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Clinical trials in "emerging markets": Regulatory considerations and other factors ☆

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ABSTRACT

Clinical studies are being placed in emerging markets as part of global drug development programs to access large pool of eligible patients and to benefit from a cost effective structure. However, over the last few years, the definition of "emerging markets" is being revisited, especially from a regulatory perspective. For purposes of this article, countries outside US, EU and the traditional "western countries" are discussed. Multiple factors are considered for placement of clinical studies such as adherence to Good Clinical Practice (GCP), medical infrastructure & standard of care, number of eligible patients, etc. This article also discusses other quantitative factors such as country's GDP, patent applications, healthcare expenditure, healthcare infrastructure, corruption, innovation, etc. These different factors and indexes are correlated to the number of clinical studies ongoing in the "emerging markets". R&D, healthcare expenditure, technology infrastructure, transparency, and level of innovation, show a significant correlation with the number of clinical trials being conducted in these countries. This is the first analysis of its kind to evaluate and correlate the various other factors to the number of clinical studies in a country.

1. Background

For a multinational biopharmaceutical company, there are multiple factors used to select countries for placement of global clinical trials. Historically, clinical studies were placed in "emerging markets" as part of global drug development programs to access large pool of eligible patients with the goal of faster drug registration in primary markets such as US and EU, with a cost effective structure.

From the perspective of the biopharmaceutical industry, the definition of "emerging markets" continues to evolve [1]. Countries or regions can be classified as "emerging" or "developing" according to a raft of different criteria such as economic status, industrial development, relative level of per capita income, human development index, etc. Most of the major biopharmaceutical companies have either created groups or reorganized to focus on emerging markets based on the market size or commercial potential of a region rather than by its regulatory systems. However, from a regulatory perspective, the definition and demarcation of "emerging markets" is rather straightforward — the world is broken into "primary markets" and "secondary markets". The "primary markets" are where the regulatory agencies conduct complete evaluation of safety, efficacy and quality of the product (usually the original ICH countries/regions). The "secondary markets" are the countries that depend on the approval of the primary countries and generally require a Certificate of Pharmaceutical Product (CPP) for drug registration. Thus from a traditional drug development paradigm, the drugs are first registered and approved in "primary markets" followed by approval in "secondary markets" which are mostly the emerging countries.

☆ The views expressed herein represent those of the author and do not necessarily represent the views or practices of the author's employer or any other party.

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For the purposes of this article, the regulatory framework for clinical trials in the top countries *other than* the "primary markets" (US, EU, Canada, Australia, Switzerland and Japan) are considered. The ranking of these countries is determined based on the number of registered clinical studies in ClinicalTrial.gov [2].

ClinicalTrials.gov has become a good consolidated source to track clinical trials conducted under an investigational new drug application (IND). While not all the global studies are reflected in this registry, it is a good surrogate to estimate for ongoing international clinical studies. This database was created as a result of the Food and Drug Administration Modernization Act of 1997 (FDAMA). FDAMA required the U.S. Department of Health and Human Services, through National Institutes of Health (NIH), to establish a registry of clinical trials information for both federally and privately funded trials conducted under investigational IND to test the effectiveness of experimental drugs for serious or life-threatening diseases or conditions. NIH and the FDA worked together to develop the site, which was made available to the public in February 2000. Geographic locations of the studies registered at ClinicalTrials.gov are illustrated in Fig. 1.

2. Choosing emerging markets for clinical trials

2.1. Regulatory considerations

Some key emerging countries (e.g., China, Korea, Taiwan, India, Vietnam, Russia) require local clinical trial data as part of the regulatory marketing application (Table 1). Consequently, clinical trials in many emerging countries no longer are primarily focused on just accessing patients as part of global studies but now use the local patients as a means to access the local markets. Thus patients from emerging markets are either part of a global study, a regional study (e.g., pan-Asian) or a local registration study. Where and when to place the clinical studies are driven by many regulatory considerations such as agency review timelines, content of the dossier, patient requirements (for registration studies), and regional regulatory requirements (Table 1).

The regulatory timelines appear to be increasing and the "drug-lag" phenomenon [3] becoming more pronounced in some of the major emerging markets where the regulatory agencies are establishing new regulatory framework outside the ICH guidelines or adapting the ICH guidelines to their local laws and regulations. There are significant differences in the top 10 emerging markets shown in Table 1 in terms of regulatory approval timelines for CTAs and patient requirements for marketing application approvals. For example, compared to other Asian countries, China has long regulatory review and approval timelines which makes China's participation in regional and global studies challenging, especially if the studies are of a shorter duration. Similarly, with China requiring 300 patients as part of a registration study, it could become impractical to include China in global or a regional study if the study design calls for fewer patients and China would then have a disproportionate number of study subjects. Thus one has to consider various regulatory factors such as review timelines, purpose of the study (global vs. local registration), and patient numbers required for local registration, and whether or not it is part of a regional registration study.

2.2. Clinical factors

The clinical trial data generated in emerging markets, whether part of the global studies or regional studies, will generally be part of the safety and efficacy analysis. To ensure

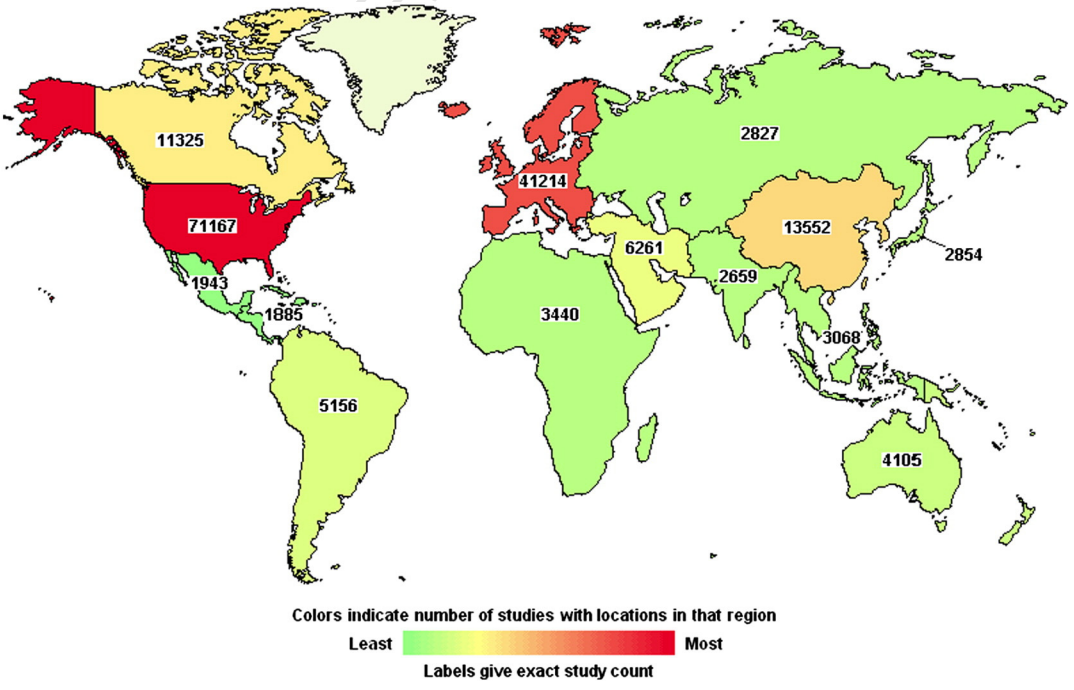

Fig. 1. Map of all studies in ClinicalTrials.gov as of September 2013.

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