S-2 [11:10～11:40]

Procedures for the Development of Generic Products in Japan

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Summary

For the approval application of generic products of oral conventional dosage form in Japan, we must submit the following data to the Ministry of Health, Labor and Welfare.

①. Data on specifications and testing methods.

②. Data on stability test.

(Acceleration test or long-term storage test)

③. Data on bioequivalence.

There are many steps for the accomplishment of these data and getting manufacture license of generic products.

Generic products nowadays have become very important social subjects for the low-cost healthy lives of Japanese people, because of increasing medicinal cost with increasing aged persons. In Japan, new "Guideline for Bioequivalence Studies of Generic Products" was established 22nd December 1997 and we try all bioequivalence tests according to this guideline.

New GCP (Good Clinical Practice) has also established 27th March 1997 and all clinical trials for approval application are conducted under this GCP regulation.

In the case of NICHI-IKO, roughly speaking, development of generic products of oral

conventional dosage form is subdivided to the following ten steps.

1. Selection of development target
2. Selection of bulk (specifications and testing methods of bulk, draft)
3. Studies on innovated products
4. Establishment of specifications and testing methods of bulk and test products
5. Manufacture of test products
6. Assessment of test products
7. Bioequivalence studies
8. Application for approval
9. Approval review
10. Application for manufacturing

At first we choose the development targets from the innovated drugs listed by Development Managing Section in accordance with the following terms.

①. Re-examination Periods shall be over in a few years.

②. Period of Substance Patent shall be over in a few years.

③. The market size of innovated products is fairy large.

A few steps (2～5) after the decision of development targets are studies of the innovated products and establishment of specifications and testing methods of bulk and test products.

Many problems that should be resolved before the final manufacture of test products are existent. Those are as follows.

- How to get bulk without interruption
- Crystal form issue on bulk
- Stabilization technique of test products
- Manufacture technique of test products

- How to improve the innovated products
- Patent issue
- Profitability

Trial manufacture of test product is repeated and the dissolubility behaviors of them are studied and prescription of test product is finally decided.

Three lots of the final test products are manufactured for stability test and one lot among them is selected for bioequivalence studies.

Step-6 is assessment of test products for approval application. Tests such as appearance, coloring, absorption spectrum, disintegration, weight variation and quantitative analysis etc. are repeated three times on the three lots of final test products manufactured for the stability test.

The conditions of stability tests are as follows.

- Acceleration test

  40℃, 75%RH,6 months≦

- Long-term storage test

  25℃,36 months≦

Dissolution tests are tried on the final test products.

Step-7 is bioequivalence studies. Bioequivalence studies are generally performed as follows.

- Selection of reference products

  ①. Purchase of three lots of innovated products.

  ②. Dissolution tests on the three lots of the innovated products.

  ③. One lot of the innovated products that shows intermediate dissolution behavior is selected for reference products.

- Equivalence of dissolution

Evaluation for equivalence of dissolution between reference products and test products is performed under specified conditions(refer to guideline*). In almost all cases, equivalence of dissolution between reference products and test products should be approved.

・Bioequivalence tests

Preliminary trial is always performed for getting the information to design the protocol for main test. In the ordinary case, preliminary trial is conducted with six to ten subjects as total number in a cross over manner. If bioequivarence has approved from the results of this trial , main test is not conducted (in the case of ten subjects). There are some cases that bioequivalence is approved in this stage.

・Determination of plasma concentration of drug

Analytical methods have been completely validated by the beginning of preliminary trial. Validation for analytical methods is performed following ICH Topic Q2B and other reference data.

Measurement of plasma concentration of drug is carried out in our laboratory in many cases but we sometimes trust the job to other organizations.

・GCP regulations

Bioequivalence test is conducted under GCP regulations including preliminary trial.

We contract for trust and entrust contract with CRO followed by the contract of secrecy agreement. (CRO means contact research organization.). Clinical trial contract among sponsor, medical institution and CRO is performed. Medical institution is selected in conformity with standard operating procedures of NICHI-IKO. Monitoring and audit are enforced by the new GCP regulations. We entrust these matters to CRO in part.

Step-8 is application for approval. The following data are submitted to OPSR (Organization for Pharmaceutical Safety and Research, Japanese semi-government organization authorized by the Ministry of Health, Labor and Welfare) by the end of March

every year and if we miss this time limit, the approval shall be delayed one year.

- Data on specifications and testing methods
- Data on stability test. (Acceleration test or long-term storage test)
- Data on bioequivalence test

Step-9 is approval review. Both review of Equivalency Review and Compliance Review are carried out by OPSR. OPSR reviews equivalency between medicines applied for approval and medicines that have been already approved (Equivalency Review) and reviews the data attached to applications in order to verify the validity of data and compliance with standards (Compliance Review). These reviews are conducted under commission of MHLW based on the Pharmaceutical Affairs Law.

After equivalency review and compliance review approvals are given to applicants by 15th of March every year. Standard period for approval review work is nowadays one year for generics.

Step-10 is application for manufacturing license. After approval application to OPSR (MHLW), manufacturing technology section begins scale up studies.

About ten times of trial manufacturing are conducted to select bulk and the most preferable manufacturing procedures and conditions.

Performance Qualification is conducted using the really manufacturing plants for the final confirmation of manufacturing procedure and conditions.

Three lots of intermediate products (before final packaging) are manufactured for Prospective Validation. About one year has passed at this point of time and application for manufacturing license is conducted to local government. After inspection to manufacturing plants approval of manufacturing license is given and final packaging process is performed.

Newly approved generic products comes into market after being listed up in NHI reimbursement price. (NHI means National Health Insurance of Japan)

The followings are outline of bioequivalence test that NICHI- IKO adopts for oral conventional formulations based on the newly established guideline mentioned above.

① Design

Crossover Method is employed in principle.

② Number of total subjects

Preliminarily test: 6~10

Main test: 20≦

③ Selection of subjects

Healthy adult volunteers are employed in principle.

④ Drug administration

- Bioequivalence test is performed by single dose studies in principle.
- One dose unit or a clinical usual dose is generally employed.
- Drugs are usually given to subjects with 150ml of water after fasting for 10 hr. Fasting lasts at least for 4 hr post-dose.

⑤ Measurement of drug substances

- Plasma sample is generally employed.
- Sampling points should be at least 7, including zero time, 1 point before Cmax, 2 points around Cmax and 3 points during the elimination phase.
  We usually sample 10~12 points.
- Sampling is continued until AUCt is over 80% of AUC∞ (more than three times the elimination half life after tmax)

⑥ Drug substances to be measured.

Parent drugs should, in principle, be measured but Major active metabolites may be

measured instead of parent drugs if it is rational.

⑦ Assay

Analytical methods should be fully validated regarding specificity, accuracy, precision, linearity, quantitation limit and stability of substances in samples and so forth.

⑧ Washout periods

Washout periods in crossover studies between administration of test and reference products should usually be more than 5 times the elimination half life of the parent drug or active metabolites.

⑨ Parameters to be assessed

When blood samples are used, AUCt and Cmax are subjected to the bioequivalence assessment in single dose studies.

⑩ Logarithmic transformation

Pharmacokinetic parameters except for tmax are in principle statistically analyzed after logarithmic transformation.

⑪ Statistic analysis

The 90% shortest confidence interval is used.

⑫ Acceptance criteria

(a). Products are considered to be bioequivalent, if the 90% confidence interval of difference in the average values of logarithmic AUCt and Cmax between test and reference products is within the acceptable range of log(0.8)-log(1.25).

(b). However, even though the confidence interval is not in the above range, test products are accepted as bioequivalent, if the following three conditions are satisfied.

①. The total sample size of the initial bioequivalence study is not less than

20(n=10/group) or pooled sample size of the initial and add-on subject studies is not less than 30.

②. The differences in average values of logarithmic AUCt and Cmax between two products are in the range of log(0.9)-log(1.11).

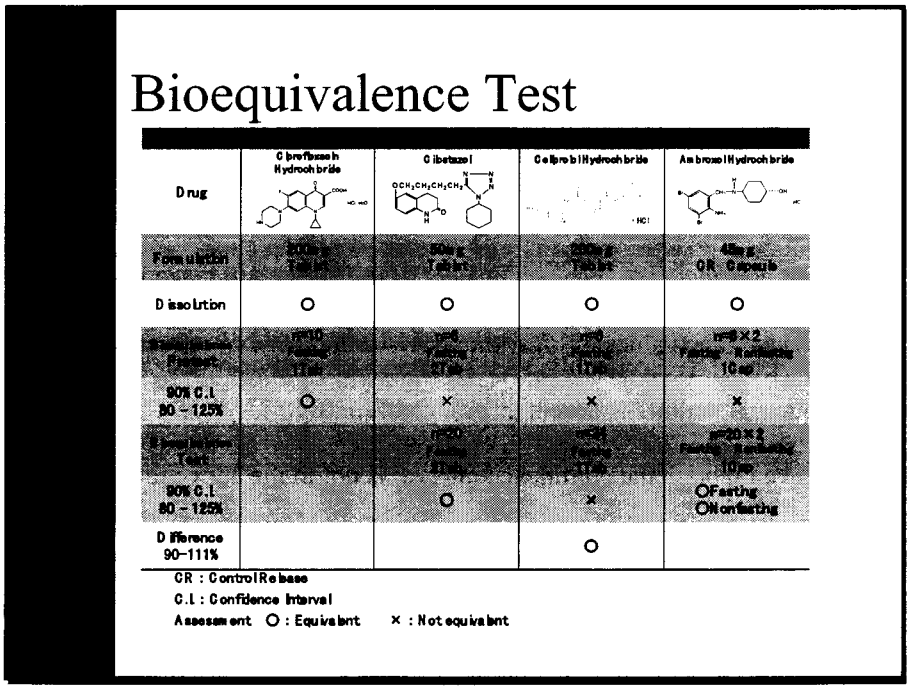
③. Dissolution rates of test and reference products are evaluated to be equal under all conditions decided.

The latter rule can not be applied to slowly dissolving products from which more than 80% of a drug does not dissolve within the final testing time (2 hr in pH 1.2 medium and 6 hr in others) under any conditions of the dissolution tests specified in guideline.

*: http://www.nihs.go.jp/drug/be-guide(e)/Generic/be97E.pdf

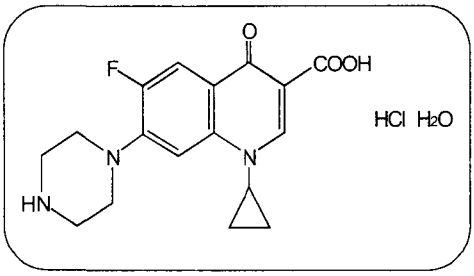
Some examples of bioequivalence tests are shown by slide and the followings are some of them.

Example of Bioequivalence Test

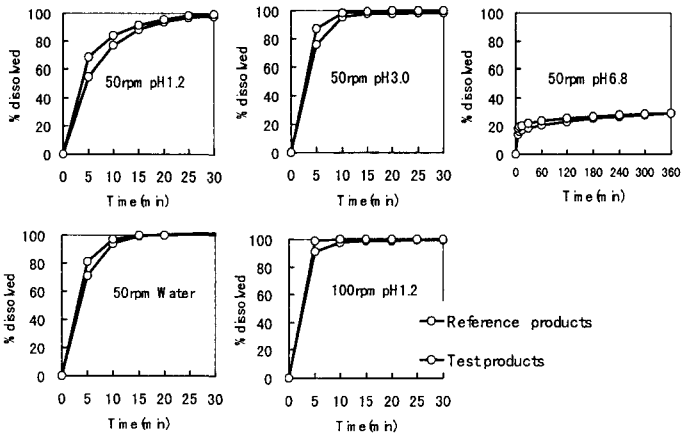


A

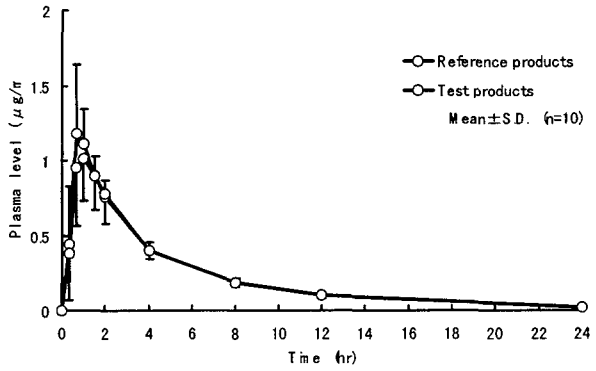
Ciprofloxacin Hydrochloride



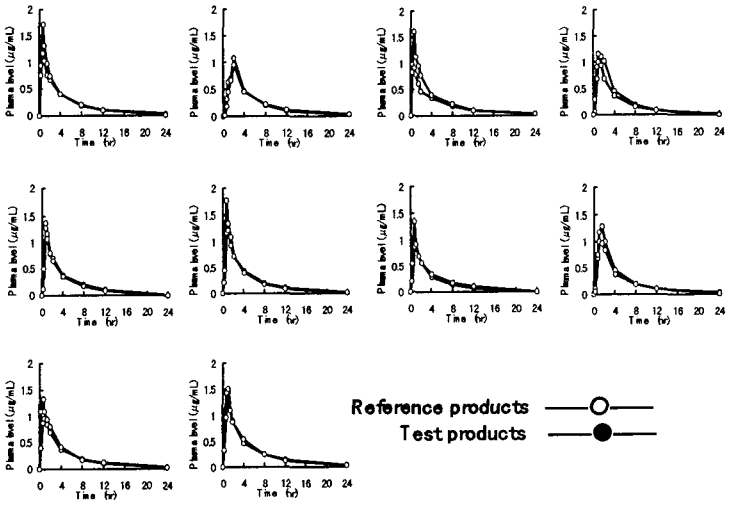
Dissolution (A)



Plasma Levels (Mean : n=10) (A)



Individual Plasma Levels (A)



Bioequivalence (A)

	Cmax		AUCt	
Mean±S.D.	(μg/mL)		(μg·hr/mL)	
Reference product	1.321 ±	0.249	5.286 ±	0.681
Test product	1.198 ±	0.255	5.172 ±	0.651
ANOVA (log)				
Between Subject	F=2.384	n.s.	F=4.215	p<0.05
Group or Seq.	F=0.027	n.s.	F=1.669	n.s.
Subject/Group	F=2.672	n.s.	F=3.923	p<0.05
Time Period	F=19.264	p<0.05	F=8.163	p<0.05
Product	F=3.460	n.s.	F=0.439	n.s.
Power $(1-\beta)$	0.839		>0.99	
Sample size	5		3	
Bioequivalence				
Difference	log (0.905)		log (0.978)	
90% confidence interval	log(0.819) ~	log(1.000)	log(0.920) ~	log(1.041)

Bioequivalence (A)

	AUC∞		MRT		tmax		kel	
Mean±S.D.	(μg·hr/mL)		(hr)		(hr)		(hr^{-1})	
Reference product	5.439 ± 0.795		5.03 ± 0.46		0.934 ± 0.410		0.139 ± 0.026	
Test product	5.343 ± 0.702		5.16 ± 0.44		1.033 ± 0.502		0.132 ± 0.023	
ANOVA								
Between Subject	F=4.715	p<0.05	F=6.688	p<0.05	F=7.157	p<0.05	F=4.262	p<0.05
Group or Seq.	F=1.415	n.s.	F=0.401	n.s.	F=7.336	p<0.05	F=0.104	n.s.
Subject/Group	F=4.507	p<0.05	F=7.165	p<0.05	F=4.200	p<0.05	F=4.733	p<0.05
Time Period	F=7.354	p<0.05	F=2.193	n.s.	F=0.108	n.s.	F=0.250	n.s.
Product	F=0.224	n.s.	F=1.896	n.s.	F=0.958	n.s.	F=0.916	n.s.
Difference	log(0.983)		log(1.028)		10.70 %		log(0.956)	

Procedures for the Development of Generic Products in Japan

(A Case of NICHI-IKO)

NICHI-IKO
PHARMACEUTICAL CO.LTD. (JAPAN)

Data Submitted with Approval Application for Generic Products in Japan

1. Data on specifications and testing methods
2. Data on stability test
   (Acceleration test or long-term storage test)
3. Data on bioequivalence

Steps for the Development of Generic Products

1. Selection of development targets
2. Selection of bulk(specifications and testing methods of bulk,draft)
3. Studies on innovated products
4. Establishment of specifications and testing methods of bulk and test products (final)
5. Manufacture of test products
6. Assessment of test products for approval application
7. Bioequivalence studies
8. Application for approval
9. Approval review
10. Application for manufacturing license

Step-1 Selection of Development Target (1)

In our company we ordinarily choose the development targets from the list that meets the following terms.

1. Reexamination Period shall be over in a few years.
2. Period of Substance Patent shall be over in a few years.
3. Market size of innovated product is fairy large.

The final targets are decided by Products Developing Conference.

Step-2 Selection of Bulk (Establishment of Specifications and Testing Methods of Bulk, Draft)

1. We try to develop the drafts of specifications and testing methods for bulk.
2. We evaluate bulk samples and select preferable one.

Step-3 Studies on Innovated Products

1. Purchase of innovated products
2. Check of indications
3. Research of related papers and some other published data
4. Dissolution test
5. Examining of compositions

Step-4 Establishment of Specifications and Testing Methods for Bulk and Products (Final)

1. Establishment of specifications and testing methods for bulk and products
2. Carrying out of validations for analytical procedures
3. Carrying out of bulk acceptance tests
4. Trial manufacture of test products
5. Repeated assessment of dissolubility behavior of test products
6. Determination of the prescription of test products

Step-5 Manufacture of Test Products (1)

Problems that should be resolved

- How to get the bulk with out interruption
- Crystal form issue on the bulk
- Stabilization technique of test products
- Manufacture technique of test products
- How to improve the innovated products
- Patent issue
- Profitability et.al

Step-5 Manufacture of Test Products (2)

Three lots of final test products are manufactured for stability test of six months and one lot among them is selected for bioequivalence studies.

Step-6 Assessment of Test Products for Approval Application (1)

Tests* are repeated three times on the three lots of final test products manufactured for stability test following the specifications and testing methods.

(Tests*: appearance, coloring, absorption spectrum, disintegration,weight variation, quantitative analysis etc.)

Step-6 Assessment of Test Products for Approval Application (2)

- One lot of final test product is selected for "test products" of bioequivalence studies.
- Dissolution tests are carried out on the test products for the verification of equivalence of dissolution.

Step-6 Assessment of Test Products for Approval Application (3)

Acceleration test or long-term storage test
is performed on the three lots of final test product.
Test conditions are as follows.

- Acceleration test
  40℃, 75%RH,6months ≦
- Long-term storage test
  25℃,36months≦

Step-7 Bioequivalence Studies (1)

Selection of reference products

1. Purchase of three lots of innovated products
2. Carrying out of dissolution test on the three lots of innovated product
3. Selection of reference products from the three lots of innovated products

(Innovated products that shows intermediate dissolution behavior is selected for reference products.)

Step-7 Bioequivalence Studies (2)

Determination of plasma concentration of drug

1. Development of the methods for the analysis of drug concentration in plasma.
2. Preliminary test
3. Main test
4. Data management and statistic analysis
5. Monitoring and audit

Step-7 Bioequivalence Studies (3)

Development of the methods for the analysis of drug concentration in plasma

1. Research of papers
2. Development of the methods for the determination of drug concentration in plasma or blood
3. Carrying out of validation for analytical procedures

Step-7 Bioequivalence Studies (4)

Preliminary Test-1

1. Selection of contract research organization
   (Medical institution is determined in accordance with SOP)
2. Preparing of the following documents.
   - Protocol
   - Investigator' brochure
   - Case report form
   - Written information and informed consent form. (draft)

Step-7 Bioequivalence Studies (5)

Preliminary test-2

3. Review by Institutional Review Board (in-company)
4. Contracts
   - Secrecy Agreement (sponsor and CRO)
   - Trust and Entrust Contract (sponsor and CRO)
   - Clinical Trial Contract(sponsor,CRO and medical institution)
5. Review by Institutional Review Board (medical institution)
6. Dosing and plasma sampling(clinical trial)
7. Measuring of plasma concentration of drug

Step-7 Bioequivalence Studies (6)

Preliminary test-3

8. Assessment of pharmacokinetic parameters and bioequivalence
9. Preparing of clinical trial report

Step-7 Bioequivalence Studies (7)

Main Test

When bioequivalence is not approved from the preliminary test, main test is conducted.

Almost the same procedures as those of the preliminary test are repeated.

Design including sampling times,sample size,dose etc. are sometimes altered based on the data obtained from the preliminary test.

Step-7 Bioequivalence Studies (8)

Clinical trial

Clinical trial should be carried out under GCP and SOP.

1.Monitoring and Audit

- Monitoring is entrust to CRO partially.
- Audit on clinical institution is entrust to CRO.
- Audit on GCP regulations is conducted by the section staffs of our company.

2.Statistic analysis on pharmacokinetic parameters

According to "Guideline for Bioequivalence Studies of Generic Products".

3.Quality control of drug concentration and clinical data

Conducted by data management section

Step-8 Application for Approval

1. Data submitted to OPSR with approval application
   - Data on specifications and testing methods
   - Data on stability test
   - Data on bioequivalence
2. Time limit for approval application
   - The last week day of March every year

   (If we miss this time limit, the approval shall be delayed one year.)

Step-9 Approval Review (1)

Equivalency Review and Compliance Review

OPSR reviews equivalency between medicines applied for approval and medicines which have been already approved (Equivalency Review) and reviews the data attached to applications in order to verify the validity of data and compliance with standards (Compliance Review) These reviews are conducted under commission of MHLW based on the Pharmaceutical Affairs Law.

Step-9 Approval Review (2)

Approval

- After Equivalency Review and Compliance Review approvals are given to applicants by the middle of March every year.
- Standard periods for approval review work is nowadays one year for generics

Step-10 Application for Manufacturing License (1)

- After approval application to OPSR, manufacturing technology section begins scale up studies.
- Ten times of trial manufacturing are usually conducted to select bulk and the most preferable manufacturing procedures and conditions.
- Performance Qualification is conducted using the really manufacturing plants for the final confirmation of manufacturing procedures and conditions.

Step-10 Application for Manufacturing License (2)

- Three lots of products are manufactured for Prospective Validation.
- Application for manufacturing license to local government
- Inspections to manufacturing plants by local government
- Approval of manufacturing license
- Coming into market after listing in NHI reimbursement price.

(NHI:National Health Insurance of Japan)

Outline of Bioequivalence Test (1)

The followings are outline of bioequivalence test that NICHI-IKO usually adopts based on the "Guideline for Bioequivalence Studies of Generic Products,December 22,1997"

1. Design

   Crossover studies is employed in principle.

2. Number of total subjects(generally)

   Preliminary test: 6-10

   Main test: 20≦

3. Selection of subjects

   Healthy adult volunteers are employed in principle.

Outline of Bioequivalence Test (2)

4. Drug administration

- Bioequivalence test is performed by single dose studies in principle.
- One dose unit or a clinical usual dose is generally employed.
- Drugs are usually given to subjects with 150ml of water after fasting for 10 hr. Fasting lasts for at least 4 hr post-dose.

Outline of Bioequivalence Test (3)

5. Measurement of drug substances

- Plasma sample is generally employed.
- Sampling points should be at least 7,including zero time ,1 point before Cmax, 2 points around Cmax and 3 points during the elimination phase.

  We usually sample from 10-12 points.
- Sampling is continued until AUCt is over 80% of AUC∞ (normally more than 3 times the elimination half life after tmax)

Outline of Bioequivalence Test (4)

6. Drug substances to be measured
   - Parent drugs should, in principle, be measured. Major active metabolites may be measured instead of parent drugs, if it is rational.

Outline of Bioequivalence Test (5)

7. Assay
   - Analytical methods should be fully validated regarding specificity, accuracy, precision, linearity, quantitation limit and stability of substances in samples and so forth.
8. Washout periods
   - Washout periods in crossover studies between administration of test and reference products should usually be more than 5 times the elimination half life of the parent drug or active metabolites.

Outline of Bioequivalence Test (6)

9. Parameter to be assessed

- When blood samples are used, AUCt and Cmax are subjected to the bioequivalence assessment in single dose studies.

Outline of Bioequivalence Test (7)

10. Logarithmic transformation

- Pharmacokinetic parameters except for tmax are in principle statistically analyzed after logarithmic transformation.

11. Statistic analysis

- The 90% shortest confidence interval is used.

Outline of Bioequivalence (8)

12.Acceptance criteria

- Two products are considered to be bioequivalent, if the 90% confidence interval of difference in the average values of logarithmic AUCt and Cmax between test and reference products is within the acceptable range of log(0.8)-log(1.25).
- However, even though the confidence interval is not in the above range, test products are accepted as bioequivalence, if the following three conditions are satisfied.

Outline of Bioequivalence Test (9)

1.The total sample size of the initial bioequivalence study is not less than 20 (n=10/group) or pooled sample size of the initial and add-on subject studies is not less than 30.

2.The differences in average values of logarithmic AUCt and Cmax between two products are between log(0.9)-log(1.11).

3. Dissolution rates of test and reference products are evaluated to be equivalent under all dissolution testing conditions decided.

Outline of Bioequivalence Test (10)

But the latter rule can not be applied to slowly dissolving products from which more than 80% of a drug does not dissolve within the final testing time (2 hr in pH 1.2 medium and 6 hr in others) under any conditions of the dissolution tests specified.

Examples of Bioequivalence Test

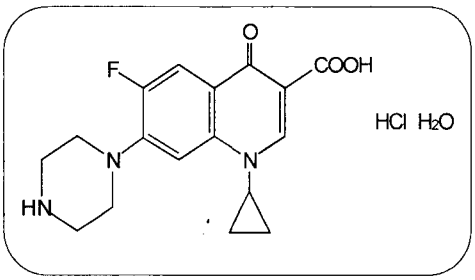
Bioequivalence Test

Drug	Ciprofloxacin Hydrochloride	Cilostazol	Ceftibuten Hydrochloride	Ambroxol Hydrochloride
Formulation	200mg Tablet	50mg Tablet	200mg Tablet	45mg CR Capsule
Dissolution	○	○	○	○
Bioequivalence Protocol	n=16 Fasting 1Tab	n=8 Fasting 2Tab	n=8 Fasting 1Tab	n=8×2 Fasting, Nonfasting 1Dap
90% C.I 80 ~ 125%	○	×	×	×
Bioequivalence Test		n=20 Fasting 2Tab	n=24 Fasting 1Tab	n=20×2 Fasting, Nonfasting 1Dap
90% C.I 80 ~ 125%		○	×	○Fasting ○Nonfasting
Difference 90~111%			○	

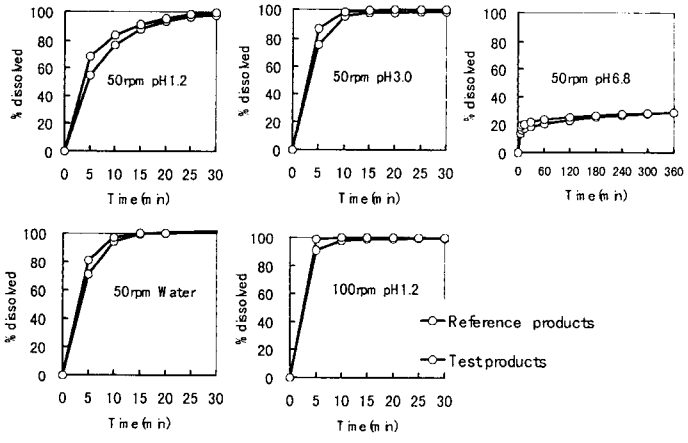
CR : Control Release
C. I. : Confidence Interval
Assessment ○ : Equivalent × : Not equivalent

A

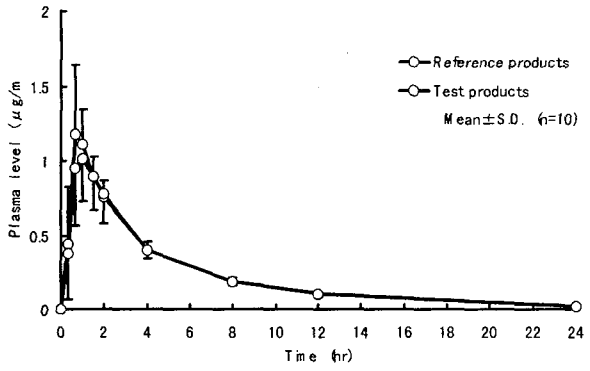
Ciprofloxacin Hydrochloride



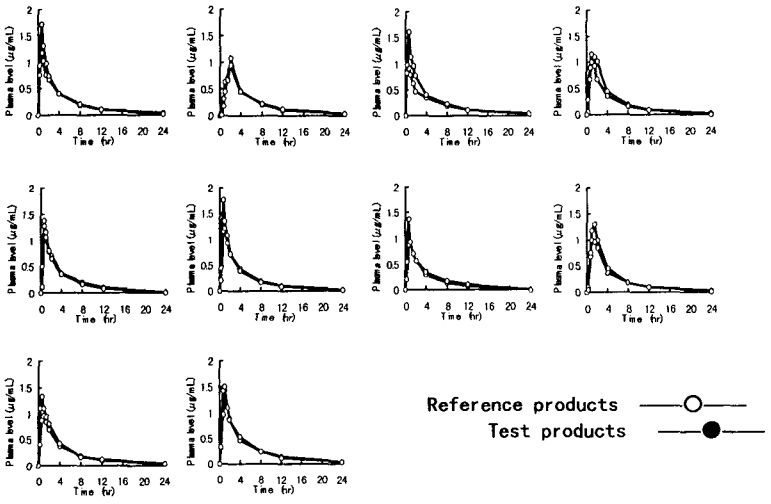
Dissolution (A)



Plasma Levels (Mean : n=10) (A)



Individual Plasma Levels (A)



Bioequivalence (A)

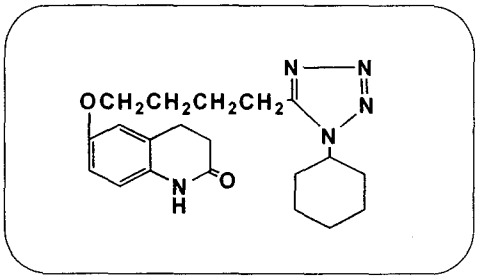
	Cmax		AUCt	
Mean±S.D.	(μg/mL)		(μg·hr/mL)	
Reference product	1.321 ± 0.249		5.286 ± 0.681	
Test product	1.198 ± 0.255		5.172 ± 0.651	
ANOVA (log)				
Between Subject	F=2.384	n.s.	F=4.215	p<0.05
Group or Seq.	F=0.027	n.s.	F=1.669	n.s.
Subject/Group	F=2.672	n.s.	F=3.923	p<0.05
Time Period	F=19.264	p<0.05	F=8.163	p<0.05
Product	F=3.460	n.s.	F=0.439	n.s.
Power (1−β)	0.839		>0.99	
Sample size	5		3	
Bioequivalence				
Difference	log (0.905)		log (0.978)	
90% confidence interval	log(0.819) ~ log(1.000)		log(0.920) ~ log(1.041)	

Bioequivalence (A)

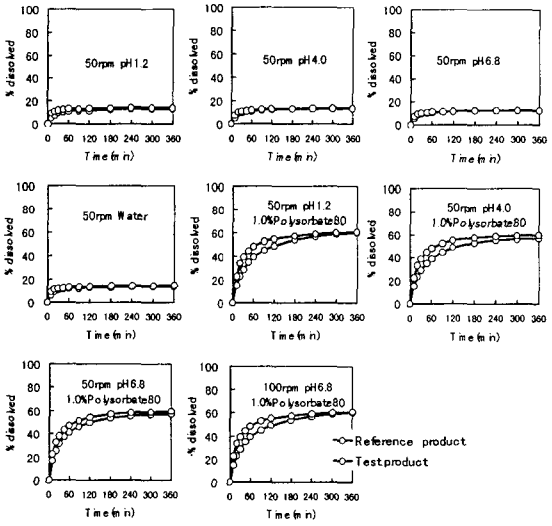
	AUC∞		MRT		tmax		kel	
Mean±S.D.	(μg·hr/mL)		(hr)		(hr)		(hr^{-1})	
Reference product	5.439 ± 0.795		5.03 ± 0.46		0.934 ± 0.410		0.139 ± 0.026	
Test product	5.343 ± 0.702		5.16 ± 0.44		1.033 ± 0.502		0.132 ± 0.023	
ANOVA								
Between Subject	F=4.715	p<0.05	F=6.688	p<0.05	F=7.157	p<0.05	F=4.262	p<0.05
Group or Seq.	F=1.415	n.s.	F=0.401	n.s.	F=7.336	p<0.05	F=0.104	n.s.
Subject/Group	F=4.507	p<0.05	F=7.165	p<0.05	F=4.200	p<0.05	F=4.733	p<0.05
Time Period	F=7.354	p<0.05	F=2.193	n.s.	F=0.108	n.s.	F=0.250	n.s.
Product	F=0.224	n.s.	F=1.896	n.s.	F=0.958	n.s.	F=0.916	n.s.
Difference	log(0.983)		log(1.028)		10.70 %		log(0.956)	

B

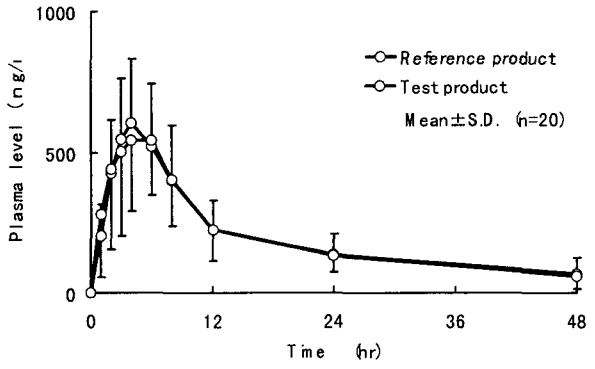
Cilostazol



Dissolution (B)



Plasma Levels (Mean : n=20) (B)



Bioequivalence (B)

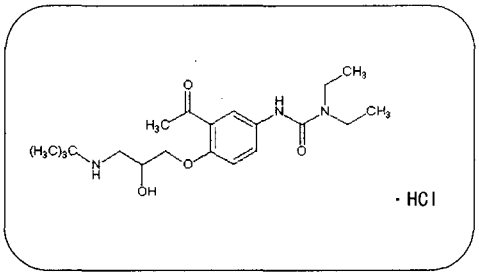
	Cmax		AUCt	
Mean±S.D.	(ng/ml)		(ng·hr/ml)	
Reference product	635.6 ±	232.2	9316.5 ±	3371.9
Test product	636.7 ±	237.5	9202.9 ±	3430.2
ANOVA (log)				
Between Subject	F=5.366	p<0.05	F=7.034	p<0.05
Group or Seq.	F=0.197	n.s.	F=2.189	n.s.
Subject/Group	F=5.603	p<0.05	F=6.620	p<0.05
Time Period	F=0.139	n.s.	F=0.576	n.s.
Product	F=0.005	n.s.	F=0.046	n.s.
Power ($1-\beta$)	0.737		0.846	
Sample size	12		9	
Bioequivalence				
Difference	log (1.005)		log (0.988)	
90% confidence interval	log(0.896) ~	log(1.127)	log(0.894) ~	log(1.091)

Bioequivalence (B)

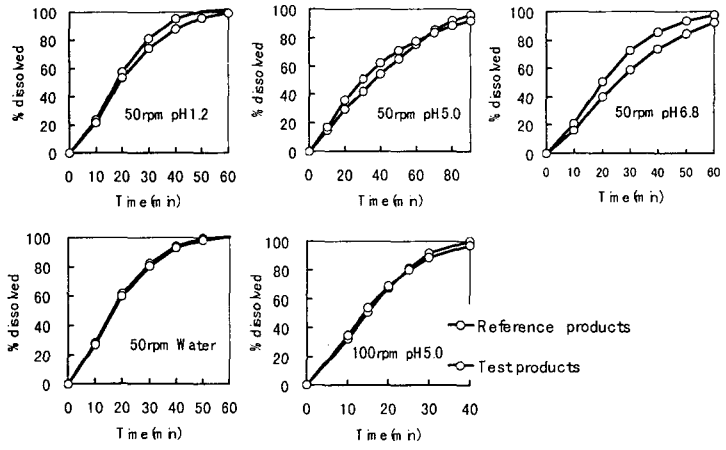
	AUC∞		MRT		tmax		kel	
Mean±S.D.	(ng·hr/ml)		(hr)		(hr)		(hr-1)	
Reference product	11331.8 ± 4997.1		15.11 ± 3.09		4.00 ± 1.17		0.05107 ± 0.02630	
Test product	11008.8 ± 4411.7		14.97 ± 3.16		4.15 ± 1.53		0.04901 ± 0.02347	
ANOVA								
Between Subject	F=5.393	p<0.05	F=6.644	p<0.05	F=0.981	n.s.	F=4.783	p<0.05
Group or Seq.	F=3.987	p<0.05	F=1.391	n.s.	F=0.325	n.s.	F=2.083	n.s.
Subject/Group	F=4.660	p<0.05	F=6.510	p<0.05	F=1.018	n.s.	F=4.525	p<0.05
Time Period	F=0.630	n.s.	F=0.061	n.s.	F=0.648	n.s.	F=0.027	n.s.
Product	F=0.111	n.s.	F=0.073	n.s.	F=0.119	n.s.	F=0.176	n.s.
Difference	log(0.979)		log(0.991)		3.75	%	log(0.968)	

C

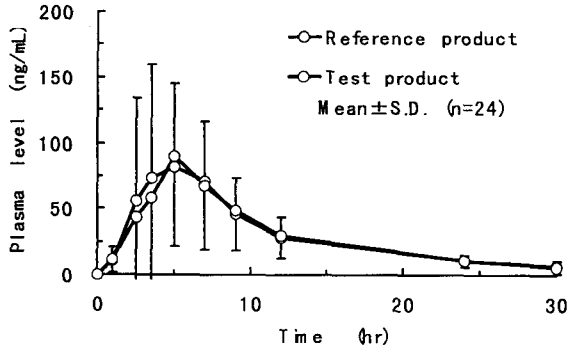
Celiprolol Hydrochloride



Dissolution (C)



Plasma Levels (Mean : n=24) (C)



Bioequivalence (C)

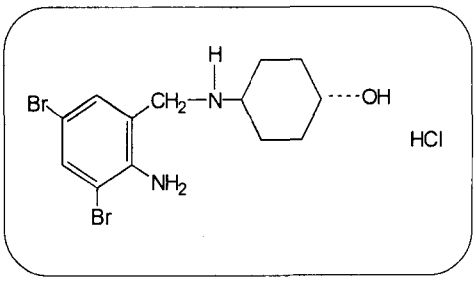
	Cmax		AUCt	
Mean±S.D.	(ng/mL)		(ng·hr/mL)	
Reference product	122.0 ± 86.2		899.4 ± 483.5	
Test product	111.6 ± 77.8		886.0 ± 530.0	
ANOVA (log)				
Between Subject	F=1.171	n.s.	F=2.374	p<0.05
Group or Seq.	F=0.365	n.s.	F=0.318	n.s.
Subject/Group	F=1.204	n.s.	F=2.446	p<0.05
Time Period	F=2.149	n.s.	F=10.777	p<0.05
Product	F=0.068	n.s.	F=0.000	n.s.
Power ($1-\beta$)	0.135		0.305	
Sample size	>20		>20	
Bioequivalence				
Difference	log (0.946)		log (1.001)	
90% confidence interval	log(0.654) ~ log(1.367)		log(0.814) ~ log(1.231)	

Bioequivalence (C)

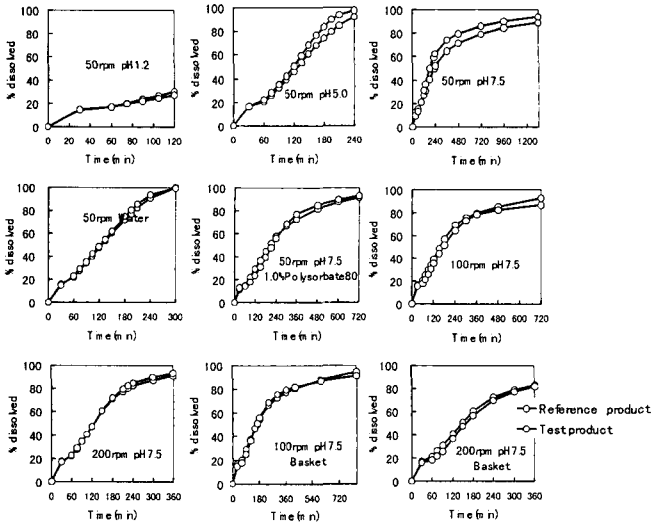
	AUC∞		MRT		tmax		kel	
Mean±S.D.	(ng·hr/mL)		(hr)		(hr)		(hr^{-1})	
Reference produc	1007.5 ± 487.5		9.92 ± 2.19		4.94 ± 1.81		0.08823 ± 0.03298	
Test product	991.3 ± 553.9		10.05 ± 1.69		5.21 ± 1.33		0.09029 ± 0.03235	
ANOVA								
Between Subject	F=2.734	p<0.05	F=1.490	n.s.	F=1.636	n.s.	F=1.840	n.s.
Group or Seq.	F=0.094	n.s.	F=0.000	n.s.	F=4.264	p<0.05	F=2.504	n.s.
Subject/Group	F=2.846	p<0.05	F=1.557	n.s.	F=1.432	n.s.	F=1.727	n.s.
Time Period	F=14.150	p<0.05	F=1.733	n.s.	F=2.015	n.s.	F=0.274	n.s.
Product	F=0.009	n.s.	F=0.190	n.s.	F=0.467	n.s.	F=0.169	n.s.
Difference	log(0.990)		log(1.023)		5.49 %		log(1.040)	

D

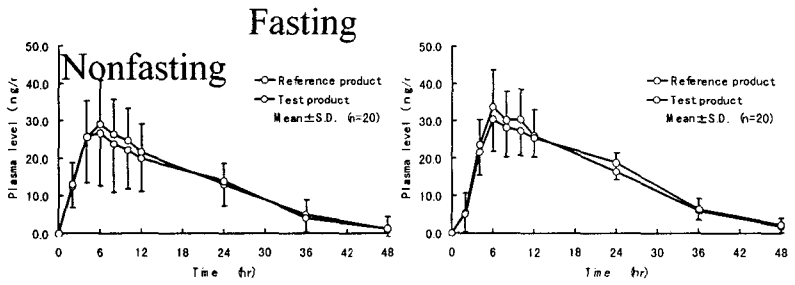
Ambroxol Hydrochloride



Dissolution (D)



Plasma Levels (Mean : n=20) (D)



Bioequivalence (D)

Fasting

	Cmax		AUCt	
Mean±S.D.	(ng/mL)		(ng·hr/mL)	
Reference product	30.01 ±	10.97	609.81 ±	236.80
Test product	28.67 ±	13.07	588.62 ±	284.50
ANOVA (log)				
Between Subject	F=5.130	p<0.05	F=11.625	p<0.05
Group or Seq.	F=2.124	n.s.	F=0.829	n.s.
Subject/Group	F=4.844	p<0.05	F=11.731	p<0.05
Time Period	F=4.944	p<0.05	F=0.322	n.s.
Product	F=0.903	n.s.	F=0.424	n.s.
Power (1−β)	0.662		0.834	
Sample size	14		10	
Bioequivalence				
Difference	log (0.934)		log (0.963)	
90% confidence interval	log(0.823) ~	log(1.058)	log(0.870) ~	log(1.065)

Bioequivalence (D)

Nonfasting

	Cmax		AUCt	
Mean±S.D.	(ng/mL)		(ng·hr/mL)	
Reference product	35.31 ± 8.84		710.89 ± 178.13	
Test product	32.24 ± 7.71		721.46 ± 137.71	
ANOVA (log)				
Between Subject	F=2.889	p<0.05	F=4.734	p<0.05
Group or Seq.	F=0.000	n.s.	F=0.510	n.s.
Subject/Group	F=3.049	p<0.05	F=4.860	p<0.05
Time Period	F=0.310	n.s.	F=0.007	n.s.
Product	F=2.676	n.s.	F=0.382	n.s.
Power ($1-\beta$)	0.886		0.984	
Sample size	9		6	
Bioequivalence				
Difference	log (0.915)		log (1.026)	
90% confidence interval	log(0.833) ~ log(1.005)		log(0.955) ~ log(1.102)	

Bioequivalence (D)

Fasting

	AUC∞		MRT		tmax		kel	
Mean±S.D.	(ng·hr/mL)		(hr)		(hr)		(hr^{-1})	
Reference product	697.74 ± 305.75		14.96 ± 2.72		8.40 ± 1.39		0.0632 ± 0.0260	
Test product	766.84 ± 379.58		15.34 ± 1.79		5.90 ± 2.47		0.0534 ± 0.0189	
ANOVA								
Between Subject	F=2.875	p<0.05	F=2.219	p<0.05	F=1.384	n.s.	F=0.514	n.s.
Group or Seq.	F=0.031	n.s.	F=0.035	n.s.	F=1.048	n.s.	F=2.139	n.s.
Subject/Group	F=3.029	p<0.05	F=2.338	p<0.05	F=1.380	n.s.	F=0.485	n.s.
Time Period	F=1.791	n.s.	F=2.755	n.s.	F=0.738	n.s.	F=3.786	n.s.
Product	F=1.088	n.s.	F=0.802	n.s.	F=0.738	n.s.	F=1.529	n.s.
Difference	log(1.115)		log(1.037)		-7.81 %		log(0.810)	

Nonfasting

	AUC∞		MRT		tmax		kel	
Mean±S.D.	(ng·hr/mL)		(hr)		(hr)		(hr^{-1})	
Reference product	785.12 ± 181.55		16.38 ± 1.92		8.60 ± 1.73		0.0627 ± 0.0139	
Test product	797.33 ± 139.61		17.29 ± 1.59		8.40 ± 4.43		0.0609 ± 0.0117	
ANOVA								
Between Subject	F=3.991	p<0.05	F=2.017	n.s.	F=1.026	n.s.	F=2.906	p<0.05
Group or Seq.	F=2.001	n.s.	F=0.655	n.s.	F=1.325	n.s.	F=1.473	n.s.
Subject/Group	F=3.791	p<0.05	F=2.054	n.s.	F=1.008	n.s.	F=2.835	p<0.05
Time Period	F=0.005	n.s.	F=0.082	n.s.	F=2.375	n.s.	F=0.014	n.s.
Product	F=0.333	n.s.	F=3.963	n.s.	F=3.006	n.s.	F=0.246	n.s.
Difference	log(1.024)		log(1.059)		27.27 %		log(0.978)	