A study on Drug Product Approval by the FDA from 1930 to 2019

By

Md. Nazmul Islam Jony

ID: 16146041

A thesis submitted to the Department of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons.)

Department of Pharmacy

Brac University

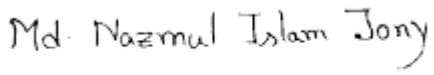
February, 2021

Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I/We have acknowledged all main sources of help.

Student's Full Name & Signature:



Md. Nazmul Islam Jony

ID : 16146041

Approval

The thesis/project titled “A study on Drug Product Approval by the FDA from 1930 to 2019” submitted by Md. Nazmul Islam Jony (16146041) of Spring 2016 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.) on 3rd May, 2021.

Examining Committee:

Supervisor: Eshaba Karim

Eshaba Karim
Lecturer, Department of Pharmacy
Brac University

Program Coordinator: _____

Dr. Hasina Yasmin
Professor, Department of Pharmacy
Brac University

Departmental Chairperson: _____

Dr. Eva Rahman Kabir
Professor, Department of Pharmacy
Brac University

Ethics Statement

The study does not involve any kind of animal or human trial.

Abstract

The Food and Drug Administration (FDA) is responsible for protecting and ensuring the safety of the American public health by approving and monitoring drug products. They do so with strict supervision. This study was done to find out any correlation between drug products approved by FDA and the nature of disease. Since chronic diseases are growing in global prevalence and directly threatening the health of the world population, this study attempted to identify if the most frequently approved drug products are for the treatment of such diseases. Data was collected from the official FDA website and analyzed to find out how frequently products containing each active pharmaceutical ingredient were approved. The ATC codes for the APIs were enlisted. This was used to identify their therapeutic classes. Most of the therapeutic classes suggested that the FDA has indeed approved more drug products for the treatment of chronic diseases than acute diseases.

Keywords: FDA; Chronic Diseases; Global Prevalence; Unique API List; ATC codes; Therapeutic Classes

Dedication

Dedicated to my parents.

Acknowledgement

I would like to thank the Almighty Allah blessing me with patience to complete this project. My journey with this project was a learning experience for me and I could come this far because of the constant support of some people who have been thoughtful with this project.

Firstly, I would like to thank my supervisor Eshaba Karim (Lecturer, Department of Pharmacy, Brac University) for her constant support and motivation that helped me to complete this project. Without her, my project would not have turned as it is. I would like to thank our honorable Chairperson, Dr. Eva Rahman Kabir (Professor and Chairperson, Department of Pharmacy, Brac University) for her valuable support. I would also like to thank Dr. Hasina Yasmin (Professor and Academic Coordinator, Department of Pharmacy, Brac University) for always looking after us. Finally, I would like to thank my family and my friends for their support which inspired me to complete this project.

Table of Contents

List of Tables

List of Figures

List of Acronyms

ADHD	Attention-Deficit/Hyperactivity Disorder
ANDA	Abbreviated New Drug Application
ATC	Anatomical Therapeutic Chemical
CDC	Centers for Disease Control and Prevention
COPD	Chronic Obstructive Pulmonary Disease
FDA	Food and Drug Administration
NCCDPHP	National Center for Chronic Disease Prevention and Health Promotion
NDA	New Drug Application

Glossary

Active pharmaceutical ingredient	An active ingredient is the ingredient in a pharmaceutical drug that is biologically active.
Acute disease	A disease characterized by a relatively sudden onset of symptoms that are usually severe.
Chronic disease	A chronic disease is defined as condition that lasts 1 year or more and require ongoing medical attention.

Chapter 1 Introduction

1.1 Literature review

The Food and Drug Administration

The Food and Drug Administration (FDA) is the agency within the U.S. Department of Health and Human Services that approves new drugs, vaccines, medical devices, biological products, dietary supplements and treatment methods. It also regulates and monitors the safety of the country's food supply. FDA consists of the Office of the Commissioner and four directorates. The directorates are in charge of overseeing the core functions of the agency that involves medical products, foods, tobacco, veterinary medicine, regulatory operations, policy making etc. Its main objective is to protect the public health by ensuring the drugs, vaccines, foods, medical devices that are marketed for public use are safe and effective. It is also in control of inspecting the safety of all cosmetics, food supply, products producing radiations and dietary supplements. FDA's regulation programs of different types of goods greatly differ between types of the products, potential risks that they may carry and the authority given to them by law. For instance, almost all aspects of prescription drugs are regulated by the FDA. This includes manufacturing, testing, marketing, monitoring efficacy and safety. However, they do not have the same authority over cosmetic products as it is centered only on the product's safety and its labeling.

The FDA is well-known for its work in regulations and control over the development of new drugs. For new drugs to be approved by the FDA, all manufacturing companies must follow the regulations and standards set by the FDA. Inspectors of the FDA ensures news drugs waiting to get approved are manufactured using standard manufacturing processes. No pharmaceutical products get FDA approval without maintaining the standard procedures. Furthermore, FDA has the authority to recall faulty and contaminated products. When there is arrival of any new drug product in the market, it is safe to say it has gone through the approval process by the FDA because it inspects and also reviews the production process thoroughly. FDA inspectors generally check if the drug product is safe and works as intended maintaining the effectiveness. The place to conduct drug testing on animals and clinical trials are also inspected by the FDA.

As the oldest consumer protection agency in the United States, the FDA is always working to ensure the safety of the consumer. But it was not always the same. Before 1938, drug

manufacturing companies were not obliged to get FDA's safety approval before marketing their products. A drug company from Tennessee marketed a new sulfa drug in 1937 which caused more than 100 deaths. That highly toxic drug did not undergo any safety regulations which initiated huge public outcry to reshape the law regarding drug safety to prevent any such incident from occurring again in future. As a result, The Federal Food, Drug and Cosmetics Act was signed in 1938 which stated that all drug products must have FDA's safety approval (*Part II: 1938, Food, Drug, Cosmetic Act | FDA*, 2018). This act of 1938 was expanded by "Kefauver-Harris Amendments" in 1962. This amendment established that all medicines must be proven safe and also effective in order to be approved by FDA (Wilensky, 2012). Although all these safety concerns made sure that the public get more safe and effective medicines, those strict regulations and controls generated a complicated regulatory environment for the drug developing companies. An average of 50 drugs were annually approved by FDA in the late 1950s (Norman, 2016). The number came down to approximately 17 per year after 1965. It happened mainly because of "Kefauver-Harris Amendments". Norman referred it as "drug lag". Manufacturers gradually overcame this issue by concentrating more on the drug development process to reduce adverse drug reactions. Pre-clinical and clinical trials were the major factors in accomplishing their goals.

Drug approval by the FDA

Since the beginning of FDA's journey, its work considerably increased over the decades as it focused more and more on the safety and effectiveness of the new drugs. At the beginning of the drug approval process by FDA, only small number of drugs got approval from FDA each year. But with the advancement of science, scientists and doctors all worked together to produce more drugs and vaccines for both acute and chronic diseases. As a result, the approved drug numbers by FDA increased significantly. Manufactures also worked hard to follow and maintain the FDA regulations to produce safe and effective drugs for all kinds of diseases. Nowadays, FDA approves hundreds of safe drugs each year maintaining the strict regulations. Whether it is a minor headache or a deadly cancer, nearly all diseases currently have effective drugs or treatment processes available. Manufacturers are continuously trying to produce new drugs with much more efficacy and effectiveness than the existing drugs for the same diseases. They spend billions of dollars developing new medicines for diseases such as cancers, diabetes, asthma, cardiovascular diseases, tumors etc. Manufacturers then have to

submit New Drug Application (NDA) to FDA for the approval of their product (Norman, 2016).

As a result, FDA receives many new drug applications from various companies around the world that they carefully go through to ensure if the manufactures adequately followed each steps of the FDA provided guidelines. Not to mention, only few of the new drugs pass the final hurdle of the approval process to be sold in the market. Strict regulations and controls of FDA make it possible for the safe, efficacious and effective drugs to be available for disease treatment.

Manufacturers have different categories to go through while creating a new drug for the market. The process may be different depending on the drug they are developing. Manufacturers must fulfill all the criteria before submitting applications to FDA for approving the manufacturing process and the drug. There are several types of application submitted to FDA. Two of the main types are New Drug Application (NDA) and Abbreviated New Drug Application (ANDA). Firstly, NDA is a comprehensive document that is submitted to FDA requesting the regulatory approval for a new drug. Manufacturers must include detailed evidence of standard clinical trials and each of which involves escalating standards of scientific evidence. These data help the FDA reviewer to decide if the drug is safe and effective. The chance of a new drug receiving FDA approval is very high once the NDA is submitted. However, developing a drug to the point where an NDA can be filed is extremely difficult. Evidences of pre-clinical and clinical studies are absolutely mandatory for an NDA submission. Clinical trials have several phases such as phase 0, phase I, phase II, phase III and phase IV. Each phase can take days to months to be completed. Each NDA document must contain 15 sections containing detailed experimental evidence (including both animal and human studies). The document must extensively demonstrate the proposed drug's pharmacology, toxicology, and dosage requirements as well as the intended process for manufacturing the drug (Norman, 2016).

On the other hand, ANDA is submitted to FDA for the approval of generic drugs. Generic drug applications are not required to include preclinical and clinical data to establish effectiveness and safety of the drugs. That is why they are termed "abbreviated". Instead, generic applicants must scientifically demonstrate that their developed product performs in the same manner as the innovator drug. Bioequivalence test for the generic drug is the most important test before approving a generic drug. Basically, it measures the time required by

the generic drug to reach the bloodstream in healthy volunteers. Rate of absorption and bioavailability are key factors in this test. These demonstrate if the generic drug performs the same way as the innovator drug or not. The results of the bioequivalence test are then compared with the innovator drug. The generic drug must deliver the same amount of active ingredients into a patient's bloodstream in the same amount of time as the innovator drug to be approved by FDA (Wittayanukorn et al., 2020).

WHO ATC Index

The WHO Anatomical Therapeutic Chemical (ATC) Classification System is a classification of active ingredients of drugs according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties. The classification system is maintained by the World Health Organization. This is an internationally recognized classification system for drugs under WHO. WHO assigns ATC codes to all APIs contained in medicines based on the therapeutic indication for the medicine. Using the ATC code, active substances are classified in groups at five different levels according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties. Where the relevant information is available, a full ATC code will have five elements made up of letters and numbers. An example of how an ATC code is applied for a medicine containing the active substance omeprazole for the treatment of acid reflux and ulcers in the gut is mentioned below (*Health Products Regulatory Authority*, 2014).

Table 1: ATC code for Omeprazole

Level	Classification	ATC Code
Main Group	Alimentary tract and metabolism	A
Therapeutic Group	Drugs for acid-related disorders	A02
Pharmacological subgroup	Drugs for peptic ulcer and gastro-esophageal reflux disease	A02B
Chemical subgroup	Proton pump inhibitors	A02BC
Active substance	Omeprazole	A02BC01

The ATC code A02BC011 is issued to all drugs containing omeprazole as a single active substance. A different but related ATC code is issued to drugs containing omeprazole and one or more active substances.

A table of 14 anatomical groups and each of their therapeutic subgroups is given below (Sataloff et al., 2018).

Table 2: Classes of the WHO ATC Index

Serial no.	Anatomical main group	Therapeutic subgroup
1	A: Alimentary tract and metabolism	A01 : Stomatological preparations
		A02 : Drugs for acid related disorders
		A03 : Drugs for functional gastrointestinal disorders
		A04 : Anti-emetics and anti-nauseants
		A05 : Bile and liver therapy
		A06 : Drugs for constipation
		A07 : Anti-diarrheals, intestinal anti-inflammatory/anti-infective agents
		A08 : Anti-obesity preparations, excluding diet products
		A09 : Digestives, including enzymes
		A10 : Drugs used in diabetes
		A11 : Vitamins
		A12 : Mineral supplements
		A13 : Tonics
		A14 : Anabolic agents for systemic use
		A15 : Appetite stimulants
		A16 : Other alimentary tract and metabolism products
2	B: Blood and blood forming organs	B01 : Antithrombotic agents
		B02 : Anti-hemorrhagics
		B03 : Anti-anemic preparations
		B05 : Blood substitutes and perfusion solutions
		B06 : Other hematological agents
3	C: Cardiovascular system	C01 : Cardiac therapy
		C02 : Anti-hypertensives
		C03 : Diuretics

		C04 : Peripheral vasodilators
		C05 : Vasoprotectives
		C07 : Beta blocking agents
		C08 : Calcium channel blockers
		C09 : Agents acting on the renin-angiotensin system
		C10 : Lipid modifying agents
4	D: Dermatological drugs	D01 : Antifungals for dermatological use
		D02 : Emollients and protectants
		D03 : Treatment of wounds and ulcers
		D04 : Antipyretics drugs
		D05 : Anti-psoriatic drugs
		D06 : Antibiotics and chemotherapeutics for dermatological use
		D07 : Topical dermatological corticosteroids
		D08 : Antiseptics and disinfectants drugs
		D09 : Medicated dressings
		D10 : Acne drugs
		D11 : Other dermatological drugs
5	G: Genito-urinary system and sex hormones	G01 : Gynecological anti-infectives and antiseptics
		G02 : Other gynecological drugs
		G03 : Sex hormones and modulators of the genital system
		G04 : Urological drugs
6	H: Systemic hormonal preparations, excluding sex hormones and insulins	H01 : Pituitary and hypothalamic hormones and analogues
		H02 : Corticosteroids systemic
		H03 : Thyroid therapy
		H04 : Pancreatic hormones
		H05 : Calcium homeostasis
7	J: Anti-infectives for systemic use	J01 : Antibacterial drugs
		J02 : Antimycotic drugs

		J04 : Antimycobacterials
		J05 : Antiviral drugs
		J06 : Immune sera and immunoglobulins
		J07 : Vaccines
8	L: Antineoplastic and immunomodulating agents	L01 : Antineoplastic drugs
		L02 : Endocrine therapy
		L03A : Immunostimulants drugs
		L04A : Immunosuppressants drugs
9	M: Musculo-skeletal system	M01 : Anti-inflammatory and antirheumatic drugs
		M02 : Topical products for joint and muscular pain
		M03 : Muscle relaxants
		M04A : Antigout preparations
		M05B : Drugs affecting bone structure and mineralization
		M09A : Other drugs for disorders of the musculo-skeletal system
10	N: Nervous system	N01 : Anesthetic drugs
		N02 : Analgesic drugs
		N03A : Antiepileptic drugs
		N04 : Antiparkinson drugs
		N05 : Psycholeptics drugs
		N06 : Psychoanaleptics
		N07 : Other nervous system drugs
11	P: Antiparasitic products, insecticides and repellents	P01 : Antiprotozoal drugs
		P02 : Anthelmintic drugs
		P03 : Ectoparasiticides, including scabicides, insecticides and repellents
12	R: Respiratory system	R01 : Nasal preparations
		R02A : Throat drugs
		R03 : Drugs for obstructive airway diseases
		R05 : Cough and cold drugs

		R06A : Antihistamines for systemic use
		R07A : Other respiratory system products
13	S: Sensory organs	S01 : Ophthalmological drugs
		S02 : Otologicals
		S03 : Ophthalmological and otological preparations
14	V: Various ATC structures	V01AA : Allergen extracts
		V03A : All other therapeutic products
		V04 : Diagnostic agents
		V06 : General nutrients
		V07 : All other non-therapeutic products
		V08 : Contrast media
		V09 : Diagnostic radiopharmaceuticals
		V10 : Therapeutic radiopharmaceuticals
		V20 : Surgical dressings

Chronic diseases

Chronic illness and disorders are on the rise worldwide. A chronic illness is a disorder of long term health that lasts for more than one year and induces functional limitations or requires continuous treatment or monitoring. According to the World Health Organization, chronic disease prevalence is expected to rise by 57% by the year 2020 (*PwC*, 2017)

According to 'The world health report 2002 – Reducing Risks, Promoting Healthy Life', major chronic diseases are responsible for 60% of all deaths and 43% of the global burden of diseases and by 2020, these numbers were expected to go up to 73% and 60% respectively (*WHO | Integrated Chronic Disease Prevention and Control*, n.d.). Moreover, the CDC's National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP) reported that 60% of all adults have at least one chronic disease and 40% of all adults have two or more chronic diseases in the United States (*Chronic Diseases in America | CDC*, n.d.). Chronic diseases are increasing globally at an alarming rate. A few key facts as reported by the WHO about some of the most occurring chronic diseases are summarized below (*WHO | Fact Sheets: Chronic Diseases*, n.d.).

Table 3: Some facts about chronic diseases

Chronic disease name	Key fact
Asthma	Estimated more than 339 million patient in 2016
Chronic obstructive pulmonary disease (COPD)	Estimated 251 million cases of COPD globally in 2016
Cardiovascular disease	Estimated 17.9 million people died in 2016
Diabetes	Estimated 1.6 million deaths directly caused by diabetes in 2016
Obesity	Estimated more than 1.9 billion adults (39%) were overweight. Of these over 650 million (13%) were obese in 2016
Cancer	Estimated 9.6 million deaths in 2018

These numbers indicate the necessity of more effective chronic disease drugs which, to some extent, explains why there has been a remarkable rise on the development of drugs used to treat chronic diseases.

The United States spends more money on health care than any European country (Thorpe et al., 2007). Chronic disease treatments cause most of the spending. It reflects the fact that, United States has higher rates of such disease prevalence than any European country. Notable differences have been seen between the US-European disease prevalence comparisons. The disease prevalence data from their research is mentioned below (Thorpe et al., 2007).

Table 4: Comparison of disease prevalence between the US and Europe

Disease name	United States (%)	Europe (%)
Heart disease	21.8	11.4
High blood pressure	50.0	32.9
High cholesterol	21.7	19.6
Stroke/cerebrovascular disease	5.3	3.5
Diabetes	16.4	10.9

Chronic lung disease	9.7	5.4
Asthma	4.4	4.3
Arthritis	53.8	21.3
Cancer	12.2	5.4
Obesity	33.1	17.1

Chronic diseases have influenced people's health and wellbeing globally. Furthermore, chronic diseases have been a big factor of medical costs while affecting workforce structures as well. In the United States, chronic diseases are some of the most common and expensive health conditions. More than two thirds of all deaths are caused by one or more of these five chronic diseases: heart disease, cancer, stroke, chronic obstructive pulmonary disease, and diabetes (Raghupathi & Raghupathi, 2018). They also stated that, chronic diseases are responsible for seven out of 10 deaths in the U.S., killing more than 1.7 million Americans each year; and more than 75%. The number of people in US with chronic conditions is rapidly increasing. Heart disease, stroke, diabetes, cancer, respiratory disease, injuries, kidney disease and septicemia, Alzheimer's disease, influenza and pneumonia are currently the top ten health problems in America among which most of them are chronic diseases.

A research showed that, 125 million Americans had one or more chronic conditions and between 2000 and 2030, the number of Americans with chronic conditions will increase by 37 percent, an increase of 46 million people (Wu & Green, 2010). A graph showing the increase of chronic diseases in the United States from 1995 to 2030 is given below.

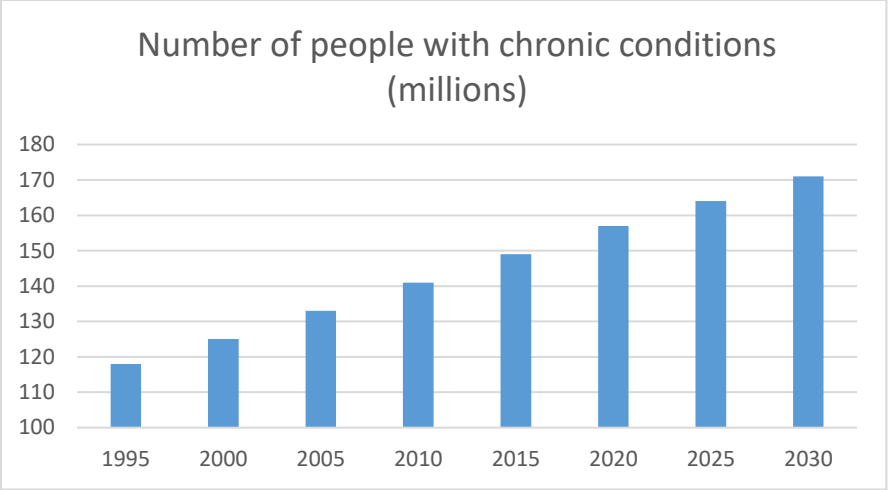


Figure 1: Cases of chronic conditions in the US (1995-2030)

1.2 Research Aim

The aim of this study is to organize and analyze big data on FDA drug approval in order to generate, highlight and extract information for easier understanding. The derived knowledge can answer specific questions about that data. The raw data is organized in such a way that can produce meaningful information and be used for further study purposes. This study was done to identify the active ingredient or combinations of active ingredients that have been frequently approved by FDA from 1930 to 2019. This information was used to verify if the FDA has indeed approved more drugs for chronic diseases than acute diseases from 1930 to 2019. The results produced by the data analysis helped to draw a conclusion on this matter.

Chapter 2 Methods

2.1 Data Collection

A compressed data file of the FDA approved drug products was downloaded from the official website of FDA (*Drugs@FDA Data Files | FDA*, n.d.). The compressed file was unzipped into 11 text tables. Next, the necessary information were extracted from the file named 'Products'.

2.2 Data Analysis

The extracted data was analyzed in Microsoft Excel spreadsheets using filters and formulas to determine the frequency at which active ingredients have been approved. The frequency was then used to classify active ingredients into different categories. Furthermore, selected APIs were classified according to the WHO ATC index.

Determination of frequency of API approval

From the 'products' data sheet, the frequency of the APIs was determined. To do this, first the unique data of the active ingredient column in the list was determined by following the steps given below.

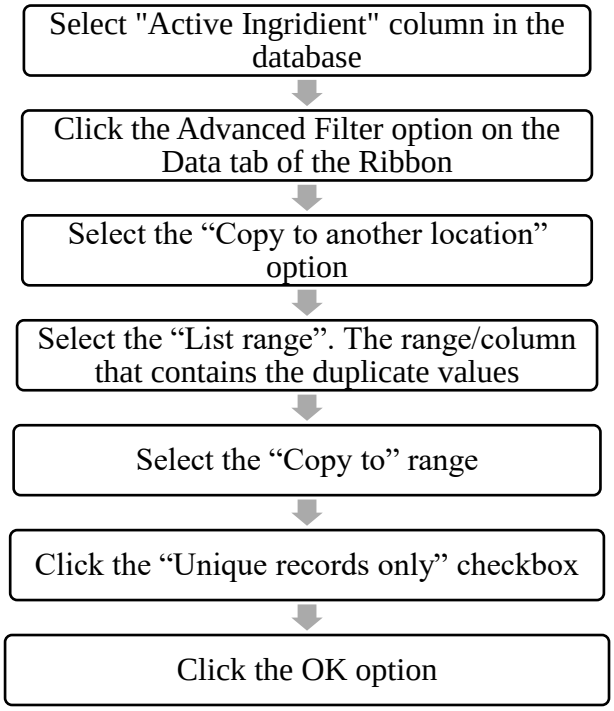


Figure 2: Steps in unique API list determination

Now that the “Unique Active Ingredient” list had been found, the frequency at which each value recurs in this non numerical list was determined by using “=Countif” on formula bar. The process is mentioned below.

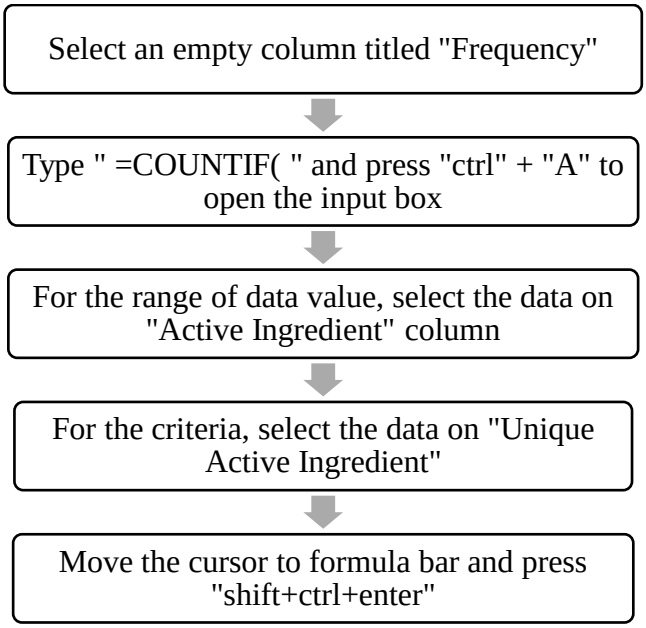


Figure 3: Steps in API frequency determination

Classification of APIs according to frequency of approval

The APIs (single or in combination) were classified according to the number of times they were approved by the FDA. The names of the classes are mentioned below.

- More than or equal to 200 times
- Less than 200 but more than or equal to 100 times
- Less than 100 but more than or equal to 50 times
- Less than 50 but more than or equal to 25 times
- Less than 25 but more than or equal to 10 times
- Less than 10 but more than 1 time
- 1 time only

The process for classifying the APIs is mentioned below.

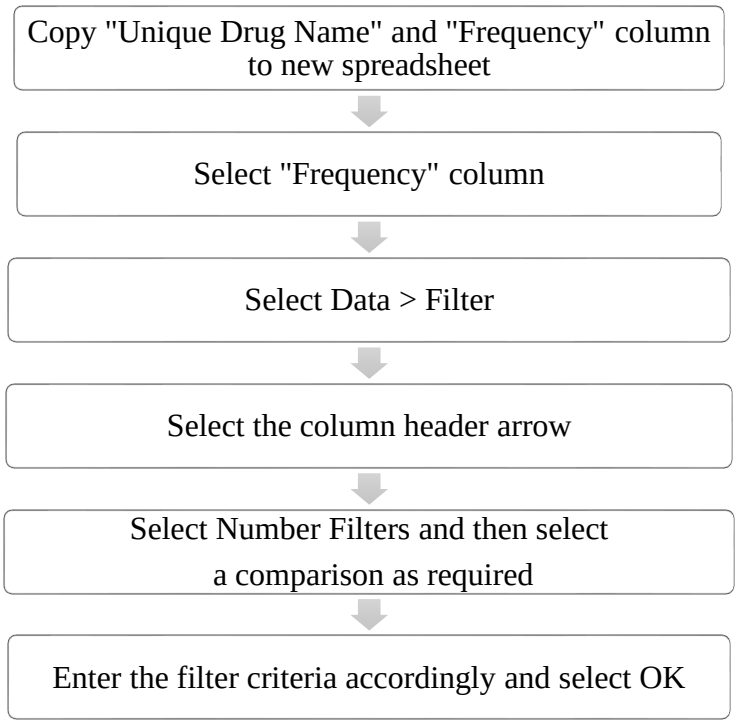


Figure 4: Steps in filtering API list

Classification of selected APIs according to the WHO ATC index

ATC codes for the active ingredients were taken from the following webpage of the WHO https://www.whocc.no/atc_ddd_index/ .

Chapter 3 Results

3.1 Data Collection

The “Products” file contained the list of 40425 FDA approved drug products, their active ingredients, strengths and dosage forms.

3.2 Data Analysis

Analysis of the data provided the information about approval frequency of the active ingredients. APIs were classified accordingly into separate categories. The Anatomical Therapeutic Chemical (ATC) codes of selected APIs were also found.

Determination of frequency of API approval

The unique data records for the “Active Ingredient” list were obtained. A total of 2842 unique active ingredients (single or in combination) were found from the database. The approval frequency for each was determined. The combination named 'Acetaminophen; Hydrocodone Bitartrate’ was approved 246 times. This is the highest for any active ingredient or combination of active ingredients.

Classification of APIs according to frequency of approval

The APIs were classified into groups according to the frequency of approval.

- **More than or equal to 200 times:** Eight APIs (single or in combination) were found whose products were approved more than 200 times. These are mentioned below.

Table 5: List of APIs with products approved more than 200 times

Serial no.	Active ingredients	Number of times approved
1	Acetaminophen; Hydrocodone Bitartrate	246
2	Ibuprofen	239
3	Pregabalin	230
4	Heparin Sodium	223
5	Methylphenidate Hydrochloride	218
6	Risperidone	206

7	Lamotrigine	203
8	Levetiracetam	201

- **Less than 200 but more than or equal to 100 times**: 58 APIs (single or in combination) were found whose products were approved less than 200 but more than or equal to 100 times. These are mentioned below.

Table 6: List of APIs with products approved less than 200 but more than or equal to 100 times

Serial no.	Active ingredients	Number of times approved
1.	Metformin Hydrochloride	193
2.	Morphine Sulfate	192
3.	Propranolol Hydrochloride	190
4.	Amitriptyline Hydrochloride	186
5.	Diltiazem Hydrochloride	180
6.	Levothyroxine Sodium	178
7.	Hydrocortisone	175
8.	Amphetamine Aspartate; Amphetamine Sulfate; Dextroamphetamine Saccharate; Dextroamphetamine Sulfate	172
9.	Pramipexole Dihydrochloride	171
10.	Quetiapine Fumarate	170
11.	Olanzapine	169
12.	Triamcinolone Acetonide	166
13.	Potassium Chloride	163

14.	Aripiprazole	162
15.	Theophylline	159
16.	Prednisone	153
17.	Lidocaine Hydrochloride	151
18.	Cetirizine Hydrochloride	151
19.	Alprazolam	143
20.	Hydroxyzine Hydrochloride	142
21.	Venlafaxine Hydrochloride	137
22.	Doxycycline Hyclate	137
23.	Dextrose; Potassium Chloride; Sodium Chloride	135
24.	Gabapentin	135
25.	Promethazine Hydrochloride	134
26.	Ropinirole Hydrochloride	133
27.	Acetaminophen; Codeine Phosphate	131
28.	Oxycodone Hydrochloride	130
29.	Hydrochlorothiazide	129
30.	Amoxicillin	129
31.	Fluconazole	127
32.	Estradiol	126
33.	Topiramate	124

34.	Fluoxetine Hydrochloride	123
35.	Minocycline Hydrochloride	123
36.	Acetaminophen; Oxycodone Hydrochloride	122
37.	Hydralazine Hydrochloride	121
38.	Ranitidine Hydrochloride	121
39.	Gentamicin Sulfate	120
40.	Amlodipine Besylate	119
41.	Warfarin Sodium	118
42.	Bupropion Hydrochloride	117
43.	Lisinopril	114
44.	Phentermine Hydrochloride	112
45.	Carboplatin	112
46.	Ampicillin Sodium	110
47.	Levofloxacin	109
48.	Lorazepam	108
49.	Fenofibrate	108
50.	Rosuvastatin Calcium	108
51.	Captopril	107
52.	Diphenhydramine Hydrochloride	105

53.	Vancomycin Hydrochloride	105
54.	Diazepam	103
55.	Verapamil Hydrochloride	103
56.	Chlorpromazine Hydrochloride	102
57.	Ondansetron Hydrochloride	102
58.	Ceftriaxone Sodium	100

- **Less than 100 but more than or equal to 50 times**: 155 APIs (single or in combination) were found whose products were approved less than 100 but more than or equal to 50 times.
- **Less than 50 but more than or equal to 25 times**: 243 APIs (single or in combination) were found whose products were approved less than 50 but more than or equal to 25 times.
- **Less than 25 but more than or equal to 10 times**: 387 APIs (single or in combination) were found whose products were approved less than 25 but more than or equal to 10 times.
- **Less than 10 but more than 1 time**: 1167 APIs (single or in combination) were found whose products were approved less than 10 but more than or equal to 1 time.
- **1 time only**: 824 APIs (single or in combination) were found whose products were approved one time only.

Classification of selected APIs according to the WHO ATC index

APIs are classified in a hierarchy with five different levels in the WHO ATC index. Only the first three levels were considered for this study purpose. The first three levels are anatomical main group, therapeutic subgroup and pharmacological subgroup respectively.

Those APIs (single or in combination) whose products were approved more than or equal to 100 times, were classified as per the WHO ATC Index.

Table 7: ATC codes and therapeutic classes of selected APIs

Serial no.	API	ATC Code	Therapeutic class
1	Ranitidine Hydrochloride	A02B	Drugs for acid related disorders

2	Ondansetron Hydrochloride	A04A	Anti-emetics and anti-nauseants
3	Phentermine Hydrochloride	A08A	Anti-obesity preparations, excluding diet products
4	Metformin Hydrochloride	A10B	Drugs used in diabetes
5	Heparin Sodium	B01A	Antithrombotic agents
6	Warfarin Sodium	B01A	Antithrombotic agent
7	Potassium Chloride	B05X	Blood substitute
8	Dextrose; Potassium Chloride; Sodium Chloride	B05X	Blood substitute
9	Lidocaine Hydrochloride	C01B	Cardiac therapy
10	Hydralazine Hydrochloride	C02D	Antihypertensive
11	Hydrochlorothiazide	C03A	Diuretic
12	Triamcinolone Acetonide	C05A	Hemorrhoid treatment
13	Propranolol Hydrochloride	C07A	Beta blocking agent
14	Amlodipine Besylate	C08C	Calcium channel blockers
15	Diltiazem Hydrochloride	C08D	Cardiac therapy
16	Verapamil Hydrochloride	C08D	Calcium channel blocker
17	Lisinopril	C09A	Agents acting on the renin-angiotensin system
18	Captopril	C09A	Agents acting on the renin-angiotensin system
19	Fenofibrate	C10A	Lipid modifying agents
20	Rosuvastatin Calcium	C10A	Lipid modifying agents
21	Diphenhydramine Hydrochloride	D04A	Antipyretic
22	Gentamicin Sulfate	D06A	Antibiotics and chemotherapeutics for dermatological use

23	Estradiol	G03C	Sex hormones and modulators of the genital system
24	Hydrocortisone	H02A	Corticosteroids
25	Prednisone	H02A	systemic use for pain
26	Levothyroxine Sodium	H03A	Thyroid therapy
27	Doxycycline Hyclate	J01A	systemic anti-infective
28	Minocycline Hydrochloride	J01A	Antibacterial
29	Amoxicillin	J01C	Antibacterial
30	Ampicillin Sodium	J01C	Antibacterial
31	Ceftriaxone Sodium	J01D	Antibacterial
32	Levofloxacin	J01M	Antibacterial
33	Vancomycin Hydrochloride	J01X	Antibacterial
34	Fluconazole	J02A	systemic anti-infective
35	Carboplatin	L01X	Antineoplastic drug
36	Ibuprofen	M01A	Musculoskeletal
37	Morphine Sulfate	N02A	Analgesic
38	Oxycodone Hydrochloride	N02A	Analgesic
39	Acetaminophen; Hydrocodone Bitartrate	N02B	Cold preparation with antipyretic action
40	Acetaminophen; Codeine Phosphate	N02B	Analgesic
41	Acetaminophen; Oxycodone Hydrochloride	N02B	Analgesic
42	Pregabalin	N03A	Antiepileptic
43	Lamotrigine	N03A	Antiepileptic
44	Levetiracetam	N03A	Antiepileptic
45	Gabapentin	N03A	Antiepileptic
46	Topiramate	N03A	Antiepileptic
47	Pramipexole Dihydrochloride	N04B	Antiparkinson drug
48	Ropinirole Hydrochloride	N04B	Antiparkinson drug
49	Risperidone	N05A	Psycholeptic
50	Quetiapine Fumarate	N05A	Psycholeptic

51	Olanzapine	N05A	Psycholeptic
52	Aripiprazole	N05A	Psycholeptic
53	Chlorpromazine Hydrochloride	N05A	Psycholeptic
54	Alprazolam	N05B	Psycholeptic
55	Hydroxyzine Hydrochloride	N05B	Psycholeptic
56	Lorazepam	N05B	Psycholeptic
57	Diazepam	N05B	Psycholeptic
58	Amitriptyline Hydrochloride	N06A	Psychoanaleptic
59	Venlafaxine Hydrochloride	N06A	Psychoanaleptic
60	Fluoxetine Hydrochloride	N06A	Psychoanaleptic
61	Bupropion Hydrochloride	N06A	Psychoanaleptic
62	Methylphenidate Hydrochloride	N06B	Psychoanaleptic
63	Amphetamine Aspartate; Amphetamine Sulfate; Dextroamphetamine Saccharate; Dextroamphetamine Sulfate	N06B	ADHD
64	Theophylline	R03D	Drugs for obstructive airway diseases
65	Cetirizine Hydrochloride	R06A	Systemic antihistamine
66	Promethazine Hydrochloride	R06A	Systemic antihistamine

Eleven anatomical main groups were found for the APIs that got approved more than or equal to 100 times.

Chapter 4 Discussion

The data file was downloaded from the official website of FDA. The downloaded file contained 11 text tables that were imported to excel spreadsheets. The file named ‘Products’ was chosen for this study as it contains the list of FDA approved drugs and its active ingredients along with the strengths and dosage forms. A total of 40425 drug products were found which were to be analyzed for this study purposes.

At first, a total of 2842 unique active ingredients (single or in combination) were found in the database. These active ingredients (single or in combination) were used for the 40425 FDA approved drug products. The combination of ‘Acetaminophen; Hydrocodone Bitartrate’ was the active ingredient most frequently found in the approved drug products. There were 246 products containing this combination. ‘Ibuprofen’ and ‘Pregabalin’ were the second and third most frequent. Products containing ‘Ibuprofen’ and ‘Pregabalin’ were approved for 239 and 230 times respectively.

APIs were categorized according to the frequency at which products containing each API (single or in combination) were approved. The following pie chart shows the classes in proportion to all products.

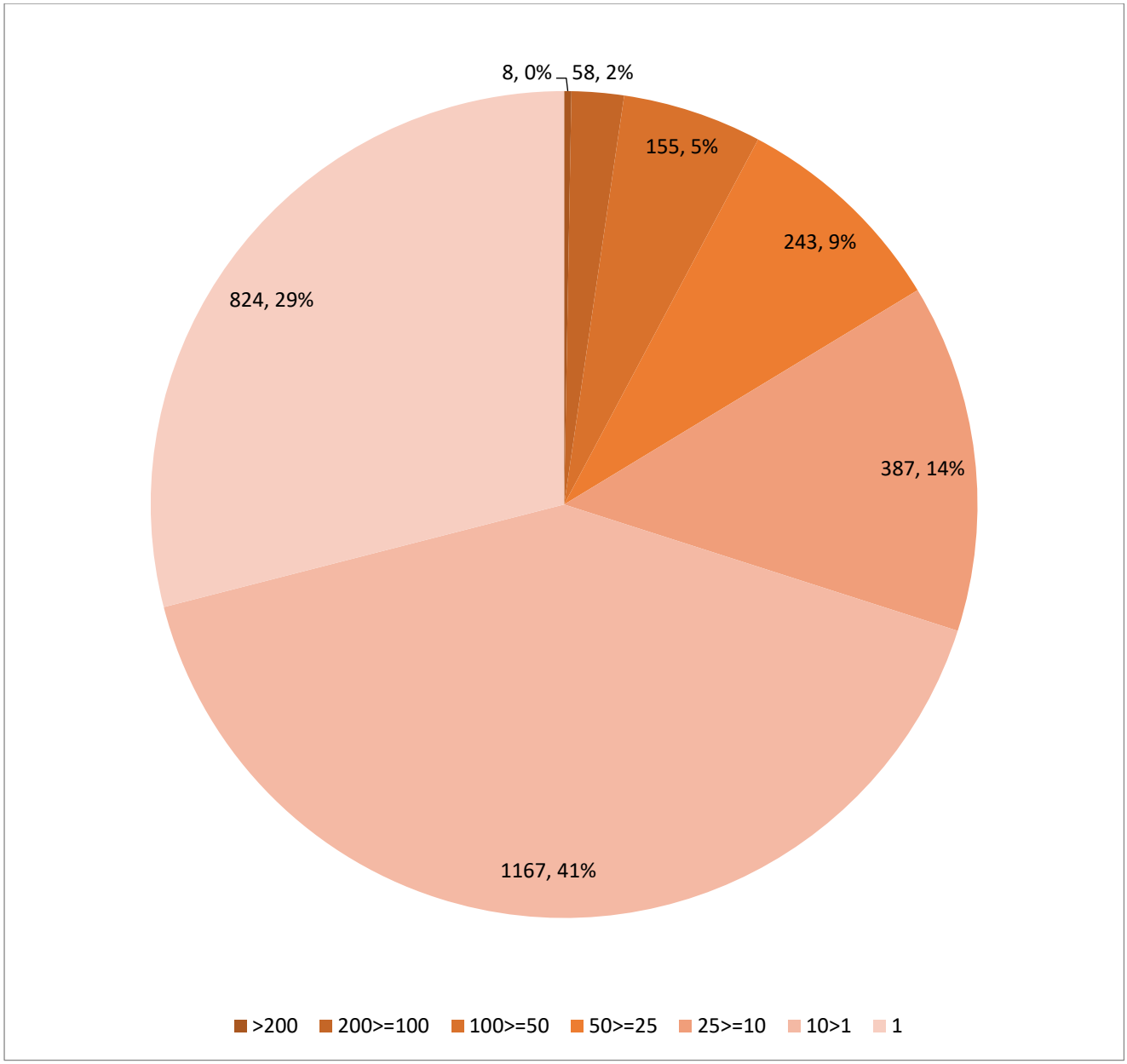


Figure 5: Pie chart showing percentage of each class out of all products

Only eight APIs fell in the category named ‘More than or equal to 200 times’ followed by 58 in the category named ‘Less than 200 but more than or equal to 100 times’. In the next four categories, the number of APIs per category increased. Products containing 824 APIs were approved one time only.

By classifying the active ingredients based on the product approval frequency, we found out the total number of drug products approved for each approval frequency class. A table showing the number of approved drugs for each category of active ingredients is given below.

Table 8: Number of drug products for each approval frequency class

Approval frequency class	Total number of approved drugs
≥200	1766
200≥100	7865
100≥50	10854
50≥25	8469
25≥10	6049
10>1	4598
1	824

A pie chart representing the percentages of approved drug numbers for each class of active ingredients is given below.

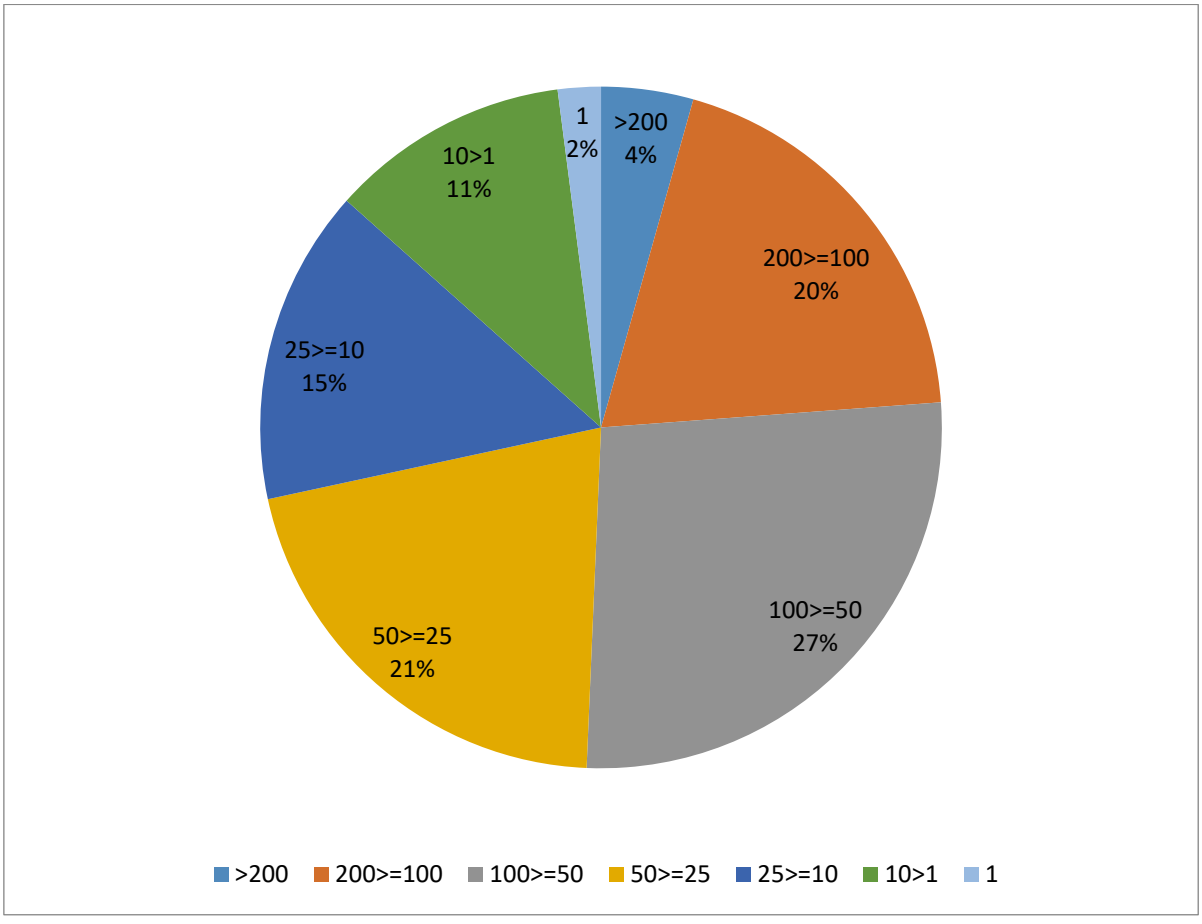


Figure 6: Pie chart showing percentages of approved drugs for each category

According to the chart, 24% of all the drug products contained active ingredients which were approved more than or equal to 100 times. As we have found out that eight and 58 active ingredients (single or in combination) were approved more than 200 times and less than 200 but more than or equal to 100 times respectively, we can say that, out of 2842 unique active ingredients, only 66 active ingredients (single or in combination) were responsible for 24% of approved drug products which is almost a quarter of all drug products approved by the FDA from 1930 to 2019.

We found 66 APIs that were approved more than equal to 100 times. These APIs were classified according to WHO ATC Index to find out the therapeutic classes of each 66 APIs. The anatomical main group and therapeutic subgroup of each ATC code specifically indicate the therapeutic classes of the APIs. Some of the APIs with same therapeutic classes were found quite a few times such as antiepileptic drugs, psycholeptic drugs, psychoanaleptic drugs, antibacterial drugs. Apart from these, there were therapeutic classes such as analgesic, diuretic, antidiabetic, antihypertensive, antiparkinson, antineoplastic ADHD etc.

A pie chart was made based on the anatomical main group of ATC codes of the APIs. We have found 11 anatomical main groups among the ATC codes of our top 66 frequently approved APIs.

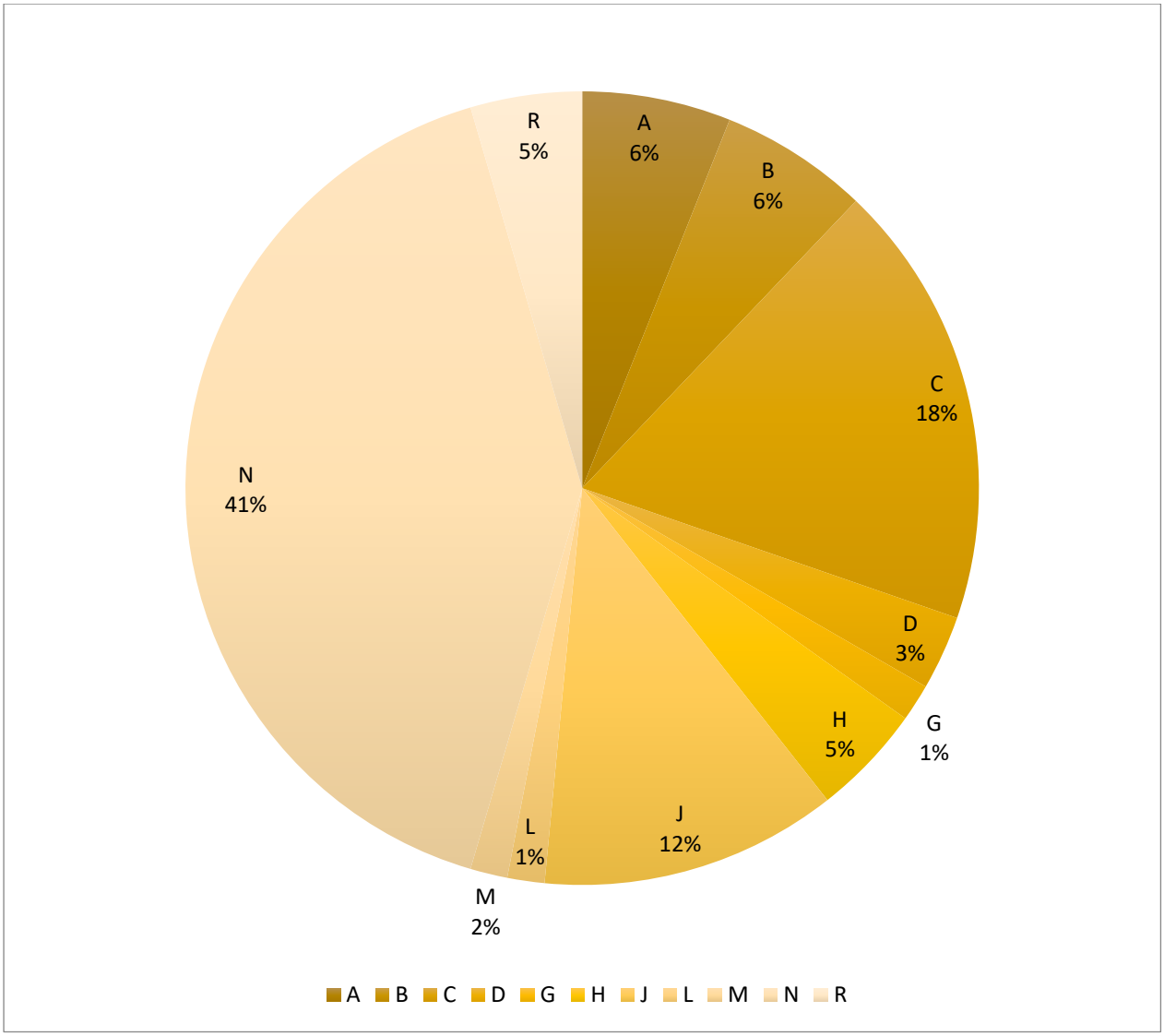


Figure 7: Percentage of anatomical classes

The chart illustrates the percentages of the selected 66 APIs that directly work on each anatomical main group of the WHO ATC Index. Overall, it can be seen that N (nervous system) is the most common anatomical main group among all 11. 41% of the selected APIs work on the nervous system. C (Cardiovascular system) and J (Anti-infectives for systemic use) are the second and third common groups occupying 18% and 12% respectively. The percentage occupied by other groups individually are notably lower than N, C and J. These other groups include A (Alimentary tract and metabolism), B (Blood and blood forming organs), H (Systemic hormonal preparations, excluding sex hormones and insulins), R (Respiratory system), D (Dermatological drugs), M (Musculo-skeletal system), G (Genito-urinary system and sex hormones) and L (Antineoplastic and immunomodulating agents).

We can see that the most common anatomical main group is N (Nervous system). Upon looking at the therapeutic subgroup for the 27 APIs in this group, it was found 9 were psycholeptics, 5 were psychoanaleptics, 5 were antiepileptics, 4 were analegics, 2 were used in the treatment of Parkinson's disease and one each were used in the treatment of ADHD and cold preparations. Twelve of the selected APIs belonged to the anatomical group C (cardiovascular system). Diseases of the cardiovascular system are chronic conditions. We have also found drug products that are used in the treatment of ulcer (Ranitidine hydrochloride), diabetes (Metformin hydrochloride), arthritis (Ibuprofen), thyroid disorder (Levothyroxine sodium), cancer (Carboplatin), obesity (Phentermine hydrochloride), asthma (Theophylline) etc. that are also chronic diseases.

Chronic diseases are on the rise worldwide. Whether it is a developed country or a developing one, chronic disease prevalence rates are increasing everywhere. Conditions such as heart disease, diabetes, obesity, cancer, cardiovascular disease, lung disease, arthritis are causing millions of death each year. As the table 01 (table number) demonstrates, huge number of people are suffering and dying from these chronic diseases. The necessity of the drugs or treatment process for these chronic diseases have also increased over the years. Manufacturers have been investing big portion of their time and money on discovering more effective and safe chronic disease drugs. As a result, we have seen that many of the drug products that have been approved are for the treatment of chronic diseases.

However, it cannot be concluded that the FDA does indeed approve more drug products for chronic diseases than for acute diseases. It cannot also be concluded that the FDA is biased towards approving drug products for diseases prevalent in the US. This is because pharmaceutical companies may be more interested in developing drug products for chronic conditions in search of profit. No effort was undertaken in this study to determine this. There were limitations in this study as well. For one, only the APIs used in chronic conditions were considered, not the number of drug products. Also, there could be a relationship between type of disease and time. This was not investigated in detail.

References

Chronic Diseases in America | CDC. (n.d.). https://www.cdc.gov/chronicdisease/resources/infographic/chronic-diseases.htm

Drugs@FDA Data Files | FDA. (n.d.). https://www.fda.gov/drugs/drug-approvals-and-databases/drugsfda-data-files

No Title. (2014). http://www.hpra.ie/homepage/medicines/medicines-information/atc-codes

No Title. (2017). https://www.pwc.com/gx/en/industries/healthcare/emerging-trends-pwc-healthcare/chronic-diseases.html#:~:text=According to the World Health,most significant in developing nations.

Norman, G. A. Van. (2016). Drugs, Devices, and the FDA: Part 1: An Overview of Approval Processes for Drugs. *JACC: Basic to Translational Science*, *1*(3), 170–179. https://doi.org/10.1016/j.jacbts.2016.03.002

Part II: 1938, Food, Drug, Cosmetic Act | FDA. (2018). https://www.fda.gov/about-fda/fdas-evolving-regulatory-powers/part-ii-1938-food-drug-cosmetic-act

Raghupathi, W., & Raghupathi, V. (2018). An empirical study of chronic diseases in the united states: A visual analytics approach. *International Journal of Environmental Research and Public Health*, *15*(3), 10–12. https://doi.org/10.3390/ijerph15030431

Sataloff, R. T., Johns, M. M., & Kost, K. M. (2018). *No 主観的健康感を中心とした在宅高齢者における 健康関連指標に関する共分散構造分析Title*.

Thorpe, K. E., Howard, D. H., & Galactionova, K. (2007). Differences in disease prevalence as a source of the U.S.-European health care spending gap. *Health Affairs*, *26*(6), 678–686. https://doi.org/10.1377/hlthaff.26.6.w678

WHO | Fact sheets: chronic diseases. (n.d.). https://www.who.int/topics/chronic_diseases/factsheets/en/

WHO | Integrated chronic disease prevention and control. (n.d.). https://www.who.int/chp/about/integrated_cd/en/

Wilensky, G. R. (2012). The Shortfalls of “Obamacare.” *New England Journal of Medicine*, *367*(16), 1479–1481. https://doi.org/10.1056/nejmp1210763

Wittayanukorn, S., Rosenberg, M., Schick, A., & Hu, M. (2020). Factors that have an Impact on Abbreviated New Drug Application (ANDA) Submissions. *Therapeutic Innovation & Regulatory Science*, *0123456789*. https://doi.org/10.1007/s43441-020-00163-x

Wu, S., & Green, A. (2010). Projection of Chronic Illness Prevalence and Cost Inflation. *RAND Corporation*, *February*, 1–47. http://www.nasuad.org/sites/nasuad/files/hcbs/files/191/9519/ChronicCareChartbook.pdf