

for established & emerging pharma markets

Globalization of the pharmaceutical market has been perceived as one of the important drivers for future growth of the biopharmaceutical industry. There are many initiatives in place to improve the biopharmaceutical R&D productivity by lowering the R&D costs, and one of these measures is designing global clinical trials and programs. Before these trials with different ethnicities can be designed, pharmaceutical companies should design bridging studies that take into account the effect of ethnic factors on pharmacokinetics and pharmacodynamics of the test substance. Data from these studies should indicate that the dosage regimen (dose and dosing frequency) has been confirmed in Caucasians, Japanese and other ethnicities involved, and especially pose no safety risk for any ethnicity. Details of the bridging study strategy have been published in the ICH E5 Guideline. Performance of bridging studies in early development may minimize duplication of clinical studies at a later stage.

Furthermore, drug regulators (i.e. US-FDA) request sponsors of NDAs to present a summary of safety and efficacy data by demographic subgroups (age, gender, race), as well as an analysis of whether modifications of dose or dosage intervals are needed for specific patient populations. Differences in patient response to drug products have already been observed in racially and ethnically distinct population subgroups. The sensitivity of the test substance to ethnic factors determines the amount of work necessary to design and complete the clinical data package.

The Gaiyo Tokyo Decree of 2006 made bioequivalence data from Japanese subjects mandatory for package inserts, also for foreign generic products. Therefore, generic products and biosimilar products should also be tested in Japanese subjects before they may be approved for use in Japanese patients.

FOCUS Phase I / Bridging Studies

- Explore and explain genetic variability and differences in PK / bioavailability / dietary effects or drug response
- Start global development or complement your core program covering major populations of established and new emerging markets

FOCUS Phase II / III International Multiethnicity Trials

- Global Clinical Trials including different ethnic populations require PK-information prior to or in parallel with a global exploratory dose-finding study.
- Design a global patient program and gain access to appropriate patient pools
- Incorporate knowledge regarding ethnic subpopulations in the process of dose selection and safety / risk assessment

FOCUS Bridging Concepts: Extending products to foreign markets

- Extend your market reach with a tailor-made ethnicity bridging project
- Gain foreign market approval at reduced cost for registered as well as for new products

FOCUS Ethnicity Studies

Worldwide markets and the global drug development approach have triggered the relevance of population subgroup studies and ethnicity data analysis.

Ethnic factors can be defined as intrinsic characteristics (e.g. genetics, metabolism, elimination, skin structure and physiology) of the patient and extrinsic characteristics associated with the environment and culture in which the subjects reside.

Extrinsic factors tend to be less genetically and more culturally and behaviorally determined. One example is local medical practice. It is widely recognized that medical practice as well as evaluation of endpoints may be more variable, and difficult to harmonize. Another example of an extrinsic factor is the wish to reduce the dose and have lower approved doses in Japan.

The available guidelines recommend using a standardized approach for collecting and reporting race and ethnicity information in clinical trials. FOCUS is performing such studies in its own clinics.

A Bridging Study is defined as a study performed in a new region or population to provide pharmacodynamic or clinical data on efficacy, safety, dosage and dose regimen in the new region that will allow extrapolation of the foreign clinical data to the population in the new region. Such studies could include additional PK information.

When no bridging study in patients is needed, a PK-study in the new region or population may be considered as a bridging study. [Source: ICH E5 (R1) Guideline (1998)]

Bridging Expertise

In the last 5 years FOCUS has completed over 25 bridging studies.

FOCUS has built up healthy volunteer panels of different origins: White (Caucasian Europeans), Asian (Japanese, Chinese) and Black (Africans), following the classification of race according to US-FDA Guidance Document Sept. 2005 / OMB-Directive 15. We are still increasing our Japanese and Chinese volunteer panel (please refer to the Figures)!

FOCUS staff and study teams include native speakers for volunteer recruitment and effective study related communication. Our experienced medical staff ensures top quality conduct and standardized interpretation of phase I studies in our clinics.

Ethnicity studies in healthy volunteers are performed in the FOCUS Clinics in Neuss & Düsseldorf while patient studies are shared between different FOCUS Clinical Research Units located in top university hospitals.

The Value which you gain when you work with FOCUS is based on the Quality of our study activities is based on our long-term EU experience in clinical research in combination with our reasonable price (relative to Japanese CRO's).

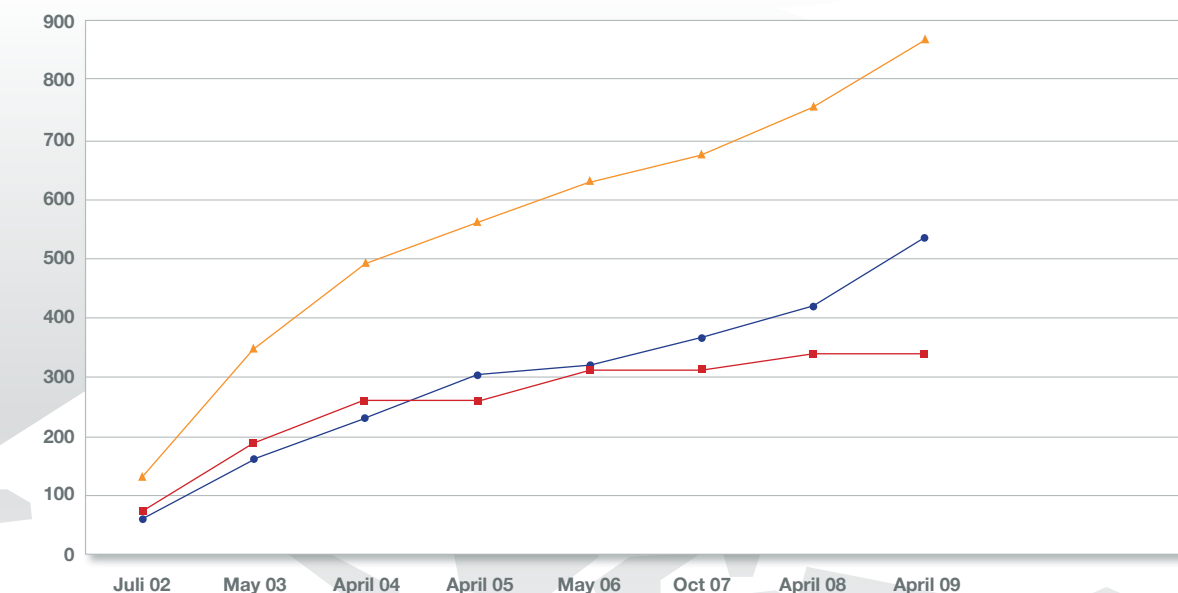
FOCUS track record:

The following study designs have been used in Japanese studies:

- PK / bioavailability
- PK / drug drug interaction
- Repeat dose tolerance study
- Effect of diet on PK and safety profile
- Female hormone PD-study
- Clinical efficacy study

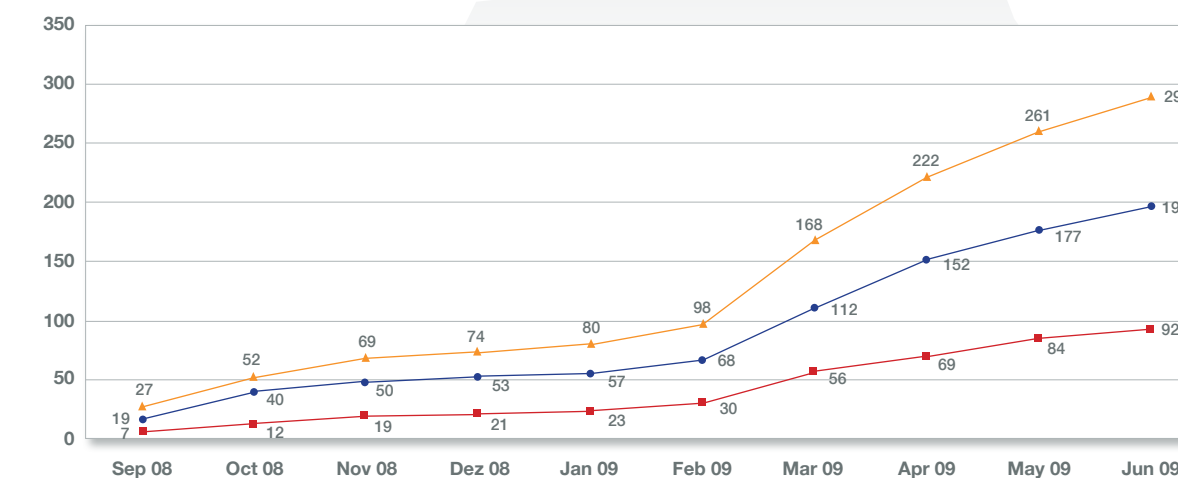
Total Number of Japanese Volunteers

● male ■ female ▲ total



Total Number of Chinese Volunteers

● male ■ female ▲ total



FOCUS Bridging Concepts

Extending products to foreign markets

Our track record:



Bridging Projects to optimize use and acceptance of existing data for foreign registrations

FOCUS has developed over 14 Bridging Concepts in the last 3 years. Our experience includes bridging from Western markets (EU and USA) to Japan, EU to Brazil, Russia to EU, Indonesia and India to EU and vice versa. By understanding the differences in local cultural, medical, legal and industry practice we can anticipate many potential short-comings before the data is reported and presented to the respective authorities for the first time.

Definition of an optimal and acceptable regulatory path for the new individual market

Except for plain generics, there is no such thing as a standard regulatory path for a given compound. The specifics of a given product require a concise description of the benefits and risks of the new product as compared to existing therapies.

Many foreign product dossiers contain too many studies. Existing guidelines provide ample space and guidance to define a stringent but convincing plan.

In the last 3 years FOCUS has, at request of our sponsors, discussed and successfully completed several development plans with the EMEA.

Communication between local project management and authorities on similar cultural and academic level

An efficient and effective communication with regulatory authorities is of paramount importance for a successful submission - before and during the development of the product.

Bridging projects comprise team members from both cultures who each understand the study activities, and jointly work to design the right study by improving existing study designs and reports, as well as by knowing and implementing differences in medical practice of the different regions.

FOCUS has industry experts from Europe, India, Indonesia, Japan, Russia, and USA who have successfully driven international and global development projects.

Involvement of key opinion leaders in advisory boards and data safety committees for novel products

FOCUS can build on a strong network of key opinion leaders from all major therapeutic areas and different regions.

FOCUS Ethnicity Studies

know-how

Proven track record in clinical pharmacology and drug development

experience

Science- & project-based expertise of multinational staff

data acceptance

West-East and East-West bridging data accepted by regulatory authorities

FOCUS Clinical Drug Development GmbH (www.focus-cdd.de) is an independent full service drug development house. The unique combination of **drug development** and **clinical pharmacology / exploratory drug development** know-how, plus an in-house infrastructure to manage different population aspects of a program ensures fast results at a high standard of quality. We provide product consultancy, regulatory strategy and development planning for New Chemical/ Biological Entities, herbal products, biosimilars, generics plus and drug combinations (FDC). We also offer to support Japanese Pharmaceutical companies to develop their drugs according to EMEA & FDA guidelines for future filing and marketing in the EU and North America.

FOCUS Headquarter is located in Neuss / Düsseldorf, Germany with affiliates in Heidelberg, Belgrade, Moscow, Dubai and Jakarta. Since its inception in 1992, FOCUS has successfully grown to become an established provider of comprehensive NCE/NBE development services to global pharmaceutical and biotech companies.

We FOCUS on:

- Regulatory Path Finding and Development Planning
- Integrated Product Development Management with internationally accepted data package
- Global Phase I and rapid Clinical Proof of Concept Phase II studies
- Biomarker & PK-genotyping Laboratory
- Ethnicity Bridging Concepts
- Clinical Research Programs covering EUROPE - AFRICA - ASIA
- Study Experiences in numerous indications with novel drugs



FOCUS on JAPAN

Exploratory Drug Development know-how
based on traditional contacts and experience



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Global reach: established & emerging markets