Serial: 00000/YYYY

Format and Content of Bioequivalence Study Report to be submitted to the Central Administration of Pharmaceutical Affairs (CAPA)

1.	**Title page**	
1.1	**Study title**	
1.2	**Name of the test drug & dosage form**	
1.3	**Name of active ingredient(s) & conc.**	
1.4	**Name of sponsor & manufacturer**	
1.5	**Name of the reference drug & dosage form**	
1.6	**Name of active ingredient(s) & conc.**	
1.7	**Name of manufacturer, sponsor & country of origin**	
1.8	**Name and address of bioequivalence center**	
1.9	**Name, affiliation and signature of: (dated)**	
1.9.1	**Chairman of the board**	
1.9.2	**Center manager**	
1.9.3	**Technical manager**	
1.9.4	**Chief analyst**	
1.9.5	**Quality assurance manager**	
1.9.6	**Sponsor representative of the company**	

2.	**Original certificate of sameness or equivalence including: (dated & signed)**	
2.1	**Test product (as stated in registration documents)**	
2.1.1	**Trade name**	
2.1.2	**Dosage form**	
2.1.3	**Strength**	
2.1.4	**Manufacturer & sponsor**	
2.1.5	**Batch number**	
2.1.6	**Manufacture date & expiry date**	
2.2	**Reference Product (as on the pack)**	
2.2.1	**Trade name**	
2.2.2	**Dosage form**	
2.2.3	**Strength**	
2.2.4	**Manufacturer, sponsor & country of origin**	

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2.2.5	Batch number	
2.2.6	Manufacture date & expiry date	
2.3	Conclusion (90% confidence interval "C.I" & point estimate) for all pharmacokinetic parameters ($AUC_{0\rightarrow t}$, $AUC_{0\rightarrow\infty}$, C_{max})	

3.	Dates of:	
3.1	Contract with sponsor	
3.2	Protocol approval	
3.3	In-vitro phase	
3.4	IRB or ethics committee approval	
3.5	Screening of volunteers	
3.6	Phase I	
3.7	Phase II	
3.8	Start of analysis	
3.10	End of analysis	
3.3	Report issue	

4.	Study protocol	
4.1	Protocol approval (signed & dated)	
4.2	Protocol justification	
4.3	Deviation from protocol with justification (if present)	
4.4	Letter of IRB or ethics committee approval (dated, signed & including study title)	
4.5	Study design	
4.5.1	Subjects assignment in the study	
4.5.1.1	Disposition of volunteers	
	No. of screened volunteers	
	No. of withdrawn volunteers	
	No. of enrolled volunteers	
	No. of excluded volunteers	
	Final no. of volunteers participated in the study	
4.5.1.2	Exclusion and inclusion criteria	

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4.5.2	Number of periods	
4.5.3	Sequence (randomization plan) for all screened volunteers	
4.5.4	Sequence (randomization plan) for final no. of volunteers participated in the study	
4.5.5	Treatments (test and reference)	
4.5.6	Half-life for each active ingredient	
4.5.7	Washout period	
4.5.8	Dosage form administration (fasting, with food, fluid intake with product, time, type of food and fluids,…etc)	
4.5.9	Procedures to minimize risk	
4.5.10	Time and frequency of sampling	
4.6	Type of obtained biological samples	
4.6.1	Sufficient number of biological samples should be collected during the absorption phase (not less than 3 points)	
4.6.2	Intensive sampling should be carried out around the time of the expected peak concentration	
4.6.3	Sufficient number of samples should be collected in the Log-linear elimination phase of the drug (A sampling period extending to at least four to five half lives of the drug is usually sufficient)	
4.6.4.	Storage conditions of biological samples	
4.7	Data analysis	
4.8	Template of informed consent form	
4.9	Template of case report	

5.	Report contents	
5.1	Study synopsis	
5.2	Abbreviations	
5.3	Study objective	
5.4	Study resume	
5.5	Drug review	
5.5.1	Pharmacokinetic characteristics	
5.5.2	Pharmacodynamics, indications	
5.5.3	Pharmacological actions	
5.5.4	Side effects & contraindications	

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6.	Product information (presented as follows)	
Item	**Test Product**	**Reference Product**
1.Product name		
2. API$_{(S)}$		
3.Molecular and structural formula		
4.Dosage form		
5.Type of the product (Immediate or modified release)		
6.Dosage regimen		
7.Strength		
8.Batch number		
9.Manufacture date		
10.Expiry date		
11.Storage conditions		

7.	Summary of bioequivalence Study	
7.1.	Analytical procedure (method of analysis)	
7.2.	Pharmacokinetic parameters	
7.3.	Statistical methods	
7.5.	Figure of mean plasma concentration- time profile (linear - semilog) with standard deviation bars	
7.6.	Figure of mean cumulative urinary excretion (if applicable)	
7.7.	Figure of mean urinary excretion rates (if applicable)	
7.8.	Results and conclusion (tables of mean parameters T_{max} ,C_{max} , $AUC_{0\rightarrow\infty}$, $AUC_{0\rightarrow t}$) "untransformed - transformed"	
7.9	90% CI (upper & lower limits) & Point estimate for all Pharmacokinetic parameters ($AUC_{0\rightarrow t}$, $AUC_{0\rightarrow\infty}$, C_{max})	
7.10	Illustrative example of the method of calculation used	

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8.	**Bio-analytical method and validation**	
8.1	**Bio-analytical method description (with reference(s) if applicable)**	
8.1.1	**Equipment, materials, solvents and their sources**	
8.1.2	**Internal standard (name, concentration, and molecular formula)**	
8.1.3	**Preparation of stock and standard solutions (in details)**	
8.1.4	**Sample extraction scheme**	
8.2	**Validation report in terms of:**	
8.2.1	**Calibration curve: (done on spiked plasma and not less than three curves)**	
8.2.1.1	**Data of individual calibration curves**	
8.2.1.2	**Regression equation**	
8.2.1.3	**Sample back calculation**	
8.2.2	**Linearity & range**	
8.2.3	**Selectivity**	
8.2.4	**Limit of quantitation (LOQ) & Limit of detection (LOD)**	
8.2.5	**Precision (interday and intraday) & (analyst to analyst)**	
8.2.6	**Accuracy**	
8.2.7	**Stability**	
8.2.7.1	**Stability of the matrix**	
8.2.7.1.1	**Short term stability**	
8.2.7.1.2	**Freeze and thaw stability**	
8.2.7.1.3	**Long term stability**	
8.2.7.1.4	**Dry extract**	
8.2.7.1.5	**Post preparative stability & Processed sample integrity (Auto sampler stability)**	
8.2.7.2	**Stability of the standard solution**	
8.2.7.3	**Dilution integrity**	
8.2.8	**System suitability**	
8.2.9	**Robustness**	
8.2.10	**QC samples (3 Levels LQC-MQC-HQC)**	
8.3	**Data of the previously mentioned parameters**	
8.4	**Figures of calibration curve(s) and chromatograms "dated" of standard and quality control samples (blank, spiked and actual subject samples should be included)**	

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9.	Pharmacokinetic parameters	
9.1	Definitions	
9.2	Tabulated plasma concentration for each volunteer at each actual sampling time & regression equation used and mark terminal plasma conc. used for calculating Ke, $T_{1/2}$.	
9.3	Calculation of plasma levels for all volunteers (including: mean - SD - CV %"RSD")	
9.4	Pharmacokinetic parameters, calculation and tables ($AUC_{0\rightarrow t}$, $AUC_{0\rightarrow\infty}$, C_{max}, T_{max}, Ke, $T_{1/2}$, AUC_{Extra}, AUC_{Extra} / $AUC_{0\rightarrow t}$ Ratio)	
9.5	Figure of mean plasma concentration - time profile with standard deviation bars	
9.6	Figures of individual subjects plasma concentration-time profile (linear & semilog)	
9.7	Figure of mean cumulative urinary excretion (if applicable)	
9.8	Figures of individual subject cumulative urinary excretion (if applicable)	
9.9	Figure of mean urinary excretion rates (if applicable)	
9.10	Figures of individual subject urinary excretion rates (if applicable)	

10.	Statistical analysis	
10.1.	Type of statistical program that was used	
10.2.	ANOVA tables "for all pharmacokinetic parameters" should include (df, SS, MS, F, P) for each of the following parameters:	
10.2.1	Treatments (drugs or formulations)	
10.2.2	Periods (phases)	
10.2.3	Sequence (group or order)	
10.2.4	Subjects within sequence	
10.2.5	Error	
10.2.6	Total	
10.3.	Logarithmic transformation of the pharmacokinetic parameters: C_{max}, $AUC_{0\rightarrow t}$ and $AUC_{0\rightarrow\infty}$, should be performed before data analysis	

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10.4.	The pharmacokinetic parameter, T_{max}, should be expressed as median values and analyzed on untransformed data	
10.5.	The two one-sided hypotheses at the alpha error = 0.05 level of significance should be performed for AUC(s) and Cmax by constructing the 90% confidence interval for the ratio between the test and the reference averages based on transformed data (90% C.I. should be based on the error value from the ANOVA tables).	
10.6.	Point estimate and 90% C.I. should be stated under each transformed ANOVA Table for all pharmacokinetic parameters (C_{max}, $AUC_{0\rightarrow t}$, $AUC_{0\rightarrow\infty}$)	
10.7.	Summary of statistical significance & parameters	

11.	Subject information	
11.1	Case report including:	
11.1.1	Tables of demographic characteristics of the subjects (gender, age, weight, height & BMI)	
11.1.2	The clinical evaluation data of subjects:	
11.1.2.1	Tabulated results of hematological tests (CBC - blood group)	
11.1.2.2	Tabulated results of biochemical tests (Fasting glucose &lipid profile "LDL - HDL"& Liver functions "GOT - GPT" and kidney functions "Serum Urea, Creatinine")	
11.1.2.3	Tabulated results of serological tests (HIV & HCV)	
11.1.2.4	Urine analysis	
11.1.2.5	Pregnancy test	
11.2	Vital signs of subjects (blood pressure, chest examination, abdomen examination, pulse rate, Temperature,….etc.)	
11.3	Adverse reactions / side effects report (during the study)	

12.	In Vitro testing
12.1	Original certificate of sameness or equivalence for the in-vitro part including: (dated & signed)
12.1.1	Test product (as stated in registration documents)

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12.1.1.1	Trade name	
12.1.1.2	Dosage form	
12.1.1.3	Strength	
12.1.1.4	Manufacturer, sponsor	
12.1.1.5	Batch number	
12.1.1.6	Manufacture date & expiry date	
12.1.2	Reference Product (as on the pack)	
12.1.2.1	Trade name	
12.1.2.2	Dosage form	
12.1.2.3	Strength	
12.1.2.4	Manufacturer & sponsor & country of origin	
12.1.2.5	Batch number	
12.1.2.6	Manufacture date & expiry date	
12.1.3	Conclusion (similarity factor "f2") for all pH	
12.2	Potency determination (done for both test and reference products, on at least ten dosage forms and taking three determinations then statistically analyzed)	
12.2.1	Assay methodology	
12.2.2	Tabulated results & acceptance values	
12.2.3	HPLC chromatograms or UV charts (dated)	
12.2.4	Assay method validation in term of calibration curve	
12.3	Uniformity of dosage unit (weight variation and / or content uniformity) "according to the official compendia" (Reference is to be attached)	
12.3.1	Description of method used	
12.3.2	Tabulated results & acceptance values	
12.3.3	HPLC chromatograms or UV charts (dated)	
12.4	Dissolution testing "on 12 dosage units"	
12.4.1	Dissolution testing method (with reference attached)	
12.4.2	Dissolution media used	
12.4.2.1	pH 1.2	
12.4.2.2	pH 4.5	
12.4.2.3	pH 6.8	
12.4.2.4	The most suitable medium (done only if there is a reference method in FDA or USP)	

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12.4.3	Equations & tabulated results including (mean - SD - CV% "RSD"….) for the 12 dosage units (peak areas or UV absorbance values and % dissolved) for all pH	
12.4.4	Tabulated similarity factor "f_2" calculation for each pH	
12.4.5	Tabulated dissimilarity factor "f_1" calculation for each pH	
12.4.6	Comparative dissolution profile for each pH	
12.4.7	HPLC chromatograms or UV charts (dated)	
12.5	Dissolution method validation	
12.5.1	Full validation report for the most suitable medium (if there is no reference for the most suitable medium, full validation will be done for only one of the three media "1.2, 4.5, 6.8" at which the drug is most soluble) as follows:	
12.5.1.1	Calibration curve (with regression equation)	
12.5.1.2	Linearity	
12.5.1.3	Selectivity	
12.5.1.4	Accuracy	
12.5.1.5	Precision (interday and intraday)	
12.5.1.6	Recovery	
12.5.2	Verification report for the other media as follows:	
12.5.2.1	Accuracy	
12.5.2.2	Precision	
12.5.3	Data of the previously mentioned parameters	
12.5.4	Represented HPLC chromatograms or UV charts (dated)	

13.	Appendices	
13.1	Bioequivalence Summary Tables (Appendix II) present in the Egyptian Guidelines for Bioequivalence Studies for Marketing Authorization of Generic Products (Page 70-88) issued by CAPA	
13.2	Chromatograms of at least 20% of subjects (all chromatograms should reveal the peak areas of the drug and internal standard used including peak area ratio & calculation equation for each) "dated"	
13.3	Clinical facilities' description	
13.4	Analytical facilities' description	

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13.5	Curricula vitae (C.V.) of the investigators (not more than 2 pages for each C.V.)	
13.6	Table of team names', responsibilities & signatures including: - Principle investigator - Clinical investigator - Analytical supervisor - Study director,…etc	

13.	Extra items can be submitted (if any)

14.	References

The study report should be submitted as follows:

1. According to the above mentioned sequence.
2. On the official papers of the bioequivalence center.
3. All the pages should be numbered.
4. Containing an index (a table of contents).
5. Separators should be used between each of the previously mentioned items.

Date: / /

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