Bridging studies: whether to bridge, how to bridge and what to bridge

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What are generic drugs and how are they approved?

Generic drugs are chemical equivalents of approved brand name drugs. Since the safety and effectiveness of the brand name drugs have already been shown, generic drugs do not have to be tested for safety and effectiveness, as long as the generic drug is shown to be the same as an already approved drug. Generic drugs are approved under abbreviated new drug applications (ANDAs).

US FDA website
Generic drugs

US FDA website except for?
The generic drug manufacturer must prove its drug is the same as (bioequivalent) the brand name drug. For example, after the patient takes the generic drug, the amount of drug in the bloodstream is measured. If the levels of the drug in the bloodstream are the same as the levels found when the brand name product is used, the generic drug will work the same.

FDA recently evaluated 2,070 human studies conducted between 1996 and 2007. These studies compared the absorption of brand name and generic drugs into a person’s body. These studies were submitted to FDA to support approval of generics. The average difference in absorption into the body between the generic and the brand name was 3.5 percent[2].


http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/ucm167991.htm#_ftnref1
Data from two compounds administered to a group of subjects.

Figure 1. Schematic diagram illustrating possible bioequivalence study outcomes. T/R = test/reference.
If a generic drug is equally bioavailable as the brand name drug, then the generic drug is considered as bioequivalent to the brand name drug.

**Underlying assumptions**

Chemically equivalent compounds showing bioequivalent bioavailability are therapeutically equivalent.
Equivalent bioavailability is the bridge between brand name drugs and generic drugs.

India is a world leader.
Can a drug travel from the West to Asia?
Can a drug travel from the West to Asia as is?

In general, yes.

General rule: Majority of drugs shown to be safe and effective in the West will also be safe and effective in Asia as is: 62% (= 85/137) in Japan and 64% (=56/88) in Korea.

ICH-E5: Although ethnic differences among populations may cause differences in a medicine’s safety, efficacy, dosage or dose regimen, many medicines have comparable characteristics and effects across regions.

There are exceptions to the general rule and bridging studies are about ruling out exceptions.

How to rule out exceptions: Requirements for extensive duplication of clinical evaluation for every compound can delay the availability of new therapies and unnecessarily waste drug development resources (from ICH E5).
Bridging studies: basic concept

How to rule out exceptions:

- X duplication of clinical evaluation: unnecessary waste
- O to generate a limited amount of clinical data in the new region

Requirements for extensive duplication of clinical evaluation for every compound can delay the availability of new therapies and unnecessarily waste drug development resources (from ICH E5).

When the regulatory authority or the sponsor is concerned that differences in ethnic factors could alter the efficacy or safety of the medicine in the population in the new region, the sponsor may need to generate a limited amount of clinical data in the new region in order to extrapolate or “bridge” the clinical data between the two regions.

“concerned”: possibly subjective judgment without scientific criteria
The primary goal of bridging studies is to determine ethnic sensitivity of the drug and to assure safety and effectiveness in the new region.

- 54 y.o. Asian female develops DVT
- Coumadin (warfarin) therapy was initiated
- Patient trips at home, falls and hits her head on the floor
- She then develops cerebral hemorrhage→ Cerebrovascular accident
- Take home: Asians are more sensitive to coumadin than Caucasians.

**Western regular dose of warfarin can harm Asian patients.**
Bridging studies: warfarin example

Warfarin activity is determined partially by genetic factors. *VKORC1* polymorphisms explain why African Americans are on average relatively resistant to warfarin (higher proportion of group B haplotypes), while Asian Americans are generally more sensitive (higher proportion of group A haplotypes). *CYP2C9* polymorphisms explain 10% of the dose variation between patients, mainly among Caucasian patients as these variants are rare in African American and most Asian populations. ([http://en.wikipedia.org/wiki/Warfarin](http://en.wikipedia.org/wiki/Warfarin))

Especially for *CYP2C9* substrates such as warfarin and phenytoin, diminished metabolic capacity because of genetic polymorphisms or drug-drug interactions can lead to toxicity at normal therapeutic doses. ([http://en.wikipedia.org/wiki/CYP2C9](http://en.wikipedia.org/wiki/CYP2C9))
Rosuvastatin PKs: Study subject under the same Environment

Rosuvastatin 40mg single oral dose

- **Chinese**  $n=36$
- **Malays**  $n=35$
- **Indians**  $n=35$
- **Caucasians**  $n=35$

Lee et al. CP&T 2005;78(4):330-41
Description of current changes to the Crestor label

In a pharmacokinetic study involving a diverse population of Asians residing in the United States, rosuvastatin drug levels were found to be elevated approximately 2-fold compared with a Caucasian control group. As a result of these findings, the “Dosage and Administration” section of the label now states that the 5 mg dose of Crestor should be considered as the start dose for Asian patients and any increase in dose should take into consideration the increased drug exposure in this patient population. Results of this pharmacokinetic study are further discussed under the “Clinical Pharmacology” and “Precautions” section of labeling.
EXAMPLES OF ETHNIC DIFFERENCES IN EXPOSURE AND RESPONSE TO MARKETED DRUGS

Labeling for the most recently approved drugs did not identify ethnicity-related differences in PK or PD leading to differences in dosing. However, several important examples of ethnicity-related safety and efficacy information are included in the labels of older marketed drugs, in some cases based on data obtained following approval of the drug. As is the case with several of the following examples, the importance of ethnicity may not be known until the postmarketing stage. (Clinical Pharmacology & Therapeutics, 417-423, vol. 84, No. 3 Sep. 2008)

Tacrolimus: $C_{\text{max}}$ and oral bioavailability of Caucasian $>$ Black
Rosuvastatin: 2-fold larger bioavailability in Asian than Caucasian
Warfarin: Black’s dose higher and Asian’s dose lower than white’s
Carbamazepine (anticonvulsant/antipsychotic): Higher incidence of Stevens-Johnson syndrome in Han-Chinese than whites
Bridging studies: examples of ethnic sensitivity

Stevens-Johnson syndrome

http://en.wikipedia.org/wiki/Stevens%E2%80%93Johnson_syndrome
FDA Rule of generics: If the levels of the drug in the bloodstream are the same as the levels found when the brand name product is used, the generic drug will work the same.

Rule of bridging: If the levels of a drug in the bloodstream in Asians are the same as the levels found in Caucasians, then the drug will work the same in both populations. Namely comparability of ADME should be the basic evaluation (ICH E5, Appendix C).

Drug dose producing comparable bioavailability in the new region

Comparable therapeutic effect in the new region

Ethnic factors, intrinsic and extrinsic factors, may impact on drug performance.
Bridging studies: ethnic factors

Intrinsic factors: genetic, physiological and pathological condition

Drug Performance

?
Bridging studies: ethnic factors

Extrinsic factors: culture, environment

Effect on Drugs
Bridging studies: ethnic factors

Dose Ratios (US/Japan) of 137 drugs approved in Japan

Japanese dose higher $9/137 = 6.6\%$
Japanese dose the same $85/137 = 62.0\%$
Japanese dose lower $43/137 = 31.4\%$

Clin Pharm Ther 87:714, 2010
Review existing data, the Complete Clinical Data Package (CCDP).

1. Are Koreans included in the CCDP?
2. Are Asians, in particular Japanese and/or Chinese, included?
3. Are other Asians included?
4. Do Asian PK/PD data and/or early phase data exist?
5. Are Asians included in pivotal studies?
6. Do Korean/Asian efficacy data exist?
7. Review drug-drug interaction data and food-drug interaction data.
8. Are PK/PD data consistent within and across ethnic groups?
9. Any questionable data from the CCDP?
Following factors are assessed.

- Linear PK
- A flat PD curve for both efficacy and safety in the range of the recommended dosage and dose regimen
- A wide therapeutic dose range
- Minimal metabolism or metabolism by multiple pathways
- High bioavailability, thus less susceptibility to dietary absorption effects
- Low potential for protein binding
- Little potential for drug-drug interaction, drug-diet and drug-disease interactions
- Non-systemic effect
- Little potential for inappropriate use

From ICH E-5 Appendix D
Assessment outcome from new drug

At least one Bridging Study (Global or Local)

Bridging exemption

Bridging data=Data from Koreans in Korea or abroad
Bridging study=Clinical trial conducted in Korea
Bridging Waiver Categories

- Orphan drugs or drugs that used to be orphan drugs
- Drugs for AIDS or other life-threatening disease
- Anticancer therapy for the following
  - No standard therapy
  - Therapy after failure of a standard therapy
- New drugs for which clinical trials will be conducted on Koreans
- Diagnostic or Radioactive drugs
- Topical drugs having no systemic effect
- No ethnic differences
Types of Bridging Studies

- Pharmacokinetics
- Pharmacodynamics with pharmacological endpoints
- Dose-response study
- Phase III confirmatory study
- Phase III with surrogate marker
Bridging studies: Korean experience

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<tr>
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</tr>
<tr>
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KFDA statistics
Bridging based on Korean data contained in multinational phase III studies

• Generally no statistically meaningful sample sizes: A desirable sample size is 15-25% Korean data contained in multinational studies.

• Design parameters such as inclusion/exclusion criteria and dosing may not be consistent with requirements in Korea.

• Comparative analysis: Korean data versus non-Korean data; Korea data versus other Asian data; and Asian versus Caucasian.

• Analysis of ethnic sensitivity according to ICH E5 Appendix D.
Bridging study example: phase III regional study

Drug: Antidiabetics

Global pivotal phase 3 study: 2% Koreans

Asian regional bridging study: Placebo controlled study with 530 China, India and Korea (n=95)

Ethnic sensitivity: Unlikely according to ICH E5 appendix D

Safety and efficacy: No evidence for significant difference between Koreans and Caucasians.

PK/PD: Similar PK/PD profile between Japanese and Caucasian after multiple dosing

KFDA action: Approval without change in dose

From KFDA file
Bridging in Korea

Bridging based on Korean data contained in multinational phase II studies

• Evaluation of ethnic sensitivity according to ICH E5 Appendix D
• Wide therapeutic dose range
• Good dose response
• Good prediction of safety/efficacy from PK/PD parameters
• KFDA will need PK/PD data for review
Bridging in Korea

Bridging based on phase II global study

Drug: Antihypertensive drug

Global pivotal study: BP outcome in essential hypertensive patients

- Placebo arm: 27 Koreans (n=142)
- 150mg arm: 28 Koreans (n=143)
- 300 mg arm: 29 Koreans (n=141)
- 600mg arm: 29 Koreans (n=142)

Dose dependent effect

Statistically significant effect both in Koreans and non-Koreans

No significant difference in effect between Koreans and non-Koreans.

Low frequency of adverse events in Koreans

PK/PD: Similar between Japanese and Caucasian data

Ethnic sensitivity: Unlikely according to ICH E5 appendix D

Safety and efficacy: No evidence of significant difference between Koreans and non-Koreans

KFDA action: Approval without change in dosage

From KFDA file
Bridging study example: phase III Korean study

Indication: osteoporosis

Ethnic sensitivity: Unlikely according to ICH E5 appendix D

PK: Similar between Korean and Caucasian data

Safety and efficacy: No evidence of significant difference between Koreans and Caucasians

KFDA action: Drug approved without change in dosage

<table>
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<th>Mother study</th>
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<td>Endpoint</td>
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<td>Fracture</td>
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From KFDA file
Bridging study example: Korean bridging study

Drug: Rosubastatin (HMG-Co reductase inhibitor)

Phase 3 study with primary hypercholesterolemia: Active control versus 10mg rosubastatin

Results from phase 3 study: Similar between Koreans and Caucasians

PK: Known to be different between Asians and Caucasians

Dosage in other countries: 10-40 mg once daily in Europe; 5-40 mg once daily in USA; and 2.5-20 mg once daily in Japan

KFDA action: 5-20 mg once daily in Korea

From KFDA file
Bridging in Korea

Bridging based on Korean PK data

- Design
  - Administration: Single dose or multiple dose
  - Dosing: More than 2 for checking linear PK
  - Same analysis method as the original method. Otherwise, validation report.

- Evaluation
  - Similarity between Korean data and the data from the origin (statistical equivalence or strict identical result not required)
  - Analysis of ethnic sensitivity according to ICH E5 Appendix D.

From KFDA file
Bridging based on Korean PK study

Indication: Neuropathic pain, epilepsy

Korean PK study with normal healthy volunteers with single administration

Arm 1: 10 for 100 mg & 2 for placebo
Arm 2: 10 200mg & 2 placebo
Arm 2: 10 fro 300 mg & w for placebo

PK: Similar among Koreans, Japanese and Caucasians

Population PK analysis with Koreans and Caucasians

Ethnic sensitivity according to ICH E5 appendix D

- Wide therapeutic dose range
- Sufficient experience with pivotal study data from the origin country
- Similar medical practice and design/conduct of clinical trials between Korea and the origin country

Correlation between PK-PD or PD and safety/efficacy: Good

KFDA action: Approval without change in dosage

From KFDA file
COPD drug: Korean study based on surrogate variable. Filipino data were also utilized.

Diabetes study: Asian regional study of 200 Chinese, 100 Indians and 95 Koreans (see the next file).

Immunosuppressant: Bridging exemption based on comparison between Caucasian data (corporal harvest) and Chinese data (living donor) in regard to kidney transplant.

Over reactive bladder syndrome: Because Japanese PK data were inconsistent, a smaller scale regional bridging study was planned.

Anesthetic reversal agent: KFDA agreed to exempt. But ...

Diabetes study of Japanese compound: The same protocol but different trial outcome
Present/Future Drug Development Model

USA/Europe
- Phase I
- Phase II
- Phase III
- Review
- Approval

Asia/Korea
- Phase I
- Phase II
- Phase III
- Review
- Approval
Drugs from Asia to the world

Pharmaceuticals & Medical Devices Agency

APEC Symposium, Taipei, Nov. 1st, 2008
Statistical view points

• Consistency (Shih 2001)
  – The results from the new region is consistent with the results from the original region

• Reproducibility/Generalizability (Chow et al., 2002)
  – The results from the original region is reproducible and/or generalizable at the new region

• Similarity, Equivalence/Non-inferiority (Liu et al., 2002; Hung, 2003)
  – The results from the new region can be shown to be similar, equivalent or non-inferior to that of the original region


Thank you.