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Research Article

A Comparative Study of Biological Products Regulations in USA, CANADA, AUSTRALIA, EUROPE, SINGAPORE and INDIA

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ABSTRACT
The FDA is an agency in the US Department of Health and Human Services charged with assuring the safety, efficacy, and security of human as well as veterinary drugs in addition to other areas of regulatory authority. The agency is also responsible for facilitating advances in medications. The study aims to evaluate the biological products regulations in USA, Canada, Australia, Europe, Singapore and India. Biopharmaceutical companies and their development partners increasingly use data from real-world settings to generate evidence that can support regulatory decision making and approvals of their manufactured medical products. The intent is to provide the FDA information to allow a review that assures the safety of participants. For sponsor-investigators, typically, the IND will not require the same extensive information including preclinical studies or manufacturing and process information as would be required for a commercial sponsor applying for an IND for a yet unapproved drug, especially early in its development. For the approval of follow-on biologics in the United States, current regulations depends on whether the biologic product is approved under the United States Food, Drug, and Cosmetic Act or it is licensed under the United States Public Health Service Act. For those biologic drugs marketed under the PHS Act, the BPCI Act passed by the US Congress on March 23, 2010 amends the PHS Act to establish an abbreviated approval pathway for biological products that are highly similar or interchangeable with an FDA-authorized biologic drug, and gives the FDA the authority to approve follow-on biologics under new section 351(k) of the PHS Act. A comparison of the marketing authorization requirements for regulated and emerging countries has been described that all countries follow ICH regulation. The prime objective of the rules governing medicative products in the United States, Europe, Canada, Australia, and Singapore is to protect public health.

Keywords: *Biological products, safety, efficacy, and security of human, regulatory authority.*

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C O N T E N T S

1. Introduction

Once a single compound is selected, preclinical studies are performed to evaluate a drug's safety, efficacy, and potential toxicity in animal models. These studies are also designed to prove that a drug is not carcinogenic (i.e., it does not cause cancer when it is used at therapeutic doses, even over long treatment intervals), mutagenic (i.e., it does not cause genetic alterations), or teratogenic (i.e., it does not cause fetal malformations). Because a patient's ability to excrete a drug can be just as important as the patient's ability to absorb the drug, both of these factors are studied in detail at this stage of preclinical development.

Preclinical studies also help researchers design proposed Phase I studies to be conducted with human. For example, preclinical studies with animals help determine the initial dose to be evaluated in the clinical trial and help identify safety evaluation criteria. The latter include factors such as patient signs and symptoms that should be monitored closely during clinical trials. The result of work at this stage is a pharmacological profile of the drug that will be beneficial long into the drug's future. Researchers can use the profile to develop the initial manufacturing process and pharmaceutical formulation to be used for testing with humans. Industry has particular strengths in these areas, and most development efforts at this stage are based in biotechnology or pharmaceutical companies. They can also use specifications assigned in this stage to evaluate the chemical quality and purity of the drug, its stability, and the reproducibility of the quality and purity during repeat manufacturing procedures. At this stage, and before testing with humans begins, an Investigational New Drug (IND) application is filed with the FDA. If the IND application is approved, then clinical trials can begin[1-5].

Phase I

Phase I trials are the first time that a drug is tested in humans. These trials may involve small numbers (20 to 100) of healthy volunteers, or they may include patients with specific conditions for which targeted pathways have been identified as potentially relevant to the disease under study. A Phase I study may last for several months. The focus of a Phase I study is the evaluation of a new drug's safety, the determination of a safe dosage range, the identification of side effects, and the detection of early evidence of effectiveness if the drug is studied in patients with disease, for example in patients with cancer. From Phase I clinical trials, researchers gain important information about the drug's effect when it is administered with another drug (the effect is often unpredictable and sometimes results in an increase in the action of either substance or creates an entirely new adverse effect not usually associated with either drug when it is used alone); the drug's pharmacokinetics (absorption, distribution, metabolism, and excretion) to better understand a drug's actions in the body; the acceptability of the drug's balance of potency, pharmacokinetic properties, and toxicity or the ability of the drug to zero in on its target and not another biological process; and the tolerated dose range of the drug to minimize its possible side effects.

Phase II. Clinical Trials

In Phase II clinical trials, the study drug is tested for the first time for its efficacy in patients with the disease or the condition targeted by the medication. These studies may have up to several hundred patients and may last from several months to a few years. They help determine the correct dosage, common short-term side effects and the best regimen to be used in larger clinical trials. This usually begins with Phase IIa clinical trials, in which the goal is to obtain an initial proof of concept. The POC demonstrates that the drug did what it was intended to do, that is, interacted correctly with its molecular target and, in turn, altered the disease. Phases I and IIa are sometimes referred to as "exploratory development.

Phase III. Clinical Trials

Phase III clinical trials are designed to prove the candidate drug's benefit in a large targeted patient population with the disease. These trials confirm efficacy, monitor side effects, and sometimes compare the drug candidate to commonly used treatments. Researchers also use these clinical trials to collect additional information on the overall risk-benefit relationship of the drug and to provide an adequate basis for labeling after successful approval of the drug[6-10].

Phase III studies are conducted with large populations consisting of several hundred to several thousand patients with the disease or the condition of interest. They typically take place over several years and at multiple clinical centers around the world. These studies provide the proof needed to satisfy regulators that the medicine meets the legal requirements needed to be approved for marketing. The study drug may be compared with existing treatments or a placebo. Phase III trials are, ideally, double blinded; that is, neither the patient nor the researcher knows which patients are receiving the drug and which patients are receiving placebos during the course of the trial. Phase III trials are usually required for FDA approval of the drug. If the trials are successful, then a New Drug Application is

submitted to the FDA. The process of review usually takes 10 to 12 months and may include an advisory committee review, but such a review is at the discretion of the FDA.

Phase IV. Clinical Trials: Marketing and Safety Monitoring

Phase IV trials are studies conducted after a drug receives regulatory approval from the FDA. They may be used primarily for medical marketing. In some cases, the FDA may require or companies may voluntarily undertake post approval studies to generate additional information about a drug's long-term safety and efficacy, including its risks, benefits, and optimal use. These studies may take a variety of forms, including studies that use data from the administrative databases of health plans as well as observational studies and additional clinical trials.

Post approval trials may also be designed to test the drug with additional patient populations (e.g., with children), in new delivery modes (e.g., as a timed-release capsule), or for new uses or indications (i.e., for the treatment of a different medical condition). Because these post approval trials are intended to provide the basis for FDA approval of further uses or delivery modes, they must meet the same standards as the Phase III trials conducted for initial approval.

Clinical investigators initiating a drug study invoke a number of specific regulatory requirements beyond those mandated for protection of human subjects in clinical trials.[1] These regulatory requirements for drug studies address the safety and efficacy issues unique to the use of pharmaceuticals in the clinical research setting. The US Food and Drug Administration (FDA) is charged with the regulation of most drugs in addition to other products. This extends to regulatory authority over clinical research using these agents. Therefore, to conduct drug studies, an investigator must comply with FDA requirements. Failing to meet the FDA's regulations can have legal and financial implications for the individuals conducting the research as well as the institutions associated with the research activities.

An initial part of the regulatory process involved for investigational drugs is notifying the FDA that a pharmaceutical agent will be used in an experimental way. This notification is called an Investigational New Drug (IND) application. For drug trials conducted by the pharmaceutical industry or other commercial sponsors, individuals highly trained and expert in meeting the regulations address the regulatory requirements. However, for individual investigators who are not as familiar with the requirements and regulations, filing an IND can be intimidating and may be perceived as an impediment to conducting drug studies. It is interesting to note that the majority of IND submissions are noncommercial.[3] Thus, individual clinical investigators frequently meet the regulatory requirements necessary to conduct investigational drug studies. This review is intended to address the simplest scenario in which an individual investigator initiates and conducts a drug study that requires filing and maintaining an IND with the FDA. In addition, for the sake of simplicity, this review only addresses regulatory requirements for studies conducted at a single site. Figure 1 depicts the IND application process for a sponsor-investigator.

Regulatory Environment

The FDA is an agency in the US Department of Health and Human Services charged with assuring the safety, efficacy, and security of human as well as veterinary drugs in addition to other areas of regulatory authority. The agency is also responsible for facilitating advances in medications. The FDA is a large and rather complex federal agency with a number of centers, divisions, and offices located both centrally in the Washington Metropolitan Area as well as numerous regional offices in the United States. For the purposes of regulatory supervision of investigational drugs in human clinical trials, the centers primarily involved are the Center for Drug Evaluation and Research (CDER), Center for Devices and Radiological Health, and the Center for Biologics Evaluation and Research (CBER). Within these centers are offices with regulatory, functional, or therapeutic focus. Most pharmaceutical drug products, both synthetic and biologic, fall under the regulatory supervision of CDER, including most drug studies. The CBER regulates biological and related products including blood, vaccines, allergenics, tissues, and cellular and gene therapies, so only a small number of specialized drug studies would come under CBER jurisdiction. The FDA Web site publishes comprehensive organizational charts with the names and contact information of officials[11-15].

The primary set of federal laws establishing FDA authority as well as codification of the regulations is the Federal Food, Drug, and Cosmetic Act. The specific section of these laws covering an IND is in Part 312 of the Code of Federal Regulations (CFR). There are also other parts of the CFR that impact the conduct of clinical studies using pharmaceutical products. Table 1 lists the more important sections relevant to individual investigators. All of these regulations are readily accessible at the FDA Web site in a searchable format.[7] Finally, Federal law dictates that in order for a drug to be transported or distributed across state lines, it must have an approved marketing application. Because drugs to be used in most clinical trials will be shipped across state lines, the sponsor must seek an exemption from that legal requirement. The name, "Notice of Claimed Investigational Exemption for a New Drug," refers to this exemption. The more commonly used name is an "IND."

The stated purpose of an IND is "to ensure that subjects will not face undue risk of harm" in a clinical investigation that involves the use of a drug.[8] Hence, to authorize a drug

study in humans, the FDA requires sufficient information to assess the safety of the intended research study. The IND is the mechanism by which by the investigator or sponsor provides the requisite information to obtain authorization to administer an investigational agent to human subjects (or an approved drug used for a new indication or a new population of patients). All studies that use a drug not approved for marketing by the FDA will always require an IND. By a rather broad set of definitions for a "new drug,"[9] all studies using not only new molecular entities or unapproved pharmaceuticals but also approved drugs used in unapproved indications, in new formulations, in new dosages, in a patient population that would be put at increased risk require an IND. Under specific criteria, an exemption from this IND requirement may be met.

For regulatory purposes, clinical investigations involving drugs are initiated by a "sponsor" who takes responsibility for the conduct of the study. This term applies to a number of different entities. A sponsor can be an individual, a commercial entity such as a pharmaceutical company, an organization, or a governmental agency. Sponsors may conduct large multicenter trials with unapproved drugs in the anticipation of submitting the results of such investigations in support of a New Drug Application or a change in the official labeling for an approved drug. Investigational New Drug applications for studies of this nature require a comprehensive dossier of information including animal studies, pharmacokinetic analyses, toxicology studies, and manufacturing information (CFR 312.23). A description of this type of complex commercial submission is beyond the intended scope of this article.

The FDA defines an "investigator" to be the "individual who actually conducts a clinical investigation (ie, under whose immediate direction the drug is administered or dispensed to a subject)."[2] Investigators may conduct clinical studies for a sponsor. However, individual investigators who initiate and conduct a clinical study, as well as being directly accountable for the administration or dispensing of the investigational drug, are designated as a sponsor-investigator by the FDA. Clinical investigators at academic medical centers who are initiating clinical studies with a lawfully marketed drug to be used in a patient population or indication not within the official labeling often fit within this designation. Unlike a commercial sponsor initiating studies with an unapproved drug, often at multiple sites, a sponsor-investigator conducting an investigation at a single site will have a substantially less complicated filing requirement. The sponsor-investigator obtaining the IND would then be the "holder" of the IND and thus would be responsible for the associated regulatory requirements. This "simplest case" is the subject of this review.

The use of a placebo does not require an IND if the investigation does not otherwise require submission of an IND. Clinical trials that use an FDA-approved drug within the approved labeling do not need an IND. However, clinical investigations initiated by sponsor-investigators frequently make use of FDA-approved drugs in populations or indications not addressed in the approved labeling. Clearly, such studies have a markedly different risk profile than a phase 1 or 2 study with a new molecular entity. Correspondingly, the FDA has a mechanism to bypass filing an IND if specific exemption criteria are met, which address the safety of the proposed study as well as stated limits on the noncommercial intent of the study. The exemption criteria only apply to studies using marketed pharmaceuticals commercially available in the United States. These criteria are listed in CFR 312.2 (b). Importantly, all studies must also be approved by an institutional review board (IRB), and informed consent procedures must be met as set forth in 21 CFR 50 and 56 in addition to meeting the exemption criteria. Note that studies involving an "exception from informed consent" all require an IND and cannot claim an exemption under these provisions.

For sponsor-investigators initiating a study with an approved drug, the exemption that most directly relates to safety issues is CFR 312.2 (b) (iii). This criterion addresses whether the study "significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product" specifically regarding a route of administration, dosage level, dosage form, new proportions, use in a patient population, or any other relevant study aspect that affects safety of drug use. For example, this might include an exemption for studying the use of a drug in a disease entity not in the approved labeling but is reasonably supported by the underlying pharmacology and without any anticipated increase in the risk of adverse effects from the drug for the study population. The noncommercial context of the exemptions assures that the results will not be used to support a change in labeling for a new indication or a significant change in the advertising for the product. Such studies are typically undertaken by a pharmaceutical or device manufacturing company or other commercial entity. Analogously, there must be a compliance with the requirements that the study does not amount to a commercial distribution or marketing of a new drug. The provisions do allow for charging the subject for the drug under narrow specified circumstances.

Notably, the FDA has issued additional guidance for exemption from IND for drugs used to treat cancer. Further provisions are made allowing exceptions for studies involving in vitro diagnostic biological products, blood grouping serum, reagent red blood cells, and anti–human globulin. If a study does not meet the exemption

criteria, then an IND may be required. If the sponsor-investigator has any question whether the study meets the exemption criteria, it is usually appropriate to contact the FDA to clarify the regulatory requirements. The local IRB may also be able to help the investigator determine whether the criteria for safety are adequately addressed in the study so as to avoid the need for an IND. Unless it is clear that an IND is required, contacting the FDA for clarification or discussion with the IRB can save a significant amount of time and effort. The organizational charts for CDER can be used to guide the initial telephone contact. A project manager in the relevant division can provide significant help not only in addressing exemption requirements but also in the IND application process. Note that the FDA will not accept an application or review a study that is exempt under the stated provisions[16-20].

Investigational New Drug Application

There are different categories and types of IND. For individual sponsor-investigators, the IND will be categorized as a "research IND." The other category is "commercial IND." The FDA categorizes IND applications as "commercial" if the sponsor is either a corporate entity or one of the institutes of the National Institutes of Health or if it is clear that the drug may be eventually commercialized. The FDA has issued numerous Guidances regarding filing an IND. Most (80%) of the Guidances are addressed to industry (ie, commercial).[11]

Within the stated categories are a number of other designations. An "investigator IND" is a research IND submitted by an investigator who initiates and conducts the study including the immediate supervision of the use of the study drug. This would typify the studies conducted by sponsor-investigators. Additional IND types include an "emergency IND" that allows the FDA to authorize the use of an experimental drug in emergency situations that do not allow time for filing an IND or for patients who do not have access to the drug under protocol. Similarly, the "treatment IND" allows access for subjects in serious or life-threatening situations to experimental drugs that have shown promise in early clinical testing but before final FDA review. Lastly, an "exploratory IND" is conducted early in phase 1 studies of an agent. These studies involve limited human exposure and are designed without therapeutic intent (screening, microdosing, etc) and are preliminary to conducting more descriptive traditional safety and tolerance studies and allow for greater flexibility in the drug development process.

In addition, for antimicrobial products, the FDA has a consultation program to facilitate communications between the sponsor and the FDA before filing an IND involving the treatment of bacterial, fungal, and viral infections, opportunistic infections, emerging infections (including naturally emerging diseases and potential biothreat agents), topical microbicides directed at prevention of HIV transmission, and transplant rejection.

General Principles

The general scheme for an IND includes providing information in general areas: animal pharmacology and toxicology studies, manufacturing information, and clinical protocols and investigator information. The intent is to provide the FDA information to allow a review that assures the safety of participants. For sponsor-investigators, typically, the IND will not require the same extensive information including preclinical studies or manufacturing and process information as would be required for a commercial sponsor applying for an IND for a yet unapproved drug, especially early in its development. To an extent, this is because the studies conducted by sponsor-investigators usually use FDA-approved pharmaceuticals. Note that a sponsor-investigator has responsibilities as both a sponsor and an investigator, and investigations conducted under this designation are frequently single-site studies.

2. Methodology

Biopharmaceutical companies and their development partners increasingly use data from real-world settings to generate evidence that can support regulatory decision making and approvals of their manufactured medical products. The use of such real-world evidence (RWE) can complement or, in some cases, serve as an alternative to evidence traditionally yielded by randomized controlled trials (RCTs). For example, the use of external control arms can have considerable benefits, including accelerating the development process or reducing burden on trial participants. RWE can also provide investigators the opportunity to ask more questions and to understand broader, more diverse populations, as compared to RCTs.

The US Food and Drug Administration (FDA; also referred to here as the Agency) has taken significant steps to advance the use of RWE in regulatory decision making. This momentum has grown after the 21st Century Cures Act passed in December 2016; the act required FDA to develop a program for evaluating the use of RWE to support new indications for already-approved drugs and fulfill post approval study requirements. In 2018, FDA published a framework for its RWE program and is currently drafting guidance on its regulatory expectations regarding the use of RWE in medical product approvals. As part of its broad impact, FDA's framework has helped to promote common definitions for real-world data (RWD; defined as "data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources"[4]) and RWE (defined as "the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD. This is part of a worldwide interest in the use of RWE, including by regulatory agencies, such as the European Medicines

Agency (EMA), the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan, and the National Medical Products Administration (NMPA) in China. Much of FDA's regulatory use of RWE to date has been in the context of postmarket surveillance through programs like FDA's Sentinel initiative, a system initially designed to aid the Agency in evaluating medical product safety, and which has more recently expanded in scope. Current goals include enhancing Sentinel's ability to evaluate effectiveness and extending the evaluation of safety. In parallel, FDA also created a pilot project in 2008 to provide for the evaluation of vaccine effectiveness and, in 2017, launched the Biologics Effectiveness and Safety (BEST) system to enhance FDA's use and analysis of data to assure the safety and effectiveness of biological products. Beyond post market surveillance, FDA considers RWE studies as part of the evidence package for submissions seeking authorization to market new medical products, including new drug applications (NDAs) and biologics license applications (BLAs). These submissions are reviewed and decisions are rendered primarily by two centers within the Agency: the Center for Drug Evaluation and Research (CDER), which focuses on drug products and therapeutic biological products, and the Center for Biologics Evaluation and Research (CBER), which focuses on biological products including vaccines. Studies submitted as part of a sponsor's overall evidence package will be considered in decision making. Approvals will then be based on, among other things, studies that provide "substantial evidence" (in CDER decisions) or "primary evidence" (in CBER decisions), which make the primary case for product safety and effectiveness, and "supportive evidence," which can serve to bolster the case. Submitted studies providing therapeutic context can help reviewers understand the landscape of the disease (such as disease prevalence and incidence) and any current standard of care, but may not directly affect decision making. Many submitted studies will be presented in the FDA-approved product label of an approved or licensed drug or biological product. As such, RWE studies have the potential to be directly influential in prescribers' decision making if FDA approves a product label that includes submitted RWE studies. FDA and others have directly and indirectly provided insights into FDA's current approaches by speaking to and publishing select examples of successful and unsuccessful uses of RWE studies in medical product approvals, and FDA has provided publicly available guidance for industry and staff. However, RWE methodology is evolving, and on many important topics, RWE stakeholders lack a shared understanding of FDA's expectations around the use of RWE, particularly in the context of NDAs and BLAs.

3. Results and Discussion

US (FDA)

For the approval of follow-on biologics in the United States, current regulations depends on whether the biologic product is approved under the United States Food, Drug, and Cosmetic Act (US FD&C) or it is licensed under the United States Public Health Service Act (US PHS). For those biologic drugs marketed under the PHS Act, the BPCI Act passed by the US Congress on March 23, 2010 amends the PHS Act to establish an abbreviated approval pathway for biological products that are highly similar or interchangeable with an FDA-authorized biologic drug, and gives the FDA the authority to approve follow-on biologics under new section 351(k) of the PHS Act. Some early biologic drugs, such as somatropin and insulin were approved under the FD&C Act. In this case, biosimilar versions can receive approval for New Drug Applications (NDAs) under section 505 (b)(2) of the FD&C Act[21].

Following the passage of the BPCI, in order to obtain input on specific issues and challenges associated with the implementation of the BPCI Act from a broad group of stakeholders, the US FDA conducted a two-day public hearing on Approval Pathway for Biosimilar and Interchangeable Biological Products held on November 2-3, 2010 at the FDA in Silver Spring, Maryland. The scientific issues covered in this public hearing included, but not limited to, criteria and design for biosimilarity and interchangeability, comparability between manufacturing processes, patient safety and pharmacovigilance, exclusivity and user fees.

CANADA

Health Canada, the federal regulatory authority that evaluates the safety, efficacy, and quality of drugs available in Canada also recognizes that with the expiration of patents for biologic drugs, manufacturers may be interested in pursuing subsequent entry versions of these biologic drugs, which are called Subsequent Entry Biologics (SEB) in Canada. In 2010, Health Canada issued the "Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs)", whose objective was to provide guidance on how to satisfy the data and regulatory requirements under the Food and Drugs Act and Regulations for the authorization of subsequent entry biologics (SEBs) in Canada.

The concept of an SEB applies to all biologic drug products, however there are additional criteria to determine whether the product will be eligible to be authorized as SEBs: (1) a suitable reference biologic drug exists that was originally authorized based on a complete data package, and has significant safety and efficacy data accumulated; (2) the product can be well characterized by state-of-the-art analytical methods; (3) the SEB can be judged similar to the reference biologic drug by meeting an appropriate set of pre-determined criteria. With regard to the similarity of products, Health Canada requires the manufacturer to evaluate the following factors: (1) relevant data for physicochemical and biological characterization; (2) analysis of the relevant samples from the appropriate

stages of the manufacturing process; (3) stability data and impurities data; (4) data obtained from multiple batches of the SEB and reference to understand the ranges in variability; (5) non-clinical and clinical data and safety studies. In addition, Health Canada also has stringent post-market requirements including the adverse drug reaction report, periodic safety update reports, any suspension or revocation of NOC (notice of compliance). The guidance of Canada shares similar concepts and principles as indicated in the WHO's guidelines, since it is clearly mentioned in the guidance that Health Canada has the intention to harmonize as much as possible with other competent regulators and international organizations.

Drug approval for biological process in Australia

The Australian life sciences sector is subject to regulation by both Commonwealth and state or territory legislation. The manufacture and supply of therapeutic goods is primarily regulated by Commonwealth legislation, in particular, the Therapeutic Goods Act 1989 (TG Act) and its accompanying regulations, namely the Therapeutic Goods Regulations 1990 (TG Regulations) and the Therapeutic Goods (Medical Devices) Regulations 2002 (Medical Devices Regulations). Commonwealth legislation also provides a system of pricing and reimbursement of certain pharmaceutical products, known as the Pharmaceutical Benefits Scheme (PBS), through the National Health Act 1953 (NH Act) and its associated regulations.

Also relevant are the consumer protection provisions of the Competition and Consumer Act 2010 (CCA), and the equivalent state and territory legislation, which apply to all consumer transactions. State and territory legislation may impose additional requirements, including in relation to clinical and non-clinical trials, wholesale of medicines, and possession and distribution of controlled substances.

The Therapeutic Goods Administration (TGA) is the national authority responsible for regulating medicines and medical devices. The Australian Competition and Consumer Commission (ACCC) is the national authority that administers the CCA (although the CCA also provides a private right of action for enforcement of certain consumer law provisions). The Commonwealth government's Department of Health (DOH) manages, and Services Australia administers, the PBS.

Drug approval process in Europe

In May 1990, Company Y filed an application with the German health authorities (Bundesgesundheitsamt, or BGA) based on the one filed with the FDA seven months earlier. The company chose the BGA as its rapporteur because of previous experience with the German agency. In November 1990, however, the BGA returned the application, stating that "the package was unacceptable," that the dossier was incomplete, and that additional characterization of the process was necessary. Initially discouraged, and still in the laborious process of gaining FDA approval, Company Y decided not to pursue the European application until the fall of 1991.

From November 1991 to October 1992, the company's director for regulatory affairs interacted frequently with the BGA while redesigning the application to fit the European focus. Company Y also generated new data regarding the manufacturing process. Although it was costly and timeconsuming to meet the European requirements, the German reviewer cooperated in helping company officials to understand and meet the "new" requirements. Indeed, Company Y officials came to prefer the European to the FDA process, partly because it included not only the voluminous core documentation but also a high-level summary (called Expert Report), a tabular summary, and cross references[22-23].

In October 1992, a year after it really began preparing its EU application, the company officially filed for the second time with the BGA. Six months later, following validation by the German authorities, Company Y submitted the dossier to the appropriate authorities in all EU countries. In September 1993 the BGA submitted its favorable evaluation of the application and forwarded its "assessment report" to all other member states. British regulators announced their intent to inspect Company Y's facilities in the United States.

In October 1993, a year after filing, the company received a first official list of 272 questions from all European authorities, compiled and coordinated by the rapporteur country. This is about the same length of time as the FDA's first response. Company Y responded to all questions within one month. In December 1993 a second set of nine questions was submitted to the company, followed by a third set in February 1994. In March 1994 the company's representatives made a presentation in Brussels to the CPMP Biotechnology Working Party, which remained concerned about three or four issues. On the night before the meeting, BGA representatives met with company officials to discuss and rehearse the presentation. According to Company Y's director for regulatory affairs, rather than creating an extra layer of bureaucracy, the rapporteur provided "a second set of eyes" and guided the company through the complex review process. The Biotechnology Working Party recommended the product to the CPMP, which within thirty days recommended the product for approval to the commission and the member states. The period from the second submission to the rapporteur country and final product approval by the CPMP was clearly shorter than in the United States.

Then, however, the company had to pursue marketing authorization in several member states, which were not automatically bound by CPMP approval under the concertation procedure. The Netherlands granted the authorization within two weeks of the CPMP's

recommendation, Germany within one month, the United Kingdom and France within two months, and Luxembourg, Greece, Ireland, and Spain shortly thereafter. Italy, however, did not grant approval until September 1995, almost a year and a half after the CPMP recommendation, and as of March 1996, Company Y was still awaiting authorization in Belgium. Austrian authorities approved sale but stipulated that a sample of every batch of albumin used in the manufacture of the product sold in Austria had to be submitted to Austrian regulators. Because of such member-state variation, some companies apply for marketing authorization only in countries that represent a significant market.[40] Company Y applied for marketing authorization in all twelve member states.

Drug approval process in Singapore

Biosimilars are recombinant DNA products that join DNA from different species and subsequently insert the hybrid DNA into a host cell, often a bacterium or mammalian cell, to express the target protein; this molecular chimera was first created by researchers from UC San Francisco and Stanford in 1972. Stanley Cohen of Stanford and Herbert Boyer of UCSF received the US patent in 1980. Boyer co-founded Genentech, Inc. in 1976. The Cohen-Boyer patents will eventually have more than 500 licensees to biotechnology and pharmaceutical companies and earn Stanford and UCSF more than USD 250 million in royalties. These patents have now expired.

Biosimilars include monoclonal antibodies, cytokines, growth factors, enzymes, immunomodulators, and thrombolytics, proteins extracted from animals or microorganisms, including recombinant versions of these products (except clotting factors), and other non-vaccine therapeutic immunotherapies. Billions of patients receiving biosimilars have shown therapeutic equivalence. None of these products have shown adverse events more than the reference product including immunogenicity responses. It is estimated that the cumulative exposure to EU-approved biosimilars was more than two billion patient treatment days in 2020, with no adverse event reporting or withdrawal from the market due to safety reasons and no biosimilar-specific adverse effects have been added to the product information. Such an impeccable record of safety and efficacy that is better than the record for chemical drugs needs serious consideration about the regulatory guidelines to assure that we are not wasting resources and committing unethical practices.

Drug Approval process in India

Biologics are derived from the natural resources such as human, animal, or microorganism and manufactured by various biotechnology methods such as recombinant deoxyribonucleic acid technology, controlled gene expression, and antibody technology. Biologics have benefitted the patients with rheumatologic diseases, inflammatory bowel disease, malignant conditions, dermatological conditions, and other connective tissue disorders by halting the disease progression, alleviating the symptoms, and improving the quality of life. Biologics are one of the top selling drugs worldwide as well as in the United States but the major drawback of this drug has been its exorbitant cost, which makes it unaffordable and inaccessible to many patients, especially in developing countries where a large number of people are poor and the concept of health insurance is at its nascent stage. But the silver lining is that once the innovator company loses their intellectual property right and patent protection after a stipulated period, it opens the window of opportunities for companies evince an interest in manufacturing similar products, which cost less, and at that time, it is known as biosimilar or similar biologicals.

4. Conclusion

This study of the regulatory process for a new biological product does not provide consistent support for the conventional wisdom that American regulatory processes are more legalistic, adversarial, and costly than those of European nations. The European multistep approval process, as compared with the U.S. one-step process, was *more* complex, difficult, and costly. Although Company Y, once it figured out the EU system, gained product approval in Europe in eighteen to twenty months, compared with thirtyone months at the FDA, subsequent manufacturing process changes are faster and therefore less costly in the United States than in Europe. Moreover, the U.S. FDA now consistently reviews license applications within twelve months as the agency strives to meet its performance goals established under the User Fee Act. Europe is now attempting to align its review times for applications as well as process changes for biotechnology-derived products with those of the FDA[24-25]. Therefore, differences in review times and time to market no longer constitute an obstacle for companies pursuing simultaneous submissions to European and U.S. authorities. A comparison of the marketing authorization requirements for regulated and emerging countries has been described that all countries follow ICH regulation. The prime objective of the rules governing medicative products in the United States, Europe, Canada, Australia, and Singapore is to protect public health. It is the obligation of government regulatory agencies to ensure that pharmaceutical companies follow regulations. There are laws that ensure drugs to be manufactured, evaluated, and scampered in accordance with guidelines to ensure their safety and the well-being of patients.

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