

**COMPARATIVE STUDY OF sNDA SUBMISSION AND APPROVAL
PROCEDURES IN REGULATED AND SEMI-REGULATED COUNTRIES**

A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF
THE REQUIREMENTS FOR THE DEGREE OF
MASTER OF PHARMACY

IN
DRUG REGULATORY AFFAIR

By

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ABSTRACT

Medical products, medical devices and supplementary food are the imperative categories of products that demand prime attention for their safety, efficacy and quality. To reach the market, a pharmaceutical product has to undergo various levels of analysis assuring its quality, safety and efficacy. Reports of these studies are considered by the regulatory bodies so as to corroborate their marketing and use. The data submitted to the regulatory body must be in a defined way to obtain their consent. Different types of applications are filed depending upon the need of the applicant and agency. These applications include a) Investigational New Drug Application (INDA) -The submission of an IND application is the pathway of obtaining consent from the regulatory body to conduct clinical studies on human volunteers and patients. Main objective of IND filing involves assurance of safety of human subjects participating in the study, determination of therapeutic efficacy of newly discovered drug. b) New Drug Application (NDA) - New drug application gives the sovereignty to the applicant to launch the new pharmaceutical product in the market. The applicant must submit an appropriate and acceptable pre-clinical and clinical study reports as supporting documents to the agency for obtaining consent. c) Abbreviated New Drug Application (ANDA)- ANDA give the applicant the authority to introduce a pharmaceutical product which is analogous to the registered product in terms of active ingredient, dosage, route of administration, safety, efficacy and use. It implies that for a drug product to be considered eligible for ANDA it must be identical to a listed drug product or branded product. d) Biologic License Application (BLA)- It is an application which allows the applicant to manufacture and market biological products. e) Supplemental Applications (sNDA, sANDA, sBLA)- Supplemental New Drug Application, Supplemental Abbreviated New Drug Application and Supplemental Biologic License Application is the process of obtaining consent from USFDA to introduce alterations in an already approved drug product. In order to change a label, change manufacturing process or market a new dosage, the applicant needs to submit a supplemental new drug application to the concerning regulatory body. Also, the applicant needs to provide supplement documents to substantiate that the intended change would not affect the quality, safety and efficacy adversely. The process of filing supplemental applications is more effective in regulated countries as compared to semi-regulates ones in terms of both process and quantity.

KEYWORDS- IND, NDA, ANDA, sNDA, Sanda, sBLA, Regulatory Authority,

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DECLARATION BY THE CANDIDATE

This is to submit that this written submission in my thesis entitled “**Comparative study of sNDA submission and approval procedures in regulated and semi-regulated countries**” represents original ideas in my own words and where other’s ideas or words have been included, I have adequately cited and referenced the original sources. I also declare that I have stuck to all principles of academic honesty and integrity and have not misrepresented or fabricated or falsified any idea/data/fact/source in my submission. I understand that any violation of the above will be cause for disciplinary action by the school and can also evoke penal action from the sources which have thus not been properly cited or from whom proper permission has not been taken when required. This thesis encompasses the information generated by me based on the experimental work carried out in the institute. I assure and hold full responsibility for its genuineness.

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The work described in this thesis entitled “**Comparative study of sNDA submission and approval procedures in regulated and semi-regulated countries**” has been carried out by Ms. Plakshi Misri under my supervision. I certify that this is her bonafide work. The work described is original and has not been submitted for any degree to this or any other university.

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LIST OF ABBREVIATIONS

S.NO	ABBREVIATIONS	FULL FORM
1.	IND	Investigational New Drug
2.	NDA	New Drug Application
3.	ANDA	Abbreviated New Drug Application
4.	BLA	Biologic License Application
5.	CDER	Center for Drug Evaluation and Research
6.	CBER	Center for Biologics Evaluation and Research
7.	USFDA	United States Food and Drug Administration
8.	DRA	Drug Regulatory Affairs
9.	OGD	Office of Generic Drugs
10.	CDSCO	Central Drug Standard Control Organization
11.	DCGI	Drug Controller General of India
12.	CMC	Chemistry Manufacturing & Control
13.	EMA	European Medicine Agency

CHAPTER 1

1. INTRODUCTION

Medical products, medical devices and supplementary food are the imperative categories of products that demand prime attention for their safety, efficacy and quality. Drug Regulatory Affair (DRA) is a pivotal part of a pharmaceutical organization that contributes to quality, safety and efficacy of the finished pharmaceutical product which is likely to be introduced in the market after the regulatory approval. It is the key nexus connecting pharmaceutical industries with the regulatory agencies. It is interlinked with all the departments of a pharmaceutical industry.

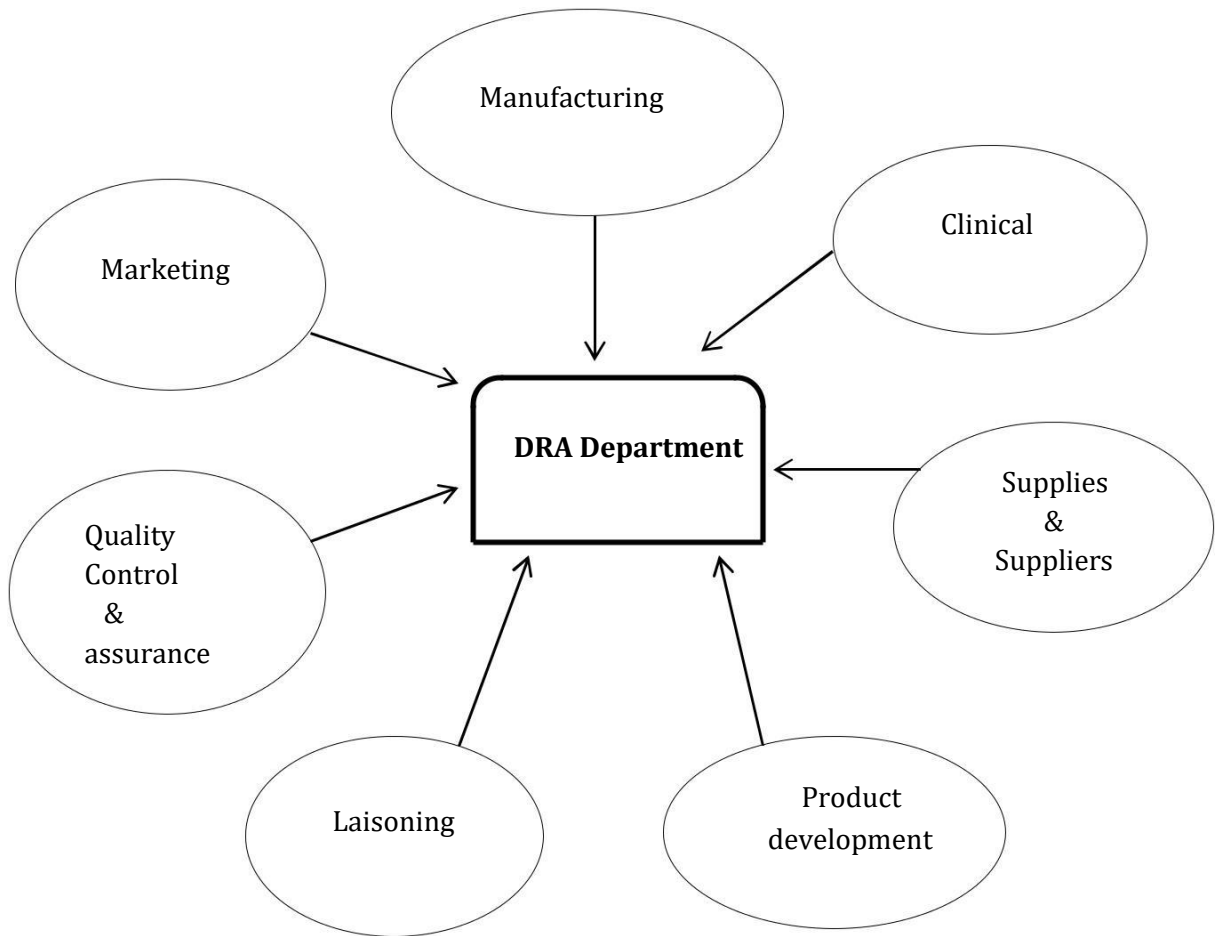


Figure 1: DRA department of a pharmaceutical industry

Major role and responsibility of DRA department is to ensure that the medical products that are manufactured under acceptable conditions and distributed that reach the patients must contain quality, safety and efficacy. It is actively involved at each step of life cycle of the finished pharmaceutical product beginning from drug discovery, development, packaging, obtaining approvals for trials, marketing to the post-marketing. This department timely appraises the legal and scientific restraints and coordinate, evaluate the scientific data generated by research and development. Regulatory department also keeps a track on changing and modified regulations in order to update the company that wishes to market their product.

To reach the market, a pharmaceutical product has to undergo various levels of analysis assuring its quality, safety and efficacy. Reports of these studies are considered by the regulatory bodies so as to corroborate their marketing and use. Here, drug regulatory department comes into action. It ensures that the information and data to be projected are conveyed in defined way and form i.e. appropriate dossier preparation (as per regulatory agency) to obtain consent and license and for the same different types of applications are filed depending upon the need of the applicant and agency.

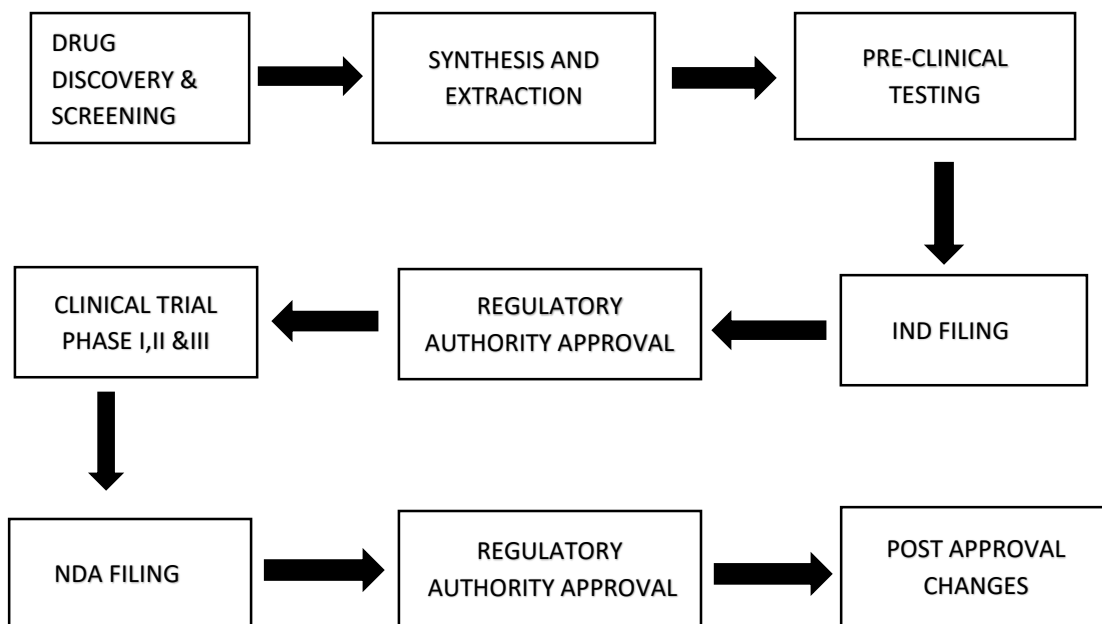


Figure 2: Conversion of a new molecular entity to a successful pharmaceutical product

1.1 TYPES OF APPLICATIONS

1.1.1 Investigational New Drug Application (INDA)

After successful pre-clinical testing of a new discovered drug/biological, it is forwarded for testing in human volunteers to discern its therapeutic potential effect along with safety for use. But the applicant/sponsor needs to seek approval from the regulatory agency, where he/she wants to conduct the study, in the form of an IND application. The submission of an IND application is the pathway of obtaining consent from the regulatory body to conduct clinical studies on human volunteers and patients. Commercial and research are major categories of an Investigational New Drug application hinged on the basis of their use. Commercial IND's are needed for filing an NDA to introduce the product in the market whereas research IND is used for research purpose. IND is further classified into three types namely-

- a) **Investigator IND:** It is submitted to the authority for drug approval by the applicant who is both initiating and conducting an investigation and for the same under immediate directions of sponsor new drug is administered to the subject.
- b) **Emergency use IND:** Such application allows the regulatory agency to authorize the use of a drug which is still under study in an emergency situation that cannot sustain submission of IND.
- c) **Treatment IND:** This application is favorable for those drug candidates which show promise in clinical testing for serious/life threatening conditions while the final clinical work is conducted and reviewed by regulatory body. It is also known as Expanded Access IND.

Once the IND is submitted, the applicant needs to wait for 30 calendar days before initiating the clinical trials. Main objective of IND filing involves assurance of safety of the human subjects participating in the study and determination of therapeutic efficacy of newly discovered drug. IND can only be filed in conditions supporting –

- a) a new indication,
- b) unusual change in already approved drug,
- c) change in priorly approved route of administration and
- d) change in approved patient population

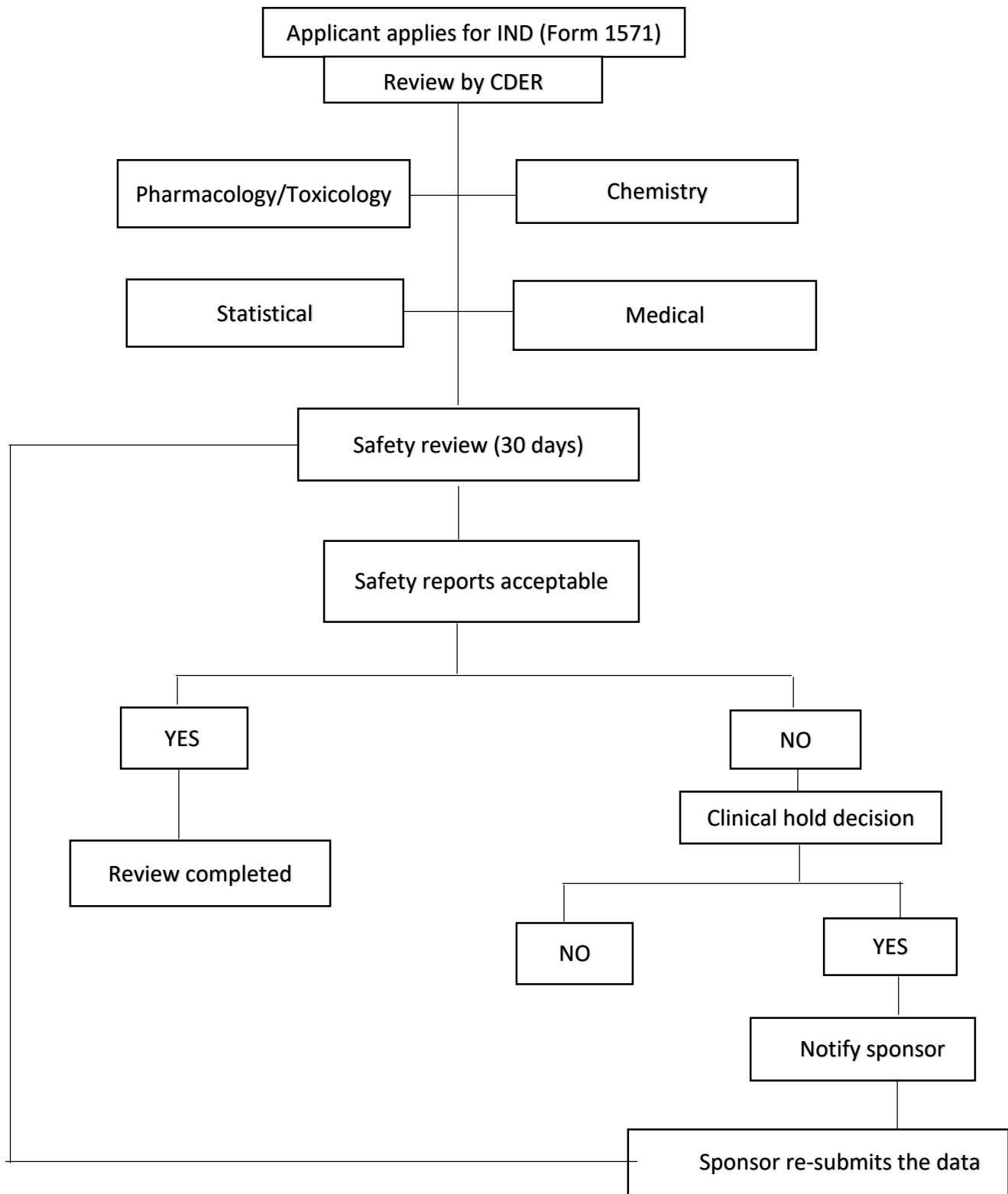


Figure 3: IND review process by the USFDA as regulated drug regulatory authority

1.1.2 New Drug Application (NDA)

New drug application gives the sovereignty to the applicant to introduce the new pharmaceutical product in the market. The applicant must submit an appropriate and acceptable pre-clinical and clinical study reports as supporting documents to assure the quality, safety and efficacy of the product. The drug product can only be considered for basis for filing a NDA application if it is:

- a) a new chemical entity,
- b) new salt of previously approved drug,
- c) new combination of two or more drugs,
- d) already marketed product (new manufacturer),
- e) new indication for already marketed product and
- f) already marketed drug product with no previously approved NDA

The sponsor/applicant must provide the regulatory agency sufficient data to allow the review to reach the following key points:

- 1) Whether benefit to patients outweighs risk of using the drug?
- 2) Is drug's proposed labeling acceptable and appropriate?
- 3) Safety and effectiveness of drug
- 4) Whether the methods used in manufacturing of the drug and the controls used to maintain the drug's quality adequate to preserve its identity, strength, quality, and purity?

The documents which support the main NDA application must project complete details of the drug, including its synthesis, manufacturing, pharmacokinetic and pharmacodynamics properties, processing, packaging and labelling.

NDA application is submitted in two copies i.e. archival and review copy. The archival copy serves as the permanent record of submission and is submitted in a blue cover jacket. Review copy is made of different technical sections & bounded in a specific color. These sections include:

- (i) chemistry manufacturing and control (CMC) in red,
- (ii) non-clinical pharmacology and toxicology in yellow,
- (iii) human pharmacokinetics and bioavailability in orange,
- (iv) microbiology in white,
- (v) clinical data in light brown and

(vi) statistical in green.

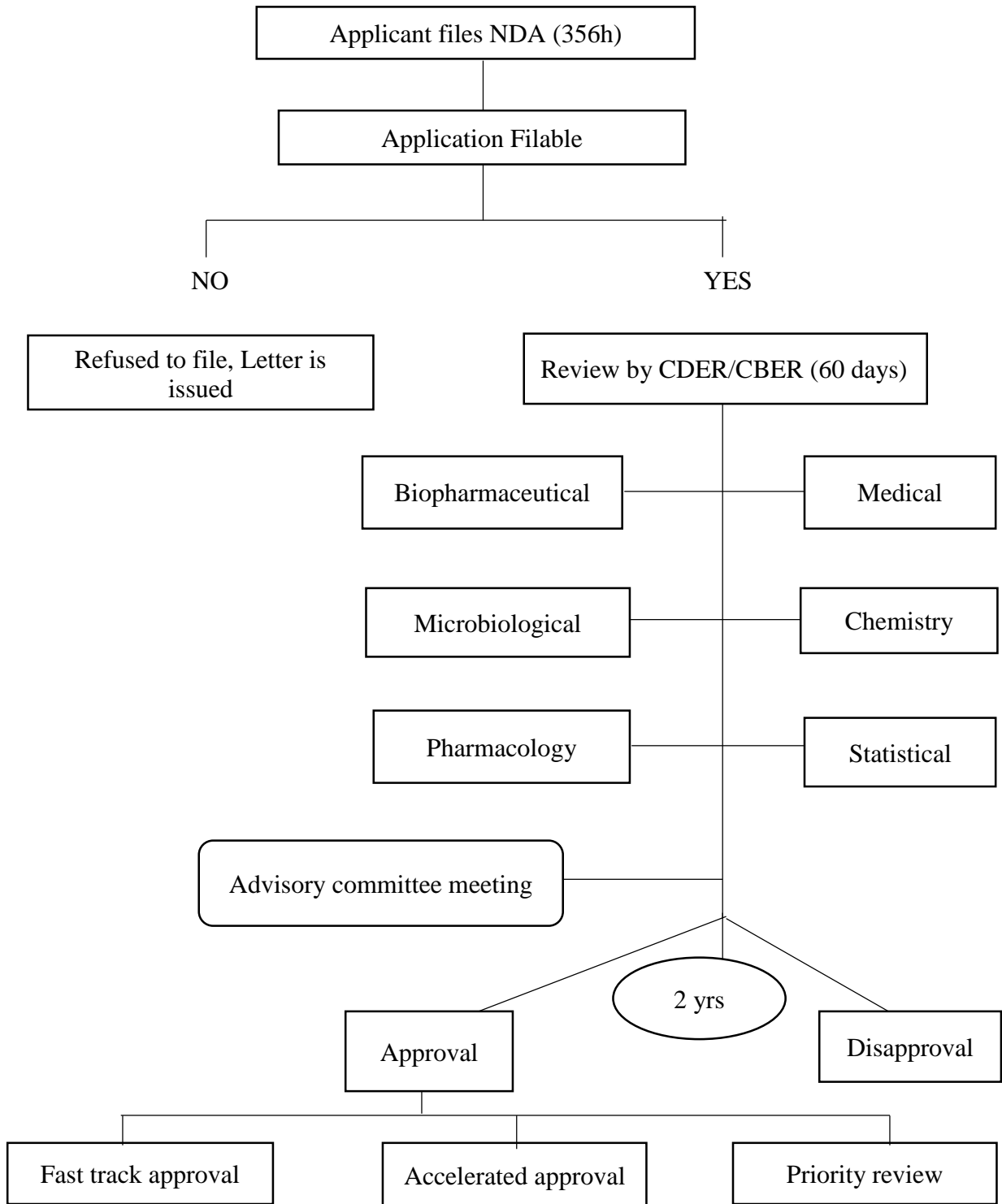


Figure 4: NDA review process by a regulated authority (USFDA)

Table 1: NDA approved in 2016 by USFDA

S. no	Drug name	Active Ingredient	Date of approval
1.	Zinplava	Bezlotoxumab	10/21/2016
2.	Lartruvo	Olaratumab	10/19/2016
3.	Exondys 51	Eteplirsen	9/19/2016
4.	Adlyxin	Lixisenatide	7/27/2016
5.	Xiidra	Lifitegrast ophthalmic solution	7/11/2016
6.	Epclusa	Sofosbuvir and velpatasvir	6/28/2016
7.	NETSPOT	Gallium Ga 68 dotatate	6/1/2016
8.	Axumin	Fluciclovine F 18	5/27/2016
9.	Ocaliva	Obeticholic acid	5/27/2016
10.	Zinbryta	Daclizumab	5/27/2016
11.	Tecentriq	Atezolizumab	5/18/2016
12.	Nuplazid	Pimavanserin	4/29/2016
13.	Venclexta	Venetoclax	4/11/2016
14.	Defitelio	Defibrotide sodium	3/30/2016
15.	Cinqair	Reslizumab	3/23/2016
16.	Taltz	Ixekizumab	3/22/2016
17.	Anthim	Obiltoxaximab	3/18/2016
18.	Briviact	Brivarasitam	2/18/2016
19.	Zepatier	Elbasvir and grazoprevir	1/28/2016

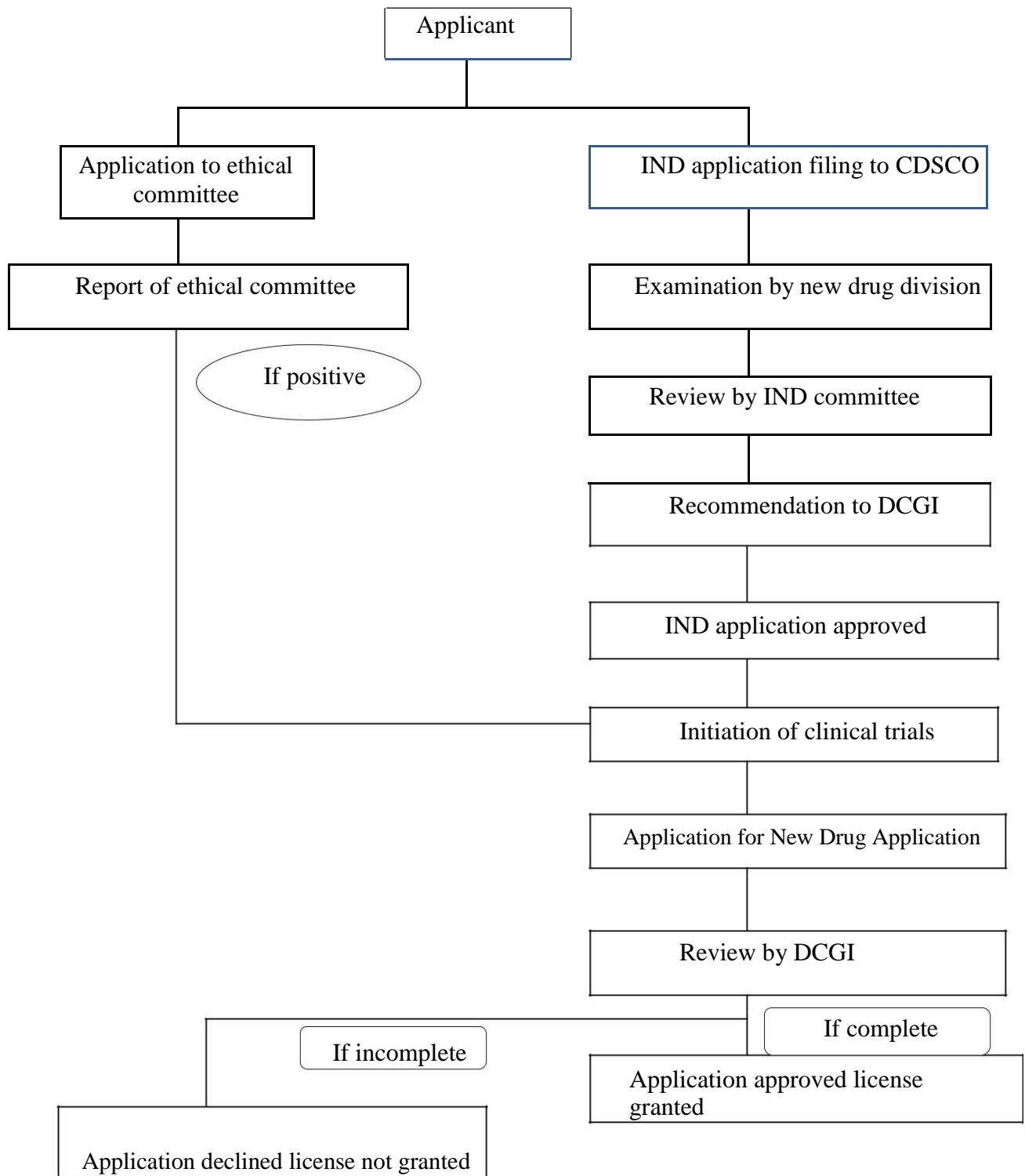


Figure 5: IND, NDA review process by a semi-regulated authority (CDSCO)

1.1.3 Abbreviated New Drug Application (ANDA)

This application is submitted by the applicant to obtain consent for marketing of a pharmaceutical product whose patent term has been expired, in countries lacking patent protection and for drugs that are not patented. For a drug product to be considered eligible for NDA it must be identical to a listed drug product (Branded drug or innovator drug) in terms of-

- a) active pharmaceutical ingredient (API),
- b) dosage form,
- c) dosage strength,
- d) route of administration and
- e) labeling

It's considered be bioequivalent to the innovator drug product if the rate and extent of absorption is same. Generic drug applications are also known as abbreviated generic drug applications as they exclude pre-clinical and clinical data to substantiate safety and effectiveness. Major goals of ANDA include reduction of drug price, reduction in time, development and enhancing the bioavailability of the product. There are four different categories of ANDA filing:

- i) Para I filing: It is filed if the innovator drug is not patented
- ii) Para II filing: It is filed when the drug patent is expired
- iii) Para III filing: It is filed when the applicant waits for innovator drug patent to expire to market its product.
- iv) Para IV filing: It is filed when the applicant ensures that its product doesn't infringe innovator's patent. In this case, the applicant has to notify the patent holder within 20 days of application filing.

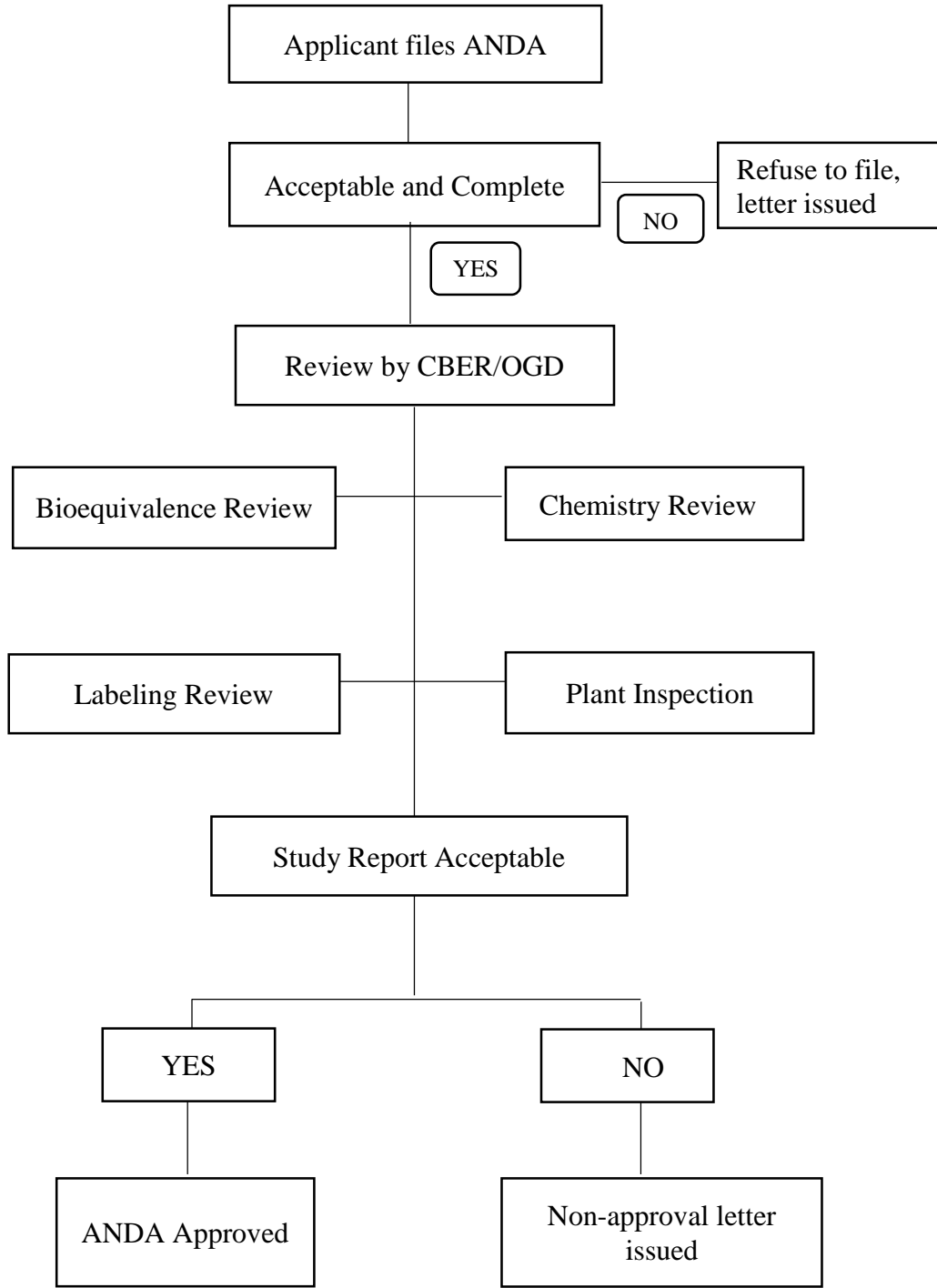


Figure 6: ANDA review process by a regulated authority (USFDA)

Table 2: ANDA approved by USFDA in 2016

S.no	Generic name	Brand name	Approval Date
1.	Quetiapine fumarate extended release tablets, 400 mg	Seroquel XR extended release tablets, 400 Mg	11/1/2016
2.	Mycophenolate mofetil Hydrochloride for injection USP, 500 mg/vial	Cellcept (Mycophenolate Mofetil Hydrochloride for injection, 500 mg/vial	10/28/2016
3.	Olmesartan Medoxomil and Hydrochlorthiazide Tablets, 20 mg/12.5mg, 40 mg/12.5mg, 40 mg/25mg	Benicar HCT, (Olmesartan Medoxomil and Hydrochlorthiazide Tablets) 20 mg/12.5mg, 40 mg/12.5mg, 40 mg/25mg	10/26/2016
4.	Olmesartan Medoxomil Tablets 5mg, 20 mg, 40 mg	Benicar (Olmesartan Medoxomil Tablets) 5mg, 20 mg, 40 mg	10/26/2016
5.	Olmesartan Medoxomil Amlodipine and hydrochlorthiazide tablets, 20mg/5mg/12.5mg, 40mg/5mg/12.5mg, 40mg/5mg/25mg, 40mg/10mg/12.5mg, 40mg/10mg/25mg,	Tribenzor (Olmesartan Medoxomil Amlodipine and hydrochlorthiazide tablets) 20mg/5mg/12.5mg, 40mg/5mg/12.5mg, 40mg/5mg/25mg, 40mg/10mg/12.5mg, 40mg/10mg/25mg,	10/26/2016

7.	Amlodipine and olmesartan Medoxomil Tablets 5mg/20mg, 5mg/40mg, 10mg/20mg 10mg/40mg	Azor (Amlodipine and Olmesartan Medoxomil Tablets) 5mg/20mg, 5mg/40mg, 10mg/20mg 10mg/40mg	10/26/2016
8.	Amlodipine and olmesartan Medoxomil Tablets 5mg/20mg, 5mg/40mg, 10mg/20mg 10mg/40mg	Azor (Amlodipine and Olmesartan Medoxomil Tablets) 5mg/20mg, 5mg/40mg, 10mg/20mg 10mg/40mg	10/26/2016
9.	Drospirenone, ethinyl estradiol and levomefolate calcium tablets, 3mg/0.3 mg/0.451 mg and Levomefolate calcium tablets 0.451 mg	Sayral (Drospirenone, ethinyl estradiol and levomefolate calcium tablets, 3mg/0.451 mg and Levomefolate calcium tablets 0.451 mg)	10/11/2016
10.	Drospirenone, ethinyl estradiol and levomefolate calcium tablets, 3mg/0.2 mg/0.451 mg and Levomefolate calcium tablets 0.451 mg	Sayral (Drospirenone, ethinyl estradiol and levomefolate calcium tablets, 3mg/0.451 mg and Levomefolate calcium tablets 0.451 mg)	10/11/2016
11.	Ribavirin for Inhalation solution USP, 6g/vial	Virazole (Ribavirin) for Inhalation solution, 6g/vial	10/6/2016
12.	Acetaminophen, caffeine and dihydrocodeine Bitartrate tablets, 325mg, 30mg, 16mg	Acetaminophen, caffeine and dihydrocodeine Bitartrate tablets, 325mg, 30mg, 16mg	09/30/2016

13.	Memantine Hydrochloride Extended release Capsules, 7mg, 14mg, 21mg, 28mg	Namenda (Memantine Hydrochloride Extended release Capsules, 7mg, 14mg, 21mg, 28mg)	09/28/2016
14.	Memantine Hydrochloride Extended release Capsules, 7mg, 14mg, 21mg, 28mg	Namenda (Memantine Hydrochloride Extended release Capsules, 7mg, 14mg, 21mg, 28mg)	09/28/2016
15.	Memantine Hydrochloride Extended release Capsules, 7mg, 14mg, 21mg, 28mg	Namenda (Memantine Hydrochloride Extended release Capsules, 7mg, 14mg, 21mg, 28mg)	09/28/2016
16.	Abacavir oral solution USP, 20mg/ml	Ziagen (abacavir) oral solution, 20mg/ml	9/26/2016
17.	Naftifine Hydrochloride cream, USP 1%	Naftin (Naftifine Hydrochloride cream) 1%*	9/8/2016
18.	Fenofibric acid delayed release capsules, 45mg, 135mg	Trilipix(Fenofibric acid delayed release capsules, 45mg, 135mg)	9/7/2016
19.	Flurandrenolide Lotion USP, 0.05%	Cordran (Flurandrenolide Lotion, 0.05%*)	8/30/2016
20.	Doxylamine succinate and Pyridoxine HCl delayed release tablets, 10mg/10mg	Diclegis (Doxylamine succinate and Pyridoxine HCl delayed release tablets, 10mg/10mg)	8/19/2016

21.	Oseltamivir Phosphate capsules USP, 30mg, 45mg, 75mg	Tamiflu (Oseltamivir Phosphate capsules USP, 30mg, 45mg, 75mg)	8/3/2016
22.	Zolpidem tartarate sublingual tablets 5mg, 10mg	Edluar (Zolpidem tartarate sublingual tablets 5mg, 10mg)	8/1/2016
23.	Nilutamide tablets 150mg	Nilandron (Nilutamide tablets 150mg)	7/15/2016
24.	Ropivcaine HCl Injection , 40mg/20ml-0.2%; 200mg/100ml-0.2%, 100mg/20ml-0.5%, 150mg/20ml-0.75%, 100mg/10ml-1%, 200mg/20ml-1%	Naropin (Ropivcaine HCl Injection , 40mg/20ml-0.2%; 200mg/100ml-0.2%, 100mg/20ml-0.5%, 150mg/20ml-0.75%, 100mg/10ml-1%, 200mg/20ml-1%)	7/13/2016
25.	Hydromorphone Extended-Release tablets, 32mg	Exalgo (Hydromorphone Extended-Release tablets, 32mg)	6/30/2016
26.	Ethacrynic acid tablets USP, 25mg	Edecrin (Ethacrynic acid tablets, 25mg)	6/30/2016
27.	Levothyroxine sodium for injection, 100mcg/vial, 500mcg/vial	Levothyroxine sodium for injection, 100mcg/vial, 500mcg/vial	6/29/2016
28.	Finofibrate Tablets USP, 40mg, 120mg	Fenoglide (Finofibrate Tablets, 40mg, 120mg)	6/23/2016

29.	Levoleucovorin for injection, 50mg/vial	Fusilev (Levoleucovorin for injection, 50mg/vial)	6/16/2016
30.	Dasatinib tablets 20mg, 50mg, 70mg, 100mg	Sprycel (Dasatinib tablets 20mg, 50mg, 70mg, 100mg)	6/10/2016
31.	Fosaprepitant Dimeglumine for injection, 150mg/vial	Emend (Fosaprepitant Dimeglumine for injection, 150mg/vial)	6/9/2016
32.	Dofetilide capsules, 0.125mg, 0.25mg, 0.5mg	Tikosyn (Dofetilide capsules, 0.125mg, 0.25mg, 0.5mg)	6/6/2016
33.	Mibelas 24FE 0.02mg, 1mg	Minastrin (Norethindrone acetate and ethinyl estradiol and ferrous fumarate) 24FE 0.02mg, 1mg	5/24/2016
34.	Doxycycline Hyclate Delayed release tablets USP, 50mg	Doryx (Doxycycline Hyclate Delayed release tablets, 50mg)	5/23/2016
35.	Rufinamide tablets USP 200mg, 400mg	Banzel (Rufinamide tablets 200mg, 400mg)	5/16/2016
36.	Rufinamide tablets USP 200mg, 400mg	Banzel (Rufinamide tablets 200mg, 400mg)	5/16/2016

37.	Estradiol valerate/Estradiol valerate/Dienogest tablets 1mg and 3mg/2/2mg and 2/3mg	Natazia (Estradiol valerate/Estradiol valerate/Dienogest tablets 1mg and 3mg/2/2mg and 2/3mg)	5/6/2016
38.	Diclofenac Potassium for oral solution 50mg	Cambia (Diclofenac Potassium for oral solution 50mg)	5/2/2016
39.	Rosuvastatin calcium tablets, 5mg, 10mg, 20mg, 40mg	Crestor (Rosuvastatin calcium tablets, 5mg, 10mg, 20mg, 40mg)	4/29/2016
40.	Lacosamide tablets 50mg, 100mg, 150mg, 200mg	Vimpat (Lacosamide tablets 50mg, 100mg, 150mg, 200mg)	4/28/2016
41.	Lacosamide tablets 50mg, 100mg, 150mg, 200mg	Vimpat (Lacosamide tablets 50mg, 100mg, 150mg, 200mg)	4/28/2016
42.	Lacosamide tablets 50mg, 100mg, 150mg, 200mg	Vimpat (Lacosamide tablets 50mg, 100mg, 150mg, 200mg)	4/28/2016
43.	Lacosamide tablets 50mg, 100mg, 150mg, 200mg	Vimpat (Lacosamide tablets 50mg, 100mg, 150mg, 200mg)	4/28/2016
44.	Lacosamide tablets 50mg, 100mg, 150mg, 200mg	Vimpat (Lacosamide tablets 50mg, 100mg, 150mg, 200mg)	4/28/2016

45.	Lacosamide tablets 50mg, 100mg, 150mg, 200mg	Vimpat (Lacosamide tablets 50mg, 100mg, 150mg, 200mg)	4/28/2016
46.	Lacosamide oral solution 10mg/ml	Vimpat (Lacosamide oral solution 10mg/ml)	4/28/2016
47.	Fosamorenvir Calcium Tablets, 700mg	Lexiva (Fosamorenvir Calcium Tablets, 700mg)	4/15/2016
48.	Flurandeolide cream USP 0.005%	Cordran (Flurandeolide cream 0.005%*)	4/13/2016
49.	Rosiglitazone Maleate and glimepiride tablets, 4mg/1mg, 4mg/2mg, 4mg/4mg, 8mg/2mg, 8mg/mg	Avandaryl (Rosiglitazone Maleate and glimepiride tablets, 4mg/1mg, 4mg/2mg, 4mg/4mg, 8mg/2mg, 8mg/mg)	4/1/2016
50.	Ibuprofen Lysine Injection, 20mg/2ml, (10mg/ml) SDV	Neoprofen (Ibuprofen Lysine Injection, 20mg/2ml) (10mg/ml)	3/30/2016
51.	Levonorgestrel and ethinyl estradiol tablets USP, 0.15mg/0.02mg, 0.15mg/0.02mg, 0.15mg/0.03mg, Ethinyl estradiol Tablets USP 0.01mg	Quartette (Levonorgestrel and ethinyl estradiol tablets USP, 0.15mg/0.02mg, 0.15mg/0.02mg, 0.15mg/0.03mg)	3/29/2016
52.	Daptomycin for injection, 500mg/vial	Cubicin (Daptomycin for injection, 500mg/vial)	3/24/2016

53.	Bendamustine Hydrochloride for injection 25mg/vial, 100mg/vial(Single dose vial)	Treanda (Bendamustine Hydrochloride for injection 25mg/vial, 100mg/vial(Single dose vial)	3/24/2016
54.	Bendamustine Hydrochloride for injection 25mg/vial, 100mg/vial(Single dose vial)	Treanda (Bendamustine Hydrochloride for injection 25mg/vial, 100mg/vial(Single dose vial)	3/24/2016
55.	Mometasone Furoate Nasal Spray, 50mcg	Nasonex (Mometasone Furoate Nasal Spray, 50mcg)	3/22/2016
56.	Diclofenac Sodium Topical Gel, 1%	Voltaren (Diclofenac Sodium Topical Gel, 1%*)	3/18/2016
57.	Magnesium Sulfate in water for injection, 40mg/ml, 80mg/ml	Magnesium Sulfate in water for injection, 40mg/ml, 80mg/ml	3/15/2016
58.	Sildenafil Citrate tablets, 25mg (base), 50mg (base), 100mg (base)	Viagra (Sildenafil Citrate tablets, 25mg (base), 50mg (base), 100mg (base)	3/9/2016
59.	Oxiconazole Nitrate cream, 1%	Oxistat (Oxiconazole Nitrate cream, 1%*)	3/7/2016
60.	Magnesium Sulfate in 5%Dextrose Injection USP, 1g/100ml	Magnesium Sulfate in 5%Dextrose Injection USP, 1g/100ml	3/2/2016

61.	Fluticasone Propionate Nasal spray USP, 50mcg/spray	Flonase (Fluticasone Propionate Nasal spray USP, 50mcg/spray)	2/29/2016
62.	Sodium Phenylacetate and sodium benzoate injection, 10%/10%	Ammonul (Sodium Phenylacetate and sodium benzoate injection, 10%/10%)	2/24/2016
63.	Diclophenac Potassium Capsules, 25mg	Zipsor (Diclophenac Potassium Capsules, 25mg)	2/23/2016
64.	Sumatriptan Nasal Spray USP, 5mg/spray 20mg	Imitrix (Sumatriptan Nasal Spray, 5mg/spray 20mg)	2/19/2016
65.	Efavirenz tablets USP, 600mg	Sustiva (Efavirenz tablets, 600mg)	2/17/2016
66.	Carbidopa tablets 25mg	Lodosyn (Carbidopa tablets 25mg)	2/17/2016
67.	Milnacipran Hydrochloride tablets, 12.5mg, 25mg, 50mg, 100mg	Savella (Milnacipran Hydrochloride tablets, 12.5mg, 25mg, 50mg, 100mg)	1/27/2016
68.	Difaraserox tablets for oral suspension, 125mg, 250mg, 500mg	Exjade (Difaraserox tablets for oral suspension, 125mg, 250mg, 500mg)	1/26/2016
69.	Vancomycin Hydrochloride for Injection USP 100mg PBP	Vancomycin Hydrochloride for Injection USP 100mg PBP	1/6/2016
70.	Adapelene Topical Solution, 0.1%	Differene (Adapelene Topical Solution, 0.1%*)	1/5/2016
71.	Naftifine Hydrochloride cream USP, 2%	Naftin (Naftifine Hydrochloride cream USP, 2%*)	1/6/2016

%*= w/v”

1.1.4 Biologics license application (BLA)

It is an application which allows the applicant to manufacture and market biological products. Therapeutic biological products include:

- ✓ monoclonal antibodies for *in-vivo* use,
- ✓ cytokines, growth factors, enzymes, immunomodulators etc.,
- ✓ proteins intended for therapeutic use extracted from animals and microorganisms, including recombinant versions of these products and
- ✓ other non-vaccine therapeutic immunotherapies

1.1.5 Supplemental New Drug Application (sNDA)

Sometimes, the applicant/sponsor wants to make alterations in an approved NDA, ANDA and BLA to enhance its quality, safety, and efficacy. For the same the applicant needs to obtain approval from the concerned regulatory body. Supplemental New Drug Application, Supplemental Abbreviated New Drug Application and Supplemental Biologic License Application is the process of obtaining consent from USFDA to introduce alterations in an already approved drug product. In order to change a label, to change in manufacturing process or to market a new dosage, the applicant needs to submit a supplemental new drug application to the concerning regulatory body. Post-approval changes applicable for supplemental applications are accordingly classified under different categories. These are followed as:

- a) components and composition change,
- b) changes in manufacturing process,
- c) changes in manufacturing site,
- d) changes in specifications,
- e) changes in container closure system,
- f) labeling changes,
- g) miscellaneous changes and
- h) multiple related changes

The applicant needs to file sNDA depending upon the category of changes stated above. Also, the applicant needs to provide supplement documents to substantiate that the intended changes would not adversely affect the quality, safety and efficacy of the drug product.

CHAPTER 2

2. OBJECTIVES OF THE STUDY

- To understand the need of supplemental applications for the drug products and biologics.
- To analyze the differences in approval procedures for supplemental applications in regulated as well as semi-regulated countries.
- To study the variation in number of submissions and approvals for supplemental applications in regulated and semi-regulated countries.
- To understand the advantages of filing the supplemental applications.

CHAPTER 3

3. LITERATURE REVIEW

1. V.Sai Kishore, Drug regulatory affairs, (2010) the author has elucidated the need of regulatory affair division along with their responsibilities. He has presented the basic role and responsibilities of drug regulatory department and agencies controlling them. The author has briefly explained the organization and working of regulatory agencies of different countries including US, UK, India, WHO, Canada etc.
2. Douglas J.Pisano et al., FDA Regulatory Affairs- A guide for prescription drugs, medical devices and biologics, the author has drawn a picture on the importance and practice of regulatory affairs along with methodology of gathering information.
3. V.Sai Kishore, Drug regulatory affairs, the author has explained concepts and fundamentals of the process of drug discovery and development. The author has also given an overview on drug approval process in countries like USA, Europe and India.
4. Sandy Weinberg, Guide book for Drug Regulatory Submissions, the author has explained the filing of IND according to FDA guidelines. He has focused on the classification, process and problem areas arising in filing process. The author has explained in detail on the resources for the application, guidance documents and organizing the submission.
5. Douglas J.Pisano et al., FDA Regulatory Affairs- A guide for prescription drugs, medical devices and biologics, the author has discussed the complete process and format of NDA. He has also highlighted the laws, regulations and the development of NDA. The author has concluded the information with maintenance and review of NDA.
6. Sandy Weinberg, Guide book for Drug Regulatory Submissions, the information presented by the author covers detailed submission requirements, process of filing along with guidance for filing NDA application.
7. Ira R. Berry et al., The Pharmaceutical Regulatory process, the author has focused on policies and procedure that the applicant needs to follow in order to obtain approval for ANDA application. The author has given overview on the Hatch-Waxman act along with orange book. He has briefly explained all the four paragraph filing procedures. He has also discussed listed drug, process of generic drug approval, submission of ANDA as an act of patent infringement.

CHAPTER 4

4. Experimental Work

4.1 USFDA

The United States Food and Drug Administration has classified three different categories of changes on the basis of the effect of the intended change. These include:

Major changes are those that have notable potential to cause an adverse effect on the identity, strength, quality, purity or potency of a drug product as they affect the safety and efficacy of the drug product forthwith. Such change demands review and prior approval by the regulatory agency before they can be implemented, hence also referred as *Prior Approval Supplement*. The applicant can also request to accelerate the review process of a prior approval supplement for public health reasons. Such supplement is called *Prior Approval Supplement-Expedited Review Requested*. Examples of major changes include changes in composition of finished pharmaceutical product, changes to manufacturing process of active pharmaceutical ingredient, etc. For such changes the applicant needs to provide sufficient evidence in order to convince the regulatory body for the proposed change.

Moderate changes are those which have mild potential to cause an adverse effect on the identity, strength, quality, purity or potency of a drug product. They are further of two types-

- a) Moderate changes which require the submission of the supplement to the concerned regulatory body at least 30 days before the distribution of the drug product, i.e. applicant must wait for 30 days before implementing a 30-day change. Such a supplement is labelled as *Supplement Changes being effected in 30 days*. Examples include changes in final process scale involving new equipment, deletion of tests in accordance with official compendia, relaxation of acceptance criteria, etc.
- b) Changes that are implemented only after being notified to the regulatory agency with the aid of supplementary are labelled as *Supplement- Changes being effected*. Examples of such change include changes to the size or shape of a container for non-sterile drug, changes to specifications or test methods intended to provide increased assurance as regards product quality, etc.

Minor changes don't require notification to the regulatory agency via supplement, but the introduction of the change in the next annual report. It involves corrections to labeling,

replacement of equipment with similar equipment, deletion/reduction in an ingredient intended to affect the colour, etc.

Table 3: Different types of changes submitted as sNDA

S.NO	CATEGORY	TYPES OF CHANGES		
		MAJOR	MODERATE	MINOR
1	Manufacturing site	-Move to new site never inspected by a regulatory official -Finished drug product sterilized by terminal process	-Manufacture of drug product that is not otherwise provided in the guidance	-Change in secondary packaging
2	Manufacturing process	-Addition or deletion of sterilization procedures -Addition of new equipment -Change in pore size of filter	-Change from single to dual sterilizing filters -Change in filtration parameters (flowrate, pressure, time etc.)	-Changes to equipment of same design -Changes in the order of addition of ingredients
3	Container closure system	-Change from ampule to vial -From single to multiple dose -Change in size of sterile container	-Change in label of drug	-Change in child resistant pack -Change in antioxidant, colorant, stabilizer etc.
4	Labeling	-Changes to clinical pharmacology	-Addition of an adverse event -Addition of precaution, warning, contraindication etc.	-Change in layout of package label

Method- The data has been archived from United States food and drug administration official website constituting all the applications approved by the USFDA from 2000 to 2016. Number of applications submitted, approved and rejected were presented on monthly basis on the website. The data was analyzed and compiled on yearly basis. Further, the data was also segregated on the basis of different categories of approved applications. Analysis was also done using statistical tool ANOVA i.e. analysis of variance (single factor).

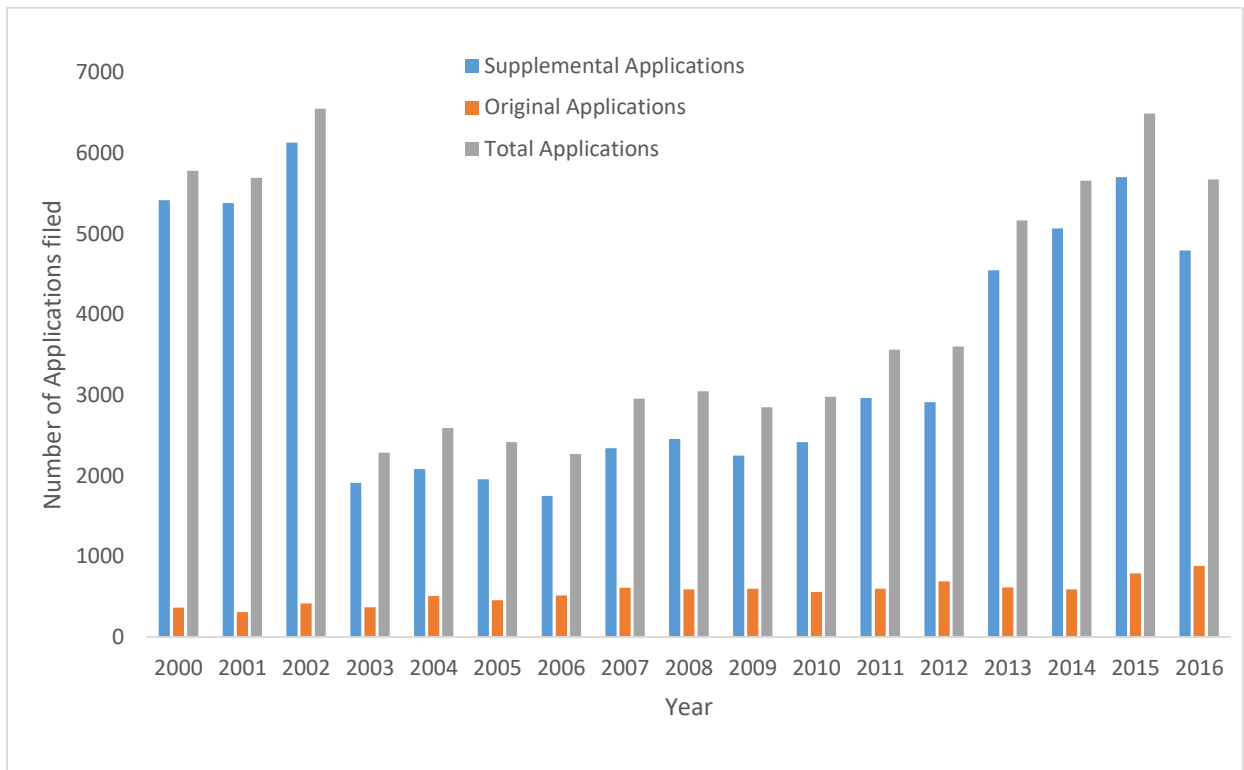


Figure 7: Data of total applications filed to USFDA (2000-2016)

From the Figure 7, it can be concluded that the major number of supplemental applications were filed in the year 2002 followed by 2015.

Table 4: Number of supplemental applications filed to USFDA (2000-2016)

S. No	Year	Total Supplemental Applications Filed	sNDA	sANDA	sBLA
1	2000	5416	2716	2678	22
2	2001	5381	2641	2715	25
3	2002	6131	3370	2722	39
4	2003	1913	1425	448	40
5	2004	2085	1463	552	70
6	2005	1959	1178	724	57
7	2006	1751	1060	615	76
8	2007	2341	1160	1118	63
9	2008	2456	1192	1195	69
10	2009	2250	1175	1016	59
11	2010	2419	1182	1150	87
12	2011	2963	1592	1250	121
13	2012	2914	1459	1355	100
14	2013	4548	3135	1309	104
15	2014	5065	3033	1929	103
16	2015	5702	2480	3113	109
17	2016	4792	2231	2453	108

As per the data analysis from table.4 out of total supplemental applications filed, major submissions belonged to the category of new drug applications followed by abbreviated new drug applications and biologic license application.

Table 5: Single factor ANOVA analysis for the applications approved by USFDA in different categories (2000 – 2016)

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	32220945.10	2	16110472.55	33.94	6.50*10 ⁻¹⁰	3.19
Within Groups	22782747.65	48	474640.57			
Total	55003692.75	50				

SS= sum of squares, **df**= degree of freedom, **MS**= mean of squares, significance value being 0.05%

Table 6: Number of applications approved under different categories of Supplemental applications by the USFDA (2000-2016)

S.No	Year	Manufacturing (cmc)	Labeling	Efficacy	Type 1 (New molecular entity)	Type 3 (New dosage form)	Type 5 (New formulation)
1.	2000	3978	1227	196	0	0	0
2.	2001	4123	1144	96	0	0	0
3.	2002	4339	1598	161	0	0	0
4.	2003	313	1355	156	0	0	1
5.	2004	196	1613	142	1	0	0
6.	2005	263	1456	150	0	0	0
7.	2006	170	1384	113	0	0	0
8.	2007	298	1846	130	0	0	0
9.	2008	276	1977	123	0	0	0

10.	2009	209	1854	110	0	0	0
11.	2010	96	2082	93	0	1	0
12.	2011	124	2413	98	0	0	0
13.	2012	203	2327	124	0	0	0
14.	2013	1840	2375	103	0	0	0
15.	2014	1921	2828	121	1	0	0
16.	2015	1559	3736	125	0	0	0
17.	2016	1130	3190	132	0	1	0

From the data as per the above table, it can be concluded that major supplemental applications filed belonged to labelling category, followed by manufacturing changes, efficacy and least in type 1,3 and 5.

Table 7: Single factor ANOVA analysis for the applications approved under different categories of supplemental applications (2000-2016)

Source of variation	SS	df	MS	F	P-value	F crit
Between Groups	63391772.56	5	12678354.51	26.91	6.45×10^{-17}	2.30
Within Groups	45228345.65	96	471128.60			
Total	108620118.2	101				

SS= sum of squares, **df**= degree of freedom, **MS**= mean of squares, significance value being 0.05%

4.2 EUROPE

According to European Medicine Agency (EMA) variations to medicinal products can be categorized under different categories, depending on the level of risk to public health and the impact on quality, safety and efficacy.

Table 8: Categorization of variations as per EMA

Minor variations		Major variations Type II	Extension of marketing authorization
Type IA	Type IB		
-Variations that has minimum or no effect on quality, safety and efficacy of medicinal product concerned	-Variations which is neither a minor variation of type IA nor a major variation of Type II nor an extension to marketing authorization	-Variation which may have major effect on quality, safety and efficacy of medicinal product and is not included in extension of marketing authorization	Variation that includes changes to active substance(s), strength, pharmaceutical form and route of administration
Examples- change in packaging material not in contact with finished product, deletion of any manufacturing site, changes made to specification of active substance or of an excipient		Examples- addition of new therapeutic indication or modification to existing one, substantial changes to manufacturing process, formulation, specification or impurity profile of active substance, changes to manufacturing site of active substance of the final dosage forms	Examples- change of bioavailability, change of pharmacokinetics, replacement of active substance by a different isomer or mixture of isomers

Table 9: Applications approved by EMA (2007-2016)

S.no	Year	Applications submitted	Applications approved
1.	2007	24540	23004
2.	2008	21612	20340
3.	2009	30636	28752
4.	2010	14184	11497
5.	2011	18625	17946
6.	2012	34792	32847
7.	2013	70092	65148
8.	2014	49632	47664
9.	2015	37464	35220
10.	2016	36577	39448*

*error in data shown on European agency website (as number of applications approved is greater than number of applications submitted)

Table 10: Variation applications approved by EMA (2007-2016)

S.no	Year	Total variation applications approved	Type IA	Type IB	Type II	Extension to marketing authorization
1.	2007	23004	9840	3504	9324	336
2.	2008	20340	9396	5544	10524	420
3.	2009	28752	10104	4944	13704	3721

4.	2010	11497	6859	4638	6043	158
5.	2011	17946	17946	7915	6101	159
6.	2012	32847	17601	9505	5741	115
7.	2013	65148	34632	19164	11352	216
8.	2014	47664	34248	23832	13236	180
9.	2015	35220	34188	22056	13164	6916
10.	2016	39448*	18918	13279	7150	101

*error in data shown on European agency website

Table 11: Single factor ANOVA analysis for the applications approved for variations (2007-2016)

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	1.66*10 ⁹	3	5.54*10 ⁸	11.18	2.47*10 ⁻⁵	2.86
Within Groups	1.78*10 ⁹	36	49529538			
Total	3.45*10 ⁹	39				

SS= sum of squares, **df**= degree of freedom, **MS**= mean of squares, significance value being 0.05%

4.3 CANADA

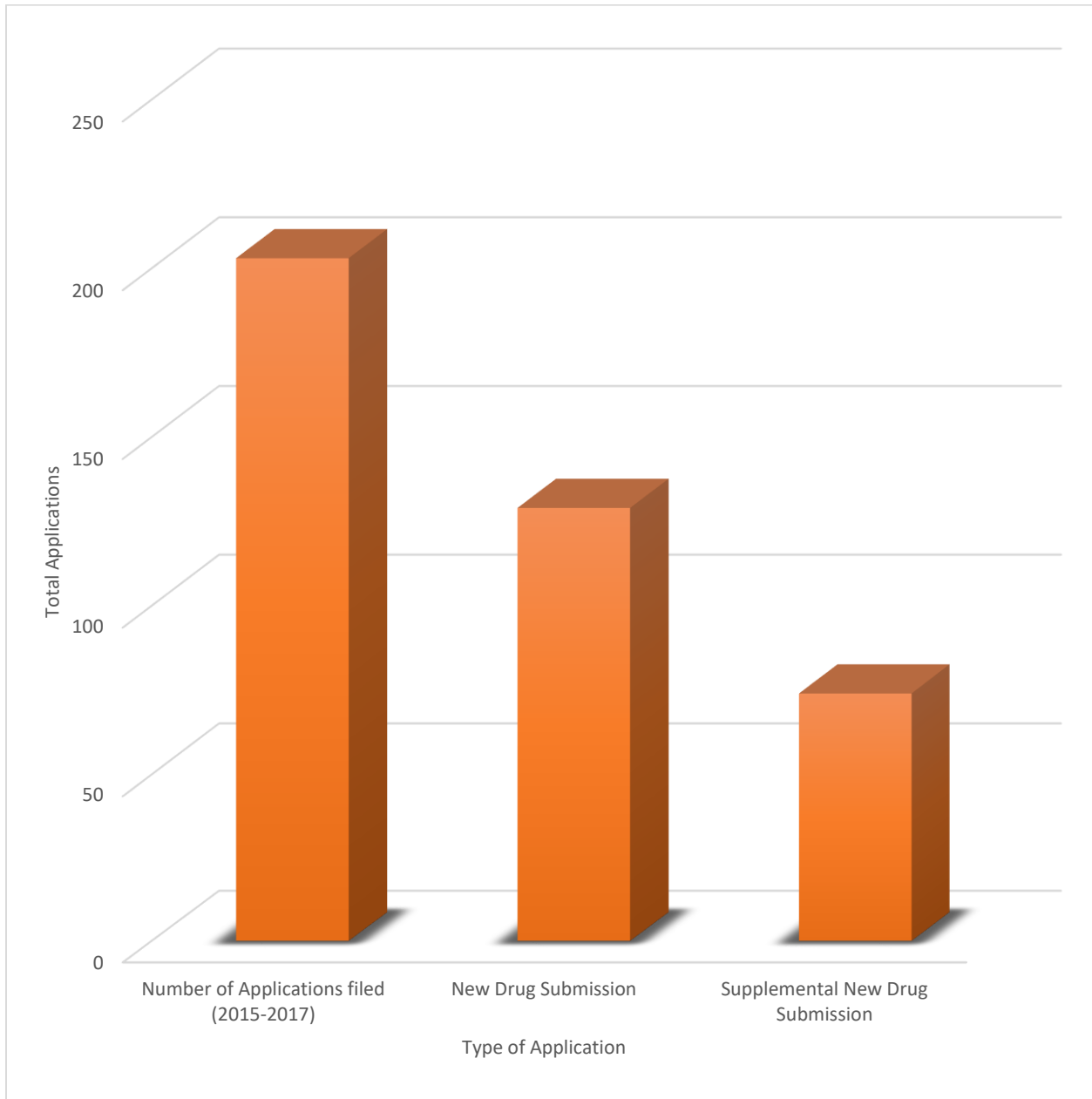


Figure.8: Applications Approved by Health Canada (2015-2017)

From the year 2015 to 2017, a total number of 203 applications were filed to Health Canada, out of which 123 applications were for New Drug Submission and remaining 80 were submitted as Supplemental New Drug Submissions.

4.3 INDIA

In India, currently the process of filing application for variation is still under process and pending category.

Table.12: Data of Subsequent New Drug Applications submitted in CDSCO

S. No	Diary number of applicant	Date of receipt	Status
1	30744	31-7-12	Pending
2	38793	19-09-12	Pending
3	44225	26-10-12	Pending
4	46259	09-11-12	Pending
5	46997	16-11-12	Pending
6	5531	07-02-13	Pending
7	7520	20-02-13	Pending
8	14025	28-03-13	Pending
9	29867	24-06-13	Pending
10	36866	31-07-13	Pending
11	35581	23-07-13	Pending
12	44776	06-09-13	Pending
13	47965	25-09-13	Pending
14	FTS-86933	12-12-13	Pending
15	63955	23-12-13	Pending
16	270	03-01-14	Pending
17	7024	17-02-14	Pending
18	11554	08-03-14	Pending
19	16938	21-04-14	Pending
20	21175	19-05-14	Pending
21	25089	12-06-14	Pending

22	44638	30-10-12	Pending
23	2546	20-01-14	Pending
24	Fts-75061	23-12-14	Pending
25	48903	23-12-14	Pending
26	1129	12-01-15	Pending
27	36866	31-07-13	Pending
28	46902	20-11-14	Pending
29	51444	31-12-14	Pending
30	47076	24-11-14	Pending
31	10040	30-3-15	Pending
32	1043	09-01-13	Pending
33	11554	08-03-14	Pending
34	8357	17-03-15	Pending
35	1029	12-01-15	Pending
36	46340	17-11-14	Pending
37	36150	04-09-12	Pending
38	30436	16-07-14	Pending
39	12488	20-03-13	Pending
40	47965	25-09-13	Pending
41	10040	30-03-15	Pending
42	12624	20-04-15	Pending
43	13628	29-04-15	Pending
44	20715	29-06-15	Pending
45	27383	19-08-15	Pending

CHAPTER 5

5. SUMMARY AND CONCLUSION

I have carried out data evaluation of data obtained, as per the data analysis done between the year 2000 to 2016 (17ys), a total number of 69,585 applications were filed to USFDA for approval. Out of the filed applications, 9499 were original applications and 60086 were supplemental applications. Out of 60086 supplemental applications 32492, 26342 and 1252 were reported to be sNDA, sANDA and sBLA respectively. Major applications filed belonged to the category of labelling changes (57.25%) followed by manufacturing changes (35.01%) and efficacy (3.61%). Other nominal changes include type 1 change, i.e. New Molecular Entity (0.003%), type 3 change, i.e. New Dosage Form (0.003%) and type 5 i.e. New Formulation or other differences (0.001%). Also, we applied ANOVA (Single Factor) to the obtained data. ANOVA is a statistical tool designed to test whether the means of more than two quantitative populations are equal. As per data presented in table 3, raise in F-value depicted large variation in submission of sNDA, sANDA and sBLA and the hypothesis is being rejected as p-value being greater than the significant value of 0.05. Similarly, from the data presented in table 5, F-value depicts a variation in different categories of supplemental application and hypothesis again being rejected as p-value being greater than the level of significance.

In case of Europe, European Medicine Agency has classified variations in different category i.e. Minor (Type IA &IB), Major (Type II) and Extension of marketing authorization. A total of 338154 applications were filed out of which 321866 were approved. There were certain errors in the data present on their official website as number of approved applications were greater than applications submitted for approval.

In case of Canada, a total of 203 applications were filed, out of which 123 applications (2015-2017) were for New Drug Submission and remaining 80 were submitted as Supplemental New Drug Submissions.

For a semi-regulated country like India, the process for filling a supplemental application is still under process. The applications filed were 45 and all of them are still under pending status.

CHAPTER 6

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