Acceptance of Foreign Clinical Data – A U.S. Perspective

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Topics

- ICH E5 Questions and Answers (2006)
- 21 CFR 312.120
- 21 CFR 314.106
- A U.S. Perspective
- Conclusions
ICH E5

- Purpose: “to facilitate the registration of medicines among ICH regions by recommending a framework for evaluating the impact of ethnic factors upon a medicine’s effect, i.e., its efficacy and safety at a particular dosage and dose regimen.”

- Provides guidance with respect to regulatory and development strategies that will permit evaluation of the influence ethnic factors, minimize duplication of studies, and expedite drug availability.
ICH E5

- Does not alter the data requirements for registration in a new region.
- All data in the clinical data package should meet the regulatory requirements of the new region.
- If there is concern that ethnic factors could alter efficacy or safety in the new region, a bridging study may be required.
- Acceptability of foreign clinical component depends on whether it can be extrapolated to the population of the new region.
E5: Assessment of Complete Clinical Data Package

- There should be adequate characterization of PK, PD, dose-response, efficacy, and safety in the population in the foreign region.
  - Trials should be conducted according to regulatory standards of new region.
  - Should be adequate and well-controlled
  - Should use appropriate endpoints
  - Should use medical and diagnostic definitions acceptable to new region

- Should characterize PK and, where possible, PD and dose response for PD in population representative of the new region
E5: Additional Study Requirements

- If foreign data do not meet new region’s regulatory requirements, may need
  - Clinical trials in different subsets, e.g., patients with hepatic or renal impairment
  - Clinical trials using different comparators at new region’s approved dosage and dosage regimen
  - Drug-drug interaction studies
E5: Drug Sensitivity to Ethnic Factors

- Potentially sensitive
  - Genetic polymorphisms
  - Steep dose-response curve

- Less likely to be sensitive
  - Lack of metabolism or active excretion
  - Wide dose range
  - Flat dose response curve
  - Experience with other drugs in a class demonstrating a lack of sensitivity
E5: Bridging Study - Definition

- Study performed in new region to provide pharmacodynamic or clinical data on efficacy, safety, dosage and dose regimen
- Allows extrapolation of foreign clinical data to the population in the new region
E5: Bridging Study - Extrapolation

- If dose response, safety and efficacy in new region are similar, the study can “bridge” the foreign data.
- If study indicates that a different dose in the new region results in a safety and efficacy profile similar to original region, it may be possible to extrapolate foreign data to new region with appropriate dose adjustment.
E5: Bridging Study - Extrapolation

- If bridging study is not of sufficient size to adequately extrapolate the foreign adverse event profile to the new population, additional safety data may be needed.

- If bridging study fails to verify safety and efficacy, confirmatory clinical trials would be necessary.
E5: Bridging Studies for Efficacy

- A bridging study may not be needed if
  - Drug is ethnically insensitive and extrinsic factors such as medical practice and conduct of trials are similar in each region
  - Drug is ethnically sensitive but the two regions are ethnically similar and there is sufficient experience with pharmacologically related compounds in the two regions
E5: Bridging Study with Pharmacologic Endpoints

- If region is ethnically dissimilar, drug is ethnically sensitive, but extrinsic factors are similar, a controlled PD study in new region using a pharmacologic endpoint or established surrogate endpoint could bridge foreign data.

- Simultaneous PK may make study more interpretable.
A controlled clinical trial in the new region may be necessary when

- There are doubts about choice of dose
- There is little or no experience with acceptance of controlled clinical trials conducted in the foreign region
- Medical practice is different between regions (e.g., concomitant meds, control arm)
- Drug class is not familiar to new region
- PD data suggest interregional differences in response
E5: Bridging Studies for Safety

- Even if foreign clinical data demonstrate safety and efficacy, there may still be a safety concern in the new region, e.g.
  - Need to accurately determine rates of common adverse events in new region
  - Need to detect serious adverse events in the new region
- An additional safety study may be needed.
E5: Strategy for Global Development

- Early in development
  - Define PK, PD, and dose response
  - Determine whether the drug is ethnically sensitive or insensitive
  - Discuss bridging study designs with regulatory agencies prior to completion of the clinical data package
- Studies should include populations representative of regions where drug is to be registered.
U.S. Development Options

- When ethnic factors are either unknown or likely to be important, there are 3 options:
  - Conduct the clinical studies entirely outside the U.S. in a population that is not representative and conduct a bridging study in one that is.
  - Conduct one study in a population that is not representative and another in a population that is.
  - Conduct all studies in a patient population that includes a wide variety of ethnic groups.
Possible to assess potential regional differences as part of a global program. Multi-regional trials with sufficient numbers of subjects from new region may allow assessment of impact of ethnic factors and determination of whether entire database is pertinent to new region.
Willingness of a region to rely on a global study depends on:
- Definition and diagnoses of disease
- Choice of control group
- Region’s objective of treatment and choice of efficacy variables
- Methods of assessment of safety
- Medical practice
- Duration of trial
- Regional concomitant medications
- Severity of disease in subjects
- Similarity of dose and dose regimens
E5: Multiregional Trials

Objectives

- Enable world-wide registration
- Show that drug is effective in each region
- Compare results between regions to show that drug is not sensitive to ethnic factors

- Primary endpoint(s) should be acceptable in all regions or data on all primary endpoints should be collected in each region for comparison purposes
- Should be powered to show an effect in each region
E5: “Hierarchy of Persuasiveness”

- Demonstration of effect in the entire study with statistically significant result in each region.
- Demonstration of effect in the entire study, but non-significant effect in region of interest. Supportive data includes:
  - Consistent trends in endpoints across regions
  - Similar dose-response relationships across regions
(a) FDA will accept as support for an IND or application for marketing approval a well-designed and well-conducted foreign clinical study not conducted under an IND, if

- The study was conducted in accordance with good clinical practice (GCP).
- The FDA is able to validate the data from the study through an onsite inspection.
- Marketing approval based solely on foreign clinical data is governed by 21 CFR § 314.106.
(b) Applicant must submit

- Description of actions taken to ensure research conformed to GCP
- Investigator qualifications
- Description of research facilities
- Detailed summary of protocol and results of study and, if requested, case records and other institutional records
- Description of drug substance and drug product
- Information showing that the study is adequate and well controlled
(b) continued

- Information on the Independent Ethics Committee (IEC)
- Summary of IEC’s decision
- Description of how informed consent was obtained
- A description of incentives, if any
- A description of how study was monitored
- A description of investigator training on GCP and study protocol
- Statement on whether written commitments by investigators to comply with GCP and the protocol were obtained
21 CFR § 314.106

(b) An application based solely on foreign clinical data meeting U.S. criteria for marketing approval may be approved if:

(1) the foreign data are applicable to the U.S. population and U.S. medical practice

(2) the studies have been performed by clinical investigators of recognized competence

(3) the data may be considered valid without need for an on-site inspection, or FDA is able to validate the data through an on-site inspection or other appropriate means.

(c) Applicants are encouraged to meet with FDA when approval based solely on foreign data will be sought.
Beyond E5: A U.S. Perspective

- Most clinical development programs are now international in scope.
- Trials submitted to the U.S. FDA often include sites in North and South America, Europe, Asia, Australia, and/or other regions/countries.
- Analyses of these trials should evaluate consistency of efficacy and safety across regions and demographic factors such as race, age, and gender.
Given the diversity of the U.S. population, multinational trials may accrue a population that adequately represents the U.S. population and additional bridging studies may not be required.

If a trial is conducted solely in a region with a population, disease, or medical practice, etc., that is not representative of the U.S., a bridging study may be required.

In oncology, a bridging study would likely be another randomized trial in a representative population.
Conclusions

- The importance of ethnic factors should be determined early in drug development.
- Regulatory agencies should be consulted early for advice on requirements for registration/approval in each region.
- In the U.S., international, randomized, controlled trials may be sufficient to support approval if they are conducted in populations that are representative of the U.S.