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Review Article

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A Comparison of the Drug Approval Process in the United States and Canada

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Abstract

The drug approval process is comparative between the United States and Canada. Without the drug approval process, consumers would be experiencing severe health consequences, therefore, the approval process is expensive, time-consuming, and lengthy for pharmaceutical companies to ensure the compound is safe and effective for its intended use.

The electronic databases utilized to recognize applicable published articles from Embase/Ovid and PubMed. The keywords utilized to recognize the pertinent articles were the following: Drug Approval, Drug Development, Food and Drug Administration, United States, Canada, and Pharmaceuticals. The research articles excluded were: non-drug, including vaccines approval process, international regulatory organizations, articles that weren't relevant to the study, and articles that are not in English language. There was no limit on the date the articles were published.

There are more similarities than differences in the drug approval process between Canada and the United States. Both countries contain a regulatory organization (Health Canada; FDA) that review and approve novel drugs to ensure safety and efficacy prior to marketing. Pharmaceutical companies must submit an IND application prior to the inception of clinical trials in humans. Drug approval by FDA is similar to Health Canada, where they develop guidance recommendations to assist pharma companies in complying with regulations.

The majority of the published articles focus on the comparison of the drug approval process between the United States and other countries, little-to-no articles discussed the advantages/disadvantages of the drug approval process and how the length of the approval process effects patient population.

Keywords: Drug Approval, FDA Approval, US Food and Drug Administration, Health Canada, Drug Development Process, Investigational New Drug, Regulatory Approval, Drug Development.

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1. Introduction

When a pharmaceutical company attempts to market a novel drug to consumers; drug company experiences increased financial risk and an extensive process where it is most common to confront failure than successes. After evaluating the thousands of compounds' pharmacology, animal pharmacokinetic, and safety studies, determining and selecting the single compound can take years to complete. The drug approval process is the most critical throughout drug development; the research process is an essential initial step for drug approval.

The published research has been mostly focused on the drug approval process outcomes, contrasting drug approvals in different countries. There are several studies that discussed drug approval times, usually discussing the difficulty of drug approval and marketing. (1-3) other countries such as United States and Canada were able to acquire the drug approval times and report the total time duration for drug approval. (4-6) For every delay in the drug approval process by the Food and Drug Administration (FDA), the pharma company loses approximately $1.3 million US dollars. (7) The assumption is that by improving the drug approval process, then that is a requirement to improve the fact that safe and effective drugs will be marketed faster, which is fulfilling the outcome in a timely manner.

The drug approval process is when the drug's efficacy and safety are reviewed by the regulatory agency, such as Health Canada or US Food and Drug Administration (FDA). (8) The investigational drug is evaluated whether its benefits outweigh its unintended risks for the target population. (8) The drug approval is a structured process and it is step-by-step where the drug company completes

requirements set by the regulatory organization in their country. Both United States and Canada claim indistinguishable purpose of the drug approval process, (9) which is ensuring that the approved drug is both safe and effective for public health. Without the lengthy pharmaceutical approval process, consumers would be experiencing severe health consequences, therefore, the approval process is in place to protect consumers' health.

Since the importance of the drug approval process is similar between United States and Canada (ensuring safety and effectiveness), this review paper discusses the comparison in the drug approval process in the United States and Canada. The drug approval process varies from each country; however, the United States and Canada can be compared since there are several similarities in the drug approval process. The drug approval process is expensive, time-consuming, and lengthy for the pharmaceutical companies. The United States and Canada are countries that utilize similar drug approval regulations and policies.

The electronic databases utilized to recognize applicable published articles from Embase/Ovid and PubMed. The keywords utilized to recognize the pertinent articles were the following: Drug Approval, Drug Development, Food and Drug Administration, United States, Canada, and Pharmaceuticals. Other websites utilized to identify applicable articles is the US Food and Drug Administration, Health Canada, and ClinRegs; National Institute of Allergy and Infectious Diseases (NIAID). The research articles excluded were the following: non-drug approval process (including vaccine approval process), international regulatory organizations, articles that weren't relevant to the study, and articles that are not in the English language. There was no limit on the dates the articles were published.

2. United States Drug Approval Process

2.1 The Development of Novel Medications

The Food and Drug Administration (FDA) is the regulatory body that regulates the review and approval process of pharmaceutical products in the United States. The FDA is responsible for regulating and permitting clinical trials utilizing an investigational medicinal or biological agent in humans according to the regulatory requirements. (10) The Center for Drug Evaluation and Research (CDER) with the FDA conduct essential tasks to ensure the safety and efficacy of drugs while enhancing the public health of the US population. (11) CDER is responsible for regulating prescription and over the counter medications, which include generic and biological medications. (8) In the US, pharmaceutical companies must investigate the novel drug prior to selling and marketing the product to the public. Through clinical trials and evaluation of results, the pharmaceutical company will forward the results to illustrate that the novel medicinal compound is both safe and effective for its intended use. (12) Shown in figure 1 is the summary of the drug approval process by the US FDA.

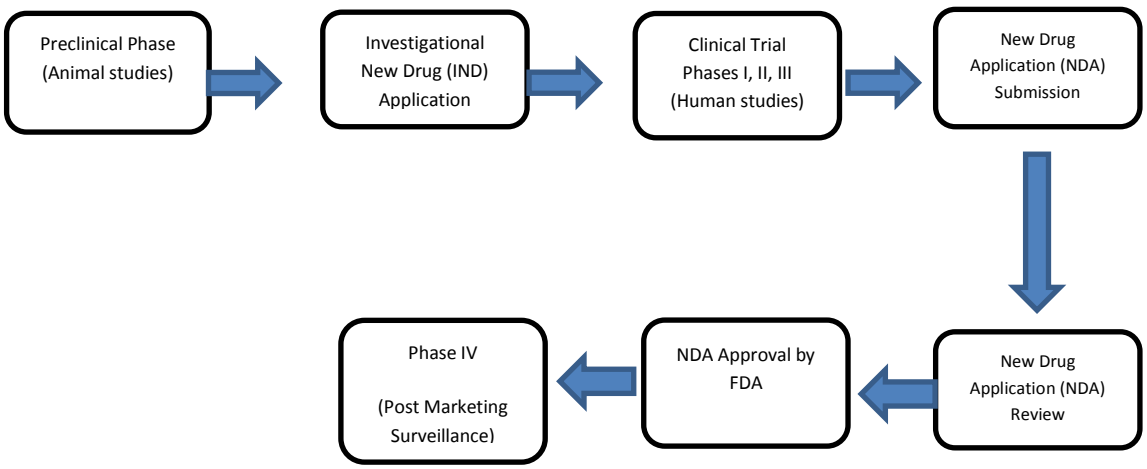

Figure 1. A Summary of the United States FDA drug approval process

2.2 The Pre-Clinical Phase

Every novel drug must be tested on animals to evaluate and determine its toxicities. (12-13) Through testing on animals in the preclinical phase, investigators collect information regarding the safety and efficacy of the pharmaceutical compound being researched. (13) In addition to determining the safety and efficacy of the novel compound, the main purpose of the preclinical phase is determining the biochemical activity of the novel medication through animal testing. (13) Additionally, toxicology research is conducted through animal testing and is conducted for years. The preclinical phase is initiated one to two years prior to the conduction of clinical studies. FDA requirements for the preclinical phase involves establishing a profile for the innovative drug, recognizing the drug's toxicity through animals, determining acute toxicities (two to three months) according to drug's intended use. (14)

2.3 Investigational New Drug Application - IND

The IND application is a requirement from the FDA prior to conducting testing on humans. (14) The FDA receives an IND application from the drug sponsor which includes the drug's initial testing (preclinical

phase), the medication's composition, and suggestion for testing the novel drug on human subjects. (14-15) The IND application also includes all previous clinical research, expected health benefits, the medication's safety data, drug's pharmacology and medicinal structure, adverse effects determined from animal clinical trials, and illustrate that human participants will not be subjected to unexpected harm in future clinical studies. (14-15) The FDA may also request an investigational drug sample during the IND process. (15) In situations where the pharma company do not receive a timely response from the FDA within thirty days from the date of submission, the sponsor may conduct the clinical trial since the FDA approval during this phase is not required. (15)

2.4 Clinical Study Initiation

The pharma company sponsor must submit a clinical study development plan preceding the conduction of clinical trials on humans. (16) The development plan is thorough and detailed describing all steps of the clinical trial process; phase I (administering drug in human subjects) until phase IV (post marketing surveillance). (16-17) The FDA provides recommendations for instructions on how to propose and evaluate data in a post-marketing study and guidelines for the various drug classes. (16) The clinical study may include thousands of subjects and multiple clinical sites. Therefore, an appropriate study design is necessary for the study to be successful and for proper conduction of the study in a timely manner. (15-16) To initiate a successful study, sponsors select proper sites for each clinical trial. (16-17) Clinical trials are conducted by physicians in practice in a research based or academic hospital. Requirements include an experienced primary investigator, access appropriate subject population, and the ability to conduct laboratory research. (17)

Clinical trial design and plan for conducting a study requires to be approved and reviewed by an ethical review committee, Institutional Review Board (IRB). Each individual study has a different IRB committee. The IRB includes members who are scientists, physicians, community members, and clergy that ensure patient safety. The FDA advisory committee members include statisticians, nurses, physicians, pharmacologists who collaborate on developing recommendations. Prior to the initiation of human subject testing, the FDA must approve the IRB. The FDA reviews the submitted data through Safety Monitoring Board and provide recommendations for continuing or adjusting the study. (17)

2.5 Clinical Trial Phases

The clinical research phases are separated into four phases. Phase I is the evaluation of the investigational drug in human subjects, mainly administered in healthy subjects. Phase I clinical trials are conducted for a short-term and consist of a small number of subjects (twenty to eighty). (18) The purpose of phase I is to evaluate the drug's safety, including the appropriate dosage range. (19) Phase II studies are larger than phase I, more thorough and its purpose is to evaluate the drug's efficacy in the subjects with the intended disease. Phase II studies include hundreds of subjects over several years. (18) The drug sponsors spend approximately $20 million to $40 million US dollars. (5,18) Phase II clinical trials evaluate drug's therapeutic effectiveness (including dose, administration frequency) and safety. (19) Phase III clinical trials examine the investigational drug in large numbers of subjects to illustrate safety and efficacy. (18) This is the most expensive, the longest and most comprehensive process since it includes thousands of subjects, and sponsors spend three years to complete this phase. Phase IV of clinical research is post marketing surveillance where the FDA gathers information such as adverse effects, safety and efficacy profile of the drug. (19) The US clinical trial three phases are summarized in Table 1.

Table 1. *Summary of the three clinical trial phases in the Drug Approval Process (The United States).*

Phase I	Phase II	Phase III
Small studies; examine drug's safety profile, i.e. dosage range	Large studies; examine drug's efficacy in target disease	Longest studies; confirm efficacy and determine adverse effects

2.6 New Drug Application - NDA

The New Drug Application is the process of approving a novel drug in the US. Pharmaceutical companies are not permitted to market the novel compound to the public unless it has been proved to be safe, effective, and approved by the FDA. (20-21) An FDA approval is based on the proposed and submitted NDA by the pharmaceutical company (sponsor). (19-20) After the completion of phase I, II, and III clinical trials, the pharma company submit the completed NDA to the FDA for review. The FDA responds to the NDA within twelve months from the date of submission. (20-21) The NDA is comprehensive and includes information such as safety, quality, efficacy of the drug, dosage and length of therapy, symptoms and adverse effects experienced by subjects, etc. (19-21)

2.7 FDA Approval

Usually, the FDA doesn't provide a clear response, the FDA doesn't always approve the novel drug. The FDA regularly inquires and requests additional study data, ask the pharma company to provide information relating to the stated drug labeling. (22) Consumers and healthcare providers utilize the drug label to gain an insight on the drug product; therefore, pharma companies promote and advertise the drug product through product labeling. (22) The purpose of the FDA's MedWatch program is for reporting adverse effects to the FDA by healthcare professionals. (22-23) The Spontaneous Reporting System (SRS) receives adverse effect reports from health care providers and hospitals. (23) The SRS can be sent straight to the FDA (through the MedWatch program), or directly to the drug sponsor, then sent to the FDA directly by the pharma company

according to regulations. (23) Pharma companies and the FDA formally coordinate to facilitate drug review and novel drug development. (22-23)

3. Canada's Drug Approval Process

3.1 The Development of Novel Medications

In Canada, the regulatory body that regulates the review and approval process of pharmaceutical products is Health Canada via Health Protection Bureau (HPB). (9,24) Health Canada develops regulations and policies for the safety and quality of pharmaceuticals in Canada. (24) The Food and Drugs Act establishes regulations for marketing drug products in Canada. (9,24) Its purpose is to ensure the safety and protection of Canadians by regulating the marketing of drugs, cosmetics, foods, and medical devices. (24) Shown in figure 2 is the summary of the drug approval process by Health Protection Bureau (HPB) within Health Canada.

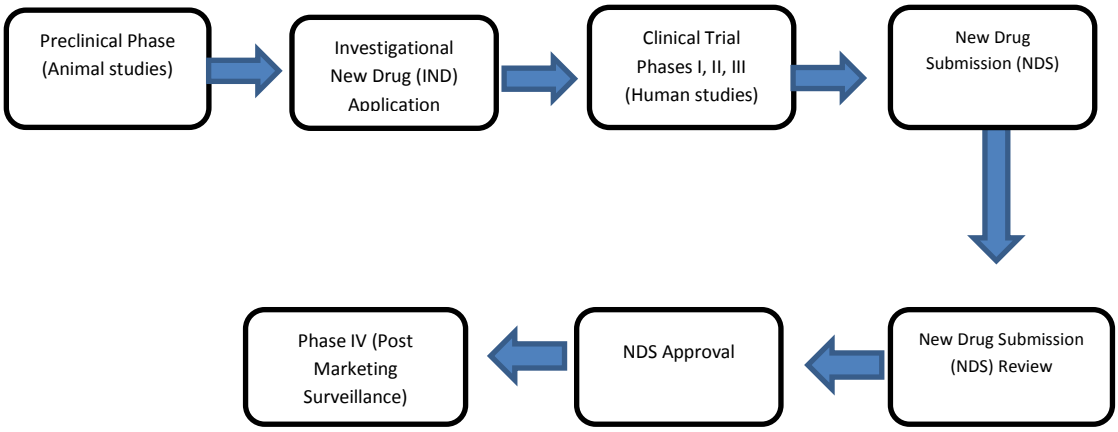

Figure 2. Summary of the drug approval process by Health Protection Bureau (HPB), Health Canada

3.2 The Pre-Clinical Phase

One of the requirements of HPB is to submit data relating to non-human subjects prior to any novel drug begin testing in human subjects. The results are according to in vivo on animals and in vitro, information received in previous studies conducted in Canada for a distinct indication. The toxicology test results from the studies are usually requested by the HPB. (25)

3.3 Investigational New Drug Application - IND

Prior to the initiation of clinical trials, an IND application must be submitted by pharma company. The sponsor must submit to the HPB with the drug development plan, the purpose of the designed clinical trial, clinical trial design, drug's chemical and manufacturer's information, and study's protocol. (26-27) This is information that must be submitted prior to the formal IND is completed and submitted. The clinical trials may be initiated when the submitted IND shows that the drug is safe for the public and that the clinical trial design won't present risk or harm to subjects. (27)

3.4 Clinical Trial Phases

The pharma company reports serious and all-other adverse effects to the Ministry of National Health and Welfare. Post-marketing studies are less controlled and are usually larger than phases I, II, III. Post-marketing studies are essential where drug sponsors acquire information of the novel drug. (25-26) The post marketing process is described as passive surveillance since the majority (more than half) of adverse reports are from providers. Results from clinical trials not conducted in Canada are acceptable by HPB. In Canada, the clinical trials three phases are the following (Table 2): phase I is for investigating information relating to the drug's safety and the drug's pharmacology. Phase II trials is for investigating information relating to drug's safety and efficacy. Phase III trials is for expanding and verifying previously gathered data relating to the drug's safety, efficacy and collect new information on the safe dosage range in humans. (26)

Table 2. Summary of the three clinical trial phases in the drug approval process (Canada)

Phase I	Phase II	Phase III
Information on Drug's safety and clinical pharmacology	Information on drug's safety and efficacy	Expand previous information on safety and efficacy; gather dosage information

3.5 New Drug Submission - NDS

The drug sponsor provides the NDS after the completion of clinical study. Through NDS, the HPB is provided with information in order for marketing the novel drug in Canada. HPB provide the Notice of Compliance if the NDS is accepted, which is valid indefinitely for the marketing of the novel drug in Canada. (28) If HPB determined that the Food and Drug Act and its regulations are unmet, the notice could be suspended, therefore notice of compliance is prone to yearly review. (27-28)

3.6 Additional Considerations – Canada's Drug Approval Process

There are further considerations relating to the Canadian drug approval process. According to the Canadian Health Act, prescription medications are not charged for outpatient or inpatients if the medication was administered in the hospital setting. Patients living in nursing or in their homes are excluded from the Act. Each territory or province must establish a plan to provide medications for residents in nursing or living at home. Originally, the programs were mainly on residents who weren't eligible for health insurance benefits or who weren't able to afford coverage. (29) Therefore, regulations from the provinces/territories adjusted access to governmental drug programs, benefits of drug, and coverage differences among territories and provinces. The adjustment in these programs resulted in pharma companies to submit the medication for review and approval. (29-30) In 1995, provinces collaborated with Health Canada to enhance and simplify the drug approval process. To streamline the approval process, Health Canada approved to monitor formulation and manufacturing processes and to declare bioequivalence among generic and reference drugs. (30)

External advisory committees are provided by Canada's government in order to enhance the review process. These committees are utilized by the government to provide expert recommendations regarding the interchangeability of drugs and recommendations regarding drug related issues. (30) Some provinces utilize one committee for all roles, whereas other provinces utilize variation in committees. (29-30) Pharmacists and medical doctors are the majority of the expert committee members. Additional committee members include clinical evaluations, pharmacologists, and economists. The economists provide pharmacokinetics examination, interchangeability conflicts, and pharmacoeconomic interpretation. (30)

4. Similarities in the Drug Approval Process between United States and Canada

The drug approval process is comparable (similarities and differences) among the United States and Canada. Table 3 shows the differences between Health Canada and the US FDA in the drug approval process. The similarities in the drug approval process among both countries is that pharma companies must submit an IND, investigational new drug application prior to the initiation of clinical research in humans. (14-15) Health Canada, similar to the US FDA, provide silent approval. (24) In situations where approval is unrejected by the Drugs Directorate (DD) within HPB, the pharma company may initiate clinical trial research. In situations where the IND is rejected by the DD, they are responsible for providing the sponsor with the reasons of the rejection. (24) Additionally, clinical trials are similar in both countries. Phase I, II, and III clinical trials testing oncology or HIV medications do not require the enrollment of healthy subjects or conducting double blind study. Phase IV in both countries are initiated after the approval of the drug and is available for the public. Canadian pharma companies conduct their studies according to the FDA's requirements, so both countries will accept the gathered data. (29-30) Similar to the US FDA, if HPB determines that the data requires clarification, they will collaborate with the manufacturer to resolve the issues. (30)

The regulation of drug approval by the US FDA is similar to Health Canada, where the FDA develops guideline recommendations and instructions to assist pharma companies in complying with the established regulations. (10,14) Generally, the process is originated with the pre-clinical trials, submission of the IND, investigational new drug application. (14,15) The approval of an IND application permits sponsors to proceed with distribution of products throughout the country to utilize in clinical trials. After the completion of clinical trials, sponsors submit the NDA (new drug application) or NDS (new drug submission), which is either approved, denied, or sent to the sponsor for inquiring about additional information. (27-28)

Similar to risk evaluation and mitigation strategy (REMS) with the US FDA, risk management in Canada is also for medications who have increased risk or unknown risk associated with its use, any medication on the market associated with recent safety concerns, and drugs that haven't been previously marketed. (31) Shown in table 4 are the similarities between Health Canada and the US FDA in the drug approval process.

Table 3. The differences in the drug approval process between Health Canada and the US FDA

Differences in Drug Approval Process	United States (Food and Drug Administration)	Canada (Health Canada)
Development/Regulations of Drugs	Food and Drug Administration (FDA); CDER	Health Canada (Health Protection Bureau)
Clinical Trial Phases I – III	Phase I: Small studies; examine drug's safety profile, i.e. dosage range Phase II: Large studies; examine drug's efficacy in target disease Phase III: Longest studies; confirm efficacy and adverse effects	Phase I: drug's safety & clinical pharmacology Phase II: drug's safety and efficacy Phase III: safety and efficacy; dosage information
Type of submitted application after clinical trial	New Drug Application (NDA)	New Drug Submission (NDS)
Reporting Adverse Effects	FDA MedWatch Program; Spontaneous Reporting System (SRS)	Ministry of National Health and Welfare

Table 4. Similarities between Health Canada and the US FDA in the drug approval process

Similarities in the drug approval process between United States and Canada
• Similar purpose is to protect public health by ensuring that approved drugs are safe and effective • Submit IND application prior to the initiation of clinical trials in humans • Phase I-III clinical trials testing oncology/HIV drugs don't require the enrollment of healthy subjects • Phase IV is initiated after the approval of the drug • Clinical trials are conducted and approved according to FDA's requirements • If data requires clarification, FDA or HPB will collaborate with drug company to resolve issues • Generally, similar drug approval process: • Preclinical → IND submission → approval of IND → distribute drugs to start clinical trial → NDA/NDS → approval/denied/sent back to sponsor → post marketing • Risk management plan = REMS

5. Discussion

The US drug approval process has progressed from where the drug can be marketed unless the FDA can prove that the drug causes increased risk/harm or ineffective into approval is required for each step from testing, marketing and promoting the drug. (32) The FDA drug approval process is both long and costly; pharma companies spend approximately $300 million to $600 million US dollars to develop and bring a novel medication into the market and it takes 10-15 years on average. (33-34) It is a selective process where only one compound in five thousand proceed on to human testing from the preclinical phase; only twenty percent of drugs are commercially marketed from the clinical trial phases. (35)

The tests conducted in the preclinical phase are the final doorway to clinical trials in humans. (36) The IND application is thorough and comprehensive where it contains the information gathered from the drug during the preclinical phase and it is where the pharma company collaborates with the FDA. (36-37) During the clinical study initiation, it is essential to strictly comply with the study's protocol and the development plan in order to submit accurate data with the regulatory applications. (37) Since there are somewhat a small number of novel drugs where an IND is submitted reach the NDA stage, the majority of pharma companies connect with the FDA in order to review both safety and efficacy data from phases I and II clinical trials. (36-37) Phases I, II, and III clinical research may be adjusted according to medical conditions, such as oncology or HIV. (37) That is because medications indicated for these medical conditions (oncology or HIV) result in significant adverse effects. Therefore, based on this condition, an informed consent from healthy volunteers are impossible to acquire and double blind trials are not possible to conduct or ethical. (38)

Not too far from now, the FDA spent about two to five years to approve a novel compound, therefore, pharma companies had to wait for long. (38) The production of Prescription Drug User Fee Act (PDUFA) of 1992 enhanced the number of employees within the FDA and improved the drug approval process. (38-39) This is an improvement in the approval process and is considered successful. FDA critics also acknowledged that the time spent from clinical trial phase to the final drug approval has been greatly enhanced. (39) Patients with more acute medical conditions, there are strategies that make drug approval readily available such as adjusting clinical trial protocols and designs, treatment IND, and formal coordination with the FDA and pharma company. (39-40) Treatment IND promote the availability of the novel drug as soon as possible in patients with life-threatening or serious conditions. In Canada, the external advisory committees' roles have increased economic focus on the cost effectiveness of the drug compared to analyzing the medicinal effectiveness of the novel drug. (40)

There are several similarities in the drug approval process between Canada and the United States. Both countries recognize the necessity for an effective drug approval process. (40) There are also differences between the US and Canada, one example is the time duration for drug approval. (39-40) In the US, it takes two to five years and in Canada, there is no time frame since it depends on the province/territory, however, in Canada, the drug approval duration is significantly longer than in the US. (40-41) It is recognized that the FDA is associated with a lengthy drug approval process, but the established procedures are the framework for Canada. The IND application is similar between US and Canada. However, the NDA application varies from Canada's NDS which is mainly an economic focus including requirements such as pharmacoeconomic analysis, supply and pricing information. (41) It is possible that the cause of the longer approval time of novel drugs in Canada is due to the increased time required by pharmacoeconomic analysts. (39,41) The drug approval process in the United States are unaffected by drug costs. (41-42) In contrast, Canada mainly relies on the clinical research conducted within the United States along with other international countries and that is utilized as the backbone for drug development, as a result, Canada will be able to maintain its focus economically. The more time spent to analyze and approve a novel drug, the costlier it is for the pharma company, where they will spend more time conducting testing and research. Delays in the drug approval process can result in death for those with serious or life-threatening conditions, therefore, it is essential for a rapid drug approval process. (42)

Strengths and Limitations of the Review

This is the first review to compare the drug approval process between the United States and Canada. A thorough literature search was conducted to select the

majority of articles that comply with the inclusion criteria. A comprehensive evaluation and analysis were conducted for each article to include in this review.

The limitation of this review is that the number of articles included is not comprehensive; there are other articles that were not included. There are other additional websites that have not been included in this review. Another limitation is that the articles selected are primarily in the English language, so articles in a different language have not been included in this review.

6. Conclusion

In conclusion, the drug approval process is comparative among Canada and the United States; without the drug approval process, the population would be experiencing harmful health consequences, as a result, the process is expensive, time-consuming and lengthy to thoroughly evaluate the compound's safety and efficacy. The majority of the published articles focus on the comparison in the drug approval process between the United States and other countries, little to no articles discussed the advantages and disadvantages of the drug approval process and how the total length of the drug approval process effects patient population.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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