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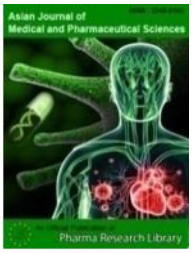

Research Article

A Comaprative Analysis of New Drugs and Clinical Trials Rules and Its Impact on Approval Process of Oncology Drugs in USA, CANADA, AUSTRALIA, EUROPE and INDIA

K. Sunil Kumar*[1], Panthagiri Thulasi[2]

[1]*Associate Professor, Department of Pharmaceutics and DRA, Sun Institute of Pharmaceutical Education and Research, Kakupalli, Nellore, Andhra Pradesh, India*
[2]*Sun Institute of Pharmaceutical Education and Research, Kakupalli, Nellore, Andhra Pradesh, India*

Abstract

The FDA approves drugs through the clinical trials process. Every clinical trial has a sponsor to fund the research process. Sponsors are usually pharmaceutical companies, government agencies, or healthcare organizations. After gathering data from animal research to determine if a potential drug is effective and safe for human testing, the sponsor of the clinical trial submits an Investigational New Drug (IND) application to the FDA. The IND application includes detailed information on the drug and explains how the trials will be conducted. The FDA regularly provides updates on approved drugs on the FDA website. Even after the FDA approves a drug, the sponsor is still required to report safety updates to the FDA as needed. If new side effects are discovered, the drug's labeling is changed and the public is informed. If a new side effect is deemed too dangerous, the FDA revokes approval. The US Food and Drug Administration (FDA) approves cancer drugs based on (1) overall survival or patient reported outcomes, (2) progression-free survival, ie, the time until cancer recurs or worsens, or (3) response rate (RR), ie, the percent of patients experiencing tumor shrinkage. The Response rate and complete response rate are typically ascertained in uncontrolled, nonrandomized studies. Because these trials have no comparator arm, drug-related adverse events may be missed among symptomatic patients because they may be mistakenly attributed to their underlying cancer. There is also uncertainty about whether and to what degree these drugs improve survival or quality of life.

Keywords: FDA, Investigational New Drug, Labeling, uncontrolled, nonrandomized studies, cancer and healthcare organizations.

Article Info

Corresponding Author
K. Sunil Kumar
Associate Professor, Department of Pharmaceutics and DRA,
Sun Institute of Pharmaceutical Education and Research,
Kakupalli, Nellore, Andhra Pradesh, India

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Contents

1. Introduction

According to the Pharmaceutical Research and Manufacturers of America (PhRMA), the United States' biopharmaceutical industry contributes substantially to the U.S. economy. PhRMA reports that the industry directly employs over 800,000 workers in well-paid jobs and diverse fields, and supports an additional 2.5 million jobs across the country. Moreover, PhRMA asserts that it supports over $789 billion in total economic output. For several years, though, the increased time and money necessary to develop a new compound, the failure rate of prospective products, and a decrease in venture capital investments, among other strains on the industry, have propelled concerns that innovative research in the U.S. might wither, stop, or move to other nations or regions, decreasing the potential short term access for U.S. patients to some new products, potentially leaving others unexplored entirely, and hurting a significant segment of the U.S. economy[1-7].

As a result, Congress, the Food and Drug Administration (FDA), and the pharmaceutical industry have sought to nurture an "ecosystem" conducive to the development of innovative, safe, and effective new compounds in the U.S. Among the mechanisms developed are four expedited approval mechanisms, the most recent of which the Breakthrough Therapy designation Congress created in 2012 through the Food and Drug Administration Safety and Innovation Act (FDASIA). Sponsors of new drug and biologic products (sponsors) have embraced the new Breakthrough Therapy designation: as of roughly December 2014, FDA reported having received 260 requests for Breakthrough Therapy designation, of which it granted 74 and denied 139.[7] Of the 41 designated compounds, four have been approved for marketing.

This article seeks to discuss the development of these mechanisms and describe when a sponsor may use each mechanism and what benefits that mechanism will provide. It argues that the four mechanisms each apply in slightly different circumstances and provide slightly different benefits. But the new Breakthrough Therapy designation essentially establishes a hierarchical layer over the Fast Track designation for a subset of compounds that appear especially promising, most likely through medical and scientific advances in targeted therapies. In addition to the tools already available through the Fast Track mechanism which may include a high likelihood of receiving Priority Review a Breakthrough Therapy designation focuses agency resources on product review primarily through the commitment of personnel.

The first part provides background information on the standard requirements and process for approving a new drug for marketing. This section includes an explanation of the standard every new drug product must meet for approval, a description of the traditional clinical trial phases and endpoints, and general trends in the time and finances required to develop successfully a new drug product. The second part describes the historical development of expedited approval mechanisms for new drug products. It describes the FDA's original prioritization classification system that was formalized during the 1970s up to and including the most recent Breakthrough Therapy designation. The third part explains each of the four expedited approval mechanisms currently used by FDA, while the fourth part goes one step further by comparing and contrasting the similarities and differences of the older expedited approval mechanisms with the Breakthrough Therapy designation.

Background on the FDA Approval Process for a New Drug Product

History of the FDA approval process A: The modern safety and efficacy requirements that govern FDA's review and approval of a new drug[9] product evolved out of a series of legislative enactments, beginning in 1938 with the Federal Food, Drug and Cosmetic Act of 1938 (the FDCA), after the tragic deaths of more than 100 people from a poisonous ingredient in Elixir Sulfanilamide. The law overhauled the regulatory system that had existed for almost 30 years. Recognizing that post-marketing monitoring alone was insufficient to protect the public's health from dangerous drugs, the FDCA required manufacturers to apply to FDA to market a new drug. If a specified period of time passed without action by FDA, the law deemed the application to be approved. The law also required a manufacturer to show that a new product was safe.

In October 1962, following the tragic discovery that a drug marketed as a sleeping pill led to substantial malformations in thousands of newborns in Western Europe, Congress expanded the pre-market requirements for manufacturers of new drug and biologic products through the Kefauver-Harris Drug Amendments to the FDCA. The amendments replaced the automatic approval provisions if FDA failed to act with a requirement for affirmative FDA approval.[15] The law further mandated that manufacturers demonstrate substantial evidence of efficacy for a new drug, laying the foundation for the current system of development and clinical trial phases. Numerous acts have amended the FDCA since 1962, but the heart of these two requirements remains the same[8-15].

The safety and efficacy standards for new drug product approval B: To receive approval for marketing, a sponsor must show that a new drug is safe[17] and effective.[18] To establish effectiveness, the sponsor must present "substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof."[19] "Substantial evidence" is: evidence consisting of adequate and well-controlled

investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

By its terms, § 505(d) of the FDCA permits FDA to find that data from one adequate and well-controlled clinical investigation and confirmatory evidence constitutes substantial evidence of effectiveness,[21] but FDA has typically only applied this provision where the lone study was statistically significant at a very high level or for products addressing orphan diseases, where more than one trial is not logistically feasible. In determining whether an investigation is adequate and well-controlled, FDA considers specific characteristics, including whether the study design permits a valid comparison between the investigational drug and the control to permit quantitative assessment of the drug's effect and whether the recruitment, allocation to treatment arms, observation of patients, and method of analysis permit inference, by, for example, limiting bias and assuring comparability.

A sponsor must also establish safety "for use under conditions prescribed, recommended, or suggested in the proposed labeling." Neither the statutes nor regulations governing marketing approval define safety. To assess safety, FDA uses a risk-benefit framework. This analysis weighs the benefits against the risks of approving a new compound and considers all of the evidence submitted regarding safety and efficacy, the type and severity of the condition the new compound addresses, other available therapies for that condition, and risk management tools that potentially could ensure the benefits outweigh the risks.

Clinical trials and phases of drug development C.

To develop the evidence necessary to satisfy the FDCA's safety and efficacy requirements, sponsors use a series of pre-clinical and three pre-marketing human clinical trial phases. Each phase builds on data from the prior phases and examines a different component of the drug's mechanisms, safety, and efficacy. While the three human clinical trial phases are theoretically distinct experiments, some modern investigations have blurred the lines between them or excluded components altogether. The process begins with preclinical research through *in vitro* (test tube) tests, tissue cell cultures, computer driven data analysis, and/or live animal models to obtain basic information about the new drug's toxicity, pharmacodynamics, and pharmacokinetics. If these studies appear sufficiently promising, the manufacturer files an Investigational New Drug (IND) Application to obtain an exemption from the FDCA's prohibition against shipping experimental drugs without FDA approval in interstate commerce and to allow FDA to assess the safety of the study.

After the submission of an IND, the investigator introduces the investigational drug to humans for the first time in Phase 1. These trials are small, typically composed of about twenty to eighty healthy individuals, and are not controlled. The investigator seeks to assess the safety (including significant short-term side-effects), toxicity, dosage range, and the pharmacokinetics of the investigational drug. Some studies may have an extension component, in which the optimal dose determined from a dose escalation series is tested without controls in a group of study participants.

For those investigational drugs that survive Phase 1, the investigator then generally conducts a randomized, controlled trial of 80 to 200 subjects who have the disease or condition the drug is intended to treat. Phase 2 trials provide more information on safety, and, by testing on patients with the disease or condition of interest, these trials present the first data on the efficacy of the investigational drug and any dose-response relationships. The success of Phase 2 relies on the adequacy of the design of Phase 1. For example, if Phase 1 provided inadequate information on dosage levels, Phase 2 may test the investigational drug "for activity at too low or [too] high a dose."

In the usual case, the safety and efficacy data from these two phases do not in themselves satisfy FDA's requirements of "adequate tests by all methods reasonably applicable to show whether or not such drug is safe" and of "substantial evidence" of efficacy, making Phase 3 trials necessary Phase 3 clinical trials are expanded controlled and uncontrolled studies. Phase 3 trials involve significantly more patients (on the order of hundreds to thousands of patients) and apply stricter exclusionary criteria to the patients who may enroll than Phase 2 trials. These trials provide more extensive data on safety and efficacy, including any side effects associated with long-term use, to enable FDA "to evaluate the overall benefit-risk relationship of the drug …

2. Methodology

Clinical trials were earlier conducted in accordance with the requirements set out in Schedule Y of the Drugs and Cosmetics Rules, 1945 (**D&C Rules**). However, there were concerns regarding patient safety and compensation provided to patients in cases of adverse effects suffered by them due to participation in clinical trials. In 2012, a Public Interest Litigation was filed by a patient-centric NGO before the Hon'ble Supreme Court of India, alleging malpractices in the conduct of clinical trials by government and non-governmental organisations, as well as by independent investigators. While hearing this matter,

regulatory aspects of clinical trials were discussed by the Court. In an order dated October 21, 2013, the Hon'ble Supreme Court opined that approvals for clinical trials should be based on all relevant aspects of safety and efficacy, particularly in terms of assessment of risk versus benefit to the patients, innovation vis-a-vis existing therapeutic options and unmet medical need in the country.

In 2013, certain amendments were made to the D&C Rules, to regulate the clinical trials conducted in India. Rule-122DAB was inserted into the D&C Rules, *vide* the Drugs and Cosmetics (First Amendment) Rules, 2013. This Rule, *inter alia,* provided for compensation to an affected clinical trial subject in case of injury or death during a clinical trial. The clinical trial subject was made eligible for financial compensation over and above free medical management. The quantum of compensation was to be determined by the Licensing Authority[16-20].

Rule-122DAC was inserted into the D&C Rules, *vide* the Drugs and Cosmetics (Second Amendment) Rules, 2013, which lists out the conditions for the conduct of clinical trials. These conditions include, *inter alia,* the requirement to comply with Schedule Y of the D&C Rules, obtaining approval of an Ethics Committee, registration of the trial with the Clinical Trials Registry of India, submission of reports of serious adverse events, etc. Further, the guidelines in relation to composition and registration of ethics committees were notified *vide* the Drugs and Cosmetics (Third Amendment) Rules, 2013.

3. Results and Discussion

Approval Process of Oncology Drugs in USA

The US Food and Drug Administration (FDA) approves cancer drugs based on (1) overall survival (OS) or patient reported outcomes, (2) progression-free survival, ie, the time until cancer recurs or worsens, or (3) response rate (RR), ie, the percent of patients experiencing tumor shrinkage.[1,2] Response rate and complete response rate are typically ascertained in uncontrolled, nonrandomized studies. Because these trials have no comparator arm, drug-related adverse events may be missed among symptomatic patients because they may be mistakenly attributed to their underlying cancer. There is also uncertainty about whether and to what degree these drugs improve survival or quality of life.

The FDA has noted that a high RR in early phase trials justifies granting expedited approval. The agency has stated, "for drugs demonstrating unprecedented activity in early clinical development in cancers with few effective options, the ability to randomly allocate patients to either an agent with markedly improved durable response rates or to a toxic and marginally effective comparator may not be feasible because equipoise may not exist."[4] The FDA has used response rate to justify both accelerated and regular (traditional) approval. The accelerated approval program is often based on response rate and duration of response in a single-arm study. For accelerated approval, the FDA generally mandates post marketing efficacy requirements be fulfilled by subsequent randomized clinical trials in the same treatment setting or in an earlier disease course setting, but the agency has also accepted larger single-arm studies using RR. This is different from the regular approval pathway where post marketing commitments generally only address drug-drug interactions, dosing based on hepatic and renal impairment, short-term and long-term drug safety, and efficacy in special or subgroup populations, and not further evidence of general efficacy. The European Medicines Agency (EMA) echoes a similar perspective that "outstanding activity from a new drug in early development in high unmet need situations with no therapeutic alternatives might obviate the need for the large confirmatory trials. There is no specific definition of "unprecedented" or "outstanding," and this determination is made at the discretion of the agency. Adding to the complexity, although regular approvals do not typically require further demonstration of efficacy, accelerated approvals may be converted to regular approvals based solely on impact on a surrogate end point.

Drug Approval Process in Canada

Few medical fields have seen as many therapeutic advances in recent years as oncology. As the development of new pharmaceuticals continues to accelerate, it falls to government regulatory bodies to adjudicate the treatments to approve and to health technology agencies to determine the treatments to recommend for public reimbursement. Regulatory and funding bodies operate under the dual tensions of providing expedient access to novel treatments for life-threatening conditions and of ensuring patient safety and equitable resource allocation[1]. Thus, critical review of the drug reimbursement and approval process is of great economic and social importance.

Drug approval in Canada is undertaken by Health Canada (HC) in a review process that accounts for safety and efficacy data from preclinical and clinical trials. Successful drugs are issued a notice of compliance (NOC) that authorizes the pharmaceutical company to market the drug. On occasion, HC instead issues a notice of compliance with conditions (NOC/c), which stipulates that the developer will undertake further studies to confirm benefit; however, those stipulations are not legally binding and do not affect market access[3]. The process is analogous to the "accelerated approval" designation granted by the U.S. Food and Drug Administration[4]. In Canada, the NOC/c policy gives earlier market access to drugs for "serious, life-threatening or severely debilitating diseases," particularly when few treatments are available for such diseases or when the drug demonstrates potential for significant

improvement over existing treatment options. Cancer drugs are frequently eligible for these expedited conditional authorizations. Upon review by HC, the NOC/c conditions can subsequently be removed if early efficacy data are borne out in further trials.

Once a cancer drug has obtained federal market authorization, each province must independently decide whether to provide public reimbursement for its use. In 2010, the pan-Canadian Oncology Drug Review (pCODR) was established by provincial ministries of health to assess cancer drugs and guide funding decisions[6]. The pCODR process is independent from the Common Drug Review, which assesses all other classes of medications[7]. The pCODR expert review committee (pERC) evaluates clinical evidence, economic evidence, patient values, and adoption feasibility to generate a reimbursement recommendation that can then be used to guide provincial decision-making for all provinces except Quebec. The committee comprises medical oncologists, pharmacists, economists, an ethicist, and patient representatives. The final pERC decision can be to recommend reimbursement, to deny reimbursement, or to consider reimbursement once certain conditions have been met. With assistance from pCODR, funding decisions can be made in a way that is transparent, expert-guided, and timely. In addition, pCODR acts to reduce duplication of the review process and improve standardization between provinces. In 2014, pCODR was incorporated into the Canadian Agency for Drugs and Technologies in Health[8].

A NOC/c issued by HC expedites the progress from market authorization to funding recommendation, which is appealing to patients, providers, and manufacturers. Moreover, pCODR is able to review drugs for funding in parallel with the HC process. However, prior studies of the NOC/c approval process have raised concerns that efforts by HC to expedite access are not routinely followed by critical reappraisal or enforcement of listed conditions′

Drug Approval Process in Europe

Market authorization of new therapies granted by regulatory agencies require evidence of safety and therapeutic efficacy based on adequate and well controlled studies. The 2 largest global regulators are the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA).[1] As such, they frequently set industry standards and guidance, routinely followed by other national regulatory agencies.

The past decade has witnessed a record number of new oncology therapy approvals, including many first-in-class or breakthrough therapies, requiring timely review and authorization from regulatory agencies to provide prompt access to patients in need.[3-5] Over this same period, new review pathways have been developed by both the FDA (Breakthrough Designation) and EMA (Priority Medicines; PRIME) to enhance support for the development and review of medicines to treat serious conditions. Furthermore, expedited approval pathways (accelerated approval by the FDA and conditional marketing authorization by the EMA) have also been used to address many areas of unmet need within oncology. These approvals are made with less comprehensive clinical data but with the expectation for further data before granting regular approval.

The activities of the FDA and EMA are frequently compared, particularly in reference to approval times for new therapy and device registrations.[1,7-9] Despite differences in approval processes, prior studies have shown a close alignment between FDA and EMA in more than 90% of new therapy registrations across all therapeutic areas.[1] However, no recent comparisons of the regulatory activities of the FDA and EMA in the approval of new oncology therapies have been conducted.

Drug Approval Process in Australia

Registration and funding of new cancer medicines in Australia: Despite a high incidence of cancer, Australia has one of the lowest rates of cancer mortality in the developed world. These positive outcomes are likely due to the implementation of national cancer screening programmes, access to high quality health care services, and universal public financing of effective cancer medicines through the Pharmaceutical Benefits Scheme (PBS). Consistent with the first objective of the National Medicines Policy, the PBS aims to provide '*timely access to the medicines that Australians need, at a cost individuals and the community can afford*'. In 2013-2014, the Australian government spent AUD$1.5 billion on cancer medicines. This represented one third of the total cost of cancer care and 16 % of total PBS expenditure [6]. Patients have access to these medicines for free in hospitals, or pay a modest co-payment as out-patients ($36.90 for general and $6.00 for concessional beneficiaries for a full-course of chemotherapy treatment).

Although Australia's invests substantially in cancer medicines, a number of studies have demonstrated either lack of regulatory approval, or delayed approval, of new cancer medicines in Australia compared to similar countries. However, the delay in regulatory approval in Australia has mostly been explained by a delay in pharmaceutical companies' applications for registration, which were submitted on average 38 weeks later than applications to the US Food and Drugs Administration (FDA) and the European Medicines Agency (EMA). Another possible contributing factor is that, unlike the FDA and EMA, Australia's Therapeutic Goods Administration (TGA) does not currently have the capacity to undertake expedited approvals for medicines [9]. In the US, expedited review leads to approvals on average 3.5 months earlier than standard review, but there are serious problems with

the FDA's ability to track and report on post-approval safety following expedited review. Thus the trade-off in expedited review of less complete pre-approval data but more extensive post-market evaluation has failed to fully live up to expectations.

Challenges associated with access to cancer medicines in Australia Uncertain and limited benefits of cancer medicines

While the same type of evidentiary standards are applied to the registration and funding of cancer and non-cancer medicines, regulators and payers face particular challenges when it comes to evaluating many cancer medicines. This is largely because the quality of clinical trial evidence on cancer medicines is generally lower than for other therapeutic classes. A retrospective analysis of submissions for cancer medicines considered by the PBAC between 2005 and 2012 found that on average, half of major submissions had significant problems with supporting clinical evidence. Although some new cancer medicines provide important therapeutic benefits, many new cancer medicines, especially those marketed for advanced cancers, fail to lead to gains in survival or lead to only minimal gains over standard care and are sometimes associated with greater toxicity. This makes it very difficult to demonstrate their "value" relative to alternatives.

High prices of cancer medicines

Despite the uncertain evidence of benefit for many new cancer medicines, prices of cancer medicines have grown dramatically in all countries over the past 15 years. In Australia, expenditure on chemotherapy has been increasing faster than any other area of health care, with an average annual growth rate of 63 % from 2009-10 to 2013-14.

Strategies for improving access to cancer medicines

Australia's medicines regulation and funding processes are constantly being reviewed and revised in an effort to improve access to safe, effective and cost-effective medicines. In 2014-2015, two national reviews examined policy options for improving medicines regulatory and funding processes in Australia: the Expert Review of Medicines and Medical Devices Regulation and the Australian Senate's inquiry on '*Availability of new, innovative and specialist cancer drugs in Australia*. We believe that three issues have emerged as being particularly important, both in reviews and in other contexts: 1) the need to streamline regulatory and funding processes, 2) the need for greater consumer involvement in decision-making and 3) the need to address the problem of high cancer drug prices.

Streamlining regulatory and funding processes

A number of steps have recently been taken in Australia to shorten the approval-funding-listing cycle by streamlining administrative procedures. Since January 2011, parallel TGA and PBAC processes have been introduced, thus reducing the time lag between marketing authorization and funding approval. A single entry point has also been established for speeding applications of medicines with a 'co-dependent' diagnostic technology (such as a genetic test for a 'targeted therapy'). The two reviews mentioned above also put forward a number of new recommendations to enhance administrative processes. For example, they recommended that Australia should make better use of assessments conducted by comparable overseas regulators, and should expedite assessments in certain circumstances which are yet to be defined.

Another innovative funding pathway that is gaining increasing prominence in Australia and globally is the development of managed entry agreements (MEA). Most MEAs to date in Australia have been financial agreements that involve price or volume rebates, or agreements that link the continuation of funding to evidence of benefit documented at the individual patient level. Managed access programs have been more recently introduced in which continuation of funding is conditional on the subsequent provision of favourable scientific evidence of population-level efficacy. In most cases, the manufacturer would be expected to pay a rebate to the Government should these medicines fail to deliver on their claimed benefits. A few medicines, including four cancer medicines (pilimumab, prembrolizumab and trametinib for advanced melanoma and crizotinib for non-small cell lung cancer), have been recently listed on the PBS as part of managed access programs. However, concerns have been raised about the implementation of these programs in other countries including the quality of the methodology of studies undertaken in 'real world' settings, as well as the governance and funding of these programs. It is as yet unclear whether these programs contribute meaningfully to the evaluation of the therapeutic effects of new medicines. Detailed information on MEAs is not publicly available and this lack of transparency is a major drawback because it precludes public understanding of the ways in which decisions about initial and continued funding are made. Furthermore, potential cessation of funding of medicines which are part of MEAs requires ongoing good communication for these decisions to be understood and accepted by the public.

Increasing consumer engagement in decision-making

The Australian Senate Committee recommended expanding the role of consumers and clinicians in PBAC assessment processes, with the objective of better aligning PBAC's decisions with stakeholders' preferences. Increased levels of public and patient involvement in decision-making processes may take several forms including higher number of consumer representatives on decision-making committees, or more robust processes of public consultation. These process are important in contexts where values are likely to conflict. However, they also raise two important issues that need to be addressed if public input is to contribute meaningfully to decision-making. The first is how to manage conflicts of interest, as some patient

organisations rely on funding from pharmaceutical companies. Such funding can compromise an organisation's independence and its ability to solely represent cancer patients' interests, particularly when PBAC is considering funding of a sponsor's drug. The second issue is effective management of power imbalances, so that consumers are able to be heard and ultimately contribute to decisions.

Transparency is also important because, although PBAC decisions are not based on a strict utilitarian rationality with a fixed funding threshold, they are often assumed to be so. These assumptions—although incorrect—are able to persist in part because the rationale and the value judgements involved in PBAC decisions are not adequately communicated to the public and patients. This, in turn, is because most of the documentation submitted to the PBAC by the manufacturers and generated during the evaluation process is considered to be commercially confidential, and cannot be released publicly. While Public Summary Documents (PSD), which summarize the evidence basis and the reasons supporting the PBAC decisions have been posted on the Australian Government's website since 2005, PSDs are highly technical and may be difficult for consumers to understand. Furthermore, sensitive information such as Incremental Cost Effectiveness Ratio, financial implications, proposed prices and details of proposed risk-share arrangements are redacted, and PSDs are released only several months after the PBAC decision has been made[21-22].

Although the Australian Senate committee report noted the high cost of cancer medicines, it did not comment on the significant role of pharmaceutical companies in delaying funding decisions by making exaggerated initial price demands to secure the highest prices possible for their products. We believe that this was a significant omission in the report and its recommendations, given that independent experts around the world are now warning that high priced medicines are a major threat to the sustainability of pharmaceutical insurance schemes.

Drug Approval Process in India

Anticancer medicine market: The growing cancer patient population has created the need for anticancer medications. There's a need to make currently available medicines affordable as also increase research in potential novel therapies. This growing market base has raised the interest in further investment in the pharmaceutical sector. Currently, the pharmaceutical industry presence in the Indian market is dominated by generics. However, recognising the need for innovation and drug development, government agencies such as the Department of Science and Technology (DST) and the pharmaceutical sector on R&D have chipped in.

For instance, in the year 2005-2006, 407 patent applications were filed and 276 were approved in India2 . R&D funding as a per cent of sales has increased from 2% to 10% in recent years. DST's Drug and Pharma Research Programme is mandated to facilitate drug discovery in academia and the pharmaceutical sector. It is currently funding over 110 research projects within major academic and industrial R&D centres.

CSIR's New Millennium Indian Technology Leadership Initiative (NMITLI) programme is funding 11 R&D projects specifically relating to drug development. The first investigational new drug application (IND) in India for an herbal-based formulation was filed under a collaborative program funded by NMITLI between industry and the National Institute for Pharmaceutical Education & Research.

4. Conclusion

The drug approval process to be composed mainly in the two steps, application to conduct clinical trial and application to the regulatory authority for marketing authorization of drug. The new drug approval process of different countries is similar in some of the aspects where as it differs in some aspects[23-25]. In most of the counties, sponsor firstly files an application to conduct clinical trial, and only after the approval by the regulatory authority, the applicant conducts the clinical studies and further submits an application to the regulatory authority for marketing authorization of drug. In all countries, information submitted to regulatory authorities regarding the quality, safety and efficacy of drug is same; however, the time, fees and review process of clinical trials and marketing authorization application different. For the purpose of harmonization, the International Conference on Harmonization (ICH) has taken major steps for recommendations in the uniform interpretation and application of technical guidelines and requirements. Through The International Conference on Harmonization (ICH) process, the Common Technical Document (CTD) guidance has been developed for Japan, European Union, and United States.

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