CLINICAL LEADER

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Meeting Clinical Trial Data Requirements In Asian Markets

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Drug sponsors looking to enter the pharmaceutical markets of China, Japan, and India will be faced with regulatory requirements specific to the design, collection, and management of clinical information that are unique for each marketplace. We'll discuss potential strategies for dealing with these requirements, from planning to clinical studies, to successfully launch a product that's ready for Asia.

Pharmacokinetics And Ethnicity

The primary reason that countries oppose the use of foreign clinical data to justify a marketing authorization for new drugs is the potential influence of ethnicity on drug pharmacokinetics. Pharmacokinetics is the branch of pharmacology having to do with how a drug moves through the body. This includes the time of its absorption, bioavailability, distribution, metabolism, and excretion.[1] Extensive research has been conducted internationally about the effects of ethnicity on drug pharmacokinetics.[2] Multiple studies have demonstrated the ways a variety of drugs are metabolized differently in persons of Asian descent. These differences can result in serious side effects. An example is carbamazepine, which has a very rare side effect of skin necrosis that occurs at a higher rate in South-East Asian populations in comparison with Caucasian populations.[3]

Because of the numerous cases of pharmacokinetic differences between Asian populations and Caucasian populations, Asian countries have become very cautious about accepting foreign clinical data that does not include sufficient representation of their populations' ethnicity.

Clinical Data Requirements In Asia

Japan

Japan has issued two major notifications regarding the acceptance of foreign clinical data to support a marketing authorization application. The first requires that foreign clinical data be collected in studies that (1) use methods meeting Japanese standards, (2) are conducted at reliable medical institutions by qualified researchers, (3) are conducted in accordance with good clinical practices (GCPs), and (4) provide raw data available for review.[4] These requirements are consistent with those of every country that accepts foreign clinical data, including the United States, European Union, China, and India.

The second notification was the adoption of ICH E5, *Ethnic Factors in the Acceptability of Foreign Clinical Data*.[5] ICH E5 outlines the requirements for assessing a clinical data package for adequacy in the population of foreign regions. It goes into detail about the properties of a compound that make it likely to be sensitive to ethnic factors, highlighting pharmacokinetics and metabolism (Appendix D). The standard also describes the need for bridging studies with local populations to assess efficacy for products that provide inadequate data to extrapolate to the local population.

Japan has implemented the two notifications by assessing each application with foreign clinical data for quality, completeness, and ethnic sensitivity. When a product is unlikely to be affected by ethnicity, the product can be approved without a bridging study. However, if a product is likely to be affected by ethnicity, a bridging study is generally required unless the foreign data contains a sufficient number of Japanese patients to demonstrate safety and efficacy. There is no written guideline describing exactly how many patients that needs to be.[6]

For companies planning a new drug application (NDA) in Japan that relies on foreign clinical data, developing a careful regulatory strategy is essential. The Japanese NDA process involves several consultations with the Japanese Pharmaceuticals and Medical Devices Agency (PMDA). Manufacturers must be prepared to defend their use of foreign data during those consultations. Preparation should include the results of analytical testing demonstrating a lack of ethnic sensitivities and extrapolated analysis of clinical data from all Japanese subjects.

outlined for the first time a method by which foreign clinical data could be used to support an application. Much like Japan, the first requirement is that overseas clinical trial data be reliable, authenticated, and comply with the good clinical practice of China and ICH GCPs. If that requirement is met, China will assess the data for ethnic sensitivity. The data will then be classified as accepted, partially accepted, or rejected. Accepted data either does not demonstrate the likelihood of racial sensitivity or includes enough Chinese patients that "racial sensitivity analyses" were conducted to justify safety and efficacy for Chinese patients. Rejected data will not be accepted at all and a new clinical trial must be conducted in China. If the data suggests ethnic inconsistencies in effectiveness and safety, and racial sensitivity analyses do not demonstrate safety and efficacy for Chinese patients, it will be considered "partially acceptable," in which case a bridging study with Chinese subjects must be conducted.[8]

Much like submissions relying on foreign clinical data in Japan, Chinese NDAs should include information about ethnic sensitivities and extrapolated clinical data on Chinese subjects. China offers optional pre-NDA meetings for imported drugs. It is highly recommended that companies take advantage of those meetings to gain concurrence with the SAMR on the use of foreign clinical data. Preparing and submitting an NDA is an expensive process. While a pre-NDA meeting seems like an unnecessary expense, gaining concurrency with the agency prior to submission has the potential to avoid a rejected submission, saving time and money.

India

Like China, India has recently relaxed its clinical data requirements significantly. Before 2019, India also did not accept foreign clinical data. In March 2019, the Indian Ministry of Health and Family Welfare published the *New Drugs and Clinical Trial Rules*.[9] The rules represent a drastic change in Indian regulation and relax many of the requirements about how trials are conducted in the country. For companies wanting to expand into India, the most significant change is Rule 75, which allows for waivers of local clinical trial data.[10] The rule specifies that drugs already approved in the U.S., U.K., EU, Japan, or Australia may receive marketing authorization without a local clinical trial, as long as no major adverse effects have been reported. The rule also requires there is no likelihood of ethnic sensitivity, no existing knowledge of safety and efficacy differences in the Indian population, and no genes/enzymes or other factors affecting metabolism/pharmacokinetics. If the new drug does have any of those characteristics, a Phase IV study must be conducted in India.

Much like Japan and China, success in India will come down to the data. Pharmacokinetic clinical data demonstrating no ethnic sensitivities is essential. However, pharmacovigilance data for products on the market will also be very beneficial. Being able to demonstrate that there is no disparity in complaints or adverse drug reactions in Indian populations based on data collected from a broad population of users will go far in convincing India's Central Drugs Standard Control Organization of the product's safety.

Going International

It is possible for a company to successfully launch in China, Japan, and India without conducting multiple costly and time-consuming bridging studies, but it requires planning. The first thing a company needs to do is evaluate the likelihood that the new drug will have ethnic sensitivities. The pharmacokinetics, pharmacodynamics, metabolism, dose range, bioavailability, mode of action, and impacting genes/enzymes, among others need to be thoroughly understood. For drugs that present any likelihood of ethnic sensitivity, multi-center clinical trials are a must. India requires trials to be conducted in the country for drugs with ethnic sensitivities. Both China and Japan require a critical mass of patients of their respective ethnicities. The strongest way to get all of the necessary data is to have trial centers in all three countries, or in India and an Asian country where Chinese and Japanese patients can be found. The alternative is bridging studies conducted in each country on top of the original clinical trial. In each case, thorough documentation of pharmacovigilance data for each population will be extraordinarily helpful. If it becomes necessary to defend an internal determination that a drug does not have ethnic sensitivities, pharmacovigilance data will be the strongest evidence.

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Caitlin Bancroft, JD, is passionate about facilitating advancements in healthcare quality and medical technology by ensuring compliance for medical device, pharmaceutical, and biologic product regulatory requirements. Her experience in medical device regulation spans Class III, 510(k), PMA, De Novo, Modification, Reclassification, and IDE. Her work includes the review of FDA and EU regulations concerning quality management systems, cGMPs, clinical evidence/trials, complaint handling, risk management, and registration requirements for product classification and regulatory compliance of medical device, pharmaceutical, biotech, and human tissue/cell products. She works closely with clinical, quality management, and product and process development teams to accomplish cGMP audits and write clinical evaluation reports on behalf of Pharmatech clients.

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