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Short Communication

Future Perspectives of Pharmaceutical Research and Development

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Abstract

As more and more innovative drug products (e.g., chemical drug and biological drug products) are going off patent protection, the development of generics/biosimilars products have become the center of attention of many pharmaceutical companies. In addition, as new drug research and development has reached the bottle-neck, the pharmaceutical industry begin to focus on the search for new or alternative medicines such as traditional Chinese medicine that can treat critical and/or life-threatening diseases. To ensure that there is high probability of success, advanced technology and/or methodology and innovative thinking of trial designs are necessarily applied. The advanced technology/methodology include two-way translational process from bench-to-bedside in translational research, micro-dosing approach for safety evaluation, and big-data analytics for identifying hidden clinical benefits of some test treatments. The innovative thinking of trial designs are referred to adaptive trial designs for identifying optimal clinical benefits of the test treatment under investigation and/or biomarker induced targeted clinical trials for personalized (precision) medicine. Along this line, this short commentary provides perspectives of future pharmaceutical development of biosimilar products and traditional Chinese medicine.

Keywords: Adaptive trial design; Micro-dosing approach; Big-data analytics; Precision medicine; Biosimilars; Traditional Chinese medicine

Introduction

In pharmaceutical development of a test treatment under investigation, the process is usually lengthy and costly. This lengthy and costly process is necessary to ensure the safety and efficacy of the test treatment under investigation. In the past several decades, however, it was recognized that increasing spending of biomedical research does not reflect an increase of the success rate of pharmaceutical development [1]. indicated that the low success rate of pharmaceutical development could be due to (i) a diminished margin for improvement that escalates the level of difficulty in proving drug benefits, (ii) genomics and other new science have not yet reached their full potential, (iii) mergers and other business arrangements have decreased candidates, (iv) easy targets are the focus as chronic diseases are harder to study, (v) failure rates have not improved, and (vi) rapidly escalating costs and complexity decreases willingness and ability to bring many candidates forward into the clinic. To assist the sponsors in identifying the scientific challenges underlying the medical product pipeline problems, the United States Food and Drug Administration (FDA) kicked off a Critical Path Initiative in early 2000s. In 2006, the FDA released a Critical Path Opportunities List that outlines 76 initial projects (six broad topic areas) to bridge the gap between the quick pace of new biomedical discoveries and the slower pace at which those discoveries are currently developed into therapies. Among the 76 initial projects, the FDA calls for advanced evaluation tool and innovative trial designs in pharmaceutical/clinical development. The advanced evaluation tools include two-way translational process from bench-to-bedside in translational research, biomarker development for achieving personalized (individualized or precision) medicine, micro-dosing approach for safety evaluation, and big-data analytics for identifying hidden clinical benefits for test treatments under study). The advancing innovative trial designs are referred to targeted clinical trials under an enrichment design utilizing certain biomarkers for personalized medicine and adaptive trial designs for identifying optimal clinical benefits of a test treatment under investigation) in pharmaceutical research and development.

In recent years, as more and more innovative drug products (e.g., chemical drug and biological drug products) are going off patent protection, the development of generics/biosimilars products have become the center of attention of many pharmaceutical companies. In addition, as new drug research and development has reached the bottle-neck, the pharmaceutical industry begin to focus on the search for new or alternative medicines such as traditional Chinese medicine (TCM) that can treat critical and/or life-threatening diseases. This has led to the development of advanced technology/methodology and the use of innovative trial designs in pharmaceutical research and development, e.g., the assessment of biosimilarity and interchangeability of biosimilar products, and the study of promising TCMs. A biosimilar product is a biological product which is highly similar to the innovative (reference) product notwithstanding minor differences in clinically inactive components and there are no clinically meaningful differences in terms of safety, purity and potency [2]. A TCM, on the other hand, is defined as a Chinese herbal medicine developed for treating patients with certain diseases as diagnosed by the four Chinese major techniques of inspection, auscultation and olfaction, interrogation, and pulse taking and palpation based on traditional Chinese medical theory of global dynamic balance among the functions/activities of all organs of the body [3]. The development of biosimilars and promising TCMs will benefit patients with critical or life-threatening diseases by providing an alternative for treatment and hopefully for cure.

In this short commentary article, we will focus on the use of advanced evaluation tool (e.g., micro-dosing approach, translational research, and big data analytics) and innovative adaptive trial design for identifying optimal benefit of the test treatment under investigation in a more efficient way in pharmaceutical research and development. In addition, perspectives regarding future development of biosimilars and promising TCMs are also discussed.

Innovative Design

As indicated in the Critical Path Opportunities List, FDA recommends the use of prior experience or accumulated information and biomarker development in clinical trials to increase the probability of success. Many researchers interpret FDA's recommendation as the

encouragement for the use of the innovative adaptive design methods in clinical trials. The use of biomarkers is to identify patient populations who are most likely to respond to the treatment under investigation in an enrichment phase of a clinical trial. The ultimate goal is to achieve personalized (individualized or precision) medicine. These innovative thinking of trial designs are briefly described below.

Adaptive design methods in clinical trials

In its 2010 draft guidance, the FDA defines an adaptive design clinical study as a study that includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data) from subjects in the study (FDA, 2010). FDA's definition has the following characteristics. First, adaptation (change or modification) is a prospectively planned opportunity. Thus, the guidance does not reflect real practice (e.g., protocol amendments). Second, changes are made based on analysis of data (usually interim data). In addition, the guidance classifies adaptive designs into well-understood and less well-understood designs. According informal communications with medical/statistical reviewers, a well-understood design is referred to as a study design which has been in practice for years and the statistical methods are well established. Most importantly, FDA is familiar with the study design. On the other hand, a less well-understood design is a study design whose relative merits and limitations have not yet been fully evaluated and statistical methods have not yet been developed/established. Most importantly, FDA does not have sufficient experience for submissions utilizing such study design.

According to the 2010 FDA draft guidance, a well-understood design is usually referred to the typical group sequential design, which has been employed in clinical research for years. Less well-understood designs include the commonly considered adaptive trial designs such as adaptive randomization design, adaptive-biomarker design, adaptive dosing finding design and two-stage phase I/II (or II/III) seamless adaptive design [4,5]. Many scientific issues surrounding the less well-understood designs are posted in the draft guidance without any recommendations for resolutions. This raises the question whether the use of adaptive design methods in clinical trials (especially or those less well-understood designs) is ready for implementation in practice.

The use of adaptive design methods has the following advantages. First, an adaptive trial design allows an early decision making such as stop the trial early for safety and/or futility/efficacy. Second, it is efficient which can shorten the development process. Third, it is flexible by offering the opportunity to re-design the study after the review of the interim data. Finally, it will not only provide more accurate and reliable assessment of the treatment effect, but also increase probability of success. Despite of these advantages, an adaptive trial design regardless it is well-understood or less well-understood, it should be used with caution because (i) it may introduce operational bias, (ii) it may not be able to preserve type I error rate, (iii) the p-values may not be correct, (iv) confidence intervals may not be reliable, and (v) validity and integrity may be in doubt if more adaptation are applied during the conduct of the trial.

Future perspectives: We are moving toward the right direction and yet there is still a long way to go until we are able to address all of the scientific issues from clinical, statistical, and regulatory perspectives as described above. In the interest of validity and integrity of intended clinical trials, adaptive trial designs should not be misused and must not be abused in clinical trials. Detailed design-specific guidances, especially for those less well-understood designs are necessary developed by the regulatory agencies for implementation. From future perspectives, it is suggested that the escalating momentum for the use of adaptive design methods in clinical trials be slowed down in order to allow time for development of appropriate statistical methodologies for interested adaptive designs with various adaptations to prevent the possible misuse and abuse of the adaptive design methods in clinical trials.

Biomarker Development for Target Clinical Trials

In clinical trials, the primary goal of the inclusion and exclusion criteria is to define a homogeneous target patient population to which the inference regarding the efficacy and safety of a treatment regimen can be made. However, despite these efforts, patients in the same trial may still respond differently to the same treatment modality. This may be due to the fact that the homogeneous patient population defined by the inclusion and exclusion criteria based on phenotype characteristics fails to take genetic or genomic variability between the patients into consideration. In practice, the following four scenarios are commonly seen:

(1) the drug is efficacious for the patient without adverse effects;

(2) the drug is efficacious for the patient with adverse effects;

(3) the drug is not efficacious for the patient without adverse effects, and

(4) the drug is not efficacious for the patient with adverse effects.

This leads to the question that what the target population should be. Larger population with a smaller treatment effect would require much larger sample size. On the other hand, smaller target population with a larger size would require a smaller sample size. Thus, it is suggested that a biomarker is developed in order to select right patient population which can help in identifying patient population that are most likely to respond to the test treatment under study in enrichment process. A biomarker is defined as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. As compared to a gold standard endpoint, such as survival, a biomarker can often have following characteristics that (i) it can be measured earlier, easier, and more frequently, (ii) less subjects to competing risks, (iii) less affected by other treatment modalities, and (iv) can detect a larger effect size.

Future perspectives

Although the use of biomarker can lead to (i) better target population, (ii) larger effect size, (iii) smaller sample size, and (iv) faster decision-making, the identified biomarker need to be validated. In practice, a biomarker is often not validated adequately in terms of some required performance (validation) characteristics. In addition, sample size is often insufficient for validation. As a result, precision of prediction of treatment effect on true-endpoint is lower using biomarkers. Biomarker development is a key to the success of personalized (precision) medicine because it not only minimizes intra-subject variability, but also maximizes the treatment effect size.

Advanced Technology

Translational medicine

It defines translational medicine [6] as *bench-to-bedside* research wherein a basic laboratory discovery becomes applicable to the diagnosis, treatment or prevention of a specific disease and is brought forth by either a physician-scientist who works at the interface between the research laboratory and patient care or by a team of basic and clinical science investigators. Thus, translational medicine is referred to

the translation of basic research discoveries into clinical applications. More specifically, translational medicine is to take the discoveries from basic research to a patient and measures an endpoint in a patient. Most recently, scientists are increasingly aware that this bench-to-bedside approach to translational research is a two-way street. Basic scientists provide clinicians with new tools for use in patients and for assessment of their impact, and clinical researchers make novel observations about the nature and progression of disease that often stimulate basic investigations [7] pointed out that there are three major obstacles to effective translational medicine in practice. The first is the challenge of translating basic science discoveries into clinical studies. The second hurdle is the translation of clinical studies into medical practice and health care policy. A third obstacle to effective translational medicine is philosophical. It may be a mistake to think that basic science (without observations from the clinic and without epidemiological findings of possible associations between different diseases) will efficiently produce the novel therapies for human testing. Pilot studies such as non-human and non-clinical studies are often used to transition therapies developed using animal models to a clinical setting. Statistical process plays an important role in translational medicine. In this article, we define a statistical process of translational medicine as a translational process for (i) determining association between some independent parameters observed in basic research discoveries and a dependent variable observed from clinical application, (ii) establishing a predictive model between the independent parameters and the dependent response variable, and (iii) validating the established predictive model. As an example, in animal studies, the independent variables may include *in vitro* assay results, pharmacological activities such as pharmacokinetics and pharmacodynamics, and dose toxicities and the dependent variable could be a clinical outcome (e.g., a safety parameter).

Translational medicine is a multi-disciplinary entity that bridges basic scientific research with clinical development. As the expense in developing therapeutic pharmaceutical compounds continues to increase and the success rates for getting such compounds approved for marketing and to the patients needing these treatments continues to decrease, a focused effort has emerged in improving the communication and planning between basic and clinical science. This will likely lead to more therapeutic insights being derived from new scientific ideas, and more feedback being provided back to research so that their approaches are better targeted. Translational Medicine spans all the disciplines and activities that lead to making key scientific decisions as a compound traverses across the difficult preclinical -- clinical divide. Many argue that improvement in making correct decisions on what dose and regimen should be pursued in the clinic, the likely human safety risks of a compound, the likely drug interactions, and the pharmacologic behavior of the compound, are likely the most important decisions made in the entire development process. Many of these decisions and the path for uncovering this information within later development are defined at this specific time within the drug development process. Improving these decisions will likely lead to a substantial increase in the number of safe and effective compounds available to combat human diseases.

Future perspectives: In translation research, the concept of bench-to-bedside approach include two-way translational process: one-way from basic discovery research to clinic and the other way from clinic back to basic discovery research. In the past, the translation research is purely a one-way street from basic discovery research to clinic. This has significantly decreased the probability of success in pharmaceutical research and development, especially when there is possible loss in translation (due to miscommunication and/or misinterpretation of the results obtained from the basic discovery research). Thus, it is strongly suggested that two-way translational process between basic discovery research and clinic be established and enforced for future pharmaceutical research and development.

Micro-dosing approach

In pharmaceutical research and development, a micro-dose is defined as less than 1/100th of the dose of a test substance calculated (based on animal data) to yield a pharmacologic effect of the test substance with a maximum dose of ≤ 100 micrograms [8]. Micro-dose studies are often designed not only to evaluate pharmacokinetics or imaging of specific targets but also to induce pharmacologic effects. The risk of microdose to human subjects is considered very limited, while information adequate to support the initiation of such limited human studies can be derived from limited non-clinical safety studies [9]. In the past decade, the relationship between a micro-dose and a therapeutic dose is often studied by comparing the response of the micro-dose with that observed at a therapeutic dose [10] indicated that about 80% of the microdose pharmacokinetics available in the public domain has been shown to scale to those observed at a therapeutic dose, within a two-fold difference. Thus, [10] suggested micro-dosing approach be extended into drug (pharmacokinetics) development in situations where the concentration of a drug in cell or tissue types is relevant to its efficacy. As indicated in the [8] guidance on Exploratory IND, a typical microdose study involves very limited human exposure and it has no therapeutic or diagnostic intent. A microdose study is considered an exploratory study which focuses on the detection of safety signals. Thus, it is suggested that preclinical and clinical approaches, as well as chemistry, manufacturing, and controls (CMC) information, should be considered when planning exploratory studies in humans, including studies of closely related drugs or therapeutic biological products.

As indicated by ref. [10], the application of micro-dosing as a tool for early drug selection and development is growing and can be applied to drug-to-drug interaction by examining drug concentrations in tissues and certain cell types. Both ICH guideline and FDA guidance, however, emphasize that micro-dosing approach is for exploratory purpose and it should focus on safety in early phase of clinical/pharmaceutical development rather than on development for efficacy. [9] emphasized that the use of human microdosing in pharmaceutical development has the following benefits that (i) it takes just six months from laboratory bench to completion of clinical studies, (ii) smarter lead candidate selection, (iii) reduces expensive late stage attrition (i.e., kill ineffective compound early and cheap), (iv) substantially reduced preclinical toxicology package compared to phase I, (v) only gram quantities of non-GMP drug (typically 10 g) are needed, (vi) any route of administration possible, including intravenous, (vii) absolute oral bioavailability calculation, (viii) drugs can be tested in sensitive populations; renal impaired patients, women of child bearing age and cancer patients, and (ix) reduces use of animals in research.

Future perspectives: The concept of micro-dosing approach in pharmaceutical development is encouraging. However, there are many scientific factors and practical issues, which limit the possible application of micro-dosing in pharmaceutical research and development, remain unsolved. These scientific factors include, but are limited to, (i) the issue of placebo effect both at micro-dose and at therapeutic dose, (ii) the prediction of animal model to human model, (iii) the selection of therapeutic dose, (iv) the characterization of dose response curve, (v) accuracy and reliability of extrapolation (prediction) of the micro-dose to therapeutic dose, and (vi) the assessment of false positive/negative of

micro-dose prediction [11]. These practical issues have limitations in many aspects on drug development for efficacy.

New Pharmaceutical Development

Biosimilars

In 2009, the United States Congress passed the *Biologics Price Competition and Innovation* (BPCI) *Act*, which has given FDA the authority to review and approve follow-on biologics (similar biological products or biosimilars). The BPCI Act (as part of the Affordable Care Act) was subsequently written into law on March 23, 2010 [12]. Following the passage of the BPCI Act, FDA hosted a public hearing between November 2-3, 2010 to obtain public input regarding scientific factors for assessing biosimilarity and drug interchangeability of biosimilar products. After extensive discussions, the FDA developed and circulated three draft guidances on biosimilars on February 9, 2012 and hosted another public hearing to obtain public input and comments on the draft guidances on May 11, 2012. These guidances were finalized and published in early 2015.

As indicated in the BPCI Act, a biosimilar product is defined as a product that is *highly similar* to the reference product notwithstanding minor differences in clinically inactive components and there are no clinically meaningful differences in terms of safety, purity, and potency. At the FDA's Public Hearings, several scientific factors and/or issues were raised. These scientific factors and/or issues included (i) how similar is considered highly similar? (ii) What should the biosimilarity criteria be? (iii) Can a non-inferiority trial be considered to replace the equivalence (similarity) study? (iv) How many biosimilar studies are required for obtaining regulatory approval of a biosimilar submission? Some of these scientific factors are partially addressed by the FDA draft guidances and yet there are still scientific factors remain unresolved.

In the FDA draft guidances, FDA recommends a stepwise approach for obtaining the totality-of-the-evidence for assessment of biosimilarity between an innovative biological product and its biosimilar products. The stepwise approach starts with analytical biosimilarity assessment for critical quality attributes at various stages of manufacturing process for functional and structural characterization, followed by animal studies for assessment of toxicity. Pharmacokinetics (PK) or pharmacodynamics (PD) is then conducted for study of clinical pharmacology. At the final step, clinical studies for the assessment of immunogenicity, safety/tolerability, and/or efficacy are conducted. Following this approval pathway, Sandoz biosimilar filgrastim was recommended for approval by FDA Oncologic Drugs Advisory Committee (ODAC) on January 7, 2015, which was subsequently approved by the FDA on March 6, 2015. Biosimilar filgrastim recommended to be approved for use in all requested indications in the reference (Amgen's Neupogen) product's label. The ODAC's recommendation was based on review of extensive data from analytical, non-clinical, clinical studies and post-marketing pharmacovigilance.

Future perspectives: One the most critical issues regarding biosimilars assessment are probably the issue of drug interchangeability. BPCI defines drug interchangeability as the following. The biological product to be interchangeable with the reference product if (A) the biological product is biosimilar to the reference product; and it can be expected to produce the same clinical result in any given patient; and (B) for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch. In practice, it is not possible to show same clinical result in any given patient. In other words, for every patient, we need to show same clinical result. However, it is possible to show same clinical result in any given patient with certain assurance [13,14].

Traditional chinese medicine

In recent years, the search for complementary and alternative medicine such as botanical drug product and traditional Chinese (herbal) medicine (TCM) for treating critical and/or life-threatening diseases has received much attention. This has led to the study of the potential use of promising TCMs. As indicated by ref. [3,15] TCM originated in ancient China has evolved over several thousands of years, which usually refers to a broad range of Chinese medicine practice including various forms of herbal medicine, acupuncture, massage (Tui-Na), exercise (Qi-Gong), and dietary therapy. In pharmaceutical/clinical development of a test treatment, one of the major criticisms for the development of TCM is lack of objectively scientific evidence (documents) of clinical safety and efficacy. Unlike the Western medicines (WM), TCM often consists of multiple components (active ingredients) whose pharmacological activities are often unknown or are not fully characterized or understood. Thus, standard methods for evaluation of WM clinical trials [16] may not be appropriately applied directly to TCM clinical trials.

In TCM clinical trials, it is a concern whether a TCM can be scientifically evaluated the Western way due to some fundamental differences between a WM and a TCM. These fundamental differences include differences in formulation and drug administration, medical theory/practice, diagnostic procedure, and criteria for evaluation [3]. As an example, the Chinese diagnostic procedure for patients with certain diseases consists of four major techniques, namely, inspection, auscultation and olfaction, interrogation, and pulse taking and palpation [15]. Under these differences, it is of interest to the investigators regarding how to design and conduct a scientifically valid (i.e., an adequate and well-controlled) clinical trial for evaluation of the clinical safety and efficacy of the TCM under investigation. In addition, it is also of particular interest to the investigators as to how to translate an observed significant difference detected by the Chinese diagnostic procedure to a clinically meaningful difference based on some well-established clinical study endpoint. Although TCM has a long history of being used in humans, little or no scientifically valid documentations are available for demonstration of clinical safety and efficacy of the TCM. In the interest of modernization or Westernization of TCM development, as indicated by the FDA, substantial evidence regarding safety and effectiveness of the test treatment under investigation can only be obtained by conducting adequate and well-controlled clinical trials. In TCM clinical trials, however, it is a concern whether a TCM can be scientifically evaluated the Western way due to some fundamental differences between a WM and a TCM.

In practice, there are some basic considerations for providing substantial evidence of clinical safety and efficacy of a TCM under investigation during the conduct of TCM clinical trials in the development of TCMs the Western way. These statistical considerations include selection of study design, preparation of matching placebo, development of study endpoint, validation of an instrument, calibration of a validated instrument, and power calculation for sample size estimation. In addition, before a TCM under investigation can be used in human, sufficient information regarding CMC, clinical pharmacology, and toxicology are necessarily provided. In practice, these information, which have impact on the scientifically validity for the assessment of the TCM under investigation, are difficult, if not impossible, to obtain. Thus, it is suggested that some practical issues

such as test for consistency, stability analysis for shelf-life estimation, and animal studies for toxicity be evaluated before the conduct of the intended TCM clinical trials [11,15,16].

Future perspectives: In Chinese community (e.g., Taiwan and China), there is huge debate regarding whether the future direction for the development of TCM should be modernization the Chinese way or Westernization the Western way due to some fundamental differences (e.g., objective versus subjective, evidence-based versus experience-based, fixed dose versus flexible dose, and population versus individual) between Western medicine (most of them contain single active ingredient) and TCM (usually contains multiple components). It is realized that a direct copy of regulatory approval pathway (guidelines/guidances), which is developed for Western medicine, may not be feasible for TCM. Modernization the Chinese way or Westernization the Western way will lead to a very different review/approval pathway for development of TCMs.

Big-Data Analytics

In healthcare related biomedical research, big data analytics is referred to as the analysis of large data sets which contain a variety of data sets (with similar or different data types) from various data structured, semi-structured or unstructured sources such as registry, randomized or non-randomized studies, published or unpublished studies, and health care database. The purpose of big data analytics is to detect any possible hidden signals, patterns and/or trends of safety and efficacy of certain test treatments under study. In addition, it is to uncover any possible unknown associations and/or correlations between potential risk factors and clinical outcomes, and other useful biomedical information such as risk/benefit ratio of certain clinical endpoints/outcomes. The finding of big data analytics could lead to more efficient assessment of treatments under study and/or identification of new intervention opportunities, better disease management, other clinical benefits, and improvement of operational efficiency for planning of future biomedical studies.

As indicated in the request for proposal (RFP) at the website of the United States National Institutes of Health (NIH), biomedical research is rapidly becoming data-intensive as investigators are generating and using increasingly large, complex, multi-dimensional, and diverse data sets. However, the ability to release data, to locate, integrate, and analyze data generated by others, and to utilize the data is often limited by the lack of tools, accessibility, and training. Thus, the NIH has developed the Big Data to Knowledge (BD2K) initiative to solicit development of software tools and statistical methods for data analysis in the four topic areas of data compression and reduction, data visualization, data provenance, and data wrangling as part of the overall BD2K initiative. Details can be found in http://bd2k.nih.gov/about_bd2k.html.

It pointed [17] out that the criteria for platform evaluation including availability, continuity, ease of use, scalability, ability to manipulate at different levels of granularity, privacy and security enablement, standardization of data with incompatible formats and quality assurance [18,19] (2) typical advantages and limitations of open source platforms, (3) menu-driven, user-friendly and transparent of big data analytics, (4) real-time big data analytics as there is a lag between data collection and data processing, (5) the availability of numerous analytics algorithms, models and methods in a pull-down type of menu, (6) management of data ownership, governance and standards of continuous data acquisition and data cleansing.

As big-data include data sets from a variety of sources including registries, randomized or non-randomized clinical studies, published or unpublished data, positive or negative clinical results (data), and healthcare database, heterogeneity within and across these data sets will have an impact on the assessment of treatment effects of interest. Big-data analytics provides opportunities for uncovering hidden important medical information, determining possible associations or correlations between possible risk factors and clinical outcomes, predictive model building, validation, and generalization, critical information for planning of future studies. Statistical methodology and software development are necessary for achieving these ultimate goals. Although there are benefits for big-data analytics, statistical issues regarding representativeness of the big-data and its quality, integrity, and validity must be addressed to ensure the success of the big-data analytics [20].

Future perspectives: One of the most controversial issues in big-data analytics occurs when the finding of the big-data analytics (with a large scale) is inconsistent with that from a relatively small scale of adequate well controlled randomized clinical trial which was conducted under the similar target patient population. In this case, the representativeness of the big data is questionable which may be due to the possible selection bias of accepting *poor* data sets into the big-data. The inconsistency may indicate that there are major dissimilarities among individual data sets (collected from individual studies) in the big-data. Thus, it is suggested that similarities/dissimilarities, possible interactions, and poolability be carefully assessed for identifying the possible causes of inconsistencies [21].

Concluding Remarks

For future pharmaceutical research and development, the use of innovative design (e.g., adaptive trial design or biomarker enrichment design) in conjunction with advanced technology and/or methodology (e.g., micro-dosing approach and big-data analytics) is encouraged. The innovative thinking of design and analysis of clinical trials conducted for development of biosimilars and/or promising TCMs is essential. However, it should not be implemented at the risk of scientific validity and integrity [22].

In scientific community, it is always a concern whether the observed finding is reproducible if the experiment shall be conducted repeatedly under similar experimental conditions. Thus, for future pharmaceutical research and development, it is suggested that the probability of reproducibility always be evaluated based on the observed treatment effect and the variability associated with the observation. The probability of reproducibility is an indicator whether the observed finding is by chance alone or it is reproducible [23].

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