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Regulatory Requirements for the Approval of Generic Inhalation And Nasal Products and Its Marketing Scenario in USA, Canada and EU

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ABSTRACT

In this study work a comparative and differentiation has been put forwarded to make some recommendations of the regulatory framework. Now a day's it's too hard to invent a new drug so, the major pharmaceutical companies mainly depend up on the generic production of drugs. The generic drugs are very cheap when compared to innovator drugs in production cost and these generic products are customer friendly. . In this study the information was extracted from certain journals, text books, and related websites and from the authorized regulated authorities of the particular countries. The Topics covered in this study are introduction to regulatory affairs as well as regulated authorities in USA, CANADA and EUROPEAN UNION. About the data exclusivity and patent protection term information and the comparison among USA, CANADA and EUROPEAN UNION are enlisted in this topic. The comparison between the number of NDA approvals and ANDA approvals of USA, CANADA and European Union are represented statistically from 2006 to 2013 are labeled. The number of total molecule wise approvals in these countries is represented through pie charts and the top most pharmaceutical firms and their brand names of inhalation and nasal products are mentioned.

Keywords: Nasal Products, NDA, MAA.

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INTRODUCTION

About Pharmaceutical Regulatory Affairs

It is proved that, on an average, a drug takes 10 - 12 years from initial research to reach the marketing stage. The cost of this process is estimated to be more than US$ 1 billion. Typically, several thousands of compounds are screened and tested, and only a few makes it onto the market as drug products. Of the 5000-10,000 compounds that show initial response, five will go into human clinical trials, and only one will become an approved drug. Customers want the drugs that are prescribed for them to be safe and effective to treat their diseases. It is the duty of public regulatory authorities to ensure that pharmaceutical companies stick with regulations or not. There are legislations that require drugs to be developed, tested, trialed, and manufactured in accordance to guidelines so that they are safe and patients' well-being is protected. Regulatory authorities perform the watchdog role to ensure that animal studies comply with Good Laboratory Practice (GLP), clinical trials are performed in accordance with Good Clinical Practice (GCP), and drugs are manufactured under current Good Manufacturing Practice (cGMP) conditions. The regulatory authorities also carry out surveys to ensure that labels and advertising materials are accurate and in accordance with approved claims. To achieve the goal of protection of public health, the regulations rely on a number of core principles and concepts:

- Safety
- Efficacy
- Purpose
- Risk / Benefit
- Quality

Since new drug development is a time taking and costly performance, pharmaceutical companies also manufacture generic versions of innovator products for which patents have expired. A generic drug product, also referred to as a multi-source pharmaceutical product, is considered to be 'essentially similar' or bioequivalent to an innovator (brand name) product. Bioequivalence implies that a generic drug product is essentially identical to the brand name (reference) drug product in terms of active ingredient(s), strength, and dosage form, route of administration, quality, safety, efficacy performance characteristics, and therapeutic indication. Generic drug products market is increasing day by day in the world market.

Regulatory Authorities of US, Canada and European Union

The scope of this study includes a comparative study of the guidelines and guidance documents

for generic approval of inhalation and nasal drug products issued by the regulatory authorities of USA, Canada and European Union.

United States of America (USA)

In the USA, the regulatory agency is Food and Drug Administration (FDA) which is established within the U.S. Department of Health and Human Services[1]. It consists of six product centers, one research center, and two offices.

FDA is responsible for:

- Protecting the public health by assuring the safety, effectiveness and security of human and veterinary drugs, vaccines and other biological products, medical devices, food, cosmetics, dietary supplements and products that give off radiation.
- Regulating tobacco products.
- Advancing the public health by helping to speed product innovations.
- Helping the public to get accurate science-based information they need to use medicines, devices, and foods to improve their health.

The various centers and offices within the FDA include:

1. Center for Biologics Evaluation and Research (CBER), which regulates products such as vaccines, blood and gene therapy.
2. Center for Devices and Radiological Health (CDRH), which regulates medical devices ranging from thermometers to kidney dialysis machines, and electronic products that give off radiation, such as microwave ovens.
3. Center for Drug Evaluation and Research (CDER).

Canada

In Canada, the regulatory agency is Health Canada which is engages in various activities and has numerous responsibilities related to health[2].

The main goals of Health Canada are:

- Preserve and modernize
- Canada's health-care system.
- Enhance and protect the health of Canadian public.
- Work in partnership with other departments, and Communicate health promotion and disease prevention.

The overall organization of Health Canada which includes several branches and an agency is shown in Table 1

Table 1: Organization of Health Canada

MINISTRIES AND OFFICERS	
Minister of Health	Deputy Minister
Associate Deputy Minister	Chief Public health Officer
BRANCHES, OFFICES AND BUREAUS	
Audit and Accountability Bureau	Chief Financial Officer Branch
Corporate Services Branch	Secretariat Departmental
Healthy Environments & Consumer Safety branch	Health Products & Food Branch
Pest management regulatory Agency	Legal Services
Regions and Programs Branch	Public Affairs, Consultation and Communication
AGENCIES	
Assisted Human Reproduction Canada	Canadian institute of Health Research
Hazardous Materials Information review Commission	Patented Medicines Prices Review Board
Public Health Agency of Canada	

European Union

The European Union (EU) is a unique economic and political partnership between 27 European Countries. The EU has developed a single market also known as the internal market through a standardized system of laws which apply in all member states. However, the agreement of the European Economic Area (EEA) which entered into force in January 1994, allows 3 member states of the European Free Trade Association (EFTA) i.e. Norway, Iceland and Liechtenstein to participate in the internal market. Thus, a total of 30 countries are included in the EEA within which there is freedom of movement of goods, persons, services and capital in all industrial sectors except agriculture and fishery[3].

These scientific committees are:

- Committee for Medicinal Products for Human Use (CHMP)
- Committee for Medicinal Products for Veterinary Use (CVMP)
- Committee for Orphan Medicinal Products (COMP)
- Committee on Herbal Medicinal Products (HMPC)
- Pediatric Committee (PDCO)
- Committee for Advanced Therapies (CAT)

These scientific committees are further divided into working parties having expertise in particular scientific fields. Apart from the above mentioned committees, EMA also contains two coordinating bodies which co-ordinate the marketing authorization of a medicinal product in two or more member states in accordance with the mutual recognition procedure or the decentralized procedure.

These are:

- Mutual Recognition & Decentralized Procedure - Human [CMD(h)]
- Mutual Recognition & Decentralized Procedure - Veterinary [CMD(v)]

The specific functions and responsibilities of each of the above mentioned committees and coordinating groups can be obtained from the official EMA website. The information regarding Data Exclusivity and Patent Protection (Table 2), Patent Protection Term in US (Table 3), Canada and European Union (Table 4) and Current Market Scenario and Sales of Inhalation Products (Table 5) was mentioned below in tabular format.

Table 2: Data Exclusivity and Patent Protection

	Data Exclusivity Term
Country	**Term**
U.S.A	5 years for New Chemical Entities as per Hatch - Waxman Act Beginning on the date of marketing[4] approval. 4 years if the application contains a certification of patent invalidity or non-infringement (Paragraph IV filing). 3 years for supplementary applications in relation to previously approved chemical entities with new clinical investigation reports for new indication. 3 years for changes in an approved drug product that affect its active ingredient(s), strength, dosage form, route of administration or conditions of use if they meet the clinical investigations criteria of a) having not been previously relied upon by the FDA for approval of a product and b) do not duplicate the results of such an investigation. 6 months extension to any data exclusivity or patent protection on a drug for which FDA has requested pediatric studies and the manufacturer has conducted such studies in accordance with the requirements of FDAMA (Food & Drug Modernization Act, (1997). 7 years exclusivity if the drug product gets orphan drug status. 6 months exclusivity for first-to-file ANDA's with patent challenge (Paragraph IV) certification.
Canada	5 years for new products approved before 17th June 2006 Containing new pharmaceutical actives not previously approved by Health Canada. 8 years for new products approved on or after 17th June 2006 including 6 years data exclusivity during which no generic applications are accepted followed by market exclusivity for 2 years during which approval will not be granted to the generic application. 6 months extension to any of the above for pediatric studies designed and conducted with the purpose of increasing knowledge about the use of the drug in pediatric populations. No additional exclusivity for new dosage forms, routes of administration, indications or combinations with other active ingredients.
European Union	8 years data exclusivity with additional exclusivity. 1 year maximum extension if authorization is granted for new therapeutic indications having significant clinical benefit in comparison with existing therapies. 10 years market exclusivity if the drug product gets orphan drug status.

Table 3: Patent protection term in US, Canada and European Union.

Patent Protection Term	
Country	**Patent Term**
U.S.A	20 years from the date of filing of the application[5] (for applications filed after 08/06/1995)
Canada	20 years from the date of filing of the application[6] (for applications filed after 01/10/1989)
European Union	20 years from the date of filing of the[7] application

Table 4: Current Market Scenario

Top Firms in the Inhalation and Nasal Market	
GlaxoSmithKline	Sanofi Aventis
Boehringer Ingelheim	Mylan Inc
Baxter Healthcare	Watson Pharmaceuticals
Teva Pharmaceutical Industries	AstraZeneca
Novartis	Abbott

Table 5: Sales of Inhalation Products

Firm	Brand Name	Active Ingredient	Sales (US Million $)
GlaxoSmithKline	Seretide / Advair	Fluticasone Propionate / Salmeterol	8,000(Approx)
Boehringer Ingelheim	Spiriva	Tiotropium	3,077(Approx)
AstraZeneca	Symbicort	Budesonide / Formeterol	2,500(Approx)

Pictorial Representation of Statistical Data of NDA's and ANDA's approved from 2006 to 2013

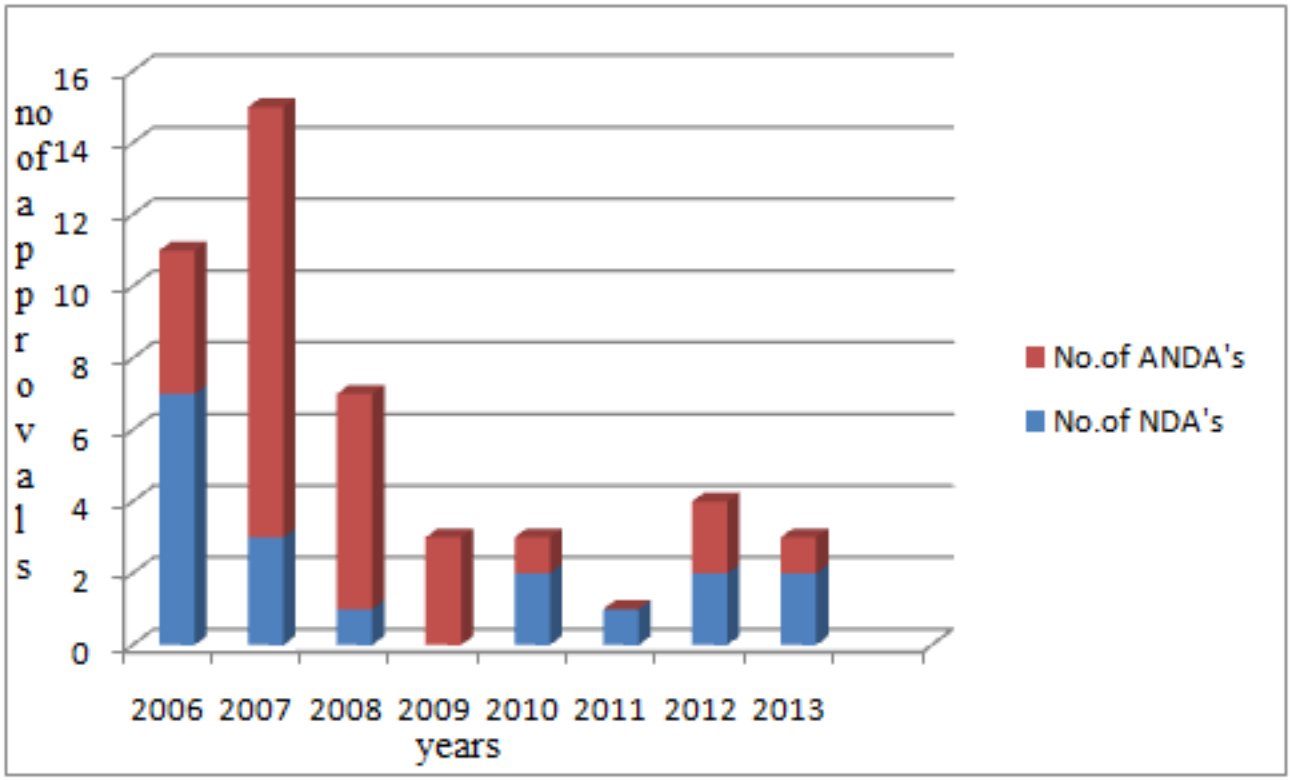

Figure1: Approval Statistics of Inhalation and Nasal Products in USA

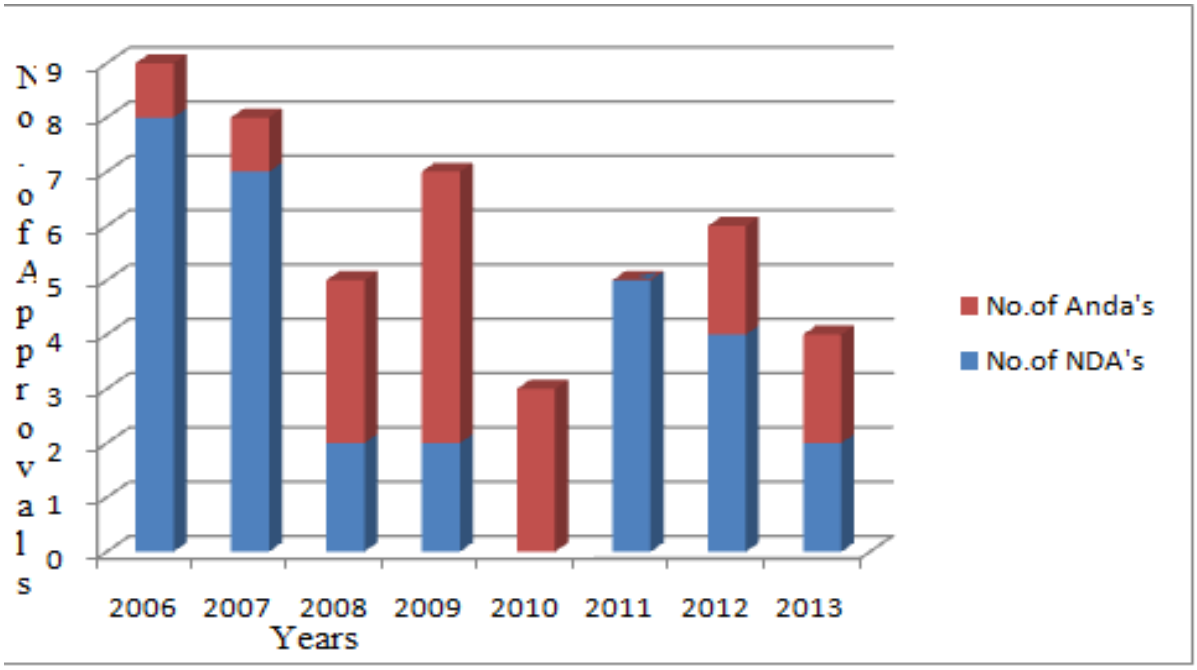

Figure 2: Approval Statistics of Inhalation and Nasal Products in Canada

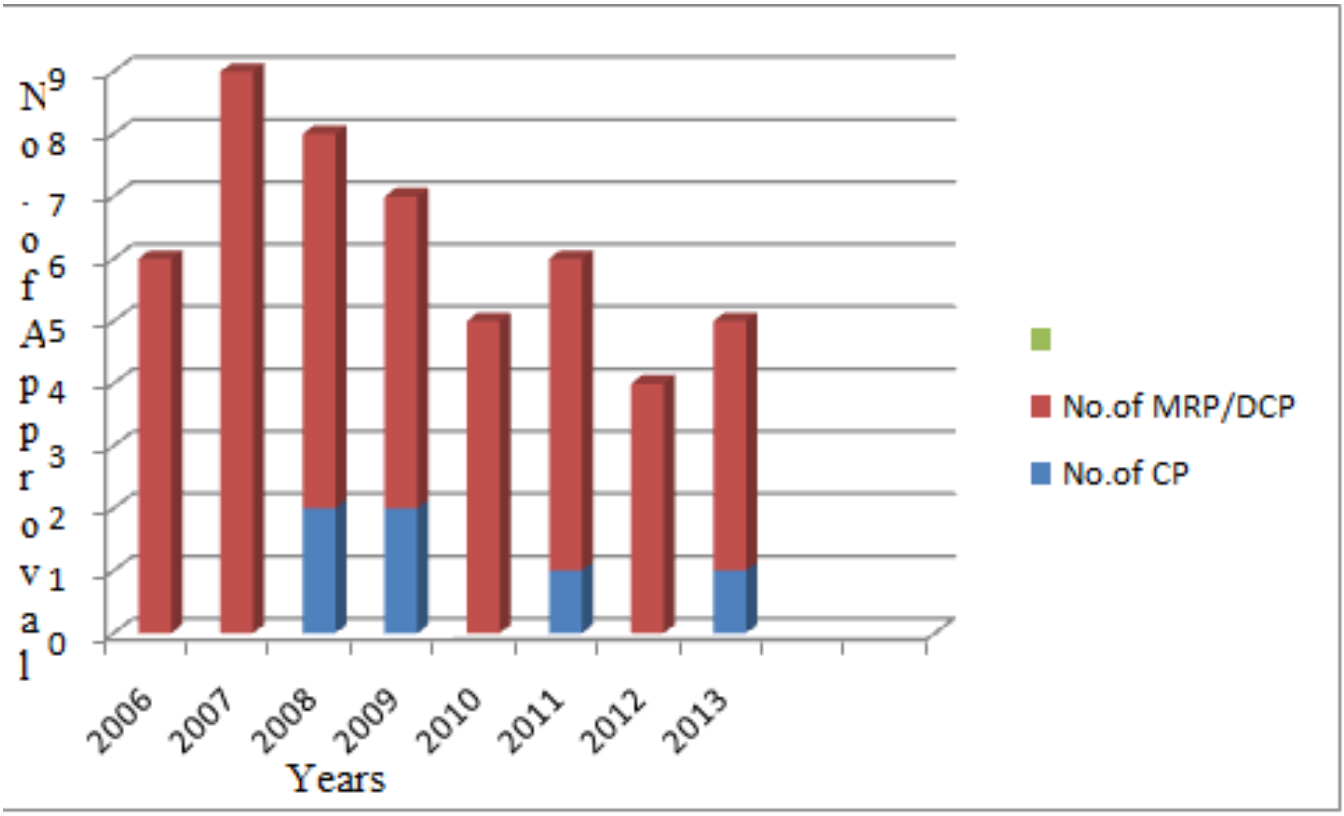

Figure 3: Approval Statistics of Inhalation and Nasal Products in European Union

Pictorial Representation of Statistical Data of Drug wise Approvals from 2006 to 2013

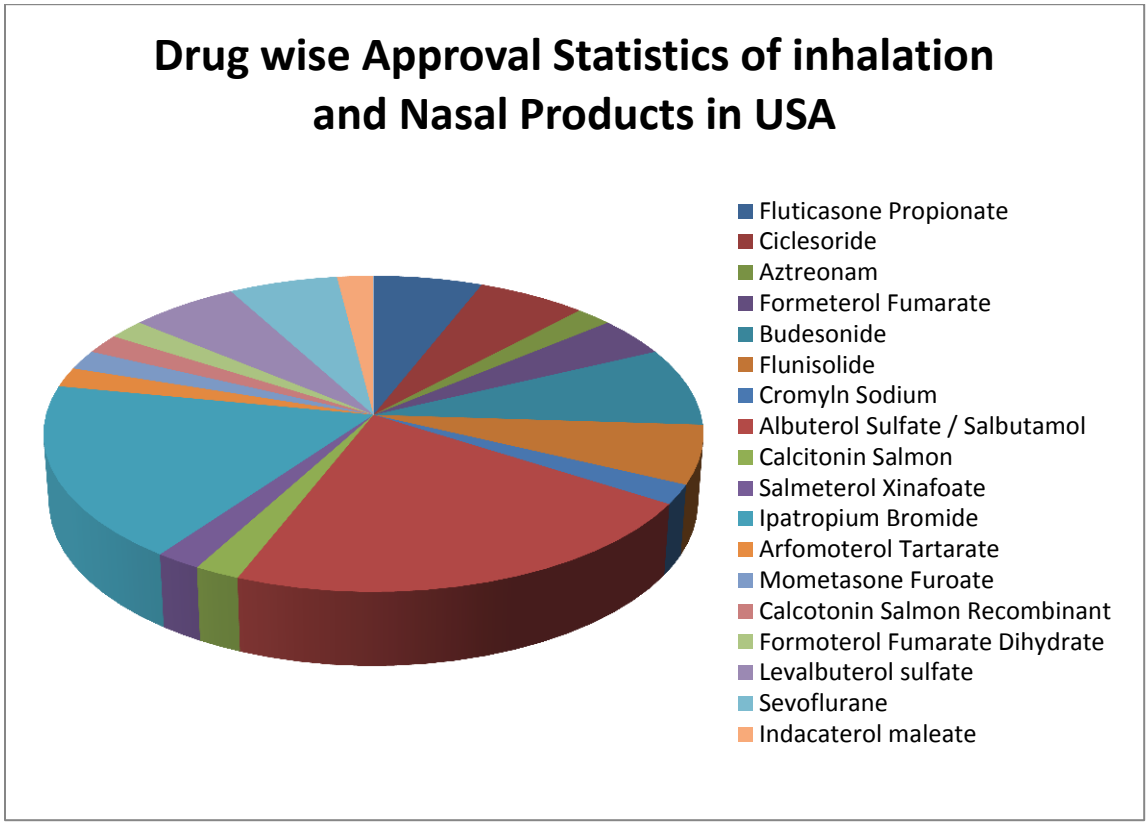

Figure 4: Drug wise Approvals of Inhalation and Nasal Products in USA

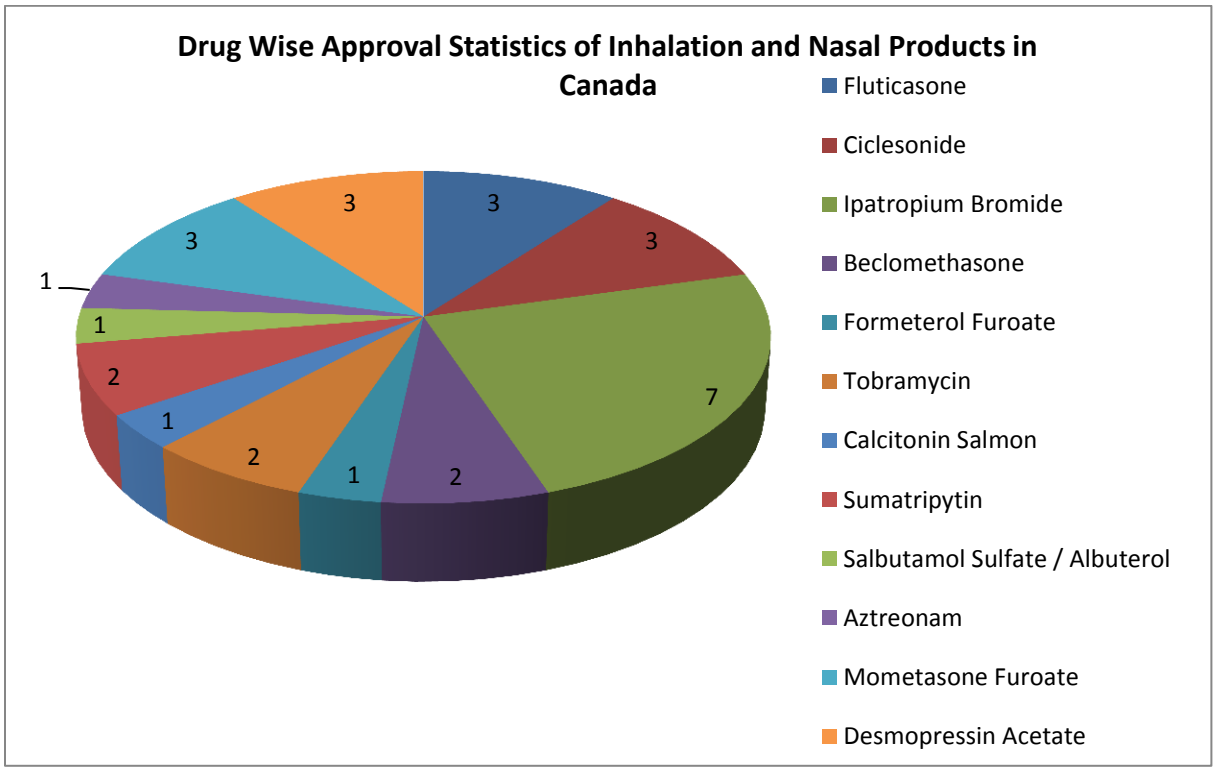

Figure 5: Drug wise Approvals of Inhalation and Nasal Products in Canada

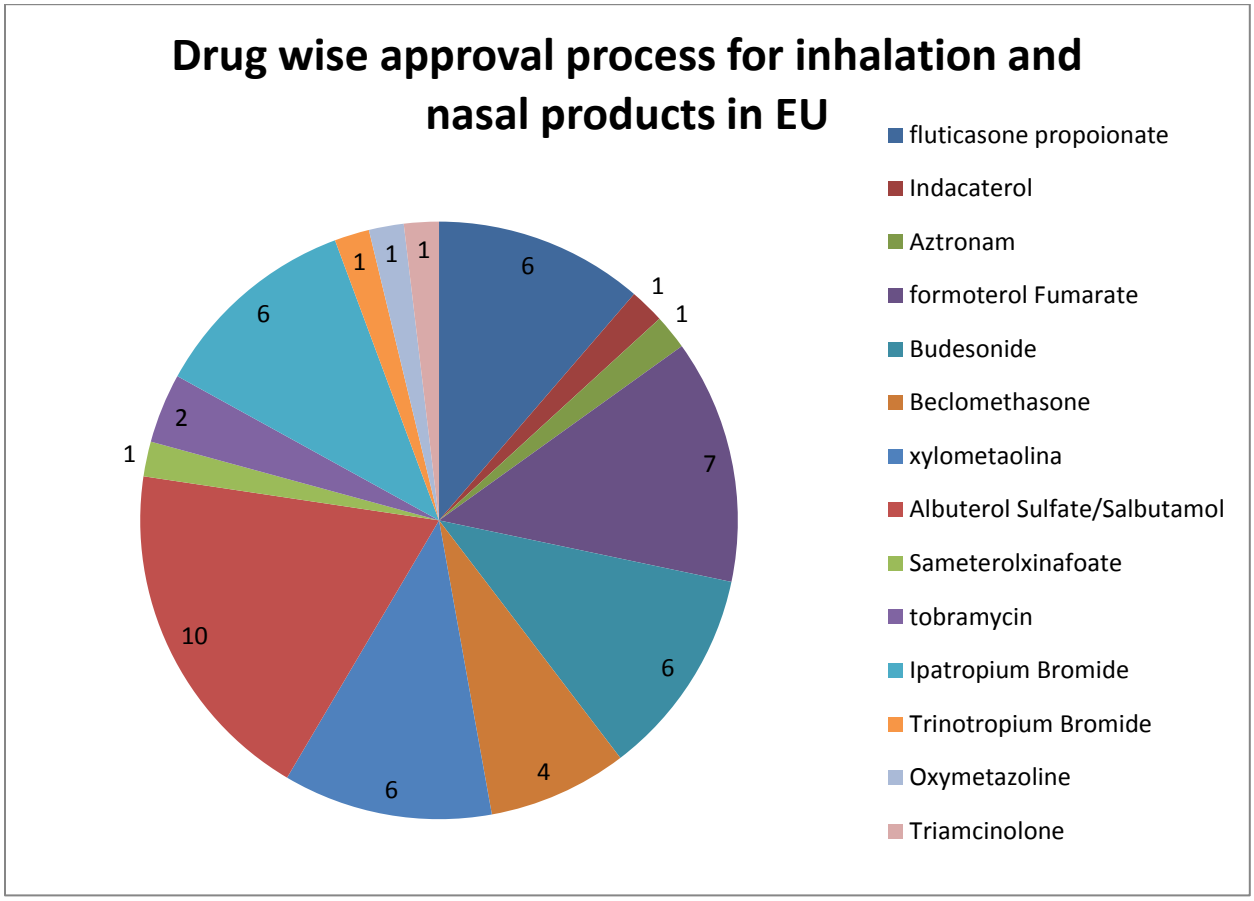

Figure 6: Drug wise Approvals of inhalation and Nasal Products in EU

CONCLUSIONS

The various brand names of drugs and their molecule name available in the market to be administered via the inhalation and nasal route were determined. The market scenario with respect to approval history of innovator and generic inhalation and nasal formulations was researched and plotted. The authorized organisations, functions and registration procedures of the regulatory authorities of USA (FDA), Canada (Health Canada) and European Union (EMA) was studied and compared. The data exclusivity and patent term approach should be followed in order to overcome regulatory back steps. If the regulated hurdles are prevented successfully, inhalation and nasal drugs market scope is available for generic pharmaceutical companies for the coming decade. Thus it can be concluded that the registration of generic inhalation and nasal products can be achieved if the necessary regulatory requirements are maintained successfully. The pharmaceutical companies can develop their share in the market if they follow the proper regulations and guidelines of the respected regulatory authorities.

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