Perhitungan :

Bobot rata-rata tablet = 261,41

Bobot kandungan hidroklorotiazide = 12,5 mg

Bobot kandungan irbesartan = 150 mg

Bobot Sampel yang ditimbang

Didapatkan AUC :

1. 5128,4
2. 5004,1

3. 5009,7

Persamaan Regresi Linear

y = 52,64 x + 297,3249

1. AUC ke-1 hidroklorotiazide

52,64 = 5128,4 – 297,3249
= 91,78 µg/ mL

Konsentrasi induk(Ci) = Cs x fp
= 91,78 µg/ mL x 1,43
= 131,24 µg/ml

Massa annalit = Ci X Vi
= 131,24 µg/ml X 25 ml
=3281 µg – 3,28 mg

Bobot hidroklorotiazide / Tablet

$$= \text{Bobot Terukur x } \frac{bobot\ rata{-}rata\ tablet}{bobot\ yang\ ditimbang} \text{ x FK}$$

$$= 3{,}28 \text{ mg x } \frac{261{,}41\ mg}{75\ mg} \text{ x } 1.04$$

= 11,9 mg

$$\% \text{ Kadar hidroklorotiazide} = \frac{Bobot\ Amoxicilin\ Per\ Tablet}{Bobot\ Teori} \text{ x } 100\ \%$$

$$= \frac{11{,}9\ mg}{12{,}5mg} \text{ x } 100\ \%$$

= 95.2 %