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A RESEARCH WORK ON COMPARISON OF REGULATORY REQUIREMENTS FOR SUBMISSION OF DOSSIER FOR GENERIC DRUGS IN USA, CANADA AND SAUDI ARABIA

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Abstract: International pharmaceutical trade and patient access to reasonably priced drugs are affected by the considerable differences in generic drug approval procedures between nations. With a focus on significant parallels and distinctions, this abstract analyzes the regulatory regimes that regulate generic medication submissions in Saudi Arabia, Canada, and the United States (USA). Compelling evidence of bioequivalency to the reference listed drug (RLD) through pharmacokinetic studies and comparative dissolving testing is a prerequisite for the USA's Abbreviated New Drug Application (ANDA) procedure, which is supervised by the Food and Drug Administration (FDA). More crucial data are the chemical, production, and controls (CMC) details.

Health Canada, Canada's regulatory body, uses the Abbreviated New Drug Submission (ANDS) approach, which takes bilingual labelling (English and French) into account while placing a comparable emphasis on bioequivalency testing and CMC data. Data on bioequivalence, safety, and efficacy that are in line with Islamic values and local market demands are required as part of the New Drug Registration procedure for generic drugs in Saudi Arabia, which is mandated by the Saudi Food and Drug Authority (SFDA).

A comparative study shows that whereas CMC data and bioequivalency testing are always crucial, different regulatory contexts are distinguished by subtle differences in labelling specifications, clinical data expectations, and submission forms. Pharmaceutical firms that want to manage global marketplaces and guarantee compliance with a variety of regulatory standards must comprehend these differences.

Keyword: Generic drug, CTD, eCTD, United state, Canada, Saudi Arabia, ANDA, SFDA, Health Canada.

INTRODUCTION

The U.S. generic drug market size was valued at US$ 123.75 billion in 2021 and is expected to hit US$ 155.82 billion by 2030, growing at a compound annual growth rate (CAGR) of 2.59% from 2022 to 2030. The Canada generic drug market size reached US$ 8.9 Billion in 2022. Looking forward, IMARC group expects the market to reach US$ 14.8 Billion by 2028, exhibiting a growth rate (CAGR) of 8.5% during 2023-2028. And In Saudi Arabia, The GCC generic drug market size reached US$ 5.2 billion in 2022. Looking forward, IMARC group expects the market to reach US$ 10.3 billion by 2028, exhibiting a growth rate (CAGR) of 13.2% during 2023-2028.

The USA and CANADA are fastest growing Generic drug market in world, due increasing the life-threatening diseases government focuses on generic drug product which is Cheaper and less cost of Production and easily available to People. Saudi Arabia also largest generic drug market in West Asia region and which is having higher demand of generic medicine.

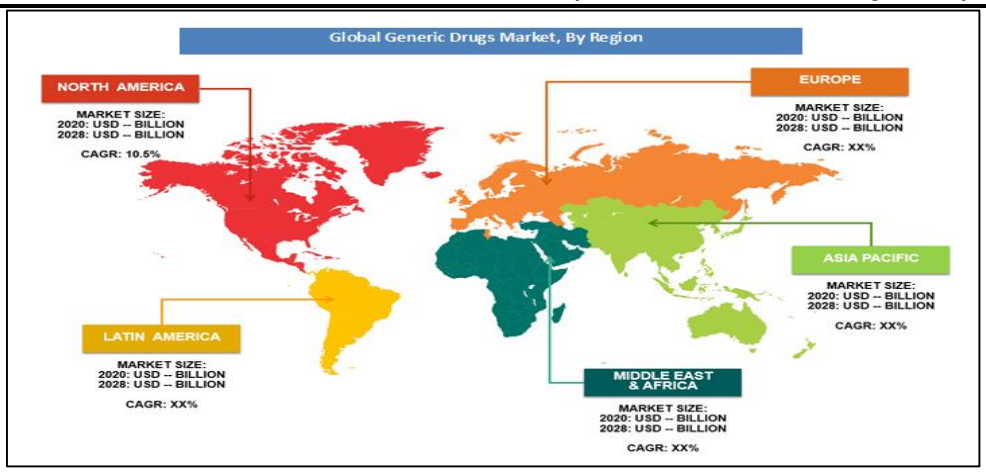

Figure 1: Global Generic Market by Region

What are Generic Drugs?

A generic drug (generic drugs, short: generics) is a drug defined as "a drug product that is comparable to a brand/reference listed drug product in dosage form, strength, quality and performance characteristics, and intended use". A generic drug must contain the same active ingredients as the original formulation. According to the U.S. Food and Drug Administration (USFDA), generic drugs are identical or within an acceptable bioequivalent range to the brand-name counterpart with respect to pharmacokinetic and pharmacodynamics properties. By extension, therefore, generics are considered (by the FDA) identical in dose, strength, route of administration, safety, efficacy, and intended use. [1]

The prices of both the original brand product and generic drugs become considerably low due to the availability of generic drugs for cheap prices in the market. The main advantage that generic drugs provide is an economic benefit. Branded drugs are expensive because most of the cost lies in research and development. [2]

Generic Drug Development:

The development of generic product in pharmaceutical industries requires lot of research and scientific review. To meet the target launching time, proper strategic planning is essential. The formulation scientist has to know and analyse the detail about the product to be developed and the target market as different market has different requirements. When a formulation scientist starts to develop a product for US, the product should comply to the physical and chemical parameter according to USP method and passes the bioequivalence study against the innovator product of US. The product developed according to US guidelines cannot be marketed in the EU/UK.

The listing of "relevant" patents and durations of "Exclusivity" for the approved drug product derives from the submission of an NDA with the FDA for a drug product developed with an NCE. The FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations," sometimes known as the "Orange Book." contains this listing. Before the expiration of the patent, innovator holds the permission to manufacturer for monopoly business. So before selecting the generic product to be developed the industries should consider the patent status and market share for sure. [3]

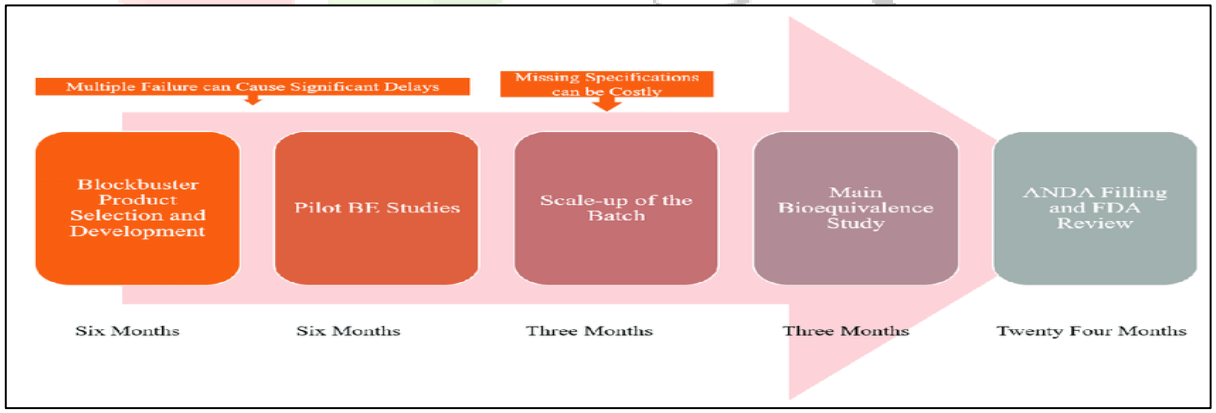

Figure 2: Generic Drug Development Process

Regulatory Agencies:

Every country having their own specific regulatory agency, which are having their own rules and regulation and guidelines for safety and efficacy of drug for public health. Regulatory agency regulates all process of drug development, clinical trials, marketing approvals, which are gives advice to manufacturer for drug development process. Agency focuses on overall process and implementing rules to all manufacturers which market their product in specific country.

To assure a drug's effectiveness, safety, and quality, drug regulation involves supporting a range of initiatives. Pharmaceutical drugs are available from many different sources. Pharmaceuticals must be safe, effective, and of high quality for people and governments to be willing to spend money on them.

Table 1: The regulatory agencies in few of the countries are as follows:

Sr. No	Country	Regulatory Authority
1.	USA	USFDA
2.	Canada	Health Canada
3.	Saudi Arabia	SFDA
4.	Australia	TGA
5.	South Africa	MCC
6.	Brazil	ANVISA
7.	European Union	EMA
8.	China	CFDA
9.	Japan	MHLW
10.	United Kingdom	MHRA
11.	New Zealand	MEDSAFE
12.	Sri Lanka	MoH

Common Technical Document: [4]
CTD are Divided into Five Dossiers:

Module 1(M1): Administrative Information

Module 2(M2): Quality Overall Summary

Module 3(M3): Quality

Module 4(M4): Non-Clinical Study Reports

Module 5(M5): Clinical Study Reports

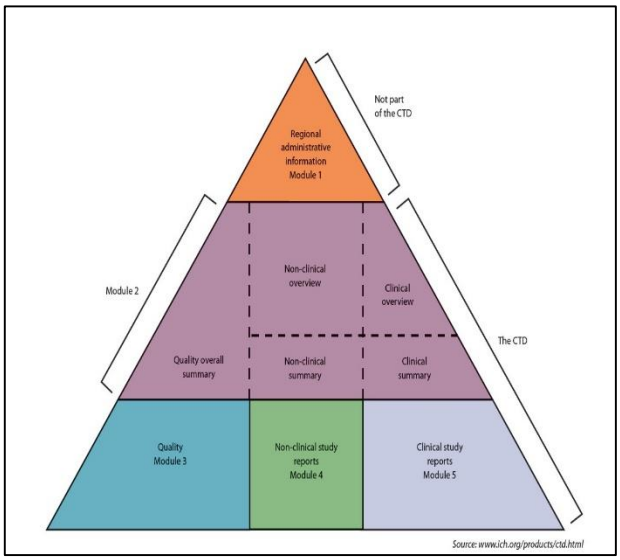

Figure 3: CTD Triangle

METHODOLOGY

United States of America (USA)

Over the past three decades, there has been a change in the generic drug market in the US. Less than 20% of all prescriptions are for generic medications, which now make up the majority of all prescriptions written in the US. The US generic medication market expanded at a CAGR of 13% from 2011 to 2018, and it now accounts for a multibillion-dollar business. The market for generic drugs in the US has grown to around 4 million prescriptions. The pharmaceutical industry in the US has seen a significant transition over the past several years. [5]

United States Food and Drug Administration (USFDA)

The majority of food products (aside from meat and poultry), human and animal drugs, therapeutic agents of biological origin, medicinal devices, radiation-emitting products for consumer use, medical occupational use, cosmetics, and animal feed are all under the regulatory, scientific, and public health preview of the USFDA. The organisation, which consists of four departments overseeing management, health, science, international activities, and regulatory affairs, is led by the office of the commissioner. They have a number of centres for the regulation of drugs, veterinary products, food, and medical equipment, as well as centres for toxicological research. The FDA is also in charge of promoting improvements in food and medication that will benefit public health by assisting in the development of new technologies that will make these products safer, more effective, and more inexpensive. [6]

Figure 4: Logo of USFDA

ANDA Regulation in USA

A generic drug product can be reviewed and ultimately approved with the use of an Abbreviated New Drug Application (ANDA), which must be submitted to the FDA's Centre for Drug Evaluation and Research (CDER) and Office of Generic Drugs (OGD). To offer the American public a safe, efficient, and affordable alternative, an applicant may produce and commercialise the generic drug product after receiving approval. In other terms, "it is an application that is submitted to the USFDA for approval of a generic version of an existing licenced medication or approved drug."

Facts About Generics and Generic Drug Application (ANDA)

- Preclinical (animal) and clinical (human) data to show safety and efficacy are typically not required to be included in generic medication applications, which is why they are known as "abbreviated" applications.
- Applicants for generic medications must scientifically show that their product is bioequivalent, or that it functions in the same way as the innovator drug.
- The time it takes for a generic medicine to enter the bloodstream of 24 to 36 healthy volunteers is usually used to determine bioequivalence. This information provides the generic drug's bioavailability rate, which can be compared to that of the brand-name medication.
- Like the innovator medicine, the generic version must deliver the same quantity of active chemicals into the patient's bloodstream in the same period of time.
- The basis for approving generic copies of drug products was established by the "*Drug Price Competition and Patent Term Restoration Act of 1984*," also known as the "*Hatch -Waxman Act*". [7]

Abbreviated New Drug Approval Process in USA

a) ANDA Regulatory Review Process: [8]

When a candidate submits an ANDA to the OGD (Office Generic Drugs) or CDER (Centre for Drug Evaluation and Research), the ANDA procedure gets started. The ANDA is processed by the document room staff, who give it an ANDA number and stamp the date of receipt on the cover letter. A consumer safety technician next receives the ANDA and goes over the first few sections of the checklist. The filed ANDA is examined while taking the drug's bioequivalence, chemistry, microbiology, and labelling into account. A file review is finished within the first 60 days after the submission of an ANDA.

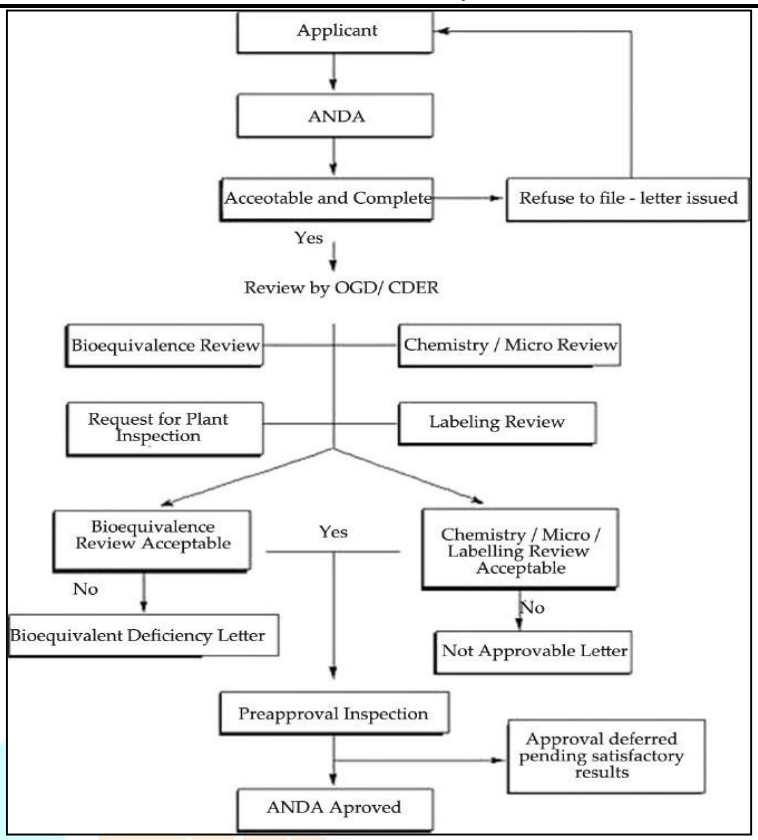

Figure 5: ANDA Review Process [9]

b) Bio Equivalence Review Process:
Pharmaceutical and bioequivalence are the two key requirements for a generic drug to be therapeutically equal to the innovator drug. The innovator medicine and the generic version should have the same potency, dosage form, and method of administration in order to be considered pharmaceutically comparable. When two products are examined under the same circumstances and show comparable bioavailability, they are said to be bioequivalent.

c) Labelling Review Process:
The purpose of the labelling review process is to guarantee that the generic drug's and innovator drug's labels are identical. The application will either receive a letter of full approval or preliminary approval after the last level of administrative review and after each discipline has corrected any issues. A complete permission letter outlines the requirements and authorises the applicant to market the generic medication product. If the reference-listed drug (RLD) is covered by patents or exclusivities that have not yet expired, a tentative approval letter is issued. [6]

d) Chemistry Review Process:
The Chemistry, Manufacturing, and Controls (CMC) part of an ANDA is assigned to the appropriate chemistry division and team based on the therapeutic category of the drug product after it has been accepted for filing by the Registration Support Branch (RSB). The CMC part of ANDAs, drug master files, supplemental ANDAs, annual reports, and controlled correspondence are all reviewed by the chemistry divisions.
The chemical review procedure's objective is to ensure that the generic medicine will be produced in a repeatable manner under controlled circumstances. The APM faxes the applicant the inadequacies in chemistry after labelling them as minor or major. When the application is prepared for final approval, the applicant is notified, and the approval package is handled through the immediate office. Prior to final approval, the chemistry division consults with all disciplines and produces a letter of final approval for the office director. [5]

USFDA Regulatory Guidelines for Prescribed Medicines
USFDA guidance documents are collection of all guidelines which are essential for the use by sponsors to provide a way to search for relevant USFDA guidance documents about prescription medicines from a single location. including basic information, CTD and general dossier requirements and forms, can be found at medicine registration fundamentals.

Following is some of the guidance documents which are important for generic drug submission process:
These Documents provides overview on USFDA registration process for application generic drug products that need to be supported by nonclinical, clinical and/or bioequivalence data.

CTD Module 1: Administrative information and prescribing information for United States.
This guidance:

- Explains the format and content for Module 1 of a dossier.
- Describes each document in Module 1.
- Outlines when each document needs to be provided.
- Details any other requirements relating to the documents.

Electronic submissions (eCTD)
It is the electronic version of a standard technical document that the applicant submits to the regulator to get permission to market the product. It is composed of various PDF documents that have been organised using the CTD structure. By employing XML as the document's backbone, cross links are used to convey the information. The regulatory authority's reviewer can benefit much from the electronic submission. The technology is cutting-edge, and there is just one application format for all apps. [10]
eCTD Structure
1) Modules: 1 to 5
2) Documents: PDF linked via XML backbone
3) The submissions are highly transparent, easy to navigate and review.

Canada

The pharmaceutical market in Canada is the eighth largest in the world by sales, making up around 2% of the global market. After China, the US, and Spain, Canada has the fourth-fastest expanding pharmaceutical industry, and it has demonstrated a consistent development pattern. The Therapeutic Products Directorate (TPD) of the Health Products and Food Branch (HPFB), Health Canada, is in charge of ensuring that all medications used by the general public are high-quality, safe, and effective for particular illnesses.

Up until 2014, the Canadian market as a whole is predicted to face persistent difficulties and uncertainty, which will have an impact on company performance. The outlook for the industry is anticipated to improve between 2014 and 2016, with annual growth ranging from 3% to 5%, more than double the anticipated slow growth for 2012 and 2013. The brand and generic segments are expected to increase at a similar rate, with the forecasted compound average annual growth rate for the 2012–2016 period being 2.8%. Although the projected growth rate is upbeat compared to recent years, Canada's growth will still lag behind that of emerging markets. Fast-growing emerging markets will continue to outperform market growth in Canada and in developed markets. [1]

Health Canada

The federal agency that controls the market for pharmaceuticals and medical devices for human use is the Therapeutic Products Directorate of the Canadian Ministry of Health (Health Canada). Pharmaceuticals are categorised as either prescription-only or over-the-counter at the federal level, with provinces further categorising medications into general sales and Schedules I through III (with Schedule I denoting prescription drugs, Schedule II denoting pharmacist-assistance drugs, and Schedule III denoting pharmacy self-selection). All retail establishments are permitted to sell unscheduled medications as general sale goods.

The department of the Canadian government in charge of national health policy. The Canadian Food Inspection Agency (CFIA) and the Public Health Agency of Canada (PHAC), among other government agencies linked to health, fall within the purview of the department itself. These groups support the enforcement of federal law in numerous healthcare, agricultural, and pharmaceutical endeavours. In order to assure the safety of food, health, and pharmaceutical products including the regulation of health research and pharmaceutical manufacturing and testing facilities this task also entails substantial collaboration with numerous other federal and provincial-level organisations.

As part of the federal health portfolio, the department reports to parliament through the current minister of health, Jean-Yves Duclos. The minister is supported by Carolyn Bennett, who is currently the associate minister of health and minister of mental health and addictions. The deputy minister of health, who is the department's senior-most civil servant, is in charge of managing day-to-day leadership and operations and answers directly to the minister. [11]

Figure 6: Logo of Health Canada

a) Responsibilities of Health Canada: [11]
Health Canada is involved in many different endeavours and is accountable for a wide range of duties. In order to control health care costs, Health Canada communicates health risks and encourages healthy lives. Health Canada also supports initiatives that:

- Preserve and modernise Canada's healthcare system.

- To improve and safeguard Canadians' health, Health Canada conducts disease outbreak surveillance, prevention, control, and research both domestically and internationally. The department also keeps an eye on risks to health and safety associated with the use and distribution of medicines, food, chemicals, pesticides, medical equipment, and some consumer goods in Canada and abroad.
- Collaborate with other organisations: Health Canada works together with other federal departments, agencies, provincial and territorial governments, and health organisations.

b) Areas Regulated by Health Canada:

- Product safety. Recalls and alerts
- Drugs and health products. Regulating drugs and health products to support public safety.
- Environmental and workplace health
- Food and nutrition
- Health care system.
- Health concerns.
- Healthy living.
- Health science and research.

c) Challenges:

1) Reduction of complexity in key operational procedures.
2) Decrease in the amount of time needed to execute inspections, provide market authorizations, and issue import licences.
3) Going forward in fostering global regulatory convergence, summarising accomplishments, adhering to best practises, and participating in harmonisation initiatives.
4) Achieving a personnel size that is appropriate for the scope of the regulatory activity.
5) Consolidating a service policy in accordance with good governance, access to information, transparency and communication values.

d) Opportunities:

- The growth potential of the Canadian generic drug market is sizeable, with the government's cost-containment policy.
- Despite being a mature market, growth is still solid and per-capita consumption is one of the highest in the world.

Drug Product Regulation in Canada [12]

Health Canada makes sure that the pharmaceuticals sold in Canada are genuine, safe, and of the highest calibre. To accomplish this goal, laws and standards must be established, health goods must be approved, safety and quality must be monitored, and compliance must be encouraged and enforced.

Establishing guidelines and norms the food and drugs act and its restrictions must be complied with by all health goods before they can be sold legally in Canada. Health Canada creates guidelines, regulations, and policies to assist businesses in better understanding their obligations and duties.

Accepting medical products Health Canada oversees and approves the sale of medications (medical products), medical devices, and natural health products by determining if the benefits of the product outweigh the risks, whether the product's health claims are supported by evidence, and whether the risks and uncertainties can be handled. Drug goods include prescription pharmaceuticals, which may only be obtained with a prescription; over-the-counter drugs, which are available without one; and biologics. Hospital beds, dental equipment, everyday objects, sophisticated technology, surgical implants and prostheses, diagnostic tools, and test kits are all examples of medical gadgets. Homoeopathic medications, vitamins, minerals, herbal cures, traditional medicines, probiotic supplements, and other goods like amino acids and essential fatty acids are examples of natural health products.

Checking for quality and safety Once a product is approved for sale, health Canada keeps an eye on its safety through safety reviews, company reports on the security of their products, assessments of changes to product formulas or designs, and evaluations of complaints and reports of adverse reactions from businesses, patients, consumers, and healthcare professionals.

Encouraging and enforcing adherence by encouraging and enforcing adherence to laws and regulations, health Canada assists in ensuring that businesses and products meet Canada's high standards for safety and quality. Clinical trials, pharmaceutical firms, medical device manufacturers, blood banks, businesses dealing with cells, tissues, and organs, and facilities dealing with donor sperm are all subject to inspection by health Canada.

The food and drug regulations are a detailed set of guidelines intended to regulate or control behaviour in relation to food, pharmaceuticals, medical devices, and cosmetics. They layout specifications for how prescription and over-the-counter medicines must be produced, packaged, labelled, stored, distributed, and sold in Canada, as well as the terms under which they must participate in clinical trials.

Part A of the food and drug regulations consists of prohibitions, powers, definitions and obligations that generally apply throughout the regulations,

Part B refers to food,

Part C deals with drugs and includes the following Divisions:

Division 1 – General; It outlines the requirements for sale or importation of drugs, enclosing labelling, packaging, testing, advertising and post authorization obligations including adverse drug reaction reporting. It also describes the requirements for obtaining, renewing, updating and cancelling a Drug Identification Number (DIN) which is required in order to sell a drug in Canada.
Division 1A – Establishment Licences (EL); A drug EL is required for any person fabricating, packaging, labelling, testing, importing or distributing drugs, or wholesaling certain drugs in Canada. This division sets out procedures related to its applications, renewals, suspensions and cancellations.
Division 2 – Good Manufacturing Practices (GMP); Division 2 sets out the GMP standards that apply to all activities in the drug supply chain: fabricating, testing, importing, packaging, labelling, storing, and transporting of the drug. To ensure that drugs are consistently produced and controlled to meet quality standards.
Division 3 – Schedule C Drugs; It sets out specific requirements for radiopharmaceutical drugs.
Division 4 – Schedule D Drugs; It sets out specific requirements for biologic drugs.
Division 5 – Drugs for clinical trials involving human subjects; It provides a mechanism to regulate the sale or importation of drugs used for clinical trials in humans and helps protect patients participating in these trials.
Division 6 – Canadian Standard Drugs; It sets standards for six specified drugs (conjugated oestrogens, digitoxin, digoxin, esterified oestrogens, gelatin and thyroid), using specific well-established standards for these drugs.
Division 7 – Sale of Drugs for the Purposes of Implementing the General Council Decision; It provides the rules for a manufacturer to export, for humanitarian purposes, a drug that cannot be sold in canada due to patent restrictions. This provision permits access to lower cost generic drugs in regions of the world, such as emerging nations, where the drug would otherwise be unavailable.
Division 8 – New Drugs; It includes drugs that have not been sold in sufficient quantity or for sufficient time to establish their safety and effectiveness. This division sets out the pre and post-authorization requirements for new drugs and adds to the requirements found in division 1. It also includes requirements for extraordinary use new drugs, clinical testing and experimental studies.
Division 9 – Non-prescription drugs; It sets out additional requirements for a few commonly used non-prescription pain or fever medications for human use.

How new drugs are authorized for sale in Canada

Part C, Division 8 of the food and drug regulations, regulates new medications. Health Canada offers numerous types of market authorization to businesses. A manufacturer receives a Notice of Compliance (NOC) when it has satisfied health Canada's regulatory standards for the safety, efficacy, and quality of a product, regardless of the type of authorization. The next section gives a quick description of the three procedures that are most frequently used to approve new medications for sale in Canada.

1) Innovator drugs ("brand name drugs"): In accordance with section C.08.002 of the food and drugs regulations, manufacturers must file a New Drug Submission (NDS) in order to be permitted to market these goods in Canada.
2) Subsequent entry drugs ("generic drugs"): By requiring them to file an abbreviated new drug submission (ANDS) in accordance with Section C.08.002.1 of the food and drug regulations, health canada frequently grants manufacturers permission to commercialise these products. According to Section C.08.004 (4), these goods will get a declaration of bioequivalence to a Canadian reference product, which will be noted on the NOC.
3) Manufacturers who desire to obtain authorization through a NOC to advertise brand-name and generic drug goods have another choice, according to the health canada changes in manufacturer's name and/or product name policy. This regulation is applicable to drug applications that are eligible for a name change after a merger, buyout, other corporate restructuring, or the creation of a licencing agreement and are filed with health canada. [11]

Drug Approval Process in Canada

The Therapeutic Products Directorate (TPD) of Health Canada oversees the medications and medical equipment used for human consumption in Canada. All pharmaceuticals used by the general public will be examined by Health Canada to ensure their efficacy and safety. They must also make sure that pharmaceuticals have been evaluated by manufacturers before being marketed.

In order to establish proof of the potential benefits and risks of the drug, regulatory drug submission evaluation in Canada is responsible for critically evaluating both the data supplied by the sponsor and their justification. All medications distributed in Canada require approval from the therapeutic products directorate. One of the biggest markets for pharmaceuticals is Canada.
For pharmaceuticals that need to be approved for marketing in Canada as well as those that have never been sold on the market previously, a new drug application is required. This submission must include details about the drug's production, labelling, intended use, and side effects. If a new drug submission is made to TPD at Health Canada, the screening process is the first step to make sure all required components of the application are included in the NDS. After receiving an NDS, the screening process should be finished within 45 days. The NDS's next step is to review medications in a therapeutic area. According to the 300-day performance guidelines, TPD completes a typical NDS review. [13]

Abbreviated New Drug Submission (ANDS)

The ANDS regulation was developed to streamline and lower the cost of the generic medicine approval procedure. A drug's manufacturer must demonstrate that their product is pharmaceutically and/or bioequivalent to the drug of the innovator in order to qualify for an ANDS. A bioequivalence study or physico-chemical comparison may be required for an ANDS by the sponsor (for parenteral medications or medications for which it is unethical to research healthy volunteers).
Steps in the review process for a drug:

1) A sponsor submits a "new drug submission" to HPFB when it determines it wants to market a medicine in Canada. This includes details and information about the quality, safety, and efficacy of the medication. It contains the outcomes of pre-clinical and clinical trials, whether they were conducted in Canada or elsewhere, information about the drug's production, packaging, and labelling, as well as facts about therapeutic claims and adverse effects.
2) The provided data is thoroughly reviewed by HPFB, which occasionally consults with outside consultants and advisory bodies.
3) To determine the possible advantages and dangers of the drug, HPFB assesses the safety, effectiveness, and quality data.

4) The HPFB examines the materials that the sponsor intends to give to consumers and healthcare professionals regarding the drug (such as the label and product brochure).
5) If, at the end of the review, it is determined that the advantages outweigh the risks and that the risks can be reduced, the drug is given a Notice of Compliance (NOC), attesting to the dossier's compliance with the food and drugs act and its regulations, as well as a Drug Identification Number (DIN), allowing the sponsor to market the drug in Canada and proving the drug's official approval in that country. [14]

Marketing Authorization: [15]
a legal document published by Health Canada that grants approval for the sale of a medication or device in accordance with the food and drug act and its regulations standards for health and safety. A drug identification number (DIN), a device licence for classes II, III, and IV medical devices, or a natural health product licence (NPN or DIN-HM) are all examples of marketing authorizations.

Saudi Arabia
Saudi Arabia, a nation in western Asia, is officially known as the Kingdom of Saudi Arabia (KSA). With a land area of over 2,150,000 km2 (830,000 sq mi), it is the second-biggest Arab nation, the largest in western Asia, and the largest in the middle east. It occupies the majority of the Arabian Peninsula. The Red Sea, Jordan, Iraq, and Kuwait border it on the west; the Persian Gulf, Qatar, and the United Arab Emirates border it on the east; and the Red Sea borders it on the north. It is a national healthcare system where the government, through a number of government organisations, provides free universal healthcare coverage. [16]

Saudi Food and Drug Authority (SFDA)

The Saudi Food and Drug Authority (SFDA) was established under the council of minister's resolution no (1) dated 07/01/1424 H, as an independent body corporate that directly reports to the president of council of ministers.
The Ministry of Health is Saudi Arabia's main regulatory body. In order to create and enforce the regulatory framework, the Saudi Food and Drug Authority was established in 2003. The management, supervision, and control of food, drugs, and medical devices whether imported or made locally as well as the establishment of legally required minimum standards for each are the main goals of the SFDA. [17]

Saudi Arabia's pharmaceutical market is governed jointly by the public and commercial sectors, with the Ministry of Health (MoH) and the Saudi Food and Drug Authority (SFDA) playing a major regulatory role. The 2003-founded SFDA oversees the registration, sale, and pricing of all drug products, as well as the licensing, inspection, and suspension of manufacturers that do not adhere to the nation's licensing standards. To fulfil this purpose, certain standards must be followed in order to provide accurate market analysis and maintain a balance between medicine supply and demand. The SFDA and the MoH have collaborated to create a chain of custody from the producer to the point of sale, which is at a neighbourhood pharmacy, and have upgraded their infrastructure to make the process of importing, manufacturing, and distributing medicines easier. [18]

The Saudi Arabian Ministry of Health transferred its oversight of pharmaceutical regulation to the SFDA in 2009. Saudi Arabia is a member of the Gulf Cooperation Council (GCC), which was founded in 1981 and consists of Saudi Arabia, Kuwait, Bahrain, Qatar, the United Arab Emirates, Oman, and Yemen. [19]

Figure 7: Logo of SFDA

Generic Drug Market in Saudi Arabia [20]

The government's promotion of generic replacement as a cost-cutting measure supports Saudi Arabia's generic medication market and serves as a primary growth driver of this trend. Although regulatory standards in the kingdom have improved somewhat, industry bias in favour of local manufacturers will also support generic drug spending in Saudi Arabia, which is anticipated to increase quickly over the short and long terms in comparison to patented counterparts. The sector is expected to develop from its current size of $2.9 billion (in 2019, contributing 35% of the entire market) to $4.4 billion by 2024 and may account for 39% of the total market at an 8.1% CAGR over the next five years.

Types of application (legal basis)
The following type of submission being presented to SFDA:
1) NEW MARKETING AUTHORIZATION APPLICATION
2) VARIATION OF MARKETING AUTHORIZATION
3) RENEWAL OF MARKETING AUTHORIZATION

1) NEW MARKETING AUTHORIZATION APPLICATION
The MAA of pharmaceutical product will be subjected to the followings processes:
A) Submission:

The process of submitting a New MAA consists of two steps:

a) Online submission:

1) The applicant shall apply through SDR system to fill the application form and pay the fees.

2) Upload the product file; The components of the file shall follow the requirements and guidelines published on SFDA website.

b) Validation:

The product file will be validated in technical and business bases to ensure the applicant fulfils the requirement.

The validation involves two steps:

1) Technical validation:

The SDR system will validate the submission automatically after the company upload the file on the SDR portal. The validation's result will be sent by email through SDR system to the applicant.

2) Business validation:

a) The product file will be validated to ensure that all information provided is according to the requirements and guidelines.

b) If any information is missing or incorrect, an electronic inquiry will be forwarded to the applicant through the SDR system. The applicant will be given an opportunity to complete the file within 30 working days.

c) The completed file will proceed to the next steps for assessment (section 3.2)

The registration request will be rejected in the following cases:

- No response from the applicant within 30 working days.
- Failure to provide acceptable clarifications after the 4th wave.

B) Assessment:

The MAA for different drug submission types subject to the following processes:

1) Evaluation / Inspection:

a) The RA will distribute the registration request to the relevant related departments to assess quality, safety and efficacy.

- For Inspection: The department will check the approval of manufacturing line; if not approved:
- Visit will be scheduled for inspection depending on the time available for both inspectors and the company.
- After the visit, the inspection report will be sent to the company (please, refer to the guidance of good manufacturing practice for medicinal product).

b) If more information or clarification is required, an electronic inquiry will be posted through SDR system as one wave for evaluation and inspection. A response should be received within 90 working days.

c) Once the evaluation and inspection are completed, the registration request will be forwarded to Pricing.

2) Testing:

a) The registration request will be forwarded to the SFDA central laboratories.

b) If more information or clarification is required, an electronic inquiry will be posted through SDR system.

c) Samples and working standards shall be delivered by the applicant to SFDA central laboratories.

3) Pricing:

a) The pricing department will review product's price according to the "SFDA's pricing rules".

b) If more information or clarification is required, an electronic inquiry will be posted through SDR system. A response should be received within 90 working days.

c) The product's price will be forwarded to registration committee.

4) Product licensing:

a) The registration committee will review the registration request for approval, rejection or ask for further information (if needed).

b) The SFDA CEO will approve the meeting minutes.

c) For approved registration request, the applicant will be notified through SDR system to issue the MA. Otherwise, submit an appeal.

2) VARIATION OF MARKETING AUTHORIZATION

Any changes on a registered product have to be submitted to the SFDA as a variation of MAA. The variations are classified into two main categories:

a) Minor changes:

- Type IA: minor variations that does not require prior approval before implementation ("Do and Tell" procedure) but require notification submitted by MAH within 60 working days after implementation.
- Type IB: minor variations that must be submitted to the SFDA by MAH before implementation, but do not require a formal approval. However, the MAH must wait a period of 60 working days to ensure that the application is deemed acceptable by the SFDA before implementing the change ("Tell, Wait and Do" procedure).

b) Major variation:

- Type II: major variations in which there might be a significant impact on the Quality, Safety or Efficacy of a pharmaceutical product and require prior approval before implementation.

The variation request subjects to the following process:

A) Submission:

The process of submitting a variation of MAA consists of two steps:

a) Online Submission:

1) The applicant shall apply through SDR system to fill the application form and pay the fees.

2) Upload the product file; The components of the file shall follow the requirements and guidelines published on SFDA website.

For applications made via the new SDR system, three parallel variation applications can be submitted at a time, each includes administrative, quality or safety variations. Each category of variations will be assigned to the related departments.

b) Business Validation:

1) The product file will be validated to ensure that all information provided is according to the requirements and/or guidelines.
2) If any information is missing or incorrect, an electronic inquiry will be forwarded to the applicant through the SDR system. The applicant will be given an opportunity to complete the file within 30 working days.
3) The completed file will proceed to the next step for assessment.

B) Assessment:

Depending on the type of variation, one or more department may review the variation application.

1) Evaluation / Inspection:

The Evaluation/Inspection process are same as that new market authorization application process.

2) Pricing:

Pricing process are same as that new market authorization application process.

3) Product Licensing:

Product licensing process are same as that new market authorization application process.

3) RENEWAL OF MARKETING AUTHORIZATION

An applicant shall submit a renewal request every five years. It is possible to request for renewal within six months of the certificate expiry.

As most of the registered drugs have gone through at least one renewal process or have been registered through SDR system; therefore, the renewal process is shorter as follows:

A) Submission:

The process of submitting a renewal of MA consists of two steps:

a) Online submission:

The applicant shall apply through SDR system to fill the application form and pay the fees.

Upload the renewal file; The components of the file shall follow the requirements and guidelines published on SFDA website.

b) Business Validation:

1) The product file will be validated to ensure that all information provided are according to the requirements and/or guidelines.
2) If any information is missing or incorrect, an electronic Inquiry will be forwarded to the applicant through SDR system. The applicant will be given an opportunity to complete the file within 30 working days.
3) The completed file will proceed to the pricing department.

1) Pricing:

1) Pricing department will review the price according to the "SFDA's pricing rules".
2) If more information or clarification is required, an electronic inquiry will be posted through SDR system. A response should be received within 30 working days.
3) The approved price will be forwarded to the product licensing.

2) Product Licensing:

1) The RA will issue the renewal of MA.
2) The applicant will be notified through SDR system. Otherwise, submit an appeal. [20]

Drug Approval Process in Saudi Arabia:

- A dossier should be submitted in eCTD or NeeS format.
- Normal time taken for registration: 6-18 Months.

The process of submitting a NEW drug application to the SFDA consists of three major steps:

1) Online submission of the APPLICATION FORM,
2) The PRODUCT FILE delivered in person,
3) DRUG SAMPLES.

Step by step procedure:

1) Applicant shall go to the Saudi Drug Registration system (SDR) website (http://sdr.sfda.gov.sa/).
2) Login to apply (each applicant should have a user ID and a Password).
3) Choose and complete the appropriate application form:

- The application form can be saved partially as the applicant may complete it in several steps.

4) Then, the applicant has to pay the submission fee (through SADAD Payment System) in order to submit the application form and schedule an appointment to deliver the hard and soft copy of the product file:

- Submission fees are mandatory in order to proceed to the next step.
- The applicant can reschedule 3 weeks before the appointment. An automatic reminder will be sent 3 days before the appointment.
- A reference number will be generated, and this number should always be used with regard to any communication with the SFDA.

5) At the appointment, the applicant will deliver the product file along with the samples.
6) The Regulatory Affairs Pharmacist will validate (Phase I) the following:

a. The application form
b. The product file (hard and soft copy)
c. The samples

- If the above are valid, an acknowledgment letter will be generated and given to the applicant. The drug application will enter the queue.

- If some of the above are missing or not satisfactory, an acknowledgment letter will be generated and given to the applicant stating the deficiencies. The applicant will have a period of 90 days to complete the requirements and the drug application will not be queued.

❖ **Comparison of Regulatory Requirement of USA, Canada and Saudi Arabia:** [21, 22]

Table 2: Comparison of Regulatory Requirement of USA, Canada and Saudi Arabia

Sr. No	Requirements	USA	Canada	Saudi Arabia
1	Agency	USFDA	Therapeutic Products Directorate (TPD), Health Canada	Saudi Food and Drug Authority (SFDA)
2	Application	ANDA	ANDS	MAA
3	Registration Process	Single	Single	Multiple (Centralized and Decentralized)
4	Dossier Format	eCTD	eCTD	eCTD and Nees
5	Approval Time	18 months	2 years	10 months
6	TSE/BSE Data	TSE/BSE Data are not attached in DMF	TSE and BSE certificates are attached for drug substance and excipients.	TSE and BSE are attached in this section.
7	Climatic Zone	Zone I and II	Zone I	Zone IVa
7 8	Minimum Stability Data Required for filling	Minimum 3- Months Stability Data are Submitted.	Minimum 6-Months Stability Data are Submitted.	Minimum 3- months Data are submitted.
9.	Pharmacopeia's	US Pharmacopeia's	BP/Ph. Eur./USP	BP/Ph.Eur./USP
10.	Fees	$178,799.00	$ 565,465	20000 SAR.
11.	Website of Regulatory authority	https://www.fda.gov/	https://www.canada.ca/en/health-canada.html	http://www.sfda.gov.sa/en
12.	Submission language	English	English or French	Arabic or English
13.	Certificate of suitability	It's Not Applicable	Preferred	Applicable
14.	Paper size for submission	Paper size (8.5 x 11) inches 11.69) inches Font 12 (New Times Roman) Table and Figures size i.e., 8-10	Paper size (8.5 x 11) inches Font 12 (New Times Roman) Table and Figures size i.e., 9	Paper size (8.5 x 11) inches Font 12 (New Times Roman) Table and Figure size i.e., 8-10.
15.	Post Approval Changes	Post Approval Changes in approval drug: Minor changes, Moderate changes, Major changes	Post Approval Changes in approval drug: Minor changes, Moderate changes, Major changes	Post Approval Changes in approval drug: Minor changes, Moderate changes, Major changes
16.	Process Validation	Not required at the time of submission	Not required at the time of submission	Required at time of Submission

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