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Research Article

Analysis of Emergency Drug Approval System in China, USA, Australia and India under Public Health Emergencies

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Abstract
Development of new drug is a complex, time-consuming, and expensive process. The time taken from discovery of a new drug to its reaching the clinic is approximately 12 years, involving more than 1 billion US$ of investments in today's context. Essentially, the new drug discovery involves the identification of new chemical entities (NCEs), having the required characteristic of drug ability and medicinal chemistry. The study aims to evaluate the emergency drug approval system in China, USA, and Australia and India under public health emergencies. China has been the second largest single-country pharmaceutical market in the world for many years. However, over the years, several hurdles in China's drug regulatory system and practice had significantly impeded drug development activities, new drug review, and approval in China. These included the overly strict requirements for clinical trial approval, lengthy regulatory review time, lack of clearly defined sponsor-agency communication channels, and the shortage of trained reviewers, to name a few. These factors had contributed to the large backlog of new drug applications and delayed access to innovative medicines and treatments. The increasing number of API manufacturing sites in China and other countries suggests that the United States' reliance on Chinese and other foreign sources of API is growing. FDA has been working diligently in collaboration with industry and other federal agencies to ensure our reliance of foreign manufacturing does not pose a national security risk.
Keywords: *New drug, China, USA, and Australia, New drug applications. Drug approval, FDA.*

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Contents

1. Introduction

Irrational prescription is a public health problem with the potential to harm both the individual and society. It is, possibly a contributory factor to the increasing pharmaceutical expenditure world-wide. Drug expenditure is a major concern for policy makers in Europe and has prompted them to suggest healthcare reforms. Several factors have been identified to influence doctors' prescribing decisions and practice. Some factors such as the physicians' age and gender, their training, the socio-economic characteristics of the practicing environment, and the healthcare demand are fixed and may not offer much opportunity for modification and improvements in prescribing behaviour. However, other factors including physicians' level of education and experience, frequency of visits by pharmaceutical sales representatives (PSRs), number of patients examined per day, and various social factors are amenable to change and can be modified to improve physicians' prescribing behavior.

Disease mongering is a potential means of creating an enormous market for drugs but its influence on the prescribing behaviour of physicians has not been explored. Many normal life processes like birth, ageing, sexuality, unhappiness and death have been medicalised and are promoted as illnesses by the pharmaceutical industry. Opinion leaders from the medical profession are used by the pharmaceutical industry to lure doctors to prescribe medicines for normal life processes when infact none is required[1-6].

Drugs play an important role in the treatment of ill patients. In Nigeria, drugs are prescribed to more than 60 percent of the patients that consult with doctors. PSRs are frequently the only source of information about medicines in developing countries where there may be as many as one representative for every five doctors.

The World Health Organization (WHO) defines pharmaceutical promotion as "all information and persuasive activities by manufacturers and distributors, the effect of which is to induce the prescription, supply, purchase and/ or use of medicinal drugs". The WHO and some NGOs are bothered about the unethical and inappropriate approach to the promotion of pharmaceutical products. At the 1997 roundtable on WHO's Ethical Criteria for Medicinal Drug Promotion there was firm agreement that inappropriate promotion of medicinal drugs remains a problem both in developing and developed countries. Alongside the concern for unethical and inappropriate drug promotion, there is also increasing concern over irrational, inappropriate, or sometimes even harmful prescribing.

Given the above problems and knowing that pharmaceutical companies play active roles in marketing their products, it is important to investigate how much influence these companies have on the prescribing behaviours of healthcare practitioners in developing African countries. Unfortunately, there is limited information on research in this area in Nigeria. This study is therefore aimed at determining the sources of drug information for doctors working in a teaching hospital in Nigeria and to assess the self-reported impact of the sources on their prescribing behaviour.

Development of new drug is a complex, time-consuming, and expensive process. The time taken from discovery of a new drug to its reaching the clinic is approximately 12 years, involving more than 1 billion US$ of investments in today's context. Essentially, the new drug discovery involves the identification of new chemical entities (NCEs), having the required characteristic of druggability and medicinal chemistry. These NCEs can be sourced either through chemical synthesis or through isolation from natural products. Initial success stories in new drug discovery came from medicinal chemistry inventions, which led to the need of development of higher number of chemical libraries through combinatorial chemistry. This approach, however, was proven to be less effective in terms of overall success rate. The second source of NCEs for potential use as drug molecules has been the natural products. Before the advent of high throughput screening and the post genomic era, more than 80% of drug substances were purely natural products or were inspired by the molecules derived from natural sources (including semi-synthetic analogs). An analysis into the sources of new drugs from 1981 to 2007 reveals that almost half of the drugs approved since 1994 were based on natural products. During the years 2005–2007, 13 natural product related drugs were approved[11-23]. There are various examples of development of new drugs from the plant sources.

Morphine was isolated from opium produced from cut seed pods of the poppy plant (Papaver somniferum) approximately 200 years ago. Pharmaceutical research expanded after the second world war to include massive screening of microorganisms for new antibiotics, inspired by the discovery of penicillin. Few drugs developed from natural sources have undoubtedly revolutionized medicine, like antibiotics (e.g. penicillin, tetracycline, erythromycin), antiparasitics (e.g. avermectin), antimalarials (e.g. quinine, artemisinin), lipid control agents (e.g. lovastatin and analogs), immunosuppressants for organ transplants (e.g. cyclosporine, rapamycins), and anticancer drugs (e.g. paclitaxel, irinotecan).

Clinical trials are ongoing on more than 100 natural product derived drugs and at least 100 molecules/compounds are in preclinical development stage. Most of these molecules in the developmental

pipeline are derived from leads from plants and microbial sources. Cancer and infections are the two predominant therapeutic areas for which the drug discovery program is based on natural products, but many other therapeutic areas also get covered, such as neuro-pharmacological, cardiovascular, gastrointestinal, inflammation, metabolic, etc. Among the different projects in various therapeutic areas, around 108 projects are based on plants. A further division of these projects indicates that 46 of them are in preclinical stage, 14 in phase I, 41 in phase II, 5 in phase III, and 2 are in pre-registration phase.

In general, there are six classes of sources for NCEs. The four classes are botanical sources, fungi, bacteria, and marine sources. In addition to these four classes, modern pharmaceutical chemistry added two categories of man-made substances, i.e. synthetic chemistry and combinatorial chemistry. Of these natural sources, botanical sources are of specific importance in the context of this review. The botanical sources are known to provide the following classes of NCEs for drug discovery processes.

Drug Discovery from Natural Resources: Advantages and Disadvantages: Usage of botanical sources as starting point in the drug development program is associated with few specific advantages: Mostly, the selection of a candidate species for investigations can be done on the basis of long-term use by humans (ethnomedicine). This approach is based on an assumption that the active compounds isolated from such plants are likely to be safer than those derived from plant species with no history of human use. At certain time point afterward, one may attempt upon synthesis of active molecule and reduce pressure on the resource. Drug development from Rauwolfia serpentina, Digitalis purpurea, etc. in the past fall under this category of approach.

Sometimes, such approaches lead to development of novel molecules derived from the source due to inherent limitations of the original molecule. For instance, podophyllin derived from Podophyllum hexandrum was faced with dose-limiting toxicities. Such limitations could be overcome to a great extent by semi-synthesis of etoposide, which continues to be used in cancer therapy today. Similar was the case with camptothecin (originally isolated from Camptotheca sp. and subsequently from Mappia sp.), which led to development of novel anticancer molecules like topotecan and irinotecan. Natural resources as starting point has a bilateral promise of delivering the original isolate as a candidate or a semi-synthetic molecule development to overcome any inherent limitations of original molecule.

On the other hand, drug development from natural resources is also associated with certain disadvantages:

More often than not, drug discovery and eventual commercialization would pressurize the resource substantially and might lead to undesirable environmental concerns. While synthesis of active molecule could be an option, not every molecule is amenable for complete synthesis. Hence, certain degree of dependence on the lead resource would continue. For instance, anticancer molecules like etoposide, paclitaxel, docetaxel, topotecan, and irinotecan continue to depend upon highly vulnerable plant resources for obtaining the starting material since a complete synthesis is not possible. On the other hand, it is expected that some 25,000 plant species would cease to exist by the end of this century. Over a period of time, the intellectual property rights protection related to the natural products is going haywire. By and large, the leads are based upon some linkage to traditional usage. With larger number of countries becoming the parties to the Convention on Biological Diversity (CBD), the process of accessing the basic lead resource, benefit sharing during the commercial phase, etc. became highly complex in many countries. These processes tend to impede the pace of discovery process at various phases irrespective of the concerns leading to such processes.

Druggability of Isolated Phytochemical Compounds

Challenges in the new drug development are mainly encountered from two categories: the prevailing paradigm for drug discovery in large pharmaceutical industries and technical limitations in identifying new compounds with desirable activity. Koehn and Carter have enumerated the following unique features of the compounds isolated from natural products:

- Greater number of chiral centers
- Increased steric complexity
- Higher number of oxygen atoms
- Lower ratio of aromatic ring atoms to total heavy atoms
- Higher number of solvated hydrogen bond donors and acceptors

Grater molecular rigidity

Broader distribution of molecular properties such as molecular mass, octanol water partition coefficient, and diversity of ring systems. These unique features of chemical entities of natural origin pose a string of challenges for medicinal chemists as they start working upon development of analogs, either to improve the absorption or to reduce the toxicity and improve upon efficacy which is often achieved by addition or deletion of selected functional groups. As per a review by Ehrman et al., different bioactive plant compounds were isolated in China from 1911 to 2000 like alkaloid, steroid, triterpene, limonoid, diterpene, sesquiterpene, monoterpene, tanin, isoflavonoid, flavonoid, polycyclic aromatic, lignan, coumarin, simple phenoloic, aliphatic, etc. Alkaloid may be distributed as 20%, flavonoids as 15%, triterpenes and simple phenolics around 10%, and remaining others below that, with limonoid being the least.

It can be safely presumed that large number of natural products, despite being biologically active and having favorable ADMET profile (absorption, distribution, metabolism, excretion, and toxicity), do not satisfy the criteria "drug likeness." The challenge is of building a physio-chemical tuned natural products library in line with the lead generation to promote natural products to their full potential. Lipinski propagated simple set of calculated property called "rule of five" basis the drug candidates reaching Phase II clinical trials. This rule is an algorithm consisting of four rules in which many of the cutoff numbers are five or multiples of five, thus originating the rule's name. To be drug-like, a candidate should have:

- less than five hydrogen bond donors;
- less than 10 hydrogen bond acceptors;
- molecular weight of less than 500 Da; and
- Partition coefficient log P of less than 5.

The aim of the "rule of five" is to highlight possible bioavailability problems if two or more properties are violated. Had Lipinski's rule been applied, paclitaxel would never have become a drug. Since it does not comply with "rule of five," a biggest challenge is to find alternative druggability criteria for the compounds of natural origin. Therefore, the biggest challenge is to find alternative druggability criteria for the compounds of natural origin.

Selection of Candidate Plant Species for Screening

To available estimates, the total number of higher plants species (comprising angiosperms and gymnosperms) is approximately 250,000 species. Of them, only 6% have been reportedly screened for biological activity and about 15% have been screened for phytochemical activity. Initial listing of the candidate species for screening of biological activity is a major task of specific importance in itself. Fabricant and Farnsworth have enumerated the following approaches being used so far by researchers for this purpose.

Random approach

Two approaches have been followed for screening of the plants selected randomly for the purpose of new drug discovery.

a) Screening for selected class of compounds like alkaloids, flavonoids, etc.: While this route is simple to perform, however, it is flawed in the sense that it provides no idea of the biological efficacy. However, chances of getting novel structures cannot be denied following this approach.

b)Screening of randomly selected plants for selected bioassays: Central Drug Research Institute, a premier R and D organization of Council of Scientific and Industrial Research of India, followed this approach about three decades ago. They screened almost 2000 plants for biological efficacy. However, the screening did not yield any new drug. National Cancer Institute (NCI) of National Institute of Health, USA, studied about 35,000 plant species for anticancer activity, spending over two decades from 1960 to 1980. It resulted in proving two success stories, which were those of paclitaxel and camptothecin. This route, therefore, has been applied for both focused screening as well as general screening, showing some success in focused screening. If target-based bioassays are used, e.g. screening against PTP1B, chances of success would probably be more. This approach, however, needs a huge library of extracts, which very few organizations in the world are having.

Ethnopharmacology approach

The approach of ethnopharmacology essentially depends on empirical experiences related to the use of botanical drugs for the discov-ery of biologically active NCEs. This process involves the observation, description, and experimental investigation of indigenous drugs, and is based on botany, chemistry, biochem-istry, pharmacology, and many other disciplines like anthropology, archaeology, history, and linguistics. This approach based on ethnomedicinal usage history has seen some success, e.g. Andrographis paniculata was used for dysentery in ethnomedicine and the compounds responsible for the activity were isolated as andrographolide. Morphine from Papaver somniferum, Berberine from Berberis aristata, and Picroside from Picrorrhiza kurroa are some examples of this approach. Some of the plants which are not selected on the basis of ethnomedical use also had some success stories, like L-Dopa from Mucuna prurita and paclitaxel from Taxus brevifolia.

Traditional system of medicine approach

Countries like India and China have a rich heritage of well-documented traditional system of medicine in vogue. Though these codified systems of medicine use largely botanical sources as medicines, however, these stand apart from ethnomedicine specifically on three accounts:

The ethnomedicinal practice is based on empirical experiences. On the other hand, these codified systems built up the empirical practices on strong conceptual foundations of human physiology as well as of pharmacology (though the tools of their investigations in those times were far different from the existing ones). The pharmaceutical processes have been more advanced as against the use of crudely extracted juices and decoctions in ethnomedicinal practices. Due to this phenomenon, the concept of standardization was known to the system.

They are well documented and widely institutionalized. On the other hand, the ethnomedicinal practices are localized and may be largely controlled by few families in each of the community. However, in terms of historicity, ethnomedicinal practices might be older than codified systems of medicine. Discovery of artemisinin from Artemesia alba for malaria, guggulsterones from Commiphora mukul (for hyperlipidemia), boswellic acids from Boswellia serrata (anti-inflammatory), and bacosides from Bacopa monnieri (nootropic and memory enhancement) was based on the leads from these codified systems of medicine prevailing in China and India. However, it can be stated that such approach for selecting candidates in drug discovery programs has not been

adopted much so far. Nonetheless, the approach has a distinct promise in terms of hit rates. But the distinct example for this approach has been the discovery of reserpine from Rauwolfia serpentine, which was based on the practices of Unani medicine.

Zoo-pharmacognosy approach

Observation of the behavior of the animals with a view to identify the candidate plants for new drug discovery is not a distant phenomenon. Observation of straight tails linked to cattle grazing habits in certain regions of South America led to identification of a plant Cestrum diurnum and three other plant members of family Solanaceae, which probably are the only known plant sources of the derivatives of Vitamin D_3. This approach, however, needs close observation and monitoring of the behavior of animals.

A clinical trial is a systematic process that is intended to find out the safety and efficacy of a drug/device in treating/preventing/diagnosing a disease or a medical condition. Clinical trial includes various phases that include phase 0 (micro-dosing studies), phase 1, phase 2, phase 3, and phase 4. Phase 0 and phase 2 are called exploratory trial phases, phase 1 is termed the non-therapeutic phase, phase 3 is known as the therapeutic confirmatory phase, and phase 4 is called the post-approval or the post-marketing surveillance phase. Phase 0, also called the micro-dosing phase, was previously done in animals but now it is carried out in human volunteers to understand the dose tolerability (pharmacokinetics) before being administered as a part of the phase 1 trial among healthy individuals.

2. Methodology

'China has been the second largest single-country pharmaceutical market in the world for many years. However, over the years, several hurdles in China's drug regulatory system and practice had significantly impeded drug development activities, new drug review, and approval in China. These included the overly strict requirements for clinical trial approval, lengthy regulatory review time, lack of clearly defined sponsor-agency communication channels, and the shortage of trained reviewers, to name a few. These factors had contributed to the large backlog of new drug applications and delayed access to innovative medicines and treatments.

In August, 2015, the State Council of China issued a policy document entitled "Opinions on the Reform of Review and Approval Process for Drugs and Medical Devices," marking the beginning of the regulatory reform through the next several years. Implementation of a series of reform policies has led to the revision of the Drug Administration Law, the adoption of the new Vaccine Administration Law, and the re-write of many important regulations. All of these have fundamentally reshaped the regulatory environment in China.

In June 2017, the Assembly of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) approved the then Chinese regulatory agency, China Food and Drug Administration (CFDA, predecessor of today's National Medical Products Administration, NMPA) as a Regulatory Member of ICH. China's joining ICH was an important milestone in its regulatory history. It signified that the agency was prepared to adopt ICH technical requirements for drug registration and to become a global player in drug approval and regulation.

It has been more than six years since the landmark reform started. However, there is a lack of reports examining the impact of the reform measures on the metrics of drug review and approval across therapeutic areas and modalities. Therefore, we set out to investigate quantitatively the trend and characteristics of regulatory review and approval of new drugs in 2011–2021, comparing the results in 2017–2021 with those in prior years. The speed with which a drug regulatory agency evaluates and approves new drugs is an important indicator of regulatory capability and efficiency. In this research, we analyzed the temporal trends of the number of new drugs approved and the approval times by the Chinese regulatory agency. We also examined how other characteristics such as regulatory programs, oncology drugs, rare disease drug status, and number of the review cycles may have influenced the trends. At the same time, Chinese domestic pharma and biotech companies have evolved rapidly over the past few years. They develop new drugs through in-license or in-house discoveries. Since the Chinese regulatory system has historically instituted different drug application processes for domestic (locally manufactured) drugs and for imported drugs, it was also of interest to analyze the data comparing domestic drug approvals with import drug approvals.

3. Result and Discussion

Emergency Drug Approval Process in USA

The United States, through its investment in biomedical research, has become a world leader in drug discovery and development, but is no longer in the forefront of drug manufacturing. Historically, the production of medicines for the U.S. population has been domestically based. However, in recent decades, drug manufacturing has gradually moved out of the United States. This is particularly true for manufacturers of active pharmaceutical ingredients (APIs), the actual drugs that are then formulated into tablets, capsules, injections, etc. As of August 2019, only 28 percent of the manufacturing facilities making APIs to supply the U.S. market were in our country. By contrast, the remaining 72 percent of the API manufacturers supplying the U.S. market were overseas, and 13 percent are in China. FDA's

data show that the number of registered facilities making APIs in China more than doubled between 2010 and 2019. While there are many reasons for this shift, underlying factors that are often cited include the fact that most traditional drug production processes require a large factory site, often have environmental liabilities, and can utilize a low-cost labor force. A 2009 paper by the World Bank, "Exploratory Study on Active Pharmaceutical Ingredient Manufacturing for Essential Medicines," stated that if a typical Western API company has an average wage index of 100, this index is as low as 8 for a Chinese company and 10 for an Indian company. China has lower electricity, coal, and water costs. Chinese firms are also embedded in a network of raw materials and intermediary suppliers, and so have lower shipping and transaction costs for raw materials. They also face fewer environmental regulations regarding buying, handling, and disposing of toxic chemicals, leading to lower direct costs for these firms. FDA's 2011 report, "Pathway to Global Product Safety and Quality," noted that both China and India enjoy a labor cost advantage and that API manufacturing in India can reduce costs for U.S. and European companies by an estimated 30 percent to 40 percent[7-11].

Using traditional pharmaceutical manufacturing technology, a U.S.-based company could never offset the labor and other cost advantages that China enjoys simply by achieving higher productivity. However, FDA believes that advanced manufacturing technologies could enable U.S.-based pharmaceutical manufacturing to regain its competitiveness with China and other foreign countries, and potentially ensure a stable supply of drugs critical to the health of U.S. patients. Advanced manufacturing is a collective term for new medical product manufacturing technologies that can improve drug quality, address shortages of medicines, and speed time-to-market. Every field has a different set of production techniques that are considered advanced. Examples of some cross-cutting advanced manufacturing technologies include continuous manufacturing and 3D printing. Advanced manufacturing technology, which FDA supports through its Emerging Technology Program (ETP), has a smaller facility footprint, lower environmental impact, and more efficient use of human resources than traditional technology, as will be explained later in this testimony.

Emergency Drug Approval Process in CHINA

The reform that started in 2015 has brought about an overhaul to the Chinese regulatory system. The initial focus of the reform was to reduce the massive backlog of drug clinical trial and marketing applications, which stood at its peak of 22,000 in September 2015, and to improve the efficiency of the regulatory review process. A series of measures were implemented. For examples, a mandatory self-examination and inspection program of clinical trial data for 1622 applications was carried out in 2015 to ensure data authenticity and integrity in regulatory filing and to crack down on potential data fraud. Other key measures included a new set of criteria for priority review, an updated requirement of filing a notification instead of obtaining approval for bioequivalent studies of chemical drugs, an enhanced sponsor-reviewer communication mechanism, as well as streamlined internal working procedures and expansion of reviewing staff in the Center for Drug Evaluation (CDE). These measures had helped eliminate the backlog of applications by the end of 2017. The outstanding number of applications has since remained stable in the proximity of 4500.

Starting in late 2016, the scope of the reform was broadened, deepening to the fundamental regulatory processes. The goals were shifted to become focused on comprehensively restructuring the regulatory system and encouraging innovation. A broad range of policy proposals was introduced, many of which were codified in the revision of the Drug Administration Law in December, 2019, or included in the subsequent re-write of key regulations, such as Drug Registration Regulation, Drug Manufacturing Regulation, Good Clinical Practice, and other regulatory directives. Many internal procedures were also updated or created to adapt to the mandates of the newly revised laws and regulations. China's joining ICH also facilitated the adoption of ICH technical guidelines. As such, the new regulatory framework was largely established and the regulatory system entered a "norming" stage.

The number of new drugs approved each year and the regulatory approval time provide suitable metrics to assess the overall performance of a regulatory review system, and in our research, the overall impact of the reform. Our analysis showed that there clearly was a surge in 2017 with 41 new drugs approved compared with only nine new drug approvals in the year before (Fig. 1). In subsequent years, the number of new drugs approved each year continued to remain at a high level, reaching a record high of 70 in 2021. The COVID-19 pandemic in 2020 and 2021 did not appear to have hindered the new drug review and approval activities in China. It is not surprising that overall, imported drugs accounted for approximately two-thirds of the new drugs approved in the period studied, because the domestic pharmaceutical industry has historically not been a source of innovative drugs for China. On the other hand, the number of approved new drugs from domestic companies has been increasing in recent years. The local biotech and pharma industry is rapidly growing and evolving, and has started to discover and develop new drugs, albeit very few first-in-class molecules, for Chinese and global markets. It is notable that the number of domestic drug approvals had surpassed imported drugs in 2021.

While it remains to be seen if such a high proportion of domestic new drug approvals will sustain, we anticipate that in future years, a substantial percentage of new drug approvals will be from local Chinese biopharma companies. This reflects the favorable regulatory policies supporting a growing local innovation ecosystem and the rapid rise of China home-grown products in global R&D pipeline.

Emergency Drug Approval Process in AUSTRALIA

The TGA registration process for prescription medicine applications, that need to be supported by nonclinical, clinical and/or bioequivalence data (category 1 and category 2). This regulatory process is designed to improve the efficiency and timeliness of the registration of prescription medicines without compromising the scientific rigour of the evaluation process, thus ensuring the maintenance of appropriate standards of quality, safety, and efficacy. This document describes this process and outlines the relevant regulatory requirements.

The key elements of this process are:

- management by milestones
- an improved quality of dossiers prepared in accordance with common technical document (CTD) format and other TGA regulatory requirements
- a pre-submission planning phase where applicants lodge details of a proposed application at least 2¼ months prior to lodgement of the dossier allowing the TGA to identify milestone dates and plan resource requirements (this is not required for submissions lodged in eCTD format if the sponsor selects the PPF-only option)
- a submission phase where the applicant must lodge a complete dossier, there being no opportunity to deliver new data after the submission date except as required by the *Therapeutic Goods Act 1989*- external site (the Act)
- requests for information under section 31 of the Act are consolidated and issued at the end of the initial evaluation phase.

Regulatory and supporting documents

Category 1 and 2 applications for new registrations are made under section 23 of the Act. Section 23 requires that applications are made in a form approved by the Secretary. The currently approved form is the CTD format. Category 1 and 2 requests to vary the entry in the Australian Register of Therapeutic Goods (ARTG) of registered therapeutic goods are made under section 9D of the Act. Section 9D requires that applications are made in a manner approved by the Secretary. The currently approved manner is the CTD format[12-17].

Emergency Drug Approval Process in INDIA

The Drug and Cosmetic Act 1940 and Rules 1945 were proclaimed by the India's parliament to regulate the import, manufacture, distribution and sale of drugs and cosmetics. The Central Drugs Standard Control Organization (CDSCO) and the office of its leader, the Drugs Controller General (DCGI) was established. In 1988, the Indian government added Schedule Y to the Drug and Cosmetics Rules 1945. Schedule Y provides the guidelines and requirements for clinical trials, which was further revised in 2005 to bring it at par with internationally accepted procedure. When a company in India wants to manufacture/ import a new drug it has to apply to seek permission from the licensing authority (DCGI) by filing in Form 44 also submitting the data as given in Schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945. In order to prove its efficacy and safety in Indian population it has to conduct clinical trials in accordance with the guidelines specified in Schedule Y and submit the report of such clinical trials in specified format [5]. Rule 122A of the Drug and Cosmetics Act says that the clinical trials may be waived in the case of new drugs which are approved and being used for several years in other countries. Section 2.4 (a) of Schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945 says for those drug substances which are discovered in India all phases of clinical trials are required. Section 2.4(b) of Schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945 says that for those drug substances which are discovered in countries other than India; the applicant should submit the data available from other countries and the licensing authority may require him to repeat all the studies or permit him to proceed from Phase III clinical trials. Demonstration of safety and efficacy of the drug product for use in humans is essential before the drug product can be approved for import or manufacturing of new drug by the applicant by Central Drugs Standard Control Organization (CDSCO). The regulations under Drugs and Cosmetics Act 1940 and its rules 1945, 122A, 122B and 122D describe the information required for approval of an application to import or manufacture of new drug for marketing. For an investigational new drug, the sponsor needs to provide detailed information to the DCGI about: 1. Generic name 2. Patent status 3. Brief description of physico-chemical/biological 4. Technical information a) Stability b) Specifications c) Manufacturing process d) Worldwide regulatory status e) Animal pharmacology and toxicity studies 5. Published clinical trial reports 6. Proposed protocol and pro forma 7. Trial duration 8. During master file 9. Undertaking to Report Serious or Life-threatening Adverse Drug Reactions. The need for local clinical trials in India depends on the status of drug in other countries[18=19]. If the drug is already approved in other countries, generally Phase III trials are required. Phase I trials are not allowed in India unless the data is available from other countries. Permission is granted by DCGI to conduct Phase 1 trials in India, if the drug has special relevance to a health problem in India, like malaria or tuberculosis. Bioavailability and bioequivalence (BABE) studies should be conducted as per BABE guidelines. The comprehensive information on the marketing status of the

drug in other countries is also required other than the information on safety and efficacy.

4. Conclusion

The increasing number of API manufacturing sites in China and other countries suggests that the United States' reliance on Chinese and other foreign sources of API is growing. FDA has been working diligently in collaboration with industry and other federal agencies to ensure our reliance of foreign manufacturing does not pose a national security risk. While FDA cannot tell industry where they can and cannot manufacture APIs, we can work with industry to utilize new technologies and new manufacturing methods to further incentivize domestic production of drugs and APIs[20]. The NDA approval time was significantly shortened compared with the pre-reform period. The newly instituted expedited regulatory pathways are taking effect. More imported drugs are entering China sooner, suggesting a positive prospect of reduction of drug lag. Therefore, patient's accessibility to innovative and the advanced treatments is being improved. Moving forward, China's regulatory system will continue to evolve as there still are many areas requiring further reform and improvement. Transforming such a complex system in an ever-changing scientific, economic, and political context is a daunting task and the course of the reform will not be uneventful.

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