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Research Article

Present Status of Supplemental Application Submission in USFDA

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ABSTRACT
Objective: In order to reach to the market, a drug product has to undergo various phases of scrutiny assuring its quality, safety and efficacy. Once the experimental drug promises its safety, efficacy and quality it is permitted to be marketed by the regulator. The drug is still present under surveillance for possibility of any adverse drug reaction or any other alteration or a new indication. If any modification is to be done, then the applicant/sponsor needs to file a supplemental application. This article provides information about present status of supplemental new drug application submitted and approved to the United States food and drug administration. Materials and methods: The data have been archived from the official website of United States food and drug administration comprising all the applications approved by this regulatory agency from the year 2000 to 2016. The data has been segregated and statistically analyzed using ANOVA on the basis of different categories of approved applications. Results: As per the analysis, from the year 2000 to 2016, a total of 69,585 applications was filed to USFDA, amongst which 9499 were original applications and 60,086 were supplemental applications.

Keywords: Indication, Specification, Generic, Biologic, Supplemental new drug application, United States food and drug administration.

INTRODUCTION

Medicinal products, medical devices and food supplements are the essential categories of products that are highly subjected to the regulations for their safety, efficacy and quality use. To obtain approval for marketing, the experimental drug needs to follow all the parameters assuring its safety, efficacy and quality. Reports of the studies on the discovered drug product are considered by the regulatory agencies in order to approve their marketing and use. The data to be submitted must be presented in the right way and form, i.e. appropriate dossier preparation (according to respective regulatory authorities). To obtain approval and a license for the same, different types of applications are filed depending upon the need of the applicant and a regulator[1]. These applications are as follows-

Investigational New Drug Application (IND) After successful pre-clinical testing of a new discovered drug/biological, it is forwarded for testing in human subjects in order to determine its therapeutic potential 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 USFDA to conduct clinical studies on human volunteers and patients[2]. 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. Only once the IND is submitted, the applicant needs to wait for 30 calendar days before initiating the clinical studies**.** Main objective of IND application filing involves assurance of the safety of human subjects participating in the study and determination of therapeutic efficacy of a newly discovered drug[3,4]. IND can only be filed in conditions supporting –

a new indication,
unusual change in already approved drug,
change in prior approved route of administration and
change in approved patient population

New Drug Application (NDA) gives the sovereignty to the applicant to introduce the new drug 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 the basis of filing an NDA application if it is:

a new chemical entity
new salt of prior approved drug,
New combination of two or more drugs,
already marketed product (new manufacturer),
new indication for already marketed product and
Already marketed drug product with no previously approved NDA[5]

The documents which support the main NDA application must project complete details of the drug, including its

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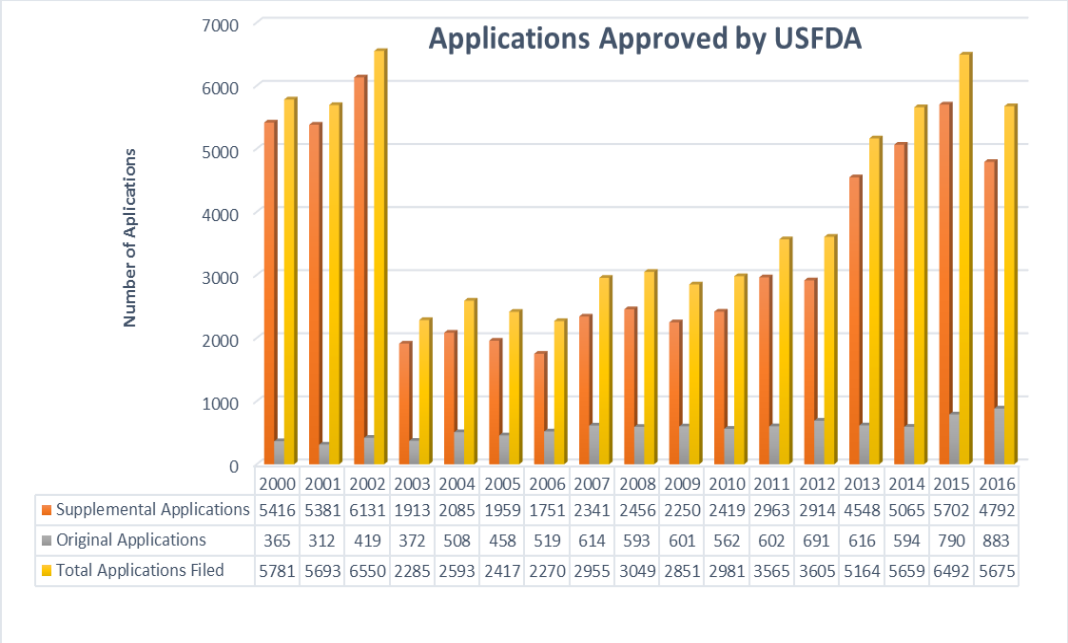
Table 1: Examples of different types of changes[11-14]

S. No	Category	Types of changes		
		Major	Moderate	Minor
1.	Manufacturing Site	-Move to a 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/Deletion of sterilization procedure -Addition of new equipment -Change in pore size of filter	-Change from single to dual sterilizing filters -Change in filtration parameters (Flow rate, pressure, time. Etc.)	-Change in 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 amount -Change in container size number of units in unit dosage form	-Change in child resistant pack -Change in antioxidant, colorant, stabilizer etc.



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Supplemental Applications	5416	5381	6131	1913	2085	1959	1751	2341	2456	2250	2419	2963	2914	4548	5065	5702	4792
Original Applications	365	312	419	372	508	458	519	614	593	601	562	602	691	616	594	790	883
Total Applications Filed	5781	5693	6550	2285	2593	2417	2270	2955	3049	2851	2981	3565	3605	5164	5659	6492	5675

Figure1: Data of total applications filed to USFDA from 2000 to 2016.

synthesis, manufacturing, pharmacokinetic properties and pharmacodynamics properties, processing, packaging and labelling. The sponsor/applicant must provide to the regulator sufficient information 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 and
4) Whether the methods used in manufacturing the drug and the controls used to maintain the drug's quality adequate to preserve its identity, strength, quality, and purity?[6]

Abbreviated New Drug Application (ANDA) is filed by the applicant to obtain approval for marketing and sale of a drug product whose patent term has been expired, in countries lacking patent protection and for the drugs that are not patented. For a drug product to be considered eligible for ANDA it must be identical to a listed drug product (branded drug or generic drug) in terms of-

active pharmaceutical ingredient (API),
dosage form,
dosage strength,
route of administration and
labeling

It is considered to be bioequivalent to the innovator drug product if the rate and extent of absorption is same[7]. Generic drug applications are also known as abbreviated

Table 2: Number of supplemental applications filed to USFDA (2000-2016)[15-17]

S. No	Year	Total Supplemental Applications Filed	Supplemental New Drug Application	Supplemental Abbreviated New Drug Application	Supplemental Biologics License Application
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

Table 3: Single factor ANOVA analysis of applications approved by USFDA in different categories from 2000 to 2016.

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	32220945.1	2	16110472.55	33.94246797	6.5034E-10	3.19072734
Within Groups	22782747.65	48	474640.576			
Total	55003692.75	50				

SS= sum of squares, df= degree of freedom, MS= mean of squares

generic drug applications as they exclude pre-clinical and clinical data to establish safety and effectiveness.

Biologic Drug 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[8]

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 of the same the applicant needs to obtain consent from the concerned regulatory body. Supplemental New Drug Application, Supplemental Abbreviated New Drug Application and Supplemental Biologic License Application is the process of obtaining approval from USFDA to introduce modifications 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 USFDA. Post-approval changes are accordingly classified under:

components and composition change,

change in manufacturing process

change in manufacturing site,

change in specifications,

change in container closure system,

labeling change,

miscellaneous change and

multiple related change

The applicant needs to file sNDA depending upon the category of changes stated above. Also, the applicant needs to provide supplemental documents to substantiate that the intended change would not affect the quality, safety and efficacy adversely. Further, there are three different categories of changes based on the effect of the intended change.

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 USFDA before they can be implemented, hence also referred as a *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 in the manufacturing process of active pharmaceutical ingredient, etc. For such changes, the applicant needs to provide sufficient evidence in order to convince USFDA for the proposed change[9,10].

Moderate changes are those which have mild potential to cause an adverse effect on the identity, strength, quality,

Table 4: Number of applications approved under different categories of Supplemental applications (2000-2016)[18-20]

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

Table 5: Single factor ANOVA analysis of applications approved under different categories of Supplemental applications from 2000-2016.

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	63391772.56	5	12678354.51	26.91060254	6.45E-17	2.309202
Within Groups	45228345.65	96	471128.6005			
Total	108620118.2	101				

SS= sum of squares, df= degree of freedom, MS= mean of squares

purity or potency of a drug product. They are further of two types-

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 labeled 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.

Changes that are implemented only after being notified to the USFDA with the aid of supplementary are labeled as *Supplement- Changes being effected.* Examples of such change include changes to the size or shape of a container for a 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 USFDA 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 color, etc[5].

MATERIALS AND METHODS

The data have been archived from United States food and drug administration official website constituting all the applications approved by the United States food and drug administration from 2000 to 2016. Number of applications submitted, approved and rejected was present on a monthly basis the data was analyzed and compiled on a 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).

RESULTS

From the Fig. 1, it can be concluded that the major number of supplemental applications were filed in the year 2002 followed by 2015 and 2002. As per the data analysis from table.2 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. 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.

DISCUSSION

We 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. There is no significant change in the number of submissions of all the three supplemental applications (Snda, sanda and sbla). It is taken as the hypothesis. 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.

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