Ethnic Factors in Drug Development

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Characteristics of Drug Metabolism Influencing Global Drug Development

- All drugs exhibit intersubject PK and PD variability
- Different populations around the world may handle drugs differently
- Influencing factors can be:
  - Intrinsic
  - Extrinsic
Some Typical Examples of Possible Ethnical Differences

• Chinese are more sensitive to the cardiovascular pharmacologic effects of beta-adrenoceptor antagonists than Caucasians
• Chinese have lower daily warfarin dose requirements than Caucasians
• Caucasians were more sensitive to the cardiovascular and respiratory effects of morphine than Chinese, although the former were less sensitive to its gastrointestinal side effects
• Etc
Intrinsic Factors

- Age
- Gender
- Body weight
- Genetic factors (polymorphism)
- Presence of diseases influencing:
  - Absorption (gastrointestinal disorders…)
  - Distribution (cardiovascular, GI…)
  - Metabolism (hepatic, genetic, ….)
  - Elimination (hepatic, renal…)
- Ethnicity/race
Extrinsic Factors

- Diet
- Medical practice
- Life style
- Tobacco use
- Alcohol use
- Concomitant medication
- Environment
- Etc
Definition of a Race

“Term once commonly used in physical anthropology to denote a division of humankind possessing traits that are transmissible by descent and sufficient to characterize it as a distinct human type (e.g., Caucasoid, Mongoloid, Negroid)”

Encyclopedia Britannica 2002
"relating to large groups of people classed according to common racial, national, tribal, religious, linguistic, or cultural origin or background"

Merriam Webster Dictionary 2001
Difficulties With Assessment of Ethnical Differences in Drug Development

- Which ethnical groups?
- Interethnical versus intraethnical differences
- Is every drug ethnically sensitive?
- Are small differences (if present) clinically important?
- Should studies on predominantly one ethnic population really always be repeated on another group? (ethics, timing, cost)
ICH E-5: Ethnic Factors in the Acceptability of Foreign Clinical Data

- Status of Implementation (Step 5)
- EU: Adopted by CPMP, March 1998, issued as CPMP/ICH/289/95
- Japan: Adopted August 98, PMSB/ELD Notification No. 672, PMSB Notification No. 739
Main Points of the E-5

• Most drugs are not ethnically sensitive
• Ethnic populations classified as
  – Asian
  – Black
  – Caucasian
• Assessment of ethnic sensitivity made from bridging data in full clinical data package
• Bridging study may be carried out in a new ethnic population if initial data assessment indicates ethnic sensitivity (Appendix D)
Appendix D

Properties of a Compound That Make It More Likely to be Sensitive to Ethnic Factors

- Nonlinear pharmacokinetics
- A steep pharmacodynamic curve for both efficacy and safety (a small change in dose results in a large change in effect) in the range of the recommended dosage and dose regimen
- A narrow therapeutic dose range
- Highly metabolized, especially through a single pathway, thereby increasing the potential for drug-drug interaction
- Metabolism by enzymes known to show genetic polymorphism
Polymorphism of Hepatic Metabolism

- Significant ethnic differences seem to exist in the enzymatic activity of several drug metabolizing enzymes (cytochrome P450):
  - CYP2C9 (S-warfarin)
  - CYP2C19 (diazepam, omeprazole, tricyclic antidepressants)
  - CYP2D6 (codeine, quinidine, haloperidol)
  - CYP1A2 (theophylline, imipramine, clozapine and olanzapine)
  - N–acetyltransferase (NAT-2 – isoniazid, hydralazid
    NAT-1 - p-aminosalicylic acid)
Polymorphism of Hepatic Metabolism

- Whites are more likely than persons of Asian and African heritage to have abnormally low levels of CYP2D6 that metabolizes drugs such as antidepressants, antipsychotics, and beta blockers.
- Slower enzyme metabolism (CYP2C19) has been observed in persons in the United States of Asian descent as compared to Whites and Blacks (diazepam, omeprazole, tricyclic antidepressants).
- Blacks respond poorly to several classes of antihypertensive agents (beta blockers and angiotensin converting enzyme (ACE) inhibitors).
- Racial differences in skin structure and physiology have been noted that can affect response to dermatologic and topically applied products.
- Clinical trials have demonstrated lower responses to interferon-alpha used in the treatment of hepatitis C among Blacks when compared to other racial subgroups.
Polymorphism of Hepatic Metabolism

• These differences can affect the PK and response profiles of drugs in different populations
• They need to be considered during the drug development process
• Compounds in development should and will be carefully screened, particularly for CYP mediated metabolic patterns
Appendix D

Properties of a Compound That Make It More Likely to be Sensitive to Ethnic Factors

• Administration as a prodrug, with the potential for ethnically variable enzymatic conversion
• High inter-subject variation in bioavailability
• Low bioavailability, thus more susceptible to dietary absorption effects
• High likelihood of use in a setting of multiple co-medications
• High potential for abuse
E-5 Concepts

- Clinical Data Package (CDP) consists of foreign data
- Bridging Study (BS)
  
  “A bridging study is defined as a study performed in the new region to provide pharmacodynamic or clinical data on efficacy, safety, dosage and dose regimen that will allow an extrapolation of the foreign clinical data to the population of the new region”
The Spirit and Intent of E5

- Not intended to request bridging studies every time
- Intended to permit the requesting of one ‘confirmatory’ phase 3 clinical trial (bridge study) in the region (not specifically defined, nor meant as ‘country’) if needed or necessary to extrapolate.
- Recognized that there would be a period of time where experience with foreign clinical studies would be accumulated and evaluated - not to be confused with always asking for a new confirmatory trial in local region
E5 Allows for a New Study in the New Region - Why is That Needed?

- When all the clinical data is derived from a foreign region and extrapolation is an issue
- When the experience with clinical trials in that region is minimal
- When there is concern with ability to confirm a finding from a study(ies)
- A confirmatory clinical trial is the bridging study
Individuality vs Population Response

- Medicines are prescribed as a treatment for an individual patient, not a population.
- The variability of response to a drug is likely to vary as much, or more, within a given population as between different populations.
- It is unusual for a population defined simply by ethnicity to share consistently enough characteristics to predict a different dose-response relationship to a drug.
- Bridging justification may be needed.
Current Issues With Bridging Studies

• Asia only
• Some authorities more frequently demanding data on ethnical differences than others
  – Japan
  – Korea
  – Taiwan
• Some others “observers”
Bridging in Japan

- Sponsor prepares a bridging package to be discussed with KIKO
- Consultation results in instructions and suggestions
- The company has to decide whether to use bridging or go into full development
- Few examples of successful bridging approach so far
Bridging - Korea

- With the new law the Koreans have indicated that local registrational trials were no longer needed.
- However, the KFDA had stated that “since the application of foreign clinical data directly to Korean population may raise problems due to ethnical differences”, the need for a bridging study would always have to be assessed.
- They require studies on Koreans living in Korea, and no data generated on Asians of other nationalities may be accepted.
Bridging - Korea

- However, there may be instances where bridging study requirement could be waived. These are as follows:
  
  - Orphan drug
  - Drugs for treating AIDS, cancers or life-threatening diseases for which a standard remedy is either unavailable or, even if it is available, not working:
  - New drugs under development inside or outside of Korea for which clinical trials will be conducted in Korea
  - Diagnostic reagents (including radiopharmaceuticals)
  - Drug that do not effect systemically but locally
  - Drugs that have demonstrated no differences by ethnic factors
Taiwan – Bridging

- Organized 2 APEC meetings on bridging
- Center for Drug Evaluation (CDE) evaluates each product for the need for bridging of data. Consultations encouraged
Considerations for Assessing the Necessity of a Bridging Study

1. **Does it meet DOH announcement on exemption of bridging study?**
   - **Yes**: Continue with the next step.
   - **No**: Continue with the next step.

2. **Is there a complete clinical data package that nature and data quality (GCP) meets Taiwan local regulatory requirements (ICH E5 and DOH guidances on clinical trials)?**
   - **Yes**: Continue with the next step.
   - **No**: Continue with the next step.

3. **Does it include data obtained in Asian population?**
   - **Yes**: Proceed to the next step.
   - **No**: Proceed to the next step.

4. **Does it include the data from the trial (early phase trials) or global clinical trials conducted in Taiwan and approved by DOH and fulfill the DOH bridging study requirement?**
   - **Yes**: Continue with the next step.
   - **No**: Continue with the next step.

5. **Can the data package reasonably show both no intrinsic and extrinsic factors sensitivities in Asian when extrapolated from foreign clinical data; or base on safety and efficacy, the clinical differences is acceptable? Ps. according to E5**
   - **Yes**: Proceed to the next step.
   - **No**: Proceed to the next step.

6. **Is it reasonable to assume similar concentration (dose)-response (C-R) relationship in Asians when extrapolated from foreign clinical data?**
   - **Yes**: Continue with the next step.
   - **No**: Continue with the next step.

7. **Is Asian* PK and/or PD data available to be used to correlate with dose or predict efficacy?**
   - **Yes**: Continue with the next step.
   - **No**: Continue with the next step.

8. **A protocol of an adequate bridging study should be designed and submitted to DOH for approval. This adequate bridging study can be a PK and/or PD study or any clinical study evaluating efficacy and safety of the medicine.**
   - **Yes**: Continue with the next step.
   - **No**: Continue with the next step.

9. **Request submit sufficient data before review**
   - **Yes**: Proceed to the next step.
   - **No**: Proceed to the next step.

10. **Whether the drug with no intrinsic sensitivities factors and the extrinsic factors between foreign and our country population is similar; or base on safety and efficacy, the clinical difference is acceptable?**
    - **Yes**: Continue to the next step.
    - **No**: Continue to the next step.

11. **Generally no bridging study required**
    - **Yes**: Proceed to the next step.
    - **No**: Proceed to the next step.

12. **Using current data for dose adjustment determination**
    - **Yes**: Proceed to the next step.
    - **No**: Proceed to the next step.

13. **If has safety concern, then bridging study is required.**
    - **Yes**: Proceed to the next step.
    - **No**: Proceed to the next step.

* When evidence indicating potential intrinsic and extrinsic factors differences between our country and other Asian populations, A Bridging study shall be conducted in our country.
Recent developments

• Literature review
• FDA Draft Guideline (January 2003)
• Questions and answers – ICH Steering Committee (February 2003)
• January 2003 – Draft “Guidance for Industry Collection of Race and Ethnicity Data in Clinical Trials”

  – A standardized approach for collecting race and ethnicity information in clinical trials conducted in the United States and abroad for certain FDA regulated products.

  – Developed by the Race and Ethnicity Working Group from the Office of the Commissioner, the Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER) of the Food and Drug Administration (FDA).
• FDA regulations require sponsors to present in certain marketing applications an analysis of data according to demographic subgroups (age, gender, race), as well as an analysis of modifications of dose or dosage intervals for specific subgroups (21 CFR 314.50 (d)(5)(vi)(a)).
Draft Guideline Recommendations:
- consistency in data collection required
- use of a two-question format
- have trial participants self-report their racial and ethnic category to enhance consistency
- individuals should be permitted to designate a multiracial identity.
Draft Guideline Recommendations:

- For **ethnicity**, the FDA recommends the following minimum choices be offered:
  - Hispanic or Latino
  - Not Hispanic or Latino

- For **race**:
  - American Indian or Alaska Native
  - Asian
  - Black or African American
  - Native Hawaiian or Other Pacific Islander
  - White
• Draft Guideline Recommendations:
  
  – In certain situations more detailed race and ethnicity information may be desired
    • e.g., White can reflect origins in Europe, the Middle East, or North Africa;
    • Asian can reflect origins from areas ranging from India to Japan.
  
  – If more detailed characterizations of race or ethnicity are collected to enhance data consistency, FDA recommends these characterizations be traceable to the five minimum designations for race and two designations for ethnicity listed before.
FDA recognizes that the categories for race and ethnicity were developed in the United States and that these categories may not adequately describe racial and ethnic groups in foreign countries.

- For ethnicity:
  - Hispanic or Latino
  - Not Hispanic or Latino

- For race:
  - American Indian or Alaska Native
  - Asian
  - Black, of African heritage
  - Native Hawaiian or Other Pacific Islander
  - White
Summary

- Influence of ethnical differences on drug development more often anecdotal (although documented) than based on hard scientific evidence
- ICH E-5 was prepared to facilitate global drug development and simplify registrations around the world
- The guideline is intentionally vague
- This may be used by some to always demand local clinical trials
- In 2003, the ICH Steering Committee prepared Q&A to facilitate global drug development and understanding of the E-5 Guideline
Summary

• Also in 2003, the US FDA issued a draft guidance with more detail concerning the ethnicity and race collection requirements than the ICH E-5
• Europe (for now) lacks a guideline concerning race and ethnicity
• The topic continues to evolve, especially given the expanding role of global drug development
Conclusions

- US, EU will continue to be the main locations for NCE clinical trials
- International, including emerging markets have an important role in global drug development
- Need to continue aligning their local regulatory requirements with developed countries
- Need to increase local clinical research expertise
- Need to accept and enforce strong patent protection