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New paradigm for drug developments—From emerging market statistical perspective

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ABSTRACT

Paradigm for new drug development has changed dramatically over the last decade. Even though new technology increases efficiency in many aspects, partially due to much more stringent regulatory requirements, it actually now takes longer and costs more to develop a new drug. To deal with challenge, some initiatives are taken by the pharmaceutical industry. These initiatives include exploring emerging markets, conducting global trials and building research and development centers in emerging markets to curb spending. It is particularly the current trend that major pharmaceutical companies offshore a part of their biostatistical support to China. In this paper, we first discuss the skill set for trial statisticians in the new era. We then elaborate on some of the approaches for acquiring statistical talent and capacity in general, particularly in emerging markets. We also make some recommendations on the use of the PDUFA strategy and collaborations among industry, health authority and academia from emerging market statistical perspective.

1. Introduction

The pharmaceutical industry experienced a boom in the 1990's. During that period, successful stories of new drug developments came out one after another. New blockbuster drugs were continuously being put into market to benefit patients tremendously. For example, with the highly active antiretroviral therapy, the annual HIV/AIDS death rate in the United States declined from 16.2 deaths in 1995 to 2.7 deaths in 2010 per 100,000 population. Additionally, medicines and interventional treatments resulted in a 45% reduction in heart attack deaths and heart failure from 1999 to 2005 [1](PhRMA 2012 profile). Nowadays, even though the industry continues to contribute strongly to the economy, the overall landscape for the industry has completely changed. The leftover diseases are much more difficult to conquer. Health authorities ask more from sponsors, with more stringent requirements on the demonstrations of safety and efficacy. It now takes longer and costs more to develop a new drug.

From 2000–2003 to 2008–2011, there were over 50% increases in clinical procedures, execution burden and patient eligibility criteria specified in clinical trial protocols. At the same time, there were over 20% reductions in volunteer enrollment rate and retention rate [2] (PhRMA 2011 profile). Furthermore, with many medical options currently available in the market as standard medical care, it is much more of a challenge to demonstrate any add-on treatment effect for a new drug. In addition, to have sufficient data to quantify safety margin and satisfy health authorities, current trials need much larger sample sizes and much longer study durations. For example, the U.S. FDA recently issued a guideline for new diabetic drug developments [3] (FDA Guidance, 2008). According to the guideline, all sponsors have to demonstrate cardiovascular (CV) safety for their compounds based on a non-inferiority assessment of not increasing the CV risk by more than 80% for the preliminary drug approval and not increasing the CV risk by more than 30% for the final drug approval. For reasonable power to meet the requirement of this guideline, besides having enough data to demonstrate

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treatment efficacy on treating diabetes, the sponsors have to have much larger data sets for the CV safety evaluation, which increases the risk of failure, delays the development timeline, and increases the cost. On average, it takes 10–15 years from drug discovery to drug approval. The cost to develop one new drug has skyrocketed, increasing from $140 million in the 1970's to approximately $1.2 billion in the early 2000's [2] (PhRMA 2012 profile). As the result, from 2004 to 2008, even though US drug companies increased R&D spending by 30% over the previous period, the number of approved new molecular entities actually declined by 33% [4].

To sustain growth and be able to continue developing safe and effective new medicines, pharmaceutical companies are making strategic changes by tapping new business territories for diversification, merging and acquiring for expanding pipelines, forming joint ventures for co-development, restructuring R&D, including outsourcing/offshoring, for cutting cost, and exploring emerging markets as significant and lucrative markets for increasing revenue [5].

To satisfy the requirements of local health authorities in order to penetrate emerging markets, multi-regional clinical trial (MRCT) strategy is an efficient way for new drug development. Conducted globally, MRCTs provide data to demonstrate treatment safety and efficacy for worldwide patients, including patients in emerging markets, simultaneously. Without the need of multiple regional trials, MRCT strategy saves resources and shortens timelines. Actually, with large patient populations in all disease categories, it is much easier to recruit patients from emerging markets such as China. The majority of Chinese patients has no medical insurance and has extremely limited access to healthcare. Participating in clinical trials provides them with a means to receive high quality medical treatment for free. Once recruited, patients in China have high retention rates and are more compliant with study protocol [6] (China Bio LLC, 2011), resulting in a lower missing data rate and a good estimate of treatment effects. Another advantage of conducting trials in emerging markets is the low operational costs. It has been estimated that trial costs in China is around only 20% of that in the West or Japan. All these factors combined can make some large-scale trial possible.

Besides participating in MRCTs for global new drug development, countries in emerging markets may also welcome clinical trials for demonstrating local treatment efficacy for drugs that have been approved in other countries. These drugs are classified as Class III drugs based on the Chinese drug classification system [7]. Many of these drugs are less expensive generic drugs and are more affordable for emerging markets. All these drugs have been used extensively elsewhere. Tremendous data on the safety and efficacy of the drugs are already available. For them, rather than using the traditional large-scale full Phase III programs, relatively small-scale bridging trials for examining consistency of treatment effects across regions should be sufficient. Nonetheless, criterion for consistency should be pre-defined in the bridging study protocols and enough patients should be recruited to have appropriate assurance probability to demonstrate consistency so that hopefully treatment effects of the original regions can be extrapolated to the new regions.

Along with more and more clinical trials conducted in emerging markets, global pharmaceutical companies have also set up R&D centers in those areas to take advantage of co-located clinical development supports and potential vast talent pool. Many companies now have R&D operations in China, starting from basic research to clinical trial design and conduct, data analysis, and final reporting. Beginning with simple and basic studies and projects to gain experience, the Chinese teams are expected to eventually function as the US counterpart and work on global trials. Among various functions and expertise for clinical development, one core expertise that many global companies have been actively establishing in China is biostatistics and programming. For example, Merck has publically announced that 40% of its future global biostatistical support would come from Asia. Correspondingly, the SFDA (State Food and Drug Administration of China) also needs to build a strong comparable statistical team to conduct statistical review. Thus, experienced statisticians are in eager demand in China.

Global clinical trials for new drug development involve many aspects such as trial conduct, trial monitoring, data management and regulatory science. In this paper, we focus on new paradigm from an emerging market statistical perspective. Since China is the largest and fastest growing emerging market, we will use China as an example in many instances. Some of the points made for China are also applicable to other emerging market countries, e.g., India. We start with the general skill set currently required for trial biostatisticians. It has a wide span, through the day after day accumulation of knowledge. We then summarize possible approaches for acquiring statistical talent and capacity in emerging markets. Some recommendations on the collaboration among the industry, agency, and academia are also provided.

2. Skill set for trial statisticians in the new era

With the explosion of new concepts and new ideas, the general required skill set for trial statisticians in the new era is also expanding. A trial statistician in a study team is involved in the whole study process from trial planning, trial design, method specification, data analysis, and result interpretation to report preparation [8,9]. Different from academia statisticians who can focus on even one specific research area for their whole career, trial statisticians must possess much broader knowledge in order to perform efficiently. Particularly, statisticians in emerging markets must quickly master these skills to become totally independent. A trial statistician can contribute in all the following areas and need the corresponding skills.

All studies are different. They are for different purposes, for different therapeutic areas and for different compounds. Different compounds have different pharmacokinetic profiles, which can impact the drug's half-life, AUC (Area Under the Curve for plasma concentration over time) and Cmax (maximum plasma concentration). These further impact the selection of doses and treatment regimens. For example, based on a drug's half-life, the drug could be administrated twice a day, once a day, or even once a month and in different formulations. Careful analysis is necessary to select the right treatment regimens for later phase trials and then the ultimate patients with great confidence. The disease area under the study determines the patient population and the