FEATURE

Can Chinese Phase I data from the West accelerate China drug development? The science of ethnobridging

This article explains the concept of ethnobridging – a way to implement cost-effective, multi-ethnic approaches to global clinical trial research and drug development

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The past decade has seen significant advances in China's healthcare as a result of a rapid rise in living standards. All individuals are guaranteed basic healthcare insurance providing access to modern diagnostics and treatments. With the Healthy China 2030 plan announced in 2016,[1] healthcare continues to be an important focus for the country. However, with nearly 1.4 billion people, an ageing population and urbanisation, there continue to be unmet medical needs, including for cancer, rare diseases and infectious diseases. China faces an ageing population (ages 60 and older), which numbers close to 178 million, or 13.3% of its population[2] (and 20% of the global population for this age category — the highest in the world). The Chinese government is committed to continuous improvement in healthcare and has made significant investments in training physicians, healthcare workers, building infrastructure and supporting medical innovations, including pharmaceuticals.

In recent years, new opportunities for biopharmaceutical companies to incorporate Asian countries into early stages of drug development programmes and accelerate product introduction have resulted from changes in greater China, Japan and South Korea's regulatory authorities. Pharmaceutical sponsors developing compounds in Europe

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and North America can collect and analyse data from native Asians living in other countries — a concept known as "ethnobridging" — to implement cost-effective, multi-ethnic approaches to global clinical trial programmes. Ethnobridging is defined as conducting an ethnic sensitivity study comparing safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) among ethnic groups. These studies can be conducted anywhere around the world if the local ethnic population has a representative sample of native populations from both intrinsic and extrinsic perspectives.[3]

The National Medical Products Administration (NMPA), formerly the China Food and Drug Administration (CFDA), was approved as a new regulatory member of the International Council for Harmonisation (ICH) in June 2017 with the goal of enabling more efficient collection and exchange of data with China.

According to the ICH website: "The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) is unique in bringing together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of drug registration. The ICH's mission is to achieve greater harmonisation worldwide to ensure that safe, effective, and high-quality medicines are developed and registered in the most resource-efficient manner."

In July 2018, the NMPA issued and finalised the "Guiding principles for the acceptance of overseas clinical trials data". The initial guidance was first published in October 2017[4] with the goal of shortening the drug approval time difference between China and other global regulatory agencies. Before the issuance, Chinese local data were required to be generated for China registration with foreign clinical data only serving as a reference. However, with reforms starting in 2015 and the issue of "Guiding principles," foreign data can be fully or partly accepted to support China registration. The overall expectation is that more Chinese data will be used in global drug development programmes and foreign data could be extensively used for Chinese registration. Thus, drug developers are encouraged to increase China's participation in global trials.

In this article, we introduce the concept of accepting overseas Chinese data to accelerate drug development in China, thereby making innovative drugs more rapidly available for Chinese physicians and their patients. We also explore the possibility of collecting overseas Chinese clinical data in support of Chinese registration. Although there may be some risks associated with this approach, there may be pragmatic, efficient and scientifically sound options to collect Chinese data globally if accurate rigorous guidelines are followed to accelerate China's drug development and make innovative drugs more readily available for Chinese patients.

The ethnic factor

Although the ICH endeavours to harmonise global drug development, the science of ethnic factors is an important consideration in drug response. Much literature is now available demonstrating scientific evidence for ethnic differences in drug safety and responses.[3]

In 1998, the ICH published guidance E5 "Ethnic factors in the acceptability of foreign

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clinical data." These guidelines recommended regulatory and development strategies on use of clinical data collected in one region to support drug and biologic registrations in another if ethnic factors were addressed using bridging studies. Bridging studies are a series of studies demonstrating similarity or differences in clinical pharmacology and clinical drug responses between populations.

The E5 guidelines facilitated drug and biologic registration among ICH regions by recommending a framework for evaluating the impact of ethnic factors on a drug's efficacy and safety. Recommended regulatory and development strategies permit adequate evaluation of the influence of ethnic factors, minimise clinical study duplication and expedite the drug approval process.

Japan was one of the first countries to apply ICH E5 but with many scientific challenges. In addition to intrinsic factors such as genetic polymorphism, there were extrinsic factors such as medical practice, environment and cultural differences. Differences in diagnostics, therapeutics, and use of concomitant herbal medicines are examples of medical practice variations. Diet, climate/sunlight, language and education levels are illustrations of potential environmental and cultural differences – all of which may impact drug response. Considerations for all these factors proved to be challenging in extrapolation of foreign clinical data.

By 2005, the industry's interest in conducting global trials involving Japan and other Asian countries early in drug development had grown significantly. At this time, European, Japanese and US pharmaceutical companies began designing trials, starting in Phase I, which included Asian volunteers, most often in the US.

In China, regulatory authorities began requiring ethnic Chinese data as a prerequisite for global trial participation. The Chinese Food and Drug Administration (CFDA) had always required Chinese PK data for product registration in the country.[4] However, the CFDA had not explicitly required Chinese Phase I data for global trial participation. This is now changing. From a scientific perspective, this information is critical in establishing safety, tolerability and PK in the new population before exposing a larger patient population in subsequent Phase II/III studies. In recent years, it appears that the NMPA is also requiring this step.

In summary, there must be data consistency between the Chinese and worldwide populations, especially related to clinical pharmacology, safety and efficacy. Such consistency ensures that overseas clinical data are applicable to the Chinese population.

Ethnobridging approach in practice

Although this type of study can be done in any region of the world, ethnobridging has been implemented most commonly in regions with large Asian populations such as Los Angeles in the US and London in the UK.

For global companies, the first investigational new drug (IND) filing for a drug candidate often occurs in the US or EU. With ethnobridging, sponsors now can incorporate Asian data into the development programme while conducting studies in the US or EU during routine Phase I development.

China and Japan require sponsors to provide PK data before any efficacy/patient studies. These data allows sponsors to include China in a Phase II/III Asian trial or a Phase III global trial.

Efficient incorporation of Asian data in a first-in-human/single ascending dose (SAD) study and/or multiple ascending dose (MAD) study can be accomplished with a careful review of the drug candidate's pharmacology profile. If designed appropriately, the entire data set should be used for Western regulatory submission, while the Asian component, along with totality of data, can be carved out for the Asian development strategy. Figure 1 explains how ethobridging studies can be done during any phase of clinical development.

Intrinsic and extrinsic factors

Intrinsic and extrinsic factors must be considered in determining the safety and efficacy of a drug before it is introduced into a new region with a unique sub-population, and they also must be considered in the conduct of ethnobridging studies.

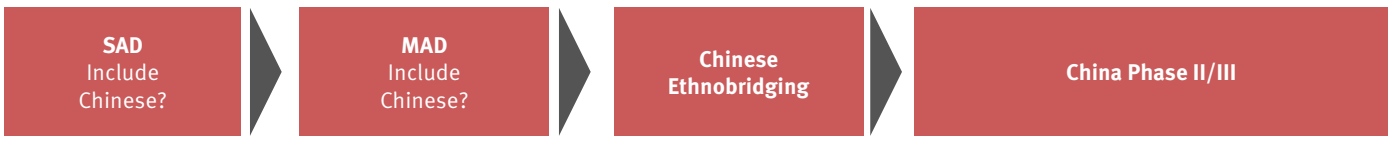
Intrinsic factors include the genetic, physiological, and pathological characteristics of an individual; these are traits that are "intrinsic" to a person rather than being determined by that person's environment. In our attempt to apply this principle to selection of Asians residing abroad, we require that all Asian volunteers were born in their native countries to both parents and maternal and paternal grandparents of their respective country's descent. The term "first generation" has been commonly used to describe this population.

In addition to genetic factors, environmental factors are important variables that impact the absorption, distribution, metabolism

FIGURE 1

Conducting an ethnobridging study at any phase of clinical development

1. Collect as part of a single ascending dose (SAD) and/or multiple ascending dose (MAD) studies
2. Conduct a separate Chinese study post-Western SAD/MAD
3. Conduct after proof-of-concept in preparation of including China into global Phase II/III studies



and elimination processes of a given drug. Although genetic factors are a major determinant of inter-individual variation, intra-individual variation is determined primarily by the environment. Diet is one major extrinsic factor. What we eat and drink may have a profound effect on the medicines that we take.[5] Diet is probably the most substantial route of exposure to environmental chemicals, including those naturally synthesised by plants or those formed during food storage and preparation. Dietary factors can affect the absorption and distribution of drugs, as well as influence Phase I and Phase II biotransformation reactions.[6] Studies have shown that cytochrome P450 and conjugating enzymes can be induced or inhibited by nutritional ingredients, dietary practices, additives and preservatives, deficiency states and even methods of food preparation.[7] Ingestion of cruciferous vegetables and charcoal broiled foods may increase the concentration of (or cause the inactivation of) certain p450 isoenzymes. The unique dietary habits of certain ethnic groups can contribute to differences in drug pharmacokinetics. Although it is outside the scope of this article, other extrinsic factors such as alcohol consumption and smoking also play a key role in drug metabolism.

Ethnobridging studies – and volunteers who participate in them – must meet strict bridging criteria to be accepted by China's and Japan's regulatory authorities. Volunteers must be natives of these countries and their lifestyles, especially in terms of diet and other health-related factors, and these must not have changed significantly since relocating. A series of questionnaires has been created to document this information. In addition, often a 10-year limit on individuals living outside of China is imposed for added confidence. Epidemiologic studies have shown it takes five to 10 years for new immigrants to acclimate to their new country with respect to diet and lifestyle.[8] Typically, these requirements mean that volunteers must live in areas with large Chinese or Japanese communities, such as Los Angeles or London, where they are more likely to maintain their native lifestyles.

Any sampling must be a true representation of a population. The strict criteria set forth provide all reasonable efforts to identify native Asians residing abroad to be a representative sample.

Parexel has conducted over 200 ethnobridging studies in the past 15 years in its Early Phase Clinical Units (EPCUs).[9,10,11] Data from these studies have been accepted to satisfy Japanese Phase I data. Based on precedents for use of ethnobriging data in Japan, similar principles may be applied to generation of data to support a Chinese marketing application.

The approach should involve early engagement with the NMPA to discuss the scientific rationale for potential ethnic difference of the compound of interest. Similar to the US FDA, China's Center for Drug Evaluation allows three types of consultation meetings: 1, 2, and 3, which corresponds to FDA's type A, B, and C. Before the 2018 "Guidance for accepting overseas clinical trial data", Chinese local clinical data had to be generated for China registration and "foreign clinical data" could only be used as a reference. The new guidance allows for the foreign clinical data to be conditionally accepted to support China registration, including, but not limited to, orphan drugs, drugs for unmet medical needs in China, and drugs for paediatric use. For this acceptance, foreign data must address the safety and efficacy applicable to the Chinese population with considerations for ethnic differences. Clinical sites must have conducted the study with ICH good clinical practice (GCP) requirements and study sites should be ready for NMPA inspection.

If the decision is to conduct the study outside China, a careful consideration of study design, inclusion/exclusion criteria to select subjects who are indeed representative of China's population, as well as the operational infrastructure (eg, bilingual staff, Chinese informed consent, Chinese diet) must be assured. With more than one million Chinese Americans residing in California and 400,000 in the UK,[12,13] applying a strict intrinsic and extrinsic criterion to ensure proper representation of people residing in China appears to be within reach.

Accelerating clinical development in China

The pharmaceutical industry and governments have a vital interest in accelerating and expanding the marketing of novel therapeutics to address unmet medical needs. Although regulatory requirements will continue to evolve, companies that understand how to leverage first-generation Chinese populations in their global development plans will gain an advantage.

Key success factors for faster product development in China are:

- Including Chinese populations at the earliest stages of development to support efficient global registration and marketing
- Establishing a broad ethnic base of data and designing studies that can bridge data between countries and regions
- Performing PK, PD and other Phase I testing with multiple populations as early as possible to reduce ethnicity-based safety risks
- Working with Chinese regulators to ensure study designs, protocols, analytical methods and ethnobridging strategies meet their individual requirements
- Ensuring all participating nations and institutions conduct trials under GCP regulations as defined by the ICH.

The future

As regulatory environments in China continue to evolve, the global scientific community will be challenged to find the best practices to address ethnicity in drug development. With the right approach, sponsors can generate early clinical data from Chinese populations living outside China. Sponsors, regulators and contract research organisations must work together to leverage the full potential of enthobridging effectively, hopefully leading to faster availability of critical medicines to patients in China. ■

References

1. Wang Wei, Zakus David. Healthy China 2030: without national health, there will be no comprehensive well-being. Family Medicine and Community Health 2016;4(4):75–76.
2. Communiqué of the National Bureau of Statistics of People's Republic of China on Major Figures of the 2010 Population Census (No. 1). National Bureau of Statistics of China. 28 April 2011. Archived from the original on 8 November 2013. Retrieved 29 April 2011.
3. Jhee S, Yen M, Moran S, Ereshefsky L. Accelerating global drug development: the science and practice of ethnobridging. Published by Parexel International, LLC, Waltham, MA, 2011.
4. National Medical Products Administration. Available at: http://english.nmpa.gov.cn/ (accessed 11 September 2020).
5. Jefferson JW, Greist JH. Brussles sprouts and psychopharmacology (understanding the cytochrome p450 enzyme system). In: Jefferson JW, Greist Jh, eds. Annals of Drug Therapy. Vol. 3, Philadelphia, PA: WB Saunders;1996:2-22.
6. Yang CS, Yoo JS. Dietary effects of drug metabolism by the mixed-function oxidase system. Pharmacol Ther 1988;38:53-72.
7. Marchand LL, Wilkinson GR, Wilkens LR. Genetic and dietary predictors of CYP2E1 activity: a phenotyping study in Hawaii Japanese using chlorzoxazone. Cancer Epidemiol Biomarker Prev 1999;8(6):495-500.
8. Kerrihard AL, Khair MB, Blumberg R et al. The effects of acclimation to the United States and other demographic factors on responses to salt levels in foods: an examination utilizing face reader technology. Appetite 2017;116:315–322.
9. Jhee SS, Lyness WH et al. Similarity of insulin detemir pharmacokinetics, safety, and tolerability profiles in healthy caucasian and Japanese american subjects. J Clin Pharmacol. 2004;44(3):258–64.
10. Frost C, Shenker A, Jhee S et al. Evaluation of the single-dose pharmacokinetics and pharmacodynamics of apixaban in healthy Japanese and Caucasian subjects. Clin Pharmacol. 2018;10:153–163. doi: 10.2147/CPAA.S169505. eCollection 2018.
11. Jhee SS, Yen M, Ereshefsky L et al. Low penetration of oseltamivir and its carboxylate into cerebrospinal fluid in healthy Japanese and Caucasian volunteers. Antimicrob Agents Chemother. 2008;52(10):3687–93. doi: 10.1128/AAC.00327-08. Epub 2008 Aug 1.
12. Selected population profiles in the United States – 2014 American community survey 1-year estimates – New York City – Chinese alone. US Census Bureau. Archived from the original on 14 February 2020. Retrieved 22 September 2015.
13. UK Office for National Statistics (ONS) – ONS. Retrieved 18 March 2015.