Texila International Journal of Clinical Research
Volume 5, Issue 1, Jun 2018

Principles, Assumptions, and Processes Established to Designate Biologics Assets as a Fast to FIH (First-in-Human) Program and the Associated Core Concepts for the Utilization of low and High-Risk Activities, Timelines and Functional Level Expectations

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Abstract

Biologics development represents a substantial advancement in the pharmaceutical industry because of their promise and huge success in the oncology, immunoscience, and cardiovascular disease areas. Prior to entering the marketed product development phase, each biopharmaceutical needs to go through series of stages that will allow or disallow the biologics asset to become a commercialized product. Each of those phases includes development planning and designing of studies to test relevant hypotheses to support the drug label if approved.

The current thesis will focus on the principles, assumptions, and processes that are established to designate an asset (biologics) as a targeted first-in-human program. First-in-human studies are included under phase 1 trials, where initial human exposure is initiated to the investigational new drug (IND). Phase 1 is critical since it affirms if a compound's mechanisms of action in humans and its development can result in a potentially new drug entity.

Subsequently, step by step initiatives and processes from the perspective of different functional groups within the pharma will be revised to outline the staged procedures, methods, critical, and non-critical paths taken when a molecule is nominated as a clinical candidate. Overall alignment of deliverables will be presented between the different functional areas that partake in the first-in-human development.

Strategic changes to the biologics development process, cell line development with multiple candidate sequences, initial platform fit assessment for a process, analytical and formulation will be acknowledged. Platform strategy for drug substance production, as well as, drug product composition will be outlined along with boilerplates for analytical method development to fit or not fit the platform approach. The functional groups that will be reviewed will be; Discovery, Cell line development, Drug Substance process development, Formulation development, Toxicology, Quality, Drug Substance manufacturing, Drug Product manufacturing, Stability and regulatory.

Keywords: Fast to First in Human, Biologics, Development, Clinical.

Introduction

The main aim of the proposed study is to find out the principles, assumptions, and processes utilized in designating biologics assets as a Fast to FIH (First-in-Human) program, as well as, streamline the processes of high and low-risk activities using Fast to First-In-Human (FIH) model and their successful implementation and subsequent readiness for regulatory submission of the clinical trial application (CTA).

Definition of the research problem

Biologics can be used as oncology and immuno-oncology therapies (Bartlett, 2011). However, the development of biologics utilizes a lengthy and complex process (Phrma, 2017; Forum on Neuroscience and Nervous System Disorders, Board on Health Sciences Policy, & Institute of Medicine, 2014; Conner et al., 2014). The methods and processes used in the development of biologics have been changing as time goes. Earlier approaches are replaced by newer ones as technology and knowledge advance (Hojjat-Farsangi, 2014). However, it has been presumed that the principles, assumptions, and processes that are used to designate biologics assets as a Fast to FIH

DOI: 10.21522/TIJCR.2014.05.01.Art002
ISSN: 2520-3096

(First-in-Human) program are still the same, despite the evident changes that have been witnessed in the pharmaceuticals industry (Atanasov, et al., 2015). In addition, organizations may have explored different approaches in the use of low and high-risk methods during the development of biologics. Consequently, there may have been changes in timelines, and functional level expectations. However, the associated changes have not been explored in terms of how they are incorporated in the development of biologics as a Fast to FIH (First-in-Human) program. The newer principles, assumptions and processes adopted in the manufacture and designation of biologics assets a fast to FIH program have not been evaluated. Therefore, given the existent scientific knowledge and an informational gap that needs to be filled. Additionally, it is necessary to explore the associated core concepts for the utilization of low and high-risk activities, timelines, and functional level expectations in the designation biologics assets as a Fast to FIH, given the changes.

Problems to be solved

The problems to be solved will test the following two hypotheses;

$H1_0$ There have been newer principles, assumptions, and processes established to designate biologics assets as a Fast to FIH (First-in-Human) program

$H1_A$ There have been no newer principles, assumptions, and processes established to designate biologics assets as a Fast to FIH (First-in-Human) program

$H2_0$ the associated core concepts for the utilization of low and high-risk activities, timelines, and functional level expectations in the designation of biologics assets as a Fast to FIH have changed significantly

$H2_A$The associated core concepts for the utilization of low and high-risk activities, timelines, and functional level expectations in the designation of biologics assets as a Fast to FIH have not changed significantly

Biologics

Biologics have revolutionized the treatment of chronic diseases as they have enhanced the treatment of rheumatoid arthritis, psoriatic arthritis multiple sclerosis, and a variety of cancers (Mócsai, Kovács, & Gergely, 2014). Existing biologics include drugs such as Humira and Avonex. Biologics are defined as a virus, therapeutic, serum, toxin, antitoxin, vaccine, blood product or derivative or an arsphenamine applicable for prevention, and treatment or cure of disease or condition (Zhao, Ren, & Wang, 2012). Zimney (2008) observes that biologics are derived from living organisms. They are obtained from humans or animals. Those that rely on Biotechnology are referred to as second-generation biologics (Zimney, 2008). Biologics include monoclonal antibodies, cytokines and growth hormones. They have unique characteristics compared to small molecules (Zhao, Ren, & Wang, 2012)

The initial preclinical testing of biologics are used in vivo animal models, in vitro studies, and also computerized algorithms. First in human tests, (also called first-in-man) are tests that initially test drugs in humans, (Eisenhauer, Twelves, & Buyse, 2015). According to the FDA and ICH, there are specific guidelines for the introduction of biologics as first-in-man tests. For example, small molecule biologics that have selective toxicity as a mechanism are not required to have genotoxicity testing prior to first in human testing (Gad, 2011). Gad further notes that In Vitro studies using liver slices, microsomes, and in some cases hepatocytes, both from human and animals are used to show the drug metabolic profile before the initiation of clinical trials. For instance, in the testing of GC33, Zhu et al. (2013) conducted clinical trials to evaluate the safety, PK characteristics and preliminary efficacy of GC33 in patients with advanced HCC.

Development and designation of biologics assets as a Fast to FIH is a critical process that is associated with several risks and requirements that should be met. For instance, there has to be evidence of the effectiveness of the biologics assets to be developed in order to secure the approval of a license application. In addition, an accurate completion of the benefit/risk assessment of the molecular entity to be introduced is required (Kudrin, 2012). Safety of the product to be introduced is a requirement that should be fulfilled too. Therefore, before the development and designation of biologics assets as a fast to FIH, there has to be a sufficient number of well-controlled studies that

would act as a pilot test (Kudrin, 2012). The main assumption here is that the term "studies" is plural. Therefore, it is a requirement that at least more than one study is carried out, which will have to be controlled and randomized clinical trials. The use of such studies is to establish the efficacy of the biologics assets to be designated as a fast to FIH.

The first step of the process of designating a biologic asset as a fast to FIH involves execution of preclinical tests (FDA, 2017a). The first step is regarded as the initial process that is succeeded by other phases that become complex at every successive step. The reason for this is that each phase should enhance testing with successful clinical results to support approval for marketing and adoption of the biologic. In this case, the biologic molecule should successfully pass the preclinical tests and prove to be effective in oncology and immuno-oncology therapeutics. Therefore, according to the Institute of Medicine (US) Committee (2010), it is imperative that the proposed drug meets the safety and efficacy standards set by FDA. Each step of the process that is followed in the development of a biologic asset is expensive and risky. Consequently, well-endowed companies with sufficient resources such as biotechnology and pharmaceutical companies have the upper hand in developing and presenting biologics to be used for treatment (Wong, 2009; Waltz, 2014). It has also been established that a majority of the new drugs that have been developed as biologic assets have successfully passed the clinical testing steps and have been approved for marketing. However, it is presumed that the discovered biologics have the potential of becoming effective oncology and immuno-oncology therapies. The reason for this is that sometimes the chances of success are very low for some drugs development efforts while the costs of development are very high. Therefore, biotechnology and pharmaceutical emphasize on a good financial return and focus on developing biologic assets that have the highest potential (Institute of Medicine (US) Committee, 2010). It has been noted that potential biologics meant to be therapies for life-threatening and rare diseases have been dropped at the very early stages of their development due to their failure in preclinical and clinical tests.

The next step of the development process of biologics for oncology therapy involves the execution of preclinical studies both in vitro and in animals to evaluate their safety potential and toxicity levels. It is through these preclinical studies that the potential effectiveness of the discovered biologic assets is reviewed (Institute of Medicine (US) Committee, 2010). The reason for this is that biotechnology and pharmaceutical companies would not like to invest in the development of therapeutic drugs that may be ineffective in the end because the process is very expensive and risky.

In the subsequent step of the development process, organizations that sponsor the development of biologic assets carry out additional clinical studies (FDA, 2017b). Such studies are meant to review and evaluate the evidence to guarantee that the drugs will evidently have no mutagenic problems (Institute of Medicine (US) Committee, 2010). Therefore, a biologic for oncology and immuno-oncology should not cause mutagenic alterations because this is very risky. In addition, the designed biologic should not have the potential of causing fetal malformations. Therefore, additional studies, beyond preclinical and clinical test ought to be carried out to ensure the potential, safety, and effectiveness of the proposed biologic drug.

In another step of the process, a determination of whether the biologic can be excreted by patients successfully (FDA, 2017c). The reason for this is that it is that a biologic drug should be excreted successfully as easily as it is absorbed or ingested by a patient (Institute of Medicine (US) Committee, 2010). Therefore, further studies and tests are required to ensure that the proposed biologic drugs meet this threshold. It is after the drug passes this test and meets the set standards that it can be passed on into the next stage of the development process.

According to Prueksaritanont and Tang, (2012), a biologic asset's Pharmacokinetics should be well-behaved such that its properties should be predictable in the long-term. With this property, high prospects biologic assets' success are expected as there will be low-attrition rates. However, it should be noted that the well-behaved property requirement for biologic assets has been challenged. The reason for this is that the property is characterized by on-target specificity while off-target monoclonal antibodies have been found to interact, placing a biologic molecule's efficacy at stake (Bumbaca et al., 2011). Such off-target antibodies are known to result in rapid clearance of the on-target specific biologic molecule, hence limiting its efficacy by enhancing poor target tissue biodistribution. In

DOI: 10.21522/TIJCR.2014.05.01.Art002
ISSN: 2520-3096

addition, non-specific interactions of antibodies with biologic molecules have a great potential of not enhancing the much needed specific cross-reactivity that is also very rare (Wang et al., 2011). Therefore, it is highly possible that the use of such biologics may result in the subjects developing some clinical conditions that the researchers did not expect. This is the reason why the biologic molecule ought to be well-behaved.

When a biologic asset exhibits poor Pharmacokinetics, they are terminated at some point during their development and designation as a fast to FIH. The reason for this is that such poor properties may have safety issues (Dostalek, Prueksaritanont, & Kelley, 2017). As much as the biologics may be recording low attrition rates during the clinical development stage, the good record may not be replicated during the subsequent stages of development. Consequently, the biologic molecule shall have violated the well-behaved requirement. However, it should be noted that preclinical development tests are usually carried out on animals; hence they are limited to *in vivo* Pharmacokinetics studies. Laboratory animals such as dogs, rats, and monkeys are used (Wang & Prueksaritanont, 2010). Therefore, an empirical allometric scaling approach has to be done to make the necessary prediction of human Pharmacokinetics (Li et al., 2016). This prediction is usually carried out without a mechanistic understanding or consideration of the molecular properties (Vugmeyster et al, 2011).

In consideration of the above-mentioned factors, a biologic molecule ought to possess well-behaved properties for a successful designation as a fast to FIH. It is required that a biologic asset to be designated as a fast to FIH behaves just like a drug because it is to be used as the treatment for cancer. The reason for the well-behaved requirement for a biologic molecule is that it is required to initiate a drug-like response in the target cell or protein (Wiley, 2016). There are some biologics meant to treat cancer, which is designed to interact with specific immune system cells.

It has been established that the existent literature majorly focuses on the processes and principles used in designating biologics assets as a Fast to FIH (First-in-Human) program. However, the assumptions that are made when developing biologics as a fast to FIH have not been explored sufficiently previously. In addition, the literature on utilization of the processes of high and low-risk activities by pharmaceutical companies using Fast to First-In-Human (FIH) model and their successful implementation and subsequent readiness for regulatory submission of the clinical trial application (CTA) is scarce. Therefore, it is implicit that insufficient research has been carried on the area. The proposed study will fill the existent gap in literature and scientific applications by exploring and ascertaining the principles, assumptions, and processes utilized in designating biologics assets as a Fast to FIH (First-in-Human) program, as well as, streamline the processes of high and low-risk activities using Fast to First-In-Human (FIH) model and their successful implementation and subsequent readiness for regulatory submission of the clinical trial application (CTA).

Methods

The proposed research will utilize a qualitative survey study approach. Therefore, a survey will be carried out on at least five leading pharmaceutical companies (Company A, B, C, D and E), using mailed questionnaires. Questionnaires will be used to collect information pertaining to the principles, assumptions, and processes utilized in designating biologics assets as a Fast to FIH (First-in-Human) program, as well as, streamline the processes of high and low-risk activities using Fast to First-In-Human (FIH) model and their successful implementation and subsequent readiness for regulatory submission of the clinical trial application (CTA). The questionnaires will be directed to the members of the research and development departments as well as analytics of the selected pharmaceutical companies. A qualitative approach has been chosen as an ideal methodology because the information required to answer the main research question and test the hypotheses cannot be quantified (Rahman, 2016; Tolley, Ulin, & Robinson, 2013). Therefore, qualitative information regarding the phenomenon under study will be collected.

Research design

The proposed research will utilize a qualitative survey study approach. Therefore, a survey will be carried out on 5 leading pharmaceutical companies, Amgen Inc. Eli Lilly and Company, AstraZeneca, Johnson & Johnson, and Merck & Company Inc., using mailed questionnaires. Questionnaires will be

used to collect information pertaining to the principles, assumptions, and processes utilized in designating biologics assets as a Fast to FIH (First-in-Human) program, as well as, streamline the processes of high and low-risk activities using Fast to First-In-Human (FIH) model and their successful implementation and subsequent readiness for regulatory submission of the clinical trial application (CTA). The questionnaires will be directed to the members of the research and development departments of the two pharmaceutical companies. A qualitative approach has been chosen as an ideal methodology because the information required to answer the main research question and test the hypotheses cannot be quantified (Rahman, 2016; Tolley, Ulin, & Robinson, 2013). Therefore, qualitative information regarding the phenomenon under study will be collected.

The proposed study will focus on the principles, assumptions, and processes utilized in designating biologics assets as a Fast to FIH (First-in-Human) program, as well as, streamline the processes of high and low-risk activities using Fast to First-In-Human (FIH) model and their successful implementation and subsequent readiness for regulatory submission of the CTA. The study will adopt an empirical research, whereby a total of 40 members will be interviewed, which means that the researcher will interview 20 informants from each of the two companies. The targeted respondents will be researchers from the two companies' research and development departments. Specifically, the informants will be required to respond to the questionnaires, which will be mailed to them electronically. It is imperative to carry out empirical research as proposed in this study because contextual information regarding the phenomenon will be acquired. In addition, the researcher will gather knowledge on the collective experiences of various organizations in the development of biologics to confirm the theoretical concepts that have been put forward. Consequently, appropriate responses to the dynamics of the phenomenon will be forged while the provision of contextual differences will be possible. In addition, empirical research may help in advancing knowledge on the basis of what is known regarding the development of biologics.

Target population

According to Subong (2005), a population is defined as the set of individuals, objects, or data from where a statistical sample can be drawn. Population is the entire group of individuals, events or objects having a common observable characteristic. A population can be the total sum of collected units from which the researcher draws conclusions of the study (Jansen, 2010). Separately, it should be noted that the target population is the group of people to whom the researcher wants the study findings to apply. Therefore, a study that seeks to find out the effects of a certain disease on a community will focus on a section of the members of that region as the target population. For instance, the study may target on people who have been affected by the disease before, but have survived. It may also target their family members and relatives, as well as, children. Another example is when a company seeks to launch a new product targeting senior citizens as they would be the appropriate users. The researcher is required to analyze the target population, which in this case is the senior citizens' population. The reason for this is that the analysis of the target population provides insights that can allow the organization to make valid inferences regarding the type of advertisements and campaigns that should be executed to different senior citizens in consideration of their income levels and attitudes.

The study population is closely related to the target population. However, the study population of a research is defined as the objects or people who meet the researcher's operational definition of the target population. The target population is a broad grouping of the objects to be studied, which is later narrowed down to study population and then it is narrowed further to arrive at the research sample. The research sample forms the members or objects of the study population from which the researcher collects information.

According to Lavrakas (2008), the target population for a survey refers to the whole set of units for which the survey information is used to make inferences. Therefore, the target population denotes the units that the results of the survey are meant to generalize. A survey is designed through a series of steps, the first of which is the establishment of the research objectives. The objectives are crucial in determining the kind of information required and the source from which such information should be obtained. They also determine how the information is analyzed and presented to make reliable and

DOI: 10.21522/TIJCR.2014.05.01.Art002
ISSN: 2520-3096

valid inferences. Consequently, the second step involves the definition of the target population. It follows that specific definition of the target population is crucial as it is the determining factor of whether the sampled objects or case can be used in survey as eligible or ineligible elements. It is also imperative that the geographic characteristics and other characteristics of the target population that may be temporary should be described or portrayed appropriately. Additionally, the researcher should specify the type of units that will be used in the target population. The researcher should ensure that the target population is made up of units that can be used to obtain reliable information easily (Lavrakas, 2008). Therefore, the target population may be restricted in some instances so that those elements that are difficult or impossible to obtain information from them are excluded. For instance, if the target population includes difficult to interview people, then the researcher will have to technically leave out such people out and focus only on those that are easier to interview.

The target population should be a population of elements that are experimentally accessible. In this case, an experimentally accessible population refers to the population that a researcher can measure practically and obtain tangible results. However, it should be noted that sometimes researchers face constraints that bar them from accessing and interviewing the ideal target population. An ideal example of the constraints that a researcher faces is budgetary limitations. When there are budgetary constraints, the researcher can only interview a limited number of people from the target population. In such cases, the experimentally accessible population differs significantly from the target population because the former is much smaller than the latter. In ideal cases, the two are supposed to be almost equal in order to achieve the threshold of representativeness. Separately, some physical factors can limit the researcher from interviewing a significant number of people from the target population. Consequently, the researcher ends up interviewing a small number of people because he or she is forced to select a smaller group for study. This is applies when the researcher is required to interview a population and finds out that it is not feasible to interview every member of the population because the members could be dispersed geographically. Therefore, the researcher settles on a smaller population or sample population that he or she interviews and generalizes the results for the entire population. However, when the experimentally accessible population is not large enough, it does not provide a significant representation of the entire target population (Mack, 2017). Therefore, the study results cannot be generalized for the entire population and offer valid and reliable inferences. The researcher should ensure that he or she chooses an ideal target population for the study sample so that to carry out investigations on a significant representative of the entire population.

In this case, the researcher will avoid interviewing just a few participants for the study because that will jeopardize the reliability and validity of the results and inferences. In addition, the researcher will choose the target population to study appropriately by using the most reliable statistical methods to ensure that the results obtained will be valid for understanding the target population at large. The number of participants to be interviewed will be increased significantly as the researcher will avoid focusing only on the conveniently located informants. Consequently, the chances of obtaining biased results that that are not true for target population will be minimized or eliminated. Alternatively, the researcher will utilize the possibility of selecting a representative sample from the experimentally accessible population. This means that the researcher will seek to base the investigation on a large enough group of informants. Additionally, the researcher will utilize appropriate and purposive selection methods to enhance the confidence the results of the research will be valid for the whole target population.

The target population of this study will be leading pharmaceutical companies, especially global companies. The researcher targets leading pharmaceutical companies because unlike the other smaller pharmaceutical companies, they engage in the manufacture of FIH drugs. Therefore, they are mostly likely to expected to utilize various principles, assumptions, and processes in designating biologics assets as a Fast to FIH (First-in-Human) program, as well as, streamline the processes of high and low-risk activities using Fast to First-In-Human (FIH) models. Moreover, they are always keen to enhance the successful implementation process to facilitate subsequent readiness for regulatory submission of the clinical trial application (CTA). Therefore, the study targets the leading pharmaceutical companies from the United States. It is not only the companies that the study will

target, but also its key employees and management teams, which are most likely to have the information that is required.

Sampling frame

A sampling frame is the list of individuals or events, source material or device from which a sample is drawn (Lavallée, 2007). It comprises of a list of all those within a population who can be sampled, and may include individuals, households, companies or institutions. According to Turner (2003), a sampling frame is the set of materials that act an informational source from which the researcher selects the sample for information gathering purposes. It follows that the sampling frame is the source of the means of particular members of the target population that the researcher can choose so that they can be interviewed during a survey. In general, there may be more than one set of materials available to be selected as the ideal sample for study. This applies to descriptive surveys, like in the case of the proposed research because it entails interviewing of a group of people with similar characteristics ideal for the provision of accurate and relevant information required by the researcher. Moreover, the proposed study will be multi-stage in nature. In this case, the researcher will identify the area frame and come up with a list that is comprised of various organizations to form a list frame. Therefore, the researcher will select the sample, first from the area frame, and then narrow it down to a list frame from which organizations for that and respective informants will be selected.

In the case of this research, the researcher will make various important considerations when choosing the appropriate sampling frame. Particularly, a consideration of the relationship between the research target population and the unit of selection will be made by the researcher. Given that the target population determines the unit of selection, the proposed study will consider organizations that manufacture Fast to FIH (First-in-Human) drugs, utilizing high and low-risk processes to enhance the successful implementation and subsequent readiness for regulatory submission of the clinical trial application (CTA). In addition, the unit of selection determines the probability of selection at the last stage. Therefore, the researcher will be guided by these principles while choosing the sampling frame and the sample for study from the target population.

The researcher will ensure that the sampling frame captures, in a statistical sense, the target population by choosing the most representative sample from the target population. The researcher will also ensure that the information to be obtained from the investigation will be as perfect as possible by choosing a complete, accurate, and up-to-date sampling frame. As much as this ideal property may be unattainable in the proposed survey, the researcher will ensure that it meets these requirements by constructing the sampling frame from scratch rather than using an existing one. Consequently, the sample frame will be up-to-date and as accurate as possible, though it may be as complete as may be required.

The researcher will ensure that the sampling frame meets the basic conditions of high-quality by assessing it in terms of how well the frame's idealized properties are related to the targeted population. Particularly, the researcher will ensure that the rules of selection are duly followed such that every member from the target population will have an equal chance of inclusion just like the rest. The chance of selection in this case will be known and non-zero. Therefore, the researcher will ensure that these conditions are met so that the sampling frame's quality may be objectively assessed.

However, it is noted that the sampling frame may not be as complete with respect to the target population as theory indicates because an ideal frame should have all of its members or the entire the universe covered. Given that these conditions will not be met in absolute terms in the case of this study, the proposed sampling frame may not be complete. However, the researcher will ensure that the sampling frame coverage is as wide as possible to facilitate its suitability for study. The researcher will also ensure that the frame meets the basic requirements, and if it does not meet them, then a determination as to whether it can be repaired or developed further to make it suitable will be made. For instance, if a survey seeks to investigate a certain aspect among the children born in medical facilities, then the sampling frame will not include those children born at home and at other places, apart from medical facilities. The reason for this is that such a survey seeks to investigate an aspect among children born in medical facilities only as the sampling unit. In such a case, there will be significant numbers of the target population that will have a zero chance of inclusion in the sample,

DOI: 10.21522/TIJCR.2014.05.01.Art002
ISSN: 2520-3096

and the condition for a probability sample is will be violated. Similarly, in this case, the researcher seeks to investigate pharmaceutical organizations that usually produce FIH drugs. This means that other pharmaceutical companies that do not manufacture FIH drugs will not be included in the study, and this would result in the violation of the probability sampling rule. However, the results will still be accurate and representative enough because the researcher's hypotheses shall have been tested using the most valid and reliable information from organizations and informants with the required information. It would not be expected that accurate and reliable information regarding the principles, assumptions, and processes established to designate biologics assets as a Fast to FIH (First-in-Human) program if organizations that do not manufacture such drugs are surveyed. Similarly, the research will not be able to establish whether there have been any significant changes in the associated core concepts for the utilization of low and high-risk activities, timelines, and functional level expectations in the designation of biologics assets as a Fast to FIH by interviewing employees from other pharmaceuticals that do not manufacture FIH drugs. Therefore, the researcher will not present biased results.

The researcher will ensure that the accuracy of the findings is enhanced by including each member of the selected member form the target population in the research only once. In this case, the researcher seeks to investigate, through the proposed study, the leading pharmaceutical companies that manufacture FIH drugs, particularly those that utilize low and high-risk activities. Therefore, it would be erroneous to include pharmaceutical companies that do not fall under the category of "leading" in terms of performance, those that do not manufacture FIH drugs, and those that do not utilize low and high-risk activities in the study. It would also be erroneous to include a company more than once in the study (Turner, 2003).

It will be ensured that the proposed study addresses the issue of coverage error appropriately. According to Turner (2003), coverage error is the items of study or people that are excluded from a study sample. In typical cases, sampling statistics are calculated assuming there is no coverage error. When some population subjects are left out systematically from the sampling frame, then it is apparent that the sampling statistics of such a research will not have to account for the cover coverage error. Examples of coverage error include a study that involves telephone users as the main subjects under investigation, where the people without telephones are excluded systematically. In addition, those who have cell phones will also be left out because they do not meet the basic requirement of owning a telephone as a cell phone is quite different from a telephone. On a separate account, a study that seeks to investigate internet users will always leave out non-internet users.

Researcher bias emanates from the nature with which the research objects are under-covered, especially when the magnitude between the covered and the uncovered subjects. For instance, a study on telephone users may not differ in terms of votes if cell phones were used. However, there is a huge possibility that they may different opinions and attitudes towards technology. In this case, the researcher will leave out pharmaceutical companies that do not manufacture FIH drugs. However, this will not affect the results in terms of bias because such organizations that will not be included will not have any significant opinion regarding the research topic.

The proposed study will use a sampling frame of organizations that manufacture FIH drugs, particularly leading pharmaceutical companies as a tool that will enable the researcher to objectively select a sample of units from the population of all units. In this case, it will be considered whether the sample results will lead to generalizable conclusions and whether the proposed sampling plan will be possible within time and budget limitations. In addition, the researcher will consider whether the sampling procedure will be practically feasible. Finally, the researcher will investigate whether the proposed sampling scheme will provide results that will address survey objectives with appropriate measures of precision. It should be noted that the quality of the sampling frame usually affects the quality of the sample. The researcher will ensure that there is adequate information on the frame available so that sampling, data collection, weighting, and non-response bias analyses can be conducted. Therefore, the researcher will ensure that the sampling frame of this proposed study up to date and includes only one record for each member of the target population.

As indicated, the sampling frame for the study will be derived from a group of the leading companies in the pharmaceuticals industry in the United States. There are numerous companies in the

US pharmaceutical industry. However, the researcher will concentrate on the top 10 companies and then choose 5 of them randomly. Therefore, the sampling frame will consist of 17 companies as indicated in Appendix 1. The companies include; Amgen Inc., Eli Lilly and Company, Johnson & Johnson, Pfizer Inc., Watson Pharmaceuticals Inc., Merck & Company Inc., AstraZeneca, Novo Nordisk, Sanofi, Bristol-Myers Squibb, AbbVie, Glaxo SmithKline, Gilead Sciences, Roche, Abbott Laboratories, Biogen Idec, and Calgine Corporation.

Table 1. Sampling frame

	Company Name
1	Amgen Inc.
2	Johnson & Johnson
3	Eli Lilly and Company
4	Pfizer Inc.
5	Watson Pharmaceuticals Inc.
6	Merck & Company Inc.
7	AstraZeneca
8	Novo Nordisk
9	Sanofi
10	Bristol-Myers Squibb
11	AbbVie
12	Glaxo SmithKline
13	Gilead Sciences
14	Roche
15	Abbott Laboratories
16	Biogen Idec
17	Calgine Corporation

Sampling techniques

Non-probability sampling will be utilized in the proposed study. The reason for this is that not all the organizational members of the two companies will have a chance of being selected as informants. Instead, the researcher will purposively select informants from among the researchers of the two companies' research and development departments. The reason for choosing purposive sampling is that it will enhance the collection of phenomenal information from people who have experience (Adler & Clark, 2014). Therefore, precise and accurate information will be collected through this kind of sampling. Purposive sampling is advantageous because it focuses on individuals who have desired characteristics to provide relevant information for answering the research question (Macnee & McCabe, 2008).

The researcher will ensure that all checks regarding the sample and its quality are carried out. For instance, the researcher will calculate the sample error, which refers to the description of describes the variability of a sample statistic across multiple hypothetical samples that could be drawn. It is calculated on samples and is based on statistical theory. An investigation of the variation between different potential samples of respondents and the entire sample frame will also be done. It should be noted that coverage error and non-response error are not accounted for in sampling statistics. There will be no bias into the study as there will be no coverage error or non-response error because they will be systematic.

Data collection instruments

The research will use a questionnaire as a data collection instrument for data. The use of a questionnaire will help the researcher to obtain the best information from the respondents because it can be tailored to suit the information requirements of the research. For instance, the questionnaires will have both closed and open-ended questions because the researcher will want respondents to provide specific information while allowing them to provide their own perceptions. Closed questions will require respondents to choose one answer to the question from a number of provided options

DOI: 10.21522/TIJCR.2014.05.01.Art002
ISSN: 2520-3096

while open-ended questions will provide respondents with an opportunity of suggesting their views. Therefore, open ended questions are ideal for gathering qualitative information. This will result into precise and rich information for the researcher because questionnaires help in the collection of straight forward information. The researcher will issue self-administered questionnaires to respondents will fill the questionnaire themselves, in the absence of the researcher. This will allow anonymity, thus allowing respondents to provide honest answers (Mitchell & Jolley, 2010). Therefore, a questionnaire will be an ideal instrument because it will enhance flexibility in formulating questions, which will help in gathering relevant information for answering the research questions. Similarly, in this case, the questionnaires will be the main data collection interviews that will be used in this research. The reason for this is that they are convenient for data collection (Creswell, 2014). The researcher will design appropriate questionnaires, comprising of questions that will seek to gather accurate information for answering the main research question and testing the hypotheses. The questionnaires will be used in a pilot study, which will entail surveys of ten randomly selected staff members from each of the two companies. The pilot test questionnaires will be used to test the validity and reliability of the data collection instrument. Therefore, questionnaires will be evaluated whether they accurately seek to gather the intended information, depending on the pilot study responses. It is expected that any adjustments to the questionnaires will be made on the basis of the pilot respondents' suggestions. Questionnaires will be sent to the respondents through email.

Results

Results are upon further discussion. It is expected that upon the completion of the proposed study, insightful and empirical information about a new the existing phenomenon regarding biologics development shall have been obtained. In this case, it is expected that the research will establish there have been newer principles, assumptions, and processes established to designate biologics assets as a Fast to FIH (First-in-Human) program. Similarly, the research expects to establish whether there have been any significant changes in the associated core concepts for the utilization of low and high-risk activities, timelines, and functional level expectations in the designation of biologics assets as a Fast to FIH. This will be further discussed in next available article to support the applied methodology.

Discussion

The above study contributes to scientific knowledge because its findings can guide drug developers, especially biotechnology and pharmaceuticals companies that develop biologics for oncology treatment and immuno-oncology purposes on the principles, processes, and assumptions to make when designating such assets as a fast to FIH. Consequently, society will benefit from the study’s findings because it is expected that with the right knowledge, scientists and biologic developers will come up with better health sustaining solutions. In addition, society will benefit from the availability of cancer-treating biologics developed by relevant companies. It is expected that biologic developing companies will utilize this study's findings to improve their approaches in new drug development. Consequently, there will be a variety of effective drugs for the treatment of cancer available at affordable costs, which will save society from the economic burden of taking care and paying for the treatment of the sick.

Conclusion

Further evaluation will be discussed to focus on established already principles, assumptions and processes that are most utilized by current pharmaceutical companies. First-in-human studies are included phase 1 trials where the initial human exposure is initiated to the investigational new drug. Clinical phase 1 is critical and will be substantially evaluated under new assumptions since it affirms if a compound’s mechanisms of action in humans and its development can result in a potentially new drug entity.

References

[1]. Adler, E. S., & Clark, R. (2014). *An invitation to social research.* Belmont, CA: Cengage Learning.
[2]. Andrew X. Zhu, P. J.-k., & Philip, P. A. (2013). *First-in-Man Phase I Study of GC33, A Novel Recombinant Humanized Antibody against Glypican-3, in Patients with Advanced Hepatocellular Carcinoma*. Clinical Cancer Research.
[3]. Atanasov, A. G., et al. (2015). *Discovery and resupply of pharmacologically active plant-derived natural products: A review.* Biotechnology Advances, 33(8), 1582–1614.
[4]. Bartlett, D. L. (2011). *Surgical Oncology: Fundamentals, evidence-based approaches and new technology.* New Delhi: Jaypee Brothers Pvt. Ltd.
[5]. Berger, A. A. (2011). *Media and communication research methods: An introduction to qualitative and quantitative approaches.* Thousand Oaks: SAGE Publications.
[6]. Bumbaca, D., et al. (2011). *Highly specific off-target binding identified and eliminated during the humanization of an antibody against FGF receptor 4*. MAbs Journal, 3(4), 376–386.
[7]. Conner, J., et al. (2014). *Biotechnology entrepreneurship.* New York: Elsevier Inc.
[8]. Creswell, J. W. (2014). *Research design: Qualitative, quantitative, and mixed methods approaches.* Thousand Oaks, CA: SAGE Publications.
[9]. Dostalek, M., Prueksaritanont, T., & Kelley, R. (2017). *Pharmacokinetic de-risking tools for selection of monoclonal antibody lead candidates.* MAbs Journal, 9(5), 756-766.
[10]. Ehnert, I. (2009). *Sustainable human resource management: A conceptual and exploratory analysis from a paradox perspective.* Heidelberg: Physica-Verlag Press.
[11]. Eisenhauer, E. A., Twelves, C., & Buyse, M. E. (2015). *Phase I Cancer Clinical Trials : A Practical Guide.* New York: Oxford University Press.
[12]. European Medicines Agency. (1988). *Pharmacokinetic Studies in Man*. Retrieved 09 15, 2017, from European Medicines Agency: Retrieved from http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001289.jsp&mid=WC0b01ac0580032ec5
[13]. FDA. (2017a). *Step 2: Preclinical research.* Retrieved from https://www.fda.gov/forpatients/approvals/drugs/ucm405658.htm
[14]. FDA. (2017b). *Step 3: Clinical research.* Retrieved from https://www.fda.gov/forpatients/approvals/drugs/ucm405622.htm
[15]. FDA. (2017c). *Inside clinical trials: Testing medical products in people.* Retrieved from https://www.fda.gov/drugs/resourcesforyou/consumers/ucm143531.htm
[16]. Feldman, E. J., Lancet, J. E., Kolitz, J. E., Ritchie, E. K., Roboz, G. J., & List, A. F. (2011). *First-In-Man Study of CPX-351.* Journaal of Clinical Oncology , 979-985.
[17]. Food and Drug Agency. (2005). *Guidance for Industry:Clinical Studies.* New York: Rockville,.
[18]. Forum on Neuroscience and Nervous System Disorders,Board on Health Sciences Policy, & Institute of Medicine. (2014). *Improving and accelerating therapeutic development for nervous system disorders: Workshop summary*. Washington DC: National Academies Press.
[19]. Gad, S. C. (2011). *Safety evaluation of Pharmaceuticals and Medical Devices : International Rregulatory Guidelines.* New York: Springer.
[20]. Giese, G. (2017). *Clinical pharmacology 1: Phase 1 studies and early drug.* Retrieved from https://www.fda.gov/downloads/training/clinicalinvestigatortrainingcourse/ucm340007.pdf
[21]. Hanauer, S. B. (2008). *The ethics of phase I trials of biologic agents*. Nature Clinical Practice Gastroenterology & Hepatology, 5(10), 533.
[22]. History of Vaccines. (2017). *Vaccine development, testing, and regulation.* Retrieved from https://www.historyofvaccines.org/content/articles/vaccine-development-testing-and-regulation
[23]. Hojjat-Farsangi, M. (2014). *Small-Molecule Inhibitors of the Receptor Tyrosine Kinases: Promising tools for targeted cancer therapies. International Journal of Molecular Sciences, 15(8), 13768–13801.*
[24]. Institute of Medicine (US) Committee. (2010). *Accelerating Rare Diseases Research and Orphan Product Development. In M. J. Field, & T. Boat, Rare Diseases and Orphan Products: Accelerating Research and Development* (p. Chapter 5: Development of New Therapeutic Drugs and Biologics for Rare Diseases). Washington DC: National Academies Press. Available from: https://www.ncbi.nlm.nih.gov/books/NBK56179/.

DOI: 10.21522/TIJCR.2014.05.01.Art002
ISSN: 2520-3096

[25]. Klein, J., & Blaser, G. (2016, Novemeber). *Expression of next generation biologics requires next generation expression systems.* Retrieved from http://bio.lonza.com/uploads/tx_mwaxmarketingmaterial/Lonza_Webinars_Next_Generation_Expression_Systems.pdf
[26]. Kudrin, A. (2012). *Overview of cancer vaccines.* Human Vaccines Immunother, 8(9), 1335–1353. doi:10.4161/hv.20518.
[27]. Li, F., et al. (2010). *Cell culture processes for monoclonal antibody production*. MAbs Journals, 2(5), 466–477.
[28]. Li, Y., et al. (2016). *Quantitation and pharmacokinetic modeling of therapeutic antibody quality attributes in human studies*. MAbs Journal, 8(6), 1079–1087.
[29]. Lybecker, K. M. (2016, January). *The biologics revolution in the production of drugs.* Retrieved from https://www.fraserinstitute.org/sites/default/files/biologics-revolution-in-the-production-of-drugs.pdf
[30]. Macnee, C. L., & McCabe, S. (2008). *Understanding nursing research: Using research in evidence-based practice*. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins.
[31]. Marion, D. (2013). *An Introduction to Biological NMR Spectroscopy.* Mol Cell Proteomics , *12*(11), 3006–3025.
[32]. Medina, C. (2003). *Compliance handbook for pharmaceuticals, medical devices, and biologics.* London: CRC Press.
[33]. Mócsai, A., Kovács, L., & Gergely, P. (2014). What is the future of targeted therapy in rheumatology: biologics or small molecules? *BMC Medicine, 12*(43), 1-9.
[34]. Phrma. (2017). *Biopharmaceutical research & development: The process behind new medicines.* Retrieved from http://phrma-docs.phrma.org/sites/default/files/pdf/rd_brochure_022307.pdf.
[35]. Prueksaritanont, T., & Tang, C. (2012). *ADME of biologics—What have we learned from small molecules*? The AAPS Journal , 14(3), 410-419.
[36]. Rahman, M. S. (2016). *The advantages and disadvantages of using qualitative and quantitative Approaches and methods in language "testing and assessment" research*: A literature review. Journal of Education and Learning, 6(1), 102-112.
[37]. Roberts, A. (2015). *Maintaining the stability of biologics*. BioPharm International Journal, 28(3), 38-41.
[38]. Rosenberg, A., & Demeule, B. (2015). *Biobetters: Protein engineering to approach the curative.* New York: Springer Publications.
[39]. Rubin, A., & Babbie, E. R. (2010). *Essential research methods for social work*. Belmont, CA: Brooks/Cole, Cengage Learning Press.
[40]. Suh, H. Y., Peck, C. C., Yu, K.-S., & Lee, H. (2016). *Determination of the starting dose in the first-in-human clinical trials with monoclonal antibodies: a systematic review of papers published between 1990 and 2013*. Drug Design, Development and Therapy.
[41]. The Conversation. (2015, August 5). *Explainer: what are biologics and biosimilars?* Retrieved from https://theconversation.com/explainer-what-are-biologics-and-biosimilars-45308.
[42]. Tibbitts, J., et al. (2016). *Key factors influencing ADME properties of therapeutic proteins: A need for ADME characterization in drug discovery and development*. MAbs Journal, 8(2), 229–245.
[43]. Tolley, E. E., Ulin, P. R., & Robinson, E. T. (2013). *Qualitative methods in public health: A field guide for applied research.* San Francisco, CA: Jossey-Bass Press.
[44]. U.S. Department of Health and Human Services, et al. (2015, July). *Analytical procedures and methods validation for drugs and biologics: Guidance for industry.* Retrieved from https://www.fda.gov/downloads/drugs/guidances/ucm386366.pdf
[45]. Vugmeyster, Y., et al. (2011). *Complex pharmacokinetics of a humanized antibody against human amyloid beta peptide, anti-abeta Ab2, in nonclinical species.* Pharmaceutical Research, 28(17), 1696–1706.
[46]. Waltz, E. (2014). *It's official: Biologics are pharma's darlings*. Nature Biotechnology, 32(2), 117.
[47]. Wang, W., & Prueksaritanont, T. (2010). *Prediction of human clearance of therapeutic proteins: Simple allometric scaling method revisited.* Biopharmaceutics & Drug Disposition Journal , 31, 253–263.
[48]. Wang, W., & Singh, M. (2014). *Biological drug products: Development and strategies.* New York: John Wiley & Sons, Inc.
[49]. Wang, W., et al. (2011). *Monoclonal antibodies with identical Fc sequences can bind to FcRn differentially with pharmacokinetic consequences*. Drug Metabolism and Disposition Journal, 39, 1469–1477.

[50]. Wiley, F. (2016, July). *What are biologics?* Retrieved from https://medshadow.org/features/what-are-biologics/.
[51]. Wong, G. (2009). Biotech scientists bank on big pharma's biologics push. Retrieved from https://www.nature.com/nbt/journal/v27/n3/full/nbt0309-293.html
[52]. Zhao, L., Ren, T.-h., & Wang, D. D. (2012). *Clinical Pharmacology Considerations in Biologics Development. Acta Pharmacologica Sinica, 1339–1347.*
[53]. Zimney, E. (2008). *Understanding biologics: How they differ from Drugs and why they cost more.* Retrieved 09 15, 2017, from Every Day health: http://www.everydayhealth.com/columns/zimney-health-and-medical-news-you-can-use/understanding-biologics-how-they-differ-from-drugs-and-why-they-cost-more/