Regulation pathway/strategy: Key considerations for foreign medical product registration in China

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The proportion of global clinical trials initiated in China has exhibited a substantial increase, rising from 25% in 2019 to 39% in 2023.

The guideline, *Clinical Data Requirement of Drug Products Marketed Abroad but Not in China* issued by China's Center for Drug Evaluation (CDE) of the National Medical Products Administration (NMPA), aims to facilitate **access to foreign medical products to address unmet medical needs in China.** This guideline is applicable to two main categories:

1. The innovative chemical products and therapeutic biological products marketed abroad
2. Generic domestic and foreign chemical products

Regulatory review criteria for foreign medical products marketed outside of China

For foreign medical products not marketed in China, the technical requirements for clinical trials supporting their market entry should be formulated in accordance with established clinical evaluation principles. These requirements should be based on a comprehensive assessment of the following key steps:

Medical need assessment	Efficacy and safety evaluation	Ethnicity sensitivity analysis	Regulatory decision based on Chinese benefit/risk assessment
› Epidemiological status, disease severity, and prognosis of the proposed indication in China › Current existing treatments in China › Differentiations from the current standard of care in China	› Full clinical efficacy and safety dataset › Evaluate the quality of clinical trial data	› Evaluation based on ICH E5 (intrinsic and extrinsic factors) › Disease characteristics and clinical practice differences between the global and Chinese populations	

Possible conclusions

1	2	3	4
› Safe and effective › Ethnicity insensitive	› Safe and effective › Unknown or ethnicity sensitive	› Safe and effective › Evidence inadequate	› Unsafe or ineffective

While the evaluation of unmet medical needs in China and ethnicity-specific sensitivity analyses are critical components in the registration process for foreign drug products, the primary emphasis remains on robust clinical data demonstrating efficacy and safety, aligning with requirements set by health authorities in other countries/regions. These foundational clinical outcomes serve as the cornerstone for regulatory assessment, complemented by China market specific and ethnicity-specific considerations.

The scenarios to be considered at each key step of the assessment process:

Scenario		Situation	Solution/Outcome
1	› Safe and effective › Ethnicity insensitive	Global data includes the subset of Chinese mainland population PK, and/or PD, safety and efficacy. When the analysis shows the benefit outweighs risk. (MRCT should follow ICH E17)	MAA directly
		No Chinese data in global trial, but ethnicity sensitivity analysis is well done among Asian, Black, and Caucasian and shows insensitive 1. Life-threatening or rare disease without effective treatment, or the drug shows significant clinical advantage to current practice in China 2. Does not show significant clinical advantage to current practice in China	1. Go to MAA directly ✓ PMC ✓ Stringent PV plan 2. Conduct trials in China to evaluate PK and/or PD, efficacy and safety
2	› Safe and effective › Unknown or ethnicity sensitive	Global clinical data demonstrates the safety and efficacy BUT lack of ethnicity comparison data or shows ethnicity sensitivity 1. Lack of ethnicity comparison data. 2. Ethnicity sensitivity may impact safety and/or efficacy	1. Apply CTA and conduct trials to evaluate PK and/or PD, efficacy and safety 2. Apply CTA and conduct trials including dose exploration trial if it is necessary
3	› Safe and effective › Evidence inadequate	Global clinical data cannot adequately demonstrate the safety and efficacy.	Generally, additional clinical trials are required. However, in cases of life threatening/ significant disease/ significant unmet medical needs, regulatory agencies may consider alternative approaches through case-by-case evaluations and discussions
4	› Unsafe or ineffective	Not effective and/or has severe safety issues	Rejection

The pharmacokinetic (PK), efficacy, and safety data in the Chinese population are mandatory for New Drug Application (NDA) or Marketing Authorization Application (MAA) approval, barring exceptional circumstances. Inclusion of China in Multi-Regional Clinical Trials (MRCT) may facilitate simultaneous NDA/Biologics License Application (BLA) approval, which is generally regarded as the most cost-effective approach. In 2023, 55% of global clinical trials included at least 1 trial location in the Asia-Pacific (APAC) region, and the number of trials initiated in APAC has surpassed those initiated in the rest of the world since 2021. Specifically, the proportion of global clinical trials initiated in China has exhibited a substantial increase, rising from 25% in 2019 to 39% in 2023.[1] The CDE typically advocates for the collection of Chinese PK data prior to initiating MRCTs.

Key regualtory considerations for evaluating foreign drug applications in China

According to the new guideline on MRCT (新药全球同步研发中基于多区域临床试验数据进行获益风险评估的指导原则) issued on December 13, 2024, the following critical factors should be considered when applying for foreign drug product registration in China:

› Safety considerations for the Chinese population

The potential safety risks for the Chinese population may be elevated compared to other regions, particularly in the following scenarios:

1. Drugs that have demonstrated significant safety concerns in clinical trials conducted in other regions.
2. Drugs with mechanisms of action that are not well elucidated.
3. Novel active ingredients without precedent products in the market.

› Body weight differences

The Chinese population generally exhibits lower average body weight compared to the Western population. Consequently, when applying dosages established in global clinical trials to the Chinese population, there may be discrepancies in drug exposure levels. These differences could potentially impact both safety and efficacy profiles.

› Genetic polymorphisms in metabolic pathways

As outlined in ICH E5, the drugs metabolized via pathways subject to genetic polymorphisms (e.g., CYP2D6, CYP2C9, CYP2C19) may exhibit altered drug exposure levels due to the differential distribution of metabolizer phenotypes between the Chinese and Western populations. Consequently, this could potentially impact both the safety profile and therapeutic efficacy in the Chinese population.

› Pharmacodynamic difference

For drugs that may exhibit ethnicity-specific pharmacodynamic differences (e.g., β receptor blocking effects, angiotensin converting enzyme inhibitory effects), it is crucial to evaluate whether the Chinese population demonstrates altered pharmacological responses compared to other populations. Such variations could potentially result in differential safety profiles and therapeutic efficacy.

Start Phase II study in China without separate Phase I PK study

Situation

A foreign pharmaceutical company was interested in conducting a Phase II study in China for an oncology asset. The sponsor asked Parexel to explore a regulatory strategy to waive the Phase I PK study in China.

Challenges

- All of the clinical studies (Phase I and ongoing global Phase II) were conducted outside of China, and there was no Chinese data.
- To minimize the prolongation of the Phase II trial and global registration timeline, the sponsor wanted to start a Phase II study in China without the safety and PK data from Chinese patients.

Solution

- Parexel provided a complete China CTA (Clinical Trial Application) service, including gap analysis, Pre-CTA meeting preparation, IB (Investigator's Brochure) development, protocol review, document translation and review, and CTA drafting and submission.
- Parexel experts carefully reviewed the data and Phase II protocol provided by the sponsors, and helped clients prepare pre-CTA BD with strong scientific justifications to demonstrate that the investigative drug was safe in Chinese. This included **extrapolated** data from non-Chinese to Chinese patients and the rationale for why a separate PK study was not necessary.

Result

- CDE accepted the pre-CTA meeting request and agreed that the sponsor could start the Phase II study in China, saving at least 9 months.
- Phase II study is currently ongoing in China.

This case study exemplifies Parexel's expertise in assisting the foreign pharmaceutical company interested in conducting Phase II clinical trials in China without prior implementation of Phase I PK studies in China.

The APAC region presents significant opportunities due to its vast population and substantial unmet medical needs. The increasing trend of including APAC in MRCT designs attests to this potential. Partnering with an entity possessing local expertise can enable sponsors to effectively leverage this trend and optimize their chances of success in the region.

References

1. Siu A, Gupta S. Exploring the Asia-Pacific Clinical trials landscape: Asking the Five W's. Citeline; October 2024. White paper.

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