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Review Article

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A comparative study on regulatory requirement of parenteral dosage form for various regulated countries

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Abstract

Parenteral products are at present extensively used for the emergency situation, as it gives maximum bioavailability. Parenteral product legislation is vital because if not sterile, nonpyrogenic can cause severe damage to health causing life-threatening danger to patient. From the above findings it is concluded that the US, being the world's biggest pharma market, also accounts for the largest chunk of the overall injectable space. For the registration of Parenteral product, TGA adopted some (not all) EU guidelines. On the other hand, health Canada mostly follows USFDA regulation guidelines for the submission of the drug product. As discussed above comparative study of regulation and registration process for Parenteral dosage form will be useful regulatory point of view as well as business development point. With this overview the Industry can harmonize dossier application in better way, which will help in reducing time for products to go in market.

Keywords: Parenteral products, USFDA, TGA, EU, New Molecular Entity (NME), ANDA, NDA, CTD.

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1. Introduction

Parenteral preparations as name suggests (par+enteral) are those which are administered other than enteral routes. Enteral route involves esophagus, stomach, intestines but parenteral route bypasses all these. Sterile dosage forms include parenteral preparations and ophthalmic preparations. Parenteral preparations include Injections, transfusions fluids, sterile solids, sterile solutions or emulsions. Ophthalmic preparations include eye drops, eye lotions, eye ointments, eye gels, eye suspensions, contact lens solutions. Typical routes of administration of a parenteral dosage form include subcutaneous, intramuscular, and intravenous delivery. Occasionally, parenteral dosage forms can also be administered via intrathecal, intracisternal, intraarterial, intraspinal, intraepidermal, and intradermal routes to achieve local or systemic effects. Although a major drawback of parenteral delivery is the pain and discomfort associated with needle injection, significant usage has been maintained in hospital environments. This is due to the unique attributes of the parenteral dosage form: rapid absorption and distribution, high bioavailability, zero enzymatic degradation in the gastrointestinal tract, and an ability to be administered to unconscious patients. Parenteral products, by nature of the fact that they are administered directly into the human bloodstream, bypass virtually all of the body's inherent barriers to infection. They are also riskier than oral solid dosage products because there is a higher propensity for improper administration of injectable products as well as the reality of patients with compromised immune systems, among other things. It is for these reasons that the utmost attention to—and assurance of—quality, safety, and efficacy are required to properly manufacture and regulate the parenteral dosage form. The Injectable Drug Delivery market is expected to reach $574.8 Billion by 2020 from $326.1 Billion in 2015, growing at a CAGR of 12.0% from 2015 to 2020. Injectable drug delivery offers a promising alternative for the delivery of drugs that are ineffective when administered orally. Injectable drug delivery is aimed to maximize patient compliance and reduce the frequency of dosage administration without compromising the effectiveness of the treatment. (1)

1.1.Regulatory Market across the Globe

The global parenteral drugs market is foreseen to register upward graph of revenues during the forecast

period of 2019 to 2029. This growth is attributed to plethora of factors. One of the key factors driving the market growth is consistent growth in the number of parenteral drug administration in all worldwide locations. This aside, the parenteral drugs market is showing promising growth owing to growing use of controlled drug delivery systems in worldwide healthcare sector. In addition to this, swift advancement in the field of biosimilars and biological products is projected to drive the parenteral drugs market growth in the years ahead.

[Figure-1: Global Regulatory Organization]

Figure 1. Global Regulatory Organization

The overall size of the injectable market during 2009 was approx. US$ 200 bn. This has grown further by 10% to US$ 220 bn in 2011 with generic penetration being 15%. In the injectable group, the segments of biologics and oncology are relatively more lucrative offering higher upside. (See Graph 1: Market Scenario of Sterile Injectables Worldwide,) US, being the world's largest pharma market, also accounts for the largest chunk of the overall injectable space. (2-4)

1.2. Parenteral drugs and recent approvals

- Over the last several years, parenteral drugs have accounted for approximately 40% of new molecular entities approved by the U.S. Food and Drug Administration each year. In 2018, there were nearly 500 parenteral drugs in the pipeline. The global market for parenteral drugs was estimated to be $451 billion in 2019 and to be expanding at a 6% compound annual growth rate (CAGR) to reach a value of $802 billion by the end of 2029. The rising prevalence of chronic illnesses and the growing importance of biologic drugs are key drivers of the rising demand for parenteral.
- The large volume parenteral (doses of 100 mL or more) subsegment is also expanding at a compound annual growth rate (CAGR) of approximately 6% through 2025. Specific drivers for the growth of these parenteral drugs, the bulk of which are nutritional and electrolyte formulations (infusions of amino acids, mannitol, dextrose, lactated Ringer's injection, Ringer's injection, sodium chloride) are increases in geriatric and paediatric patients, as well as people suffering from cancer and other chronic illnesses. (5,6)
- With respect to parenteral drug packaging, the global market was valued at $9.86 billion in 2017 and is projected to expand at a CAGR of 4.8% through 2028.5 Prefilled syringes and cartridges accounted for more than 35% of the market and are expected to increase compared with vials, bags, and ampoules. (2)

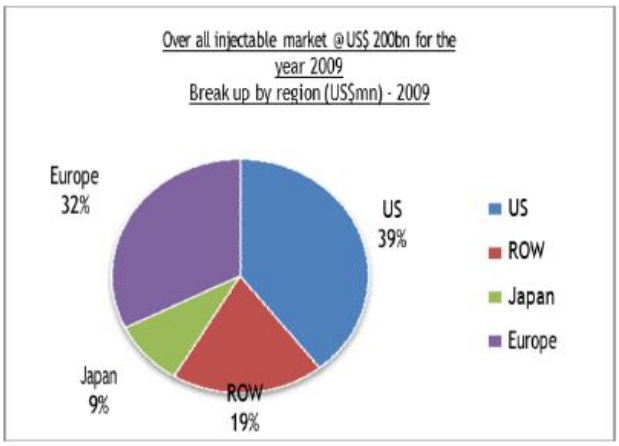

Figure 2. Market scenario of Injectables wordwide

The percentage of parenteral drugs approved as new molecular entities (NMEs) by the US Food and Drug Administration's (FDA) Centre for Drug Evaluation and Research (CDER) (see Table 1) reached a recent high of 59% in 2016 and has since trended near 40% over the past several years. (4, 7)

Table 1. Number of Parenteral Drugs Approved in Relation to Total New Molecular Entity (NME) Approved, 2015-2019 (as of Oct. 21, 2019) by the US Food and Drug Administration's Centre for Drug Evaluation and Research

Year span>	Number of New Molecular Entities (NMEs) Approved	Number of parenteral drugs approved as new molecular entities	Percentage of parenteral drugs approved as new molecular entities
2019 as of Oct. 21, 2019	33 NMEs approved	12 NME parenteral drugs approved	36%
2018	59 NMEs approved	23 NME parenteral drugs approved	39%
2017	46 NMEs approved	19 NME parenteral drugs approved	41%
2016	22 NMEs approved	13 NME parenteral drugs approved	59%
2015	45 NMEs approved	20 NME parenteral drugs approved	44%

2. Global Parenteral Drugs Market: Notable Development and Competitive analysis

Major enterprises in the global parenteral drugs market are increasing spending on research and development activities. By executing this move, these players are eyeing on the development of latest technologies and introduction of advanced products. Several players in the global parenteral drugs market are focused on growing their regional presence. To attain this aim, they are entering into partnership and collaboration agreements. All these activities by well-established players depict the future expansion opportunities for the global parenteral drugs market.

2.1. The list of important players in the global parenteral drugs market includes

- AstraZeneca plc
- Amgen Incorporated
- Baxter International Incorporated
- Abbott Laboratories
- Becton Dickinson
- AptarGroup Incorporated
- Bristol-Myers Squibb Company
- Pfizer Incorporated
- Novartis AG (4, 7)

3. Comparative study on regulatory requirement of parenteral dosage form for various regulated countries

3.1 US

The United States has perhaps the world's most stringent standards for approving new drugs. Drug approval standards in the United States are considered by many to be the most demanding in the world. The Food and Drug Administration (FDA) is responsible for protecting and promoting public health.the product must be registered with new chemical entity (NCE) filed as a 505(b) (1) Application for approval of a new drug application (NDA), Application for approval of a new drug that relies, at least in part data not developed by the applicant 505(b) (2) NDA, or Application for approval of a generic drug product 505(j) abbreviated NDA (ANDA). (7-9)

3.1.1. Application Types/Filing to USFDA

a) IND (Investigational New Drug Application):

The IND is also the vehicle through which a sponsor advances to the next stage of drug development known as clinical trials (human trials) (10)

b) NDA (New Drug Application):

When the sponsor of a new drug believes that enough evidence on the drug's safety and effectiveness has been obtained to meet FDA's requirements for marketing approval, the sponsor submits to FDA a new drug application (NDA).

c) ANDA (Abbreviated New Drug Application):

An ANDA contains data which when submitted to FDA's Center for Drug Evaluation and Research, Office of Generic Drugs, provides for the review and ultimate approval of a generic drug product.

d) OTC Application (Over-the-counter Drug Application):

OTC drug products are those drugs that are available to consumers without a prescription. CDER oversees OTC drugs.

e) BLA (Biologics License Application):

A biologics license application is a submission that contains specific information on the manufacturing processes, chemistry, pharmacology, clinical pharmacology and the medical effects of the biologic product

3.1.2. Dossier Submission in United States

FDA has issued several guidance documents specific to the CTD and eCTD submissions. The information contained in these guidance focuses on the technical aspects of filing a CTD application and should be reviewed thoroughly prior to submitting an ANDA. This guidance addresses the content of the CTD for an original ANDA. The CTD is comprised of the following modules:

- Module 1: Administrative information;
- Module 2: CTD Summaries;
- Module 3: Quality;
- Module 4: Nonclinical study reports; and
- Module 5: Clinical study reports

3.1.3. General Requirements for Submission

- The general requirements for submitting ANDAs are provided in the Regulations in 21 CFR 314.94. ANDA is submitted to FDA's Center for Drug Evaluation and Research, Office of Generic Drugs.
- Amendments and Supplements CTD format can be used to supplements to an original application or amendments to either the original application or subsequent supplements.
- Organizing Documents: All documents should be binded in separate volumes or documents separated by tab identifiers.
- Number of copies: Requires archival, review, and field copies for ANDAs.
- Paper size: U.S. letter size paper (8.5 x 11 inches) is used for all submissions.
- Paper margins: margin of at least 0.75 inches from the bound edge of the printed page prevents information from being obscured
- Fonts: Font sizes for text and tables should be of a style and size that are large enough to be easily legible, even after photocopying and narrative text is submitted in Times New Roman 12-point font. (7,8)

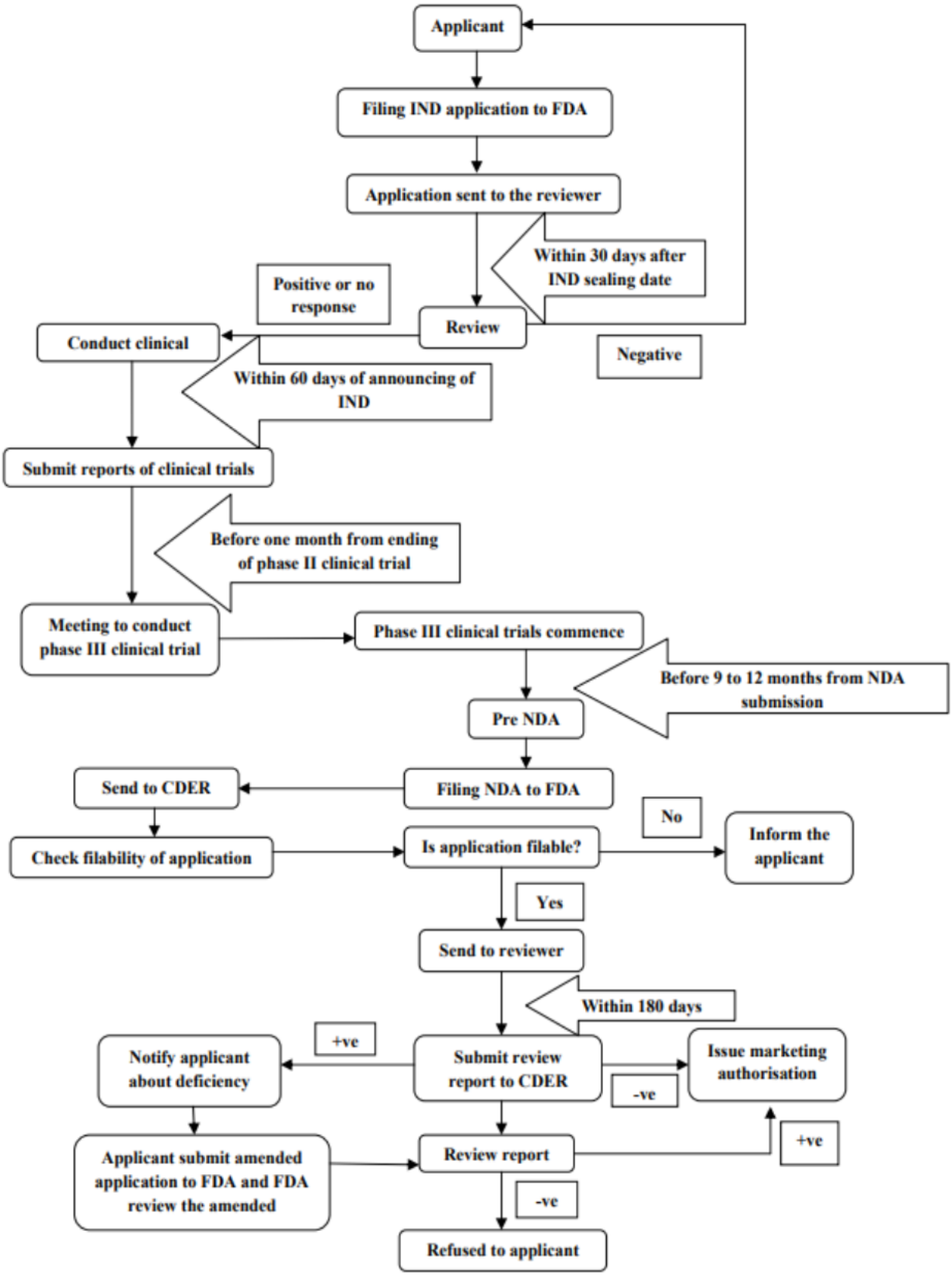

Figure 3. Drug approval process in US (7,8)

- Binding volumes: The front cover of the binder should be 9 by 11.5 inches, and the back cover should be 9 by 12 inches. Binders are used to distinguish the different copies of the applications. For ANDAs, archival copy should be blue, the review copy should be red and the field copy should be green.
- Volume size: Volumes should not be more than 2 inches thick.
- Volume numbering of the Volumes is done by module
- Volume identification: All copies of the submission, including the review copies, should use the same volume numbers.

- Pagination: Page numbering should be at the document level and not at the volume or module level.
- Cross referencing documents is done by volume, CTD module, tab identifier, and page number (5,6) 7,8

3.2. Europe

3.2.1.Regulatory Bodies

- European regulator, the European Medicines Agency (EMEA)
- EMEA works closely with United Kingdom Medicines & Healthcare Products Regulatory Agency (UK-MHRA)
- Committee for medicinal products for human use (CHMP)
- Committee for proprietary medicinal product (CPMP)
- Heads of Medicines Agency(HMA)
- National Patient Safety Agency(NPSA)

3.2.2. Regulations of Parenteral Drugs in EU

Good Manufacturing Practice Guidelines Medicinal Products for Human and Veterinary Use, Annex 1- Manufacture of Sterile Medicinal Products (Corrected version) gives the detailed guidance on Manufacturing of Sterile medicinal products. Rest of the marketing authorization procedures are general - single application for all type of approval. Medicines can be authorized throughout the EU by means of a single application procedure. (7,8, 11-13)

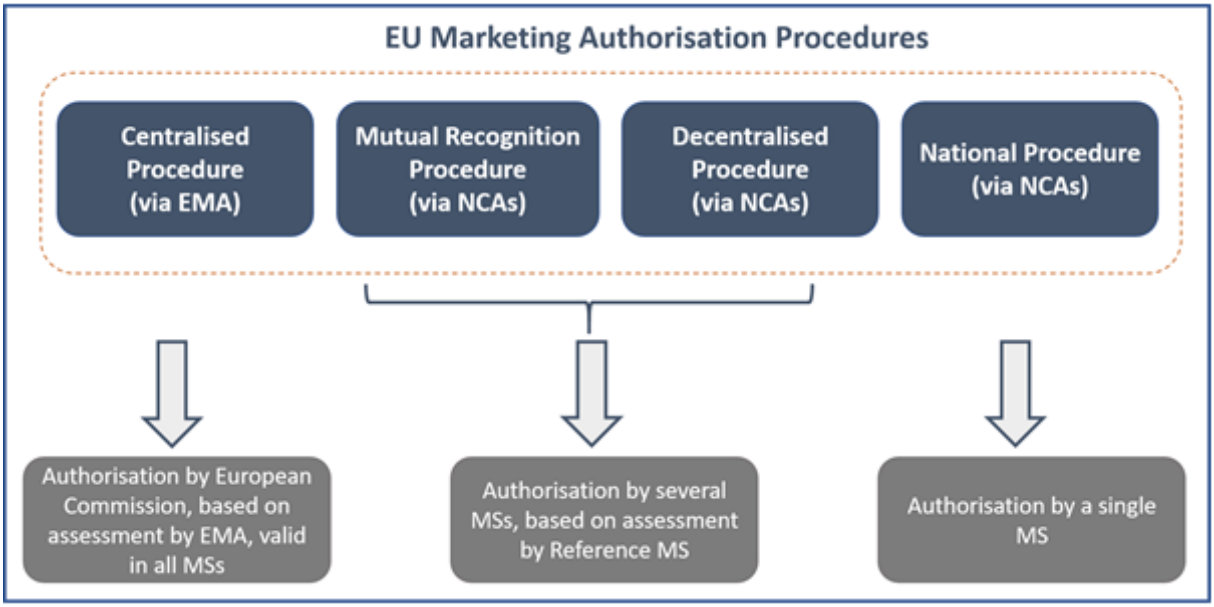

Figure 4. Marketing authorization procedure) (11-14)

3.2.3. Marketing authorization procedures in EU

I. Centralized Procedure (CP)

Applications for the centralised procedure are made directly to the European Medicines Agency (EMA) and lead to the granting of a European marketing authorisation by the Commission which is binding in all Member States. (10) 13

II. National Procedure (NP)

This procedure is used whenever a company wants to commercialize a product in onlyone EU Member State. The National procedure is specific to each country. That is, each country within the EU has its own procedures for authorizing a marketing application for a new drug.

III. Mutual Recognition Procedure (MRP)

Applicable to the majority of conventional medicinal products, is based on the principle of recognition of an already existing national marketing authorisation by one or more Member States.

IV. Decentralized Procedure (DCP)

Manufacturer can apply for simultaneous authorization in more than one EU country, that have not yet been authorized in any EU country and that do not fall the mandatory scope of the centralized procedure.

3.2.4. Dossier to be submitted

- The EMEA requires from the applicant:
- One full copy of the dossier (modules 1-5 according to the EU-CTD format), including the applicant's part of the Active Substance Master File, if any;
- Two additional copies of Modules 1 and 2 including the draft summary of product characteristics, labelling and package leaflet in English;
- One electronic copy of module 1 and 2 (at least 2.1-2.5) in WORD. (11-14)

3.3. Canada

3.3.1. Approval Process

Health Canada reviews every new drug product before it can be sold in Canada. The approval of a new medication can take around 8-12years and cost up to $1 billion dollars. (8)

- Step1:Research and Development
- Step2:Patent Protection
- Step3:Pre-clinical testing
- Step4:Clinical Trial Application
- Step5:Clinical Trials
- Step6:Health Canada's Drug Review Process
- Step7:Notice of Compliance
- Step8:Drug Scheduling
- Step9:Price Review
- Step10:Advertising
- Step11:Distribution
- Step12:Listing on Provincial Formularies
- Step13:Post-marketing Surveillance

3.3.2. Regulatory Approval Procedure in Canada (15,16)

- ***New Drug approval process in Canada***

Health Canada's Therapeutic Products Directorate (TPD) regulates pharmaceutical drugs (prescription and non-prescription) and medical devices for human use. Canada's systems for regulating drug products are very similar to those in the United States. At the federal level, the Therapeutic Products Directorate, an agency of Health Canada that regulates Canada's drug supply, is Canada's counterpart to the FDA. All drug products sold in Canada must be approved by the Therapeutic Products Directorate. Pharmacies in Canada are regulated by the provinces; a similar system to the U.S. in which states regulate pharmacies. New drug submission required for new drugs that have not been sold in Canada for a sufficient time and in sufficient quantity to establish their safety and effectiveness—includes clinical trial information and details on production, packaging, labelling, conditions for use, and side effects. When an NDS is submitted to TPD, it first undergoes an administrative screening procedure to ensure that all necessary parts are included and in the required format. This is not a review of the data. The goal is to complete the screening procedure within 45 days of receipt of the NDS. The file is then directed toward the appropriate Bureau responsible for reviewing drugs in a given therapeutic area. TPD currently has a 300-day performance guideline to complete a standard NDS review, and 180 days to complete a priority NDS.

3.3.3. Generic drugs in Canada

Generic parenteral products that are considered to be New Drugs, are subject to the requirements of Division 8 of Part C of the Food and Drug Regulations. New drug submissions (NDS) for these parenteral preparations are required to contain evidence of safety and efficacy under the proposed conditions of use in conformity with sections C.08.002 and C.08.005.1 of the Regulations. In the case of drugs intended to be used in food producing animals, evidence must also be provided that, after the proposed withdrawal time, drug residues do not exceed levels acceptable to the Directorate. For the purpose of establishing the requirements for new drug submissions for generic parenteral products, the following categories have been established:

CATEGORY I PRODUCTS:

(a) Water-soluble powders for reconstitution, no non-medicinal ingredients;

(b) Aqueous solutions, no non-medicinal ingredients other than the vehicle; Non-aqueous single solvent solutions, other than oil preparations, no non-medicinal ingredients other than the vehicle.

CATEGORY II PRODUCTS:

Lyophilized powders

Buffered powders

Aqueous solutions, with non-medicinal ingredients

Non-aqueous solutions, other than oil preparations, with non-medicinal ingredients

CATEGORY III PRODUCTS:

Oil soluble preparations involving a single oil

CATEGORY IV PRODUCTS:

Special products, such as:

- Suspensions
- Emulsions
- Preparations involving co-solvent systems
- Modified release preparations
- Special classes of drugs
- Drugs subject to Schedule D of the Food and Drugs Act

The general requirements for all categories are outlined below:

GENERAL REQUIREMENTS (CATEGORY I, II, III AND IV)

A new drug submission (Guidelines for Preparing and Filing New Drug Submissions) including:

I) complete chemistry, manufacturing and quality control data.

ii) in vitro and in vivo animal studies and clinical trials establishing safety and effectiveness of the product.

Data in the public domain may be acceptable as fulfilling this requirement. (15,16)

iii) fully annotated Product Monograph, accompanied by appropriate documents cited in the annotations.

iv) labels and any other labelling material required for the product.

v) for products intended to be used in food-producing animals, appropriate residue studies in target species.

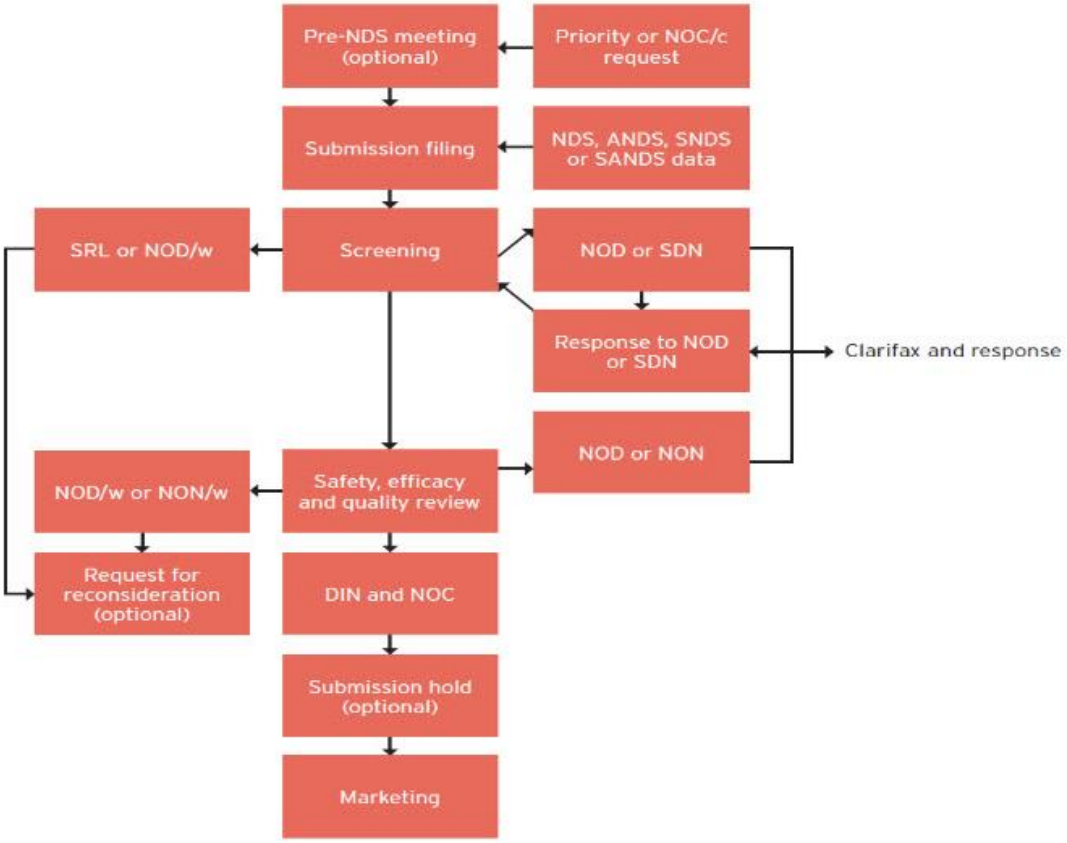

Figure 5. Overview of the Regulatory approval Procedure in Canada (15,16)

Special requirements, as specified by category:

CATEGORY I PRODUCTS

i) proof of pharmaceutical equivalence of the generic and the innovator's product, as marketed in Canada, or

ii) for products for which pharmaceutical equivalence has not been established, appropriate in vitro and/or in vivo animal studies and/or clinical trials.

CATEGORY II PRODUCTS

i) proof of pharmaceutical equivalence of the generic and the innovator's products as marketed in Canada. A product will not be considered pharmaceutically equivalent if:

- any of the non-medicinal ingredients are not generally accepted for such preparations, or

- the quantity of any of the non-medicinal ingredients fall outside the range acceptable to the Directorate;

or

ii) for products for which pharmaceutical equivalence has not been established, appropriate in vitro and/or in vivo animal studies and/or clinical trials.

CATEGORY III PRODUCTS

i) complete information on the source of the oil, the description of the purification process, and the analytical profile of the oil, and

ii) proof of pharmaceutical equivalence of the generic and the innovator's product as marketed in Canada. A product will not be considered pharmaceutically equivalent if

- any of the non medicinal ingredients are not generally accepted for such preparations, or

- the quantity of any non medicinal ingredient falls outside the range acceptable to the Directorate, or

- the oil used is different from that used in the innovator's product; or

iii) for products for which pharmaceutical equivalence has not been established, appropriate in vitro and/or in vivo animal studies and/or clinical trials. (15,16)

CATEGORY IV PRODUCTS

In view of the particular considerations that may apply to these products, a written opinion on special requirements for individual products will be provided on request, upon submission of chemistry and manufacturing data, and proposed labelling. (15,16)

3.3.4. Dossier

Presentation of Information in the Common Technical Document (CTD) Format. (15,16)

3.4. Australia

3.4.1. Therapeutic good Administration (TGA)

The Therapeutic Goods Administration (TGA) is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating therapeutic goods including medicines, medical devices,

blood and blood products. Therapeutic goods are evaluated before they are marketed by TGA. (17, 18)

3.4.2. Medicines and TGA classifications

Higher risk medicines must be registered on the Australian Register of Therapeutic Goods (ARTG), which involves individually evaluating the quality, safety and effectiveness of the product.

All registered medicines: must display an 'AUST R' number on the label as proof of registration are evaluated as either 'high risk' or 'low risk' registered.

- **Prescription (high risk) registered:**

Prescription medicines fit into the sub-category of registered medicines as high risk registered products. This group includes all prescription medicines and some specified products such as sterile injectables.

- **Non-prescription (lower risk) registered:**

Lower risk registered products do not require a prescription. Products in this category are lower risk than prescription medicines. However, they still require a high level of scrutiny, for example to ensure adequate labelling for appropriate use. Examples of products in this category are mild analgesics, cough and cold medicines, and anti-fungal creams. Lower risk medicines containing pre-approved, low-risk ingredients and that make limited claims can be listed on the ARTG.

must display an 'AUST L' number on the label as proof of listing for example, sunscreens can be a listed product yet, they must have complied with testing under the Australian standard for sunscreens. Within the regulatory framework, medicines are classified as either registered or listed.

3.4.3. Types of applications submitted to the TGA for registration of medicines

Category 1 application: These are applications submitted for new medicine, new dosage forms, new strengths, and new generics. Extensions to indications and changes to product information (PI) also constitute category 1 application.

Category 2 application: Category 2 applications are an application to register a prescription medicine with the same formulation, dosage and indications as in two acceptable countries and for which two independent evaluation reports are available.

Category 3 application: These are applications submitted when the change is made to quality information of registered medicines or medicines included in ARTG which may or may not render medicines separate and distinct (separate registration is needed). This application does not require the support of clinical, pre- clinical or bio-equivalence data.

3.4.4. Submission process

TGA has introduced new submission process "Streamline Submission process" to register the prescription medicines that require evaluation of quality, clinical and nonclinical data (category 1 and 2 applications). This new submission process was brought into force in order to improve significantly efficacy and timelines of registration of prescription medicines without compromising the scientific data of evaluation process and maintaining the appropriate standards of quality, safety and efficacy

3.4.5. Key elements of submission process

The streamline submission process consists of eight phases and eight milestones, allowing effective planning and tackling by TGA and sponsor. (9, 17-21)

Table 2. Different Regulatory phases and milestones:

Regulatory phase	Milestone
Pre-submission	Outcome of pre-submission planning sent
Submission	Outcome of submission consideration sent
1stround assessment	Outcome of 1st round assessment sent
Consolidateds.31response	End of s. 31 response period
2ndroundassessment	Outcome of assessment sent
Expert advisory review	Outcome of advisory committee sent
Decision	Decision made by delegate
Post-decision	Administrative and regulatory activities Complete

3.4.6. Pre-submission

During pre-submission phase, sponsor Completes and lodges a Pre-submission Planning Form (PPF). The PPF provides information of quality, non-clinical and clinical evidences. The PPF should be provided at least two and half months prior to actual submission dossier. The information provided in PPF allows TGA to effectively assign resources for evaluation process.

3.4.7. Submission

Sponsor must lodge well planned, high quality complete submission dossier. Sponsor must ensure submission meet the TGA requirements for format and content. When sponsor submit in complete, delayed and poor-quality submission, the submission will be considered not effective and will not be considered for evaluation.

3.4.8. Submission consideration

In this phase submissions are screened and decisions are taken to accept for evaluation or not. The previous 40 working days period for screening of submission on receipt has been replaced by shorter period for ascertaining whether the submission will be considered effective and will be accepted for evaluation or not

effective and will not be considered for evaluation in streamline submission process and thus it will be completed in 15 days.

3.4.9. Consolidated s.31 request for information

In previous process TGA may request the sponsor for information at any phase during the evaluation process through multiple requests. In streamline submission process, this multiple requests for information are replaced by single consolidation s.31 request for information. This request will be sent through pre-determined data specified in planning letter so sponsor can conduct necessary planning activities. (17-21)

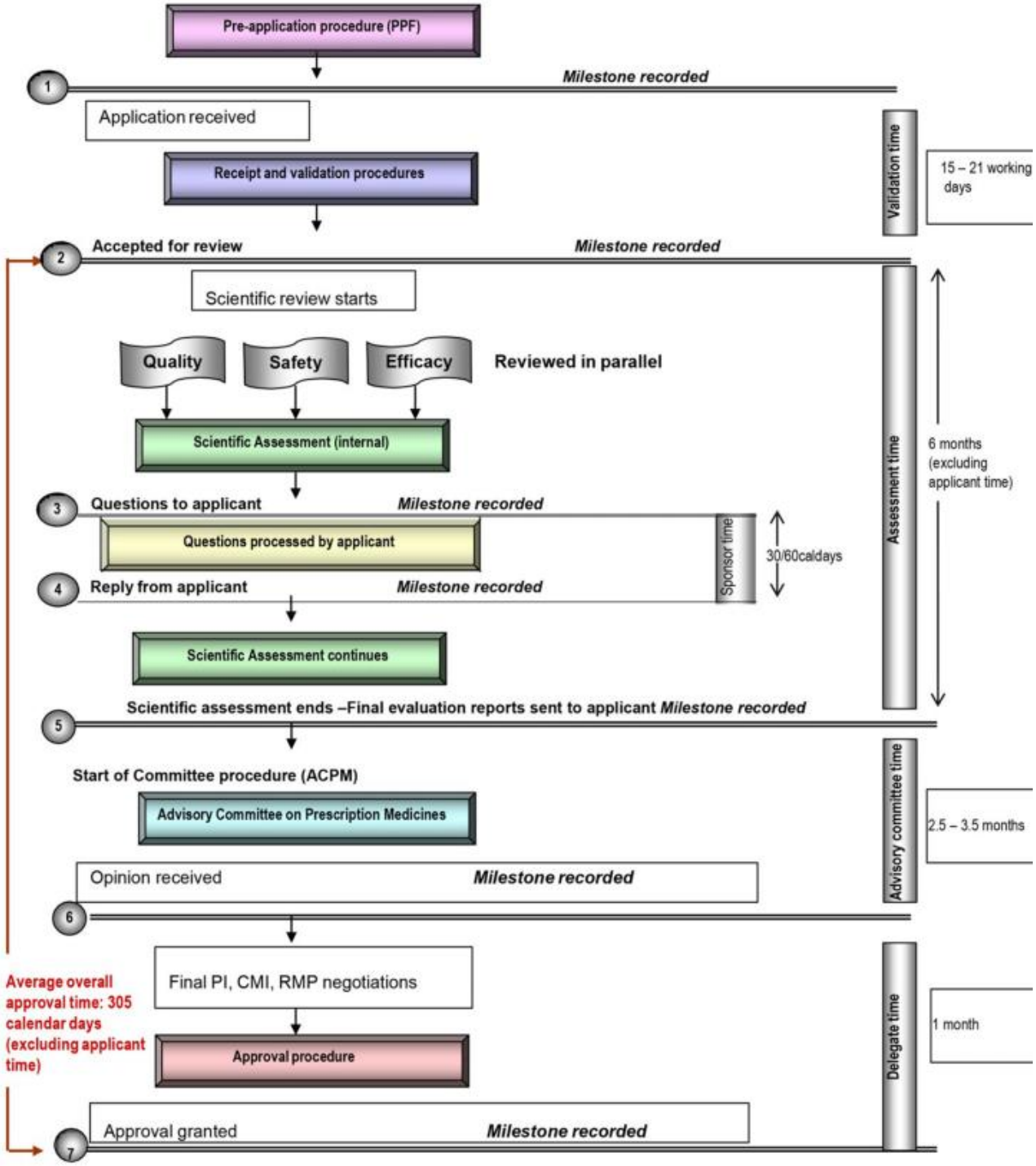

Figure 6. Submission process for TGA (17-21)

Table 3. Comparison of Regulatory Requirement of Parenteral Product in US, Europe, Canada and Australia (8,12,16,19)

Requirements	US	EU	Canada	Australia
Agency	One agency USFDA	Multiple agencies • EMEA • CHMP • National health agencies	Therapeutic Products Directorate (TPD)of the Health Products and Food Branch	Therapeutic Goods Administration (TGA)

			(HPFB), Health Canada	
Registration process	One registration process	Multiple registration process • Centralised (European community) • Decentralised (at least 2 member states) • Mutual recognition (at least 2 member states) • National (1-member state)	One Registration Process	Sponsor applies to register the product on the ARTG.
Stability data	The stability data for accelerated studies are submitted for three months at the time of original Submission	The stability data for accelerated studies are submitted for complete 6 months at the time of original submission.	The stability data for accelerated studies are submitted for complete 6 months at the time of original submission	The stability data for accelerated studies are submitted for complete 6 months at the time of original submission
Pharmacopeia	US pharmacopeia	BP/Ph. Eur.	BP/Ph.Eur./USP	BP/Ph.Eur./USP
Post approval changes	Post approval changes in the approved drug: • Minor • Moderate • major	Post variation in the approved drug: • Type IA • Type IB • Type II	Post-approval changes in the approved drug: • Minor • Moderate • major	Post variation in the approved drug: • minor • major
Application	ANDA/NDA	MAA	ANDS	Application category is identified by a number: Category 1 Category 2 Category 3
Debarment classification	Required	Not required	Not required	-
Number of copies	3	1	-	-
Approval timeline	18 months	12 months	2 years	11 months
Fees	Under $2 million – NDA application $1,520 – ANDA application	National fee (including hybrid applications): £103,059 Decentralised procedure	$37,358.25	AUD 91,600
Presentation	eCTD and paper	eCTD	CTD	CTD/eCTD
Number of batches	1	3	2	1
Packaging	A minimum of 1,00,0000	Not required	Not required	-
Process validation	Not required at the time of submission	Required	Not required at the time of Submission	Required
Batch size	1 pilot scale or minimum of 1 lakh units whichever is higher	2 pilot scale plus 1 lab batch or minimum of 1 lakh units whichever is higher	2 pilot scale batches	Minimum of two batches of at least pilot scale.

Table 4. Comparison based on Modules (8,12, 16, 19)

US	Europe	Canada	Australia
i. Administrative information is different i.e., cover letter, forms (356h), application	i. Administrative information such as cover letter specified for the particular	HC/SC 301 i. Administrative information Correspondence Table of	i. the administrative information and prescribing information (for example, the

information, field copy certification, debarment certification, financial certification, Patent information and exclusivity.	country; application form applicable in that country, exclusivity statement, proof of payment to clinical investigators, proof of establishment of the applicant in EEA.	Contents (M1 to 5) Administrative Information product Information Health Canada Summaries Environmental Assessment Statement Regional Clinical Information Clinical Trial Application and Clinical Trial Application-Amendment Specific Requirements	application form, the proposed product information and labelling) for Australia For Category 1 and 2 applications (other than applications for additional trade names), documents from different CTD modules are in separate volumes.
ii. The paper size for the submission is Letter size (8.5x11inches) with font size 12 in times new roman format. The tables and figures have small font size i.e. 8 to10.	ii. A4 (8.27x11.69inches) paper size is used for the dossier preparation with font size 12 in times new roman format.	ii. The paper size for the submission is Letter size (8.5×11 inches) with font size 12 in Times New Roman format. The table and figures have small font size i.e., 9	ii. We recommend that text is no smaller than: 12-point text, 10-point text within tables, 10-point text within footnotes.
i. Package inserts are provided for drug product in labelling.	iii. SPC (summary of product characteristic) is provided about the drug product in labelling.	iii. Package inserts are provided for drug Product in Labelling.	iii. package insert (content of labelling) submitted electronically
iv. Proposed Labels and cartons with proper dimensions similar to that of the RLD labels are provided.	iv. Mock ups and specimens of labels and cartons sent with the application as appropriate. Braille is used for the labeling conditions on the labels.	iv. Proposed Labels and Cartons with Proper dimensions similar to that of the RLD labels are provided	iv. Mock ups and specimens of labels and cartons sent with the application as appropriate
v. Request for waiver of in-vivo BE studies isprovidedinthemodule 1.	v. Request for waive is not provided inthemodule1.	v. Request for waiver of in-vivo BE studies is provided in the module 1 in module 1.6	v. Request for Waiver of In-Vivo BA/BE Study(ies)
vi. Annotated draft labeling (side by side) for labels and cartons compared with the RLD with proper annotation is provided.	vi. No annotation (side by side) for labelling is provided. Everything is provided in the SPC and package inserts.	vi. Annotated draft labelling (side by side) for labels and cartons compared with the RLD with proper annotation is provided	vi. side by side labelling (package and patient insert) comparison with all differences annotated and explained RLD label and RLD container label
vii. The EAS (Environment Assessment Statement) for Categorical exclusion certification in compliance With the law of EPA of US is provided.	vii. Environ risk Certification is given with the information for GMO or Non -GMO. The fresh/ new certificate is provided.	vii. The EAS is required for new substances in products regulated under the F&D Act as per the New Substances Notification Regulations (NSN) of the Canadian Environmental Protection Act (CEPA)	vii. Environmental Risk for non-GMOs containing medicines

3.4.10. No addition or supplementary data after submission Lodgment

The data submitted during submission phase will be considered as final and complete submission. No supplementary or additional is required to submit. Australian regulation of prescription medical products

3.4.11. Submission of dossier

This CTD contains five modules:

Module 1: Australian specific Administrative and Prescribing Information.

Module 2: Quality overall summary.

Non clinical summary

Clinical summary

Module 3: Quality Data.

Module 4: Non clinical Data.

Module 5: Clinical Data.

As dossier was compiled for Generic drug (Parental preparation), submission of Module 4& 5 data is not required

3.4.12. Approval

Final decision by the TGA

Finalise conditions of registration

Advice to sponsor for new chemical entity, advise drug information centres, forensic laboratories, etc.

3.4.13. Registration

Sponsor applies to register the product on the ARTG Supply is permitted once AustR number is allocated

The current application and annual fees (table 3) for registering or listing a medicine on the ARTG are:

Medicine type	Application Fees ($AUD)
Prescription (New chemical entity)	221,400
Prescription (Generic)	84,600

4. Conclusion

Parenteral products are nowadays widely used for the emergency situation, as it provides maximum bioavailability. Parenteral product regulation is necessary because if not sterile, non-pyrogenic can cause severe harm to health causing life-threatening risk to patient. From the above study it is concluded that the US, being the world's largest Pharmaceutical market, also accounts for the largest chunk of the overall injectable space. For the registration of Parenteral product, TGA adopted some (not all) EU guidelines. On the other hand, health Canada follows some USFDA regulation guidelines for the submission of the drug product. As discussed above comparative study of regulation and registration process for Parenteral dosage form will be useful regulatory point of view as well as business development point. We can conclude that the Industry can harmonize the dossier application in better way, which will help in reducing time for products to reach the market.

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Conflict of Interest

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

References

1. Thomas S, Mahendran S, Selvakumar R. FORMULATION AND EVALUATION OF AN INJECTABLE SOLUTION AS A DOSAGE FORM. JDDT [Internet]. 6Sep.2018 [cited 2Jan.2023];8(5):81-7. Available from: https://jddtonline.info/index.php/jddt/article/view/1854
2. Parenteral Packaging Market by Product Type, By Material and by Region: Industry Analysis, Market Share, Revenue Opportunity, Competition and Forecast 2020-2027 [Internet]. FutureWise;2023 [cited 2023 Jan 21]. Available from: https://www.futurewiseresearch.com/healthcare-market-research/Parenteral-PackagingMarket/93
3. Llamas M. How the FDA Regulates and Approves parenteral Drugs [Internet]. drugwatch;2023 Jan 31 [cited 2023 Feb 22]. Available from: https://www.drugwatch.com/fda/
4. Gorsky I. Sterile Manufacturing: Future Trends and Challenges [Internet]. contractpharma;2017 [cited 2023 Feb 23]. Available from: https://www.contractpharma.com/sterile-manufacturing-future-trends-and-challenges
5. Dongare S, Mali S, Patrekar P. Sterile parenteral products: a narrative approach. JDDT [Internet].2015 Jan 13[cited 2023 Feb 21];5(1):41-8. Available from: https://jddtonline.info/index.php/jddt/article/view/1047
6. Saad Ali H. A Comprehensive Review in Parenteral Formulations. Acta Sci Pharm Sci. 2020;4(7):33-41. doi:10.31080/asps.2020.04.0554
7. Jawahar N, Vidhya Lakshmi T. Regulatory requirements for the drug approval process in US, Europe and India. J Pharm Sci Res. 2017;9(10):1943-1952.
8. Mumeena S. Comparison of Regulatory Requirements for Generic Drugs Dossier Submission in United States, Europe and Canada. Int J Pharma Chem Res. 2017;3(2):369-396. http://www.ijpacr.com/files/07-04-2017/35.pdf.
9. Kumar M, Venkatesh MP, Kumar TMP. Review Article Strategic planning for regulatory submission of injectables / parenterals. 2020;7(2):30-36.
10. Investigational New Drug Application IND Application Template (mssm.edu) [Internet]. New York: Icahn School of Medicine at Mount Sinai;2016 Feb 24 [cited 2023 Feb 21]. Available from: https://icahn.mssm.edu/files/ISMMS/Assets/Research/Research%20Portal/ORS/6_IND_Application.pdf
11. Jawahar N, Shrivastava N, Ramachandran A, Baviya Priyadharshini R. Procedures and applications for marketing authorisation of medicinal products in European union. J Pharm Sci Res. 2015;7(4):219-225.
12. Gupta NV. Comparative Study of Generic Drug Approval process in EU, USA and China. 2017;42(14):67-73.
13. Makvana P, Maheshwari D. Regulatory Requirements for Marketing Authorization of Generic Parentral Product in European Conutries by Decentralised Procedure. JPSBR. 2014;4(2):145- 149.
14. The European regulatory system for medicines A consistent approach to medicines regulation across the European Union [Internet]. EU: europa.eu;2014 [cited 2023 Feb 22]. Available from: https://www.europarl.europa.eu/meetdocs/2014_2019/documents/envi/dv/ema_promo_/ema_promo_en.pdf
15. Sandeep D S, Raj K A, Narayanan V A, Dubey, A, & Jose J. Regulatory Approval Process for Drugs in Canada-A Challenging Task. Research Journal of Pharmacy and Technology. 2019;12(7):3206-10.
16. Meghraj S. An overview on comparative study of registration requirements for generics in US, Canada and Europe. International Journal of Research in Pharmaceutical Sciences and Technology. 2020;1(4):117-123.

17. India PEPC of Regulatory & Market Profile of Australia [Internet]. Pharmexcil;2018 [cited 2023 Feb 22]. Available from: https://pharmexcil.com/uploads/countryreports/Australia-_Regulatory_Market_Profile.pdf
18. Sai Kumari B., Sai Hanuja G., Nagabhushanam M.V., D. Nagarjuna Reddy BB. Current Regulatory Requirements for Registration of Medicines, Compilation and Submission of Dossier in Australian Therapeutic Goods Administration. Int J Adv Sci Tech Res. 2016;6(6):144-157.
19. Bhargava, N.S., Shah, D.B., Maheshwari, D.G. Comparative Study of Regulation and Registration Process of Parenteral Product in US and Malaysia. International Journal for Pharmaceutical Research Scholars (IJPRS). 2015;4(1):74-81.
20. Regulatory and market profile of Australia (pharmexcil.com) [Internet]. Pharmexcil;2018 [cited 2023 Feb 22]. Available from: https://pharmexcil.com/uploads/countryreports/Australia-_Regulatory_Market_Profile.pdf
21. Vaughan, G. The Australian drug regulatory system. Australian Prescriber. 1995;18:69-71.