REVIEW ARTICLE

A Comparative Analysis of Pharmaceutical Product Regulations in Singapore, Australia, Canada, and Europe

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ABSTRACT

This review aims to compare the pharmaceutical regulations of developed nations such as Singapore, Australia, Canada, and Europe. The present work describes the need of pharmaceutical regulations and how these regulations have evolved with time. Regulatory bodies of different countries play a huge role in the type of procedures, methodologies, and guidelines adopted by each nation. The comparison gives an insight into the different clinical trial pathways, drug registration procedure, CTD format, medical device registration, and consultation provisions offered by the following nations. Countries of interest chosen here are based on demographic parameters, population, and regulatory body establishment. These nations have a strong regulatory system that sets an example for the emerging pharmaceutical market. They account for a large number of populations ranging from 26 million in Australia, 38 million in Canada, and 738 million in Europe. Singapore is a small nation with a population of 5.8 million people. However, it has emerged to be one of the leading potential markets in the pharmaceutical industry.

Key words: Clinical Trial Application, Clinical Trial Notification, Health Sciences Authority, Therapeutic Goods Administration, Health Canada, European Medicines Agency

INTRODUCTION

Pharmaceutical regulations play an important role in all countries across the world. The need for such regulations was felt when there were no measures taken for public health protection in the United States. Harvey Washington Wiley was a chief chemist at the US Department of Agriculture who protested against this issue and spread awareness about it. He received outraging support from the people of the United States due to which the Food and Drug Administration (USFDA) was born on June 30, 1906.[1]

This was followed by the establishment of many other regulatory bodies across the globe. Australia's regulatory body Therapeutic Goods Administration (TGA) was established in 1989, Canada's competent authority Health Canada in 1993, followed by Europe's regulatory agency European Medicines Evaluation Agency (EMEA) in 1995 (Currently known as European Medicines Agency), and Singapore's regulatory authority Health Sciences Agency (HSA) in 2001.

These regulatory authorities play an important role in ensuring the safety, efficacy, and quality of a pharmaceutical product. Each country has a specific set of standards and regulations for conducting clinical trials register a pharmaceutical product, register a medical device, etc.

This review gives an insight into these different approaches, pathways, and methodologies used by Singapore, Australia, Canada, and Europe, along with offering a comparison of these regulations.

The countries chosen for comparison contribute to the pharmaceutical industry in various ways such as research, technology, infrastructure, and market share. Europe and Canada's pharmaceutical industry is a research-based industry; while Australia's pharmaceutical industry is usually called a technology-intensive industry. On the other hand, Singapore's pharmaceutical industry is known to have an extremely skilled workforce and excellent infrastructure. Europe contributes 22% of the global pharmaceutical revenue, while Canada contributes 2%. Australia and Singapore contribute 1% each.[2] Comparative demographic data for the countries of interest are shown in Table 1. It summarizes that Singapore, Australia, Canada, and Europe are located on different continents. Europe has the largest Total Land Area among the four, followed by Canada, Australia, and Singapore. The population of these regions also corresponds to the Total Land Area and follows the same order of priority, as mentioned above. This data justify its market shares in the global pharmaceutical industry.

Further, the comparison of Pharmaceutical Product Regulations is based on the parameters which are listed below:

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Table 1: Comparative demographic data for the countries of interest

Parameters	Singapore	Australia	Canada	Europe
Location	Located in Asia	Located in Oceania	Located in North America	Europe is a continent itself
Total land area	721.5 km^2	7.692 million km^2	9.985 million km^2	10.18 million km^2
Population	5.8 million	26 million	38 million	738 million

1. Clinical trial of pharmaceutical products
2. Drug registration of pharmaceutical products
3. Dossier format
4. Provision for consultation
5. Medical device registration procedure

CLINICAL TRIAL OF PHARMACEUTICAL PRODUCTS

Singapore

Initiation of a clinical trial for a therapeutic product in Singapore requires the submission of a clinical trial application (CTA) or clinical trial notification (CTN).

CTA is filed for a therapeutic product registered previously with an unapproved use or an unregistered therapeutic product. The evaluation time for CTA is 30 working days. CTN is filed for registered therapeutic products used in accordance with approved label. These clinical trials have a simple screening procedure and shorter pathway in comparison to CTA. The evaluation time for CTN is 15 working days.[3] Clinical trial submission pathway in Singapore is described in Figure 1.

Australia

Clinical trials in Australia are carried out in the same way as in Singapore. There are two pathways for conducting Clinical Trials in Australia: CTN Scheme and CTX Scheme. The pathway has been described in the flow chart above [Figure 1].

1. CTN Scheme: The CTN Scheme is called the notification scheme and is usually for earlier phase studies when there is an adequate amount of preclinical data available. Data are not reviewed or evaluated after submission. All information, including the proposed trial and trial protocol, is submitted to the Human Research Ethics Committee (HREC). The HREC assesses the validity of the trial design, risk-benefit ratio, and ethical considerations of the trial.
2. CTX Scheme: The CTX Scheme is called for novel treatment or treatments with high risk. It includes evaluation and data review by the Therapeutic Goods Administration (TGA) before a trial. Safety review, along with ethical considerations, plays an important role which is conducted by HREC.[4]

Canada

The filing of CTA needs to be done by the sponsor to initiate a clinical trial. Registration of clinical trial should be done on publicly accessible registries that accept international clinical trial information. All CTAs are screened for completeness and deficiencies. Health Canada issues a Request for Clarification or Screening Rejection letter if any deficiency is identified. During the review process, if any additional information is requested and the sponsor fails to provide the requested information within 2 working days, the application should be withdrawn. Not Satisfactory Notice (NSN) is issued in case any major deficiencies are identified in the CTA. However, if the CTA is accepted, a No Objection Letter (NOL) is issued during the review period. CTA should be sent to the appropriate directorate and reviewed by it, which is described in Figure 2.[5]

Europe

The CTA process in Europe is a centralized procedure which enables greater transparency, enhance safety, and efficacy of drugs. This process also streamlines the CTA process, authorizes clinical trials by removing duplication, and enhances efficiency of the process.[6]

CTA is filed in Europe which is followed by the complete evaluation of the application. If the application is complete, then the application is accepted and reviewed further. After this, EMA generates a review report which if possible, allows the initiation of the clinical trial. Figure 2 illustrates the clinical trial pathway of Europe.

DRUG REGISTRATION OF PHARMACEUTICAL PRODUCTS

Singapore

Registration of a therapeutic product in Singapore depends on the type of application. There are two broad categories of the applications:

1. New Drug Application (NDA): NDA is for therapeutic products that contain new biological and chemical entities.
2. Generic Drug Application (GDA): GDA is for therapeutic products that contain more than one chemical entity and is bioequivalent to the registered therapeutic product.

The evaluation time of a therapeutic product varies with the type of product and if it has been approved by any competent regulatory authority overseas. There are four evaluation routes for this, and these include:

1. Full evaluation route: This is applicable for new therapeutic products that have not been approved by any competent regulatory authority, that is, NDA.

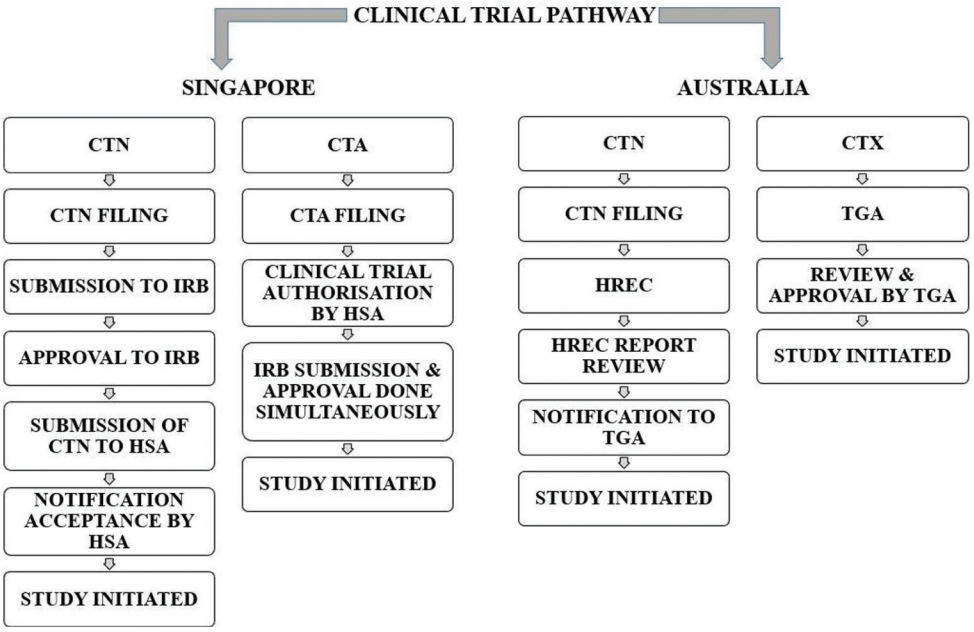

Figure 1: Clinical trial registration procedures in Singapore and Australia

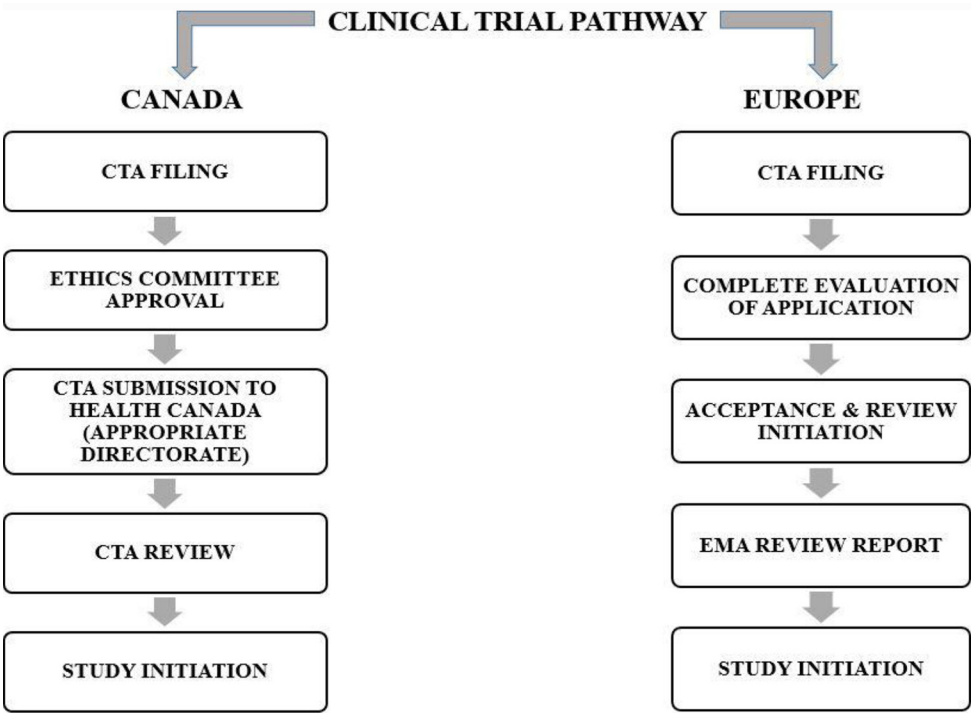

Figure 2: Clinical trial registration procedures in Canada and Europe

2. Abridged evaluation route: This is applicable for a new therapeutic or generic product that has been approved by at least one of the competent regulatory authorities, that is, it includes both NDA and GDA.
3. Verification evaluation route: This is applicable for a new therapeutic or generic product that has been approved by any reference drug regulatory authority of Health Sciences Authority (HSA), that is, it includes both NDA and GDA.
4. Verification – Comprehensive Economic Cooperation Agreement (CECA) evaluation route: This is applicable for any generic drug product manufactured in India and approved by any reference drug regulatory authority of Health Sciences Authority, that is, GDA of drug products manufactured in India.

After evaluation route determination, the application is screened to ensure that it is complete. If the application is submitted under a different type of application, the applicant can take action by filing an input request. Status and progress of evaluation are available and are listed under four broad categories:

- Acceptance for Evaluation (Stage 1): In this stage, the application is accepted for evaluation.

- Active Evaluation in Progress (Stage 2): In this stage, active evaluation is done.
- Evaluation at Midway or (Stage 3): In this stage, the application is midway through the evaluation process. Applicants can receive queries from Health Sciences Authority.
- Completed Evaluation or (Stage 4): In this stage, the evaluation has been completed for the application. The application is undergoing a regulatory decision phase and the decision will be issued shortly. Queries can be issued by the Health Sciences Authority.

A regulatory decision is issued after benefit-risk assessment by Health Sciences Authority. This decision is based on the data which was submitted in the application. Applicants are then notified with any one of the listed decisions and the procedure for registration is described in Figure 3.

- Approval: This implies that application meets registration requirements.
- Approvable: This implies that the application consists of minor deficiencies and can be approved if rectified.
- Non-approvable: This implies that the application consists of major deficiencies.
- Rejection: This implies that the response provided by the applicant fails to address the major deficiencies.

Australia

The registration procedure for prescription medicines in Australia includes eight phases. Applications are divided into five types. They include:

- Category 1/Regulatory Compliance Mark (RCM) 1: For medicines that are identical to a registered medicine.
- Category 2/RCM 2: For medicines that comply with a Therapeutic Goods Administration (TGA) medicine monograph.
- Category 3/RCM 3: For medicines where previous evaluation by TGA is done or a comparable regulatory authority (CRA) has demonstrated their safety and efficacy, for example, generic medicines and medicines evaluated by a comparable regulatory authority.
- Category 4/RCM 4: For medicines where quality, safety, or efficacy have been established.
- Category 5/RCM 5: For new medicines to be registered on the Australian Register of Therapeutic Goods (ARTG) and which have not been previously evaluated for quality, safety and efficacy, for example, new registered medicine with increase in the strength of an active ingredient, new dosage form.

1. Pre-submission is the first phase of the registration procedure for prescription medicine, which begins with filing a pre-submission planning form (PPF). Once the PPF is reviewed, pre-submission planning is initiated.
2. The second phase is submission, which includes processing activities such as payment verification of application fee, processing of registration, and issuing notification letter.
3. The third phase is the First Round Assessment, where the data submitted in the form of the dossier are evaluated. In case of any queries or clarification, a consolidated section 31 request for information is issued by TGA.
4. Consolidated Section 31 Request-Response is the fourth phase, which allows applicants to

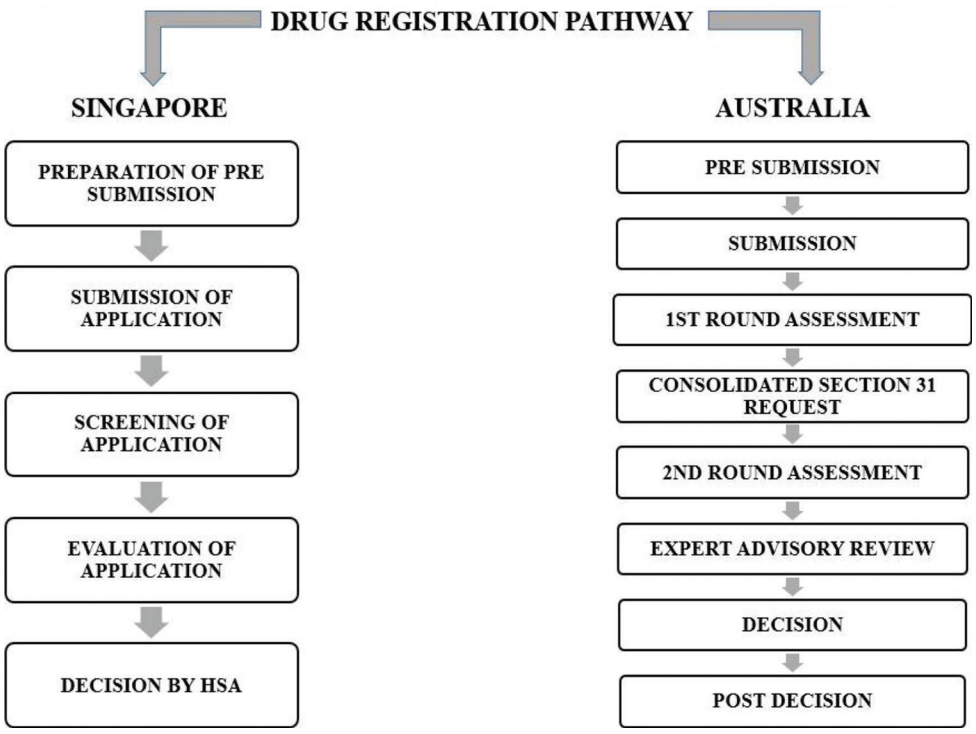

Figure 3: Drug registration procedures in Singapore and Australia

respond to the consolidated section 31 request for information issued.

5. The applicant's response is then considered, and data are evaluated in the fifth phase, which is called the Second Round Assessment.
6. After this, the evaluation reports are considered by delegates, which may seek advice on any issues concerned with the application. Comments are prepared and issued, and this phase is called Expert Advisory Review.
7. The approval decision of an application is made here. Hence, this phase is called the decision phase.
8. The last and eighth phase is the post decision phase, where all the regulatory and administrative activities are completed.[4] The process is explained in Figure 3.

Canada

The registration of a therapeutic product in Canada is done by filing a New Drug Submission (NDS) or Abbreviated New Drug Submission (ANDS). NDS is submitted to the appropriate Health Products and Food Branch (HPFB) Directorate to be marketed in Canada. NDS can also be submitted if the clinical trials are not conducted in Canada. The drug is evaluated for risk-benefit ratio, safety, and efficacy. NDS should also contain detailed information about quality, preclinical, and clinical data. This information is submitted to Health Canada in the form of an electronic Common Technical Document (eCTD) format. ANDS is submitted for approval of generic drug products. The manufacturer has to demonstrate that the generic drug product is pharmaceutically equivalent (bioequivalent) to the innovator drug product. This can be done by performing BA/BE studies. The review is then done by HPFB, considering the risk-benefit outcome in their population. If all requirements are met, the Marketing Authorization Holder receives a Notice of Compliance (NOC), which states that the drug can be introduced in the market. A drug identification number (DIN) is allotted with NOC, which is specific for a drug product to be marketed in the country. If Notice of non-compliance is received by the Marketing Authorization Holder (MAH), they can submit additional data to HPFB to support their application.[7]

Europe

Medicines need to be authorized before they can be marketed and made available to the public in Europe. This is done to safeguard public health and ensures that the medicines available are safe and efficacious for the European citizens. The system offers different routes of the marketing authorization of medicines. These include the following:

i. **Centralized procedure**
   This procedure allows the drug product to be marketed based on a single application. It has an added advantage that the drug product is available throughout Europe, and product information is available in all European languages. The assessment is carried out by the relevant scientific committee of Europe. The duration of the procedure is 210 working days.[8] Figure 4 illustrates the centralized procedure:

ii. **Decentralized procedure**
   It allows the applicant to apply for the marketing authorization of a drug in more than one EU Member State, provided that the drug has not been approved previously. As per the procedure, the applicant needs to choose one country as the reference Member State during the submission of the marketing authorization application. The reference member state has to prepare a draft assessment report to be submitted to the other member state. This allows the other member states to consider and approves the report simultaneously. The advantage here is that the member states can access the report at an early stage. Hence, they can eliminate any issues if there is any. In comparison with MRP or Mutual Recognition Procedure, there is an added advantage of the decentralized procedure, which allows marketing of the drugs simultaneously in various EU Member states.[9] Figure 5 illustrates the decentralized procedure.

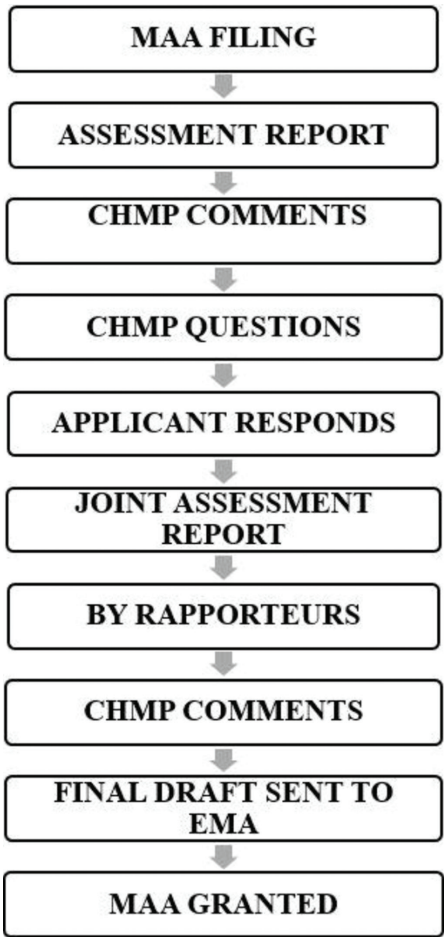

Figure 4: Centralized drug registration procedure in Europe

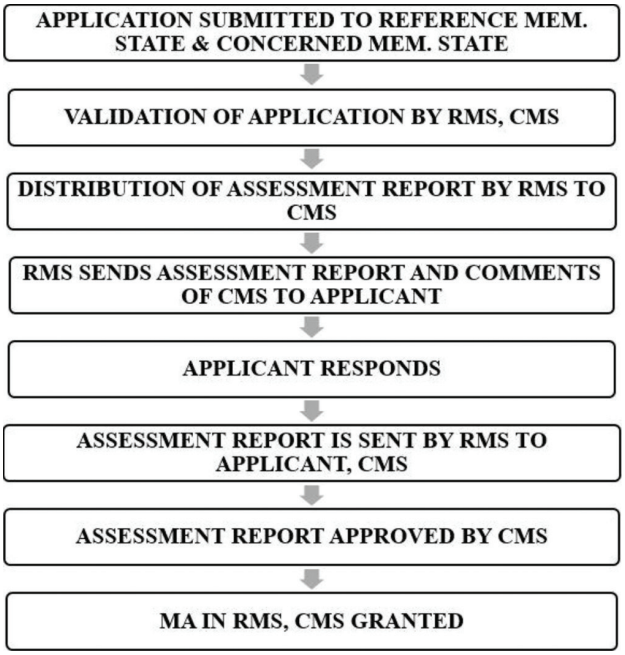

Figure 5: Decentralized drug registration procedure in Europe

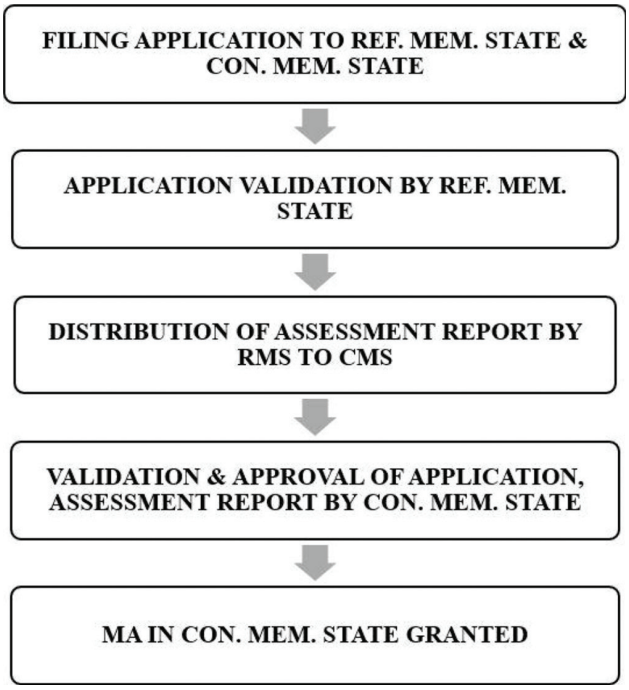

Figure 6: Mutual recognition drug registration procedure in Europe

iii. **Mutual recognition procedure**
This procedure allows the applicant to apply for marketing authorization of drugs in other member states, which has already been approved in one EU member state. This enables the member states to rely on each other's scientific assessments. This procedure has evolved from a multi-state licensing procedure. Here, the applicant should have received approval in at least one EU Member state previously, which is called the reference member state. The member state where the approval is awaited is called concerned member state. The assessment timeline by the Committee for Human Medicinal Products is 60 days.[9] Figure 6 shows the Mutual Recognition Procedure.

iv. **Nationalized procedure**
This procedure allows each European Member State to regulate its national procedures for drug approval. The applicant is expected to file for MAA separately in any European country where the drug is to be marketed.

DOSSIER FORMAT

Singapore

Singapore follows ASEAN Common Technical Dossier format or ACTD format. The association of South East Asians also known as ASEAN is an organization consisting of ten countries. These countries include Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam.[10] ACTD consists of four parts where Part I is Organization of the dossier, Part II is Quality of the document, Part III is Non-Clinical document, and Part IV is Clinical document.

Australia, Canada, and Europe

Australia, Canada, and Europe follow the International Conference of Harmonization Common Technical Document (ICH CTD). It combines all information in a standard format, which leads to the harmonized regulatory procedure and implementation of common standards. It is divided into five modules.

Module 1 contains Regional Administrative Information (not a part of CTD).

Module 2 contains Quality Overall Summary, Non-clinical Overview and Summary, and Clinical Overview and Summary.

Module 3 contains Quality related data.

Module 4 contains Non-clinical study reports.

Module 5 contains Clinical study reports.[11]

PROVISION FOR CONSULTATION

Singapore

Health Sciences Authority offers two types of consultations to applicants.

The first one is called Pre-Submission Consultation which helps the applicant to determine if the application is complete and the dossier prepared is as per the listed requirements.

The second one is Pre-Market Consultation which enables the applicant to seek regulatory advice during development of clinical trials, medical devices, etc.[3]

Australia

Therapeutic Goods Administration provides the Pre-Submission Meeting, which helps the applicant to plan and manage submissions, along with adhering to the need for any supporting documents. They also intend to clarify any queries related to existing studies.[4]

Canada

Health Canada offers consultation in the form of a Pre-Submission Meeting. It is similar to Australia's provision for consultation and can be requested for any drug product under Health Canada's jurisdiction.[12]

Europe

European Medicines Agency provides Scientific Assistance or advice to the applicant, which can be requested by the applicant during any stage of the drug development procedure.[13]

MEDICAL DEVICE REGISTRATION PROCEDURE

Singapore

Medical device registration in Singapore is done by determining the risk-based classification of the device. This helps to select an appropriate evaluation route for the medical device. Registration of the device is also based on any prior approvals granted by the reference regulatory authorities. The registrant must obtain a Dealer's License from the Health Sciences Authority to get the medical device registered.[3]

Australia

Therapeutic Goods Administration has risk-based classification system for medical devices. It emphasizes on identifying the class to which the medical device belongs, ensuring compliance, and selecting appropriate conformity assessment procedure to ensure the safety, quality, and performance of a medical device.[4]

Canada

Medical devices in Canada have to be classified as per the classification format. The manufacturer of the medical device is required to obtain a Medical Device Establishment License for Class I devices and Medical Device License for all other classes of medical device.[14]

Europe

To register a medical device in Europe, the device must undergo a conformity assessment procedure that verifies the safety as well as the performance of the device. Conformity assessment includes audit and review procedures. European Conformity (CE) certification can be placed on the medical device after it has passed the conformity assessment.[15]

COMPARATIVE ANALYSIS

All the regulatory procedures, as discussed in the above sections, are summarized in Table 2. Further, the table describes the following:

(i) Regulatory body and establishment year of the countries of interest.
(ii) Standard CTD Format.
(iii) Consultations Provisions provided by these countries.
(iv) NDA Evaluation Time.
(v) Priority Review.
(vi) Orphan drugs.

The 1st country to establish a regulatory body among these four nations was Australia which was followed by Canada, Europe, and Singapore. ACTD Dossier format is only adopted by Singapore while the other three nations follow ICH CTD format. Provision for Consultation is provided by all four nations. It is termed as "Pre-Submission Consultation" in Singapore, "Pre-Submission Meeting" in Australia and Canada, and "Scientific advice" in Europe. The data for NDA Evaluation Time implies that Europe (7 months – Centralized Procedure) and Singapore (9 months) have quick approval procedures in comparison to Australia and Canada (11 months – both).

Table 2: Comparative analysis of countries of interest

Parameters	Singapore	Australia	Canada	Europe
Regulatory body establishment	Health Sciences Authority in 2001	Therapeutic Goods Administration in 1989	Health Canada in 1993	European Medicines Agency in 1995
CTD format	ACTD	ICH CTD	ICH CTD	ICH CTD
Consultation	Pre Submission Consultation	Pre Submission Meeting	Pre Submission Meeting	Scientific Advice
NDA evaluation time	9 Months (approx.)	11 Months (approx.)	11 Months (approx.)	7 Months (approx.) (Centralized procedure)
Priority review	For Medical Devices only	For Life Saving Prescription drugs	For Life Saving Prescription drugs	PRIME Scheme by EMA to support unmet medical need
Orphan drugs	No registration pathway for Orphan Drugs	Registration pathway for Orphan Drugs available	Registration pathway for Orphan Drugs available	Registration pathway for Orphan Drugs available

It is also observed that the countries chosen for comparison provide Priority Review for drugs except for Singapore, which has this provision only for Medical Devices. Moreover, while considering the Orphan Drug Approvals, there is no registration procedure in Singapore as compared to the other three countries.

CONCLUSION

All the countries chosen for the present review are developed nations and have done exceedingly well in the regulatory sphere. The Pharmaceutical Industry in Singapore has strongly evolved in the last decade. It is well known as the "Pharmaceutical Hub of Asia" and offers an excellent infrastructure for the Research and Innovation of drugs. The pharmaceutical market has recorded a significant increase in the revenue of the country in the years 2012–2017.[16] The market is anticipated to grow and becomes worth 2.19 Billion USD by the year 2023.[17] Approximately 30 of the World's top Pharmaceutical firms such as Abbott, GlaxoSmithKline, Novartis, Sanofi, Pfizer, and many more have set up their manufacturing units along with research and development centers in the country. The amount invested by these pharmaceuticals players totaled to approximately 440 Million USD in the year 2017.[18] Although, Singapore's regulatory body was established in the year 2001, which was much later in comparison to other nations. Despite this drawback, Singapore has emerged successfully as a growing pharmaceutical industry with a strong regulatory environment which is commendable.

CONFLICTS OF INTEREST

The authors have no conflicts of interest.

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