A note on Drug Master Filings

Dynamics of Drug Master Filings at United States Food and Drug Administration

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Abstract

Drug master filing at USFDA in one of the parameters that helps in knowing the potentiality of a country in the field of pharmaceuticals. Filing a drug master file at USFDA implies that the company is claiming manufacturing drug and facility suitable for USFDA rules and regulations. Several incidences are available where a company do have a USFDA approved facility but do not have financial viability of the developed products. Patent Facilitation Center at Pharmexcil of India believes that providing lead information to develop innovative products finally leads to protection of intellectual property. The article mainly concentrates statistics relating to type II drug master filing at USFDA since manufacturing drugs in USFDA approved facilities usually comply global standards.

Introduction

As per the regulatory guidelines, it is mandatory to file a drug master file and after being approved, releasing the drug into the market. A drug master file may be for a bulk drug or for a formulation. A drug master file declared by the company provides in detail the manufacturing place, physicochemical properties, pharmacodynamic/kinetic, toxicology studies of the bulk drugs and formulations, therapeutic class, dosage form, strength, route of administration, labeling, packaging etc. Filing a drug master file at USFDA by a company is an indication that the company is claiming its capability in manufacturing and having a facility complying USFDA rules and regulations.

Filing drug master files from countries other than United States, give a provision to the US pharmaceutical organizations recommending foreign country facilities utilizing the manufactured products upon approval by the USFDA authorities to market in United States.

It is necessary to understand DMF filings by pharmaceutical industries give an indication of potential market both in terms of volume and value.

Drug master files are classified into five types by the USFDA and are as follows:

Type I : Manufacturing Site, Facilities, Operating Procedures, and Personnel (no longer applicable)

Type II : Drug Substance, Drug Substance Intermediate, and Material Used in Their Preparation, or Drug Product

Type III : Packaging Material

Type IV : Excipient, Colorant, Flavor, Essence, or Material Used in Their Preparation

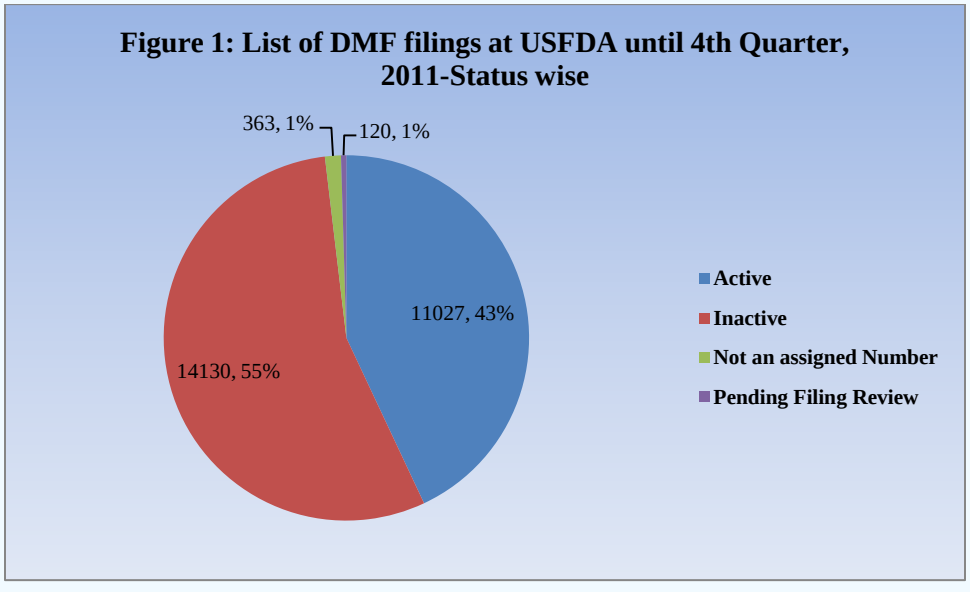
Type V : FDA Accepted Reference Information

At USFDA, DMF filings are classified as "I"-Inactive, "A"-Active, "N"-Not an assigned number, "P"-DMF Pending Filing Review

Over view of DMF statistics

All DMFs-Status wise

As on 4th quarter, 2011 a total of 25640 drug master files were filed at United States Food and Drug Administration that includes all types. Figure 1 indicates that among all the types, 55 percent of the filings are inactive and 43 percent of the filings are active. The left over are in the stage of review or not assigned with a number.

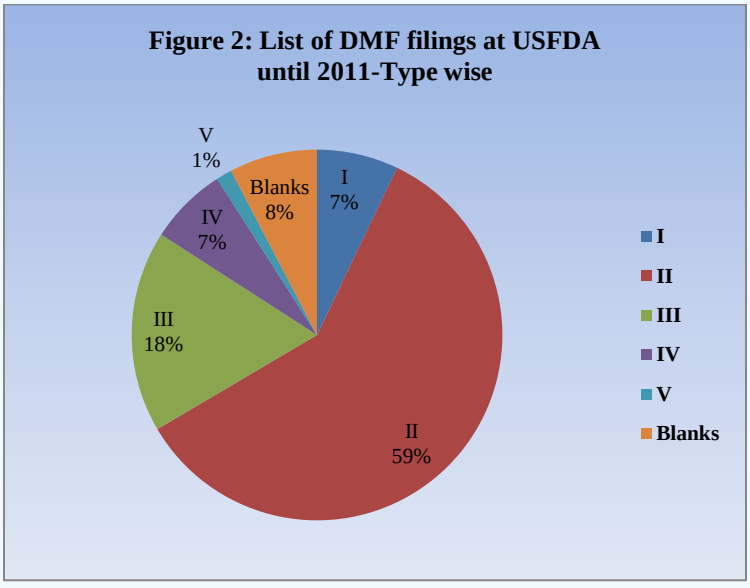


All DMFs-Type wise

A study by type wise on the number of DMFs filed at USFDA indicates from table 1, figure 2 that a maximum of 59 percent of DMF filings is relating to type II that includes all types of status. It has been observed that DMF filings of the type I are during the years 1941-2000 indicating that type I filings are withdrawn by the USFDA authorities.

Table 1: List of DMF filings at USFDA until 2011-Type wise

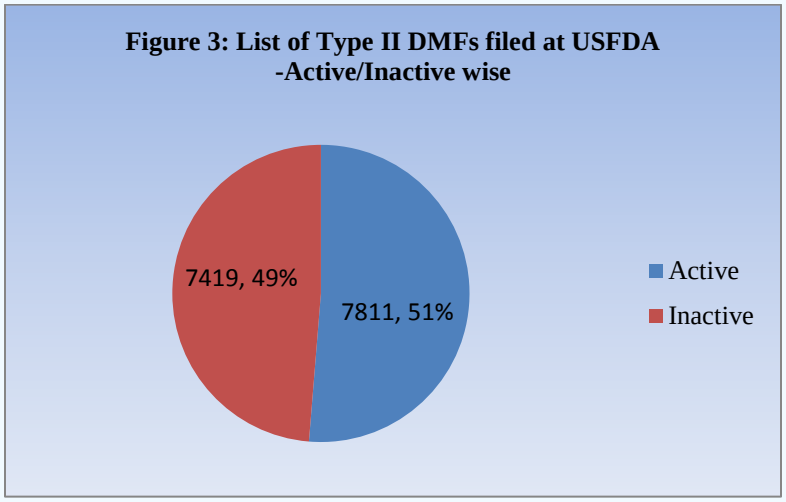
S. No	Type	Type code	No. of DMFs
1	Manufacturing Site, Facilities, Operating Procedures, and Personnel (no longer applicable)	I	1826
2	Drug Substance, Drug Substance Intermediate, and Material Used in Their Preparation, or Drug Product	II	15230
3	Packaging Material	III	4511
4	Excipient, Colorant, Flavor, Essence, or Material Used in Their Preparation	IV	1749
5	FDA Accepted Reference Information	V	355
6	Blanks	Blanks	1969
	Grand Total		**25640**



It is necessary to understand that type II filings have potential market since industries select molecules that have potential market both in terms of volume and value.

Type II DMFs in Detail

Drug Master Filings under type II includes drug substance, drug substance intermediate, and material used in their preparation, or drug product. When a study is made among the type II drug master files, figure 3 indicates that among the 15230 type II DMFs filed, 51 percent of the filings are active.

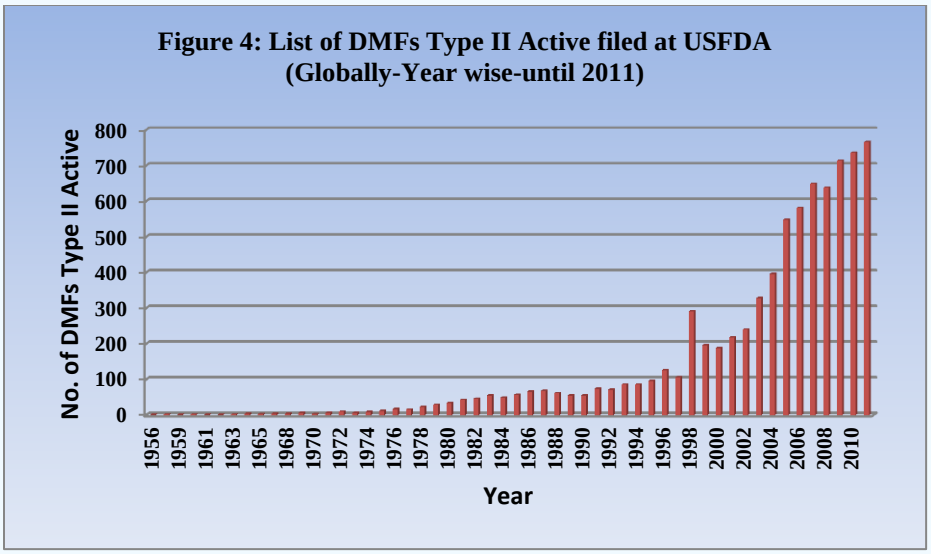


Type II DMFs Active-Global Scenario

It has been observed that a total of 57 countries have filed 7886 DMFs that are currently active. The number of DMFs type II active is higher than mentioned in figure 3 due to the reason of several DMFs belonging same company being manufactured in different countries.

When a study is made in terms of number of DMFs type II active, table 2 and figure 4 clearly indicates an uptrend in filings to market the products in United States market. During the period 1956 to 2011, the number of filings ranging a minimum of 1 to a maximum of 766 is observed.

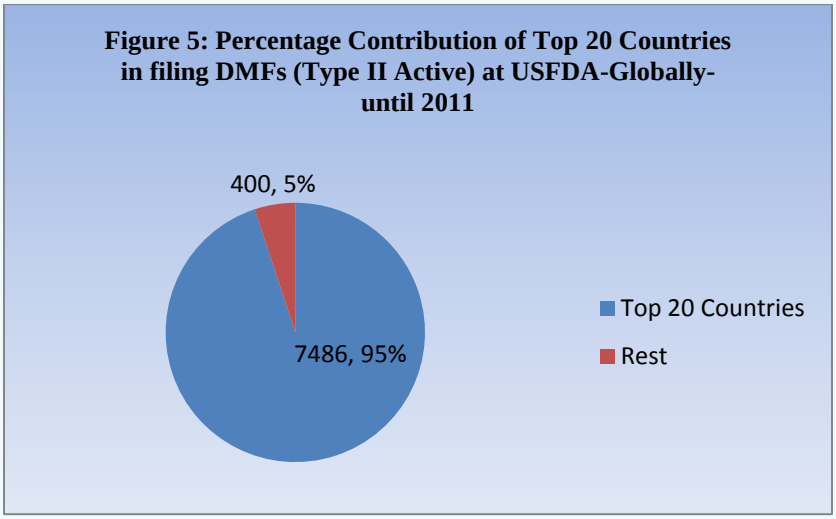
Table 2: List of DMFs Type II Active at USFDA (Globally-Year wise-until 2011)			
Year	**No. of DMFs**	**Year**	**No. of DMFs**
1956	1	**1985**	57
1957	2	**1986**	66
1959	1	**1987**	68
1960	2	**1988**	62
1961	1	**1989**	55
1962	1	**1990**	55
1963	2	**1991**	74
1964	4	**1992**	71
1965	3	**1993**	86
1967	4	**1994**	86
1968	4	**1995**	96
1969	6	**1996**	126
1970	3	**1997**	106
1971	6	**1998**	291
1972	10	**1999**	196
1973	6	**2000**	188
1974	9	**2001**	218
1975	12	**2002**	240
1976	17	**2003**	328
1977	16	**2004**	396
1978	23	**2005**	548
1979	29	**2006**	581
1980	34	**2007**	649
1981	43	**2008**	638
1982	46	**2009**	714
1983	55	**2010**	736
1984	49	**2011**	766
		Grand Total	**7886**



Type II DMFs Active-Contribution of Top 20 Countries

Even though DMF filings at USFDA starts from the year 1940, currently type II DMF filings that are active is from the year 1956 which is filed by a local company of United States. When a study is made from 1956 for the DMFs type II that are still active, the first foreign country is Mexico filing type II DMF in the year 1961.

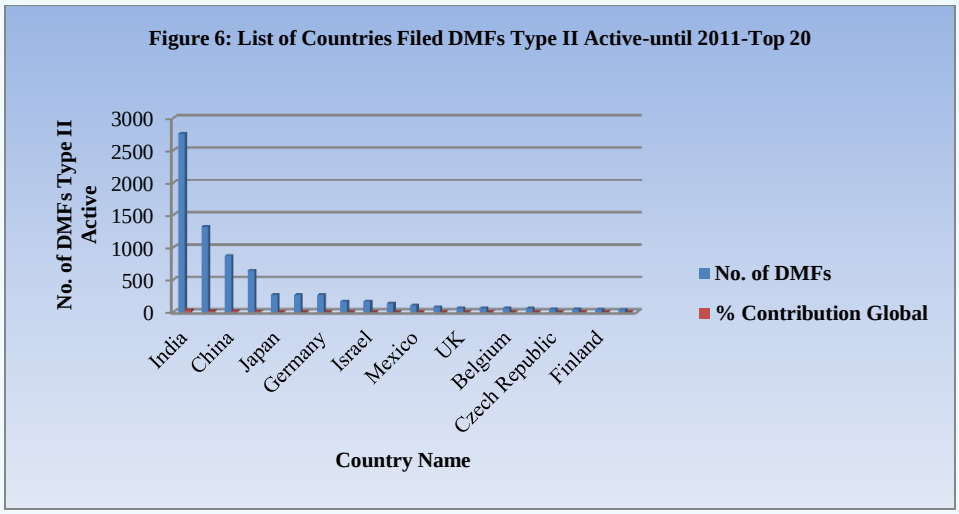
Considering the currently available type II DMFs that are active, top 20 countries that still have active DMFs (cumulative-until 2011) were considered and when compared their percentage contribution to total type II DMFs active figure 5 indicates 95 percent contribution is from these top 20 countries (including USA).



When a study is made among the top 20 countries that have filed type II DMFs and active, table 3 and figure 6, India stands first with 2759 DMFs of the type II that are currently active with a contribution of about 35 percent when compared to the total number of type II DMFs active .

Table 3: List of Countries Filed DMFs Type II Active at USFDA - until 2011-Top 20

S. No	Name of Country	No. of DMFs Type II Active Filed	% Contribution Global
1	India	2759	34.99
2	USA	1323	16.78
3	China	870	11.03
4	Italy	644	8.17
5	Japan	270	3.42
6	Spain	268	3.40
7	Germany	266	3.37
8	France	170	2.16
9	Israel	170	2.16
10	Switzerland	136	1.72
11	Mexico	102	1.29
12	Canada	80	1.01
13	UK	65	0.82
14	The Netherlands	64	0.81
15	Belgium	62	0.79
16	Hungary	61	0.77
17	Czech Republic	50	0.63
18	Austria	47	0.60
19	Finland	40	0.51
20	Ireland	39	0.49
	Sub Total Top 20	**7486**	94.93
	Grand Total	**7886**	100.00

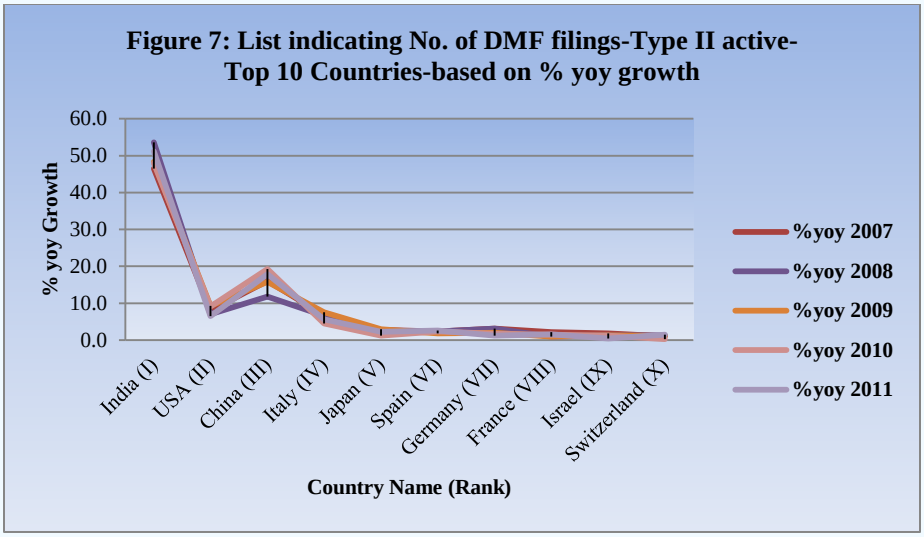


Type II DMFs Active - % yoy growth during 2007-2011

Considering the top 10 countries (based on cumulative type II DMFs active until 2011), when a study is made in terms of number of type II DMFs active and filed by different countries yearly, table 4, figure 7 indicates India standing first with 51.2 percent filings with 392 filings over a total of 766 filings when compared to other countries for the year 2011.

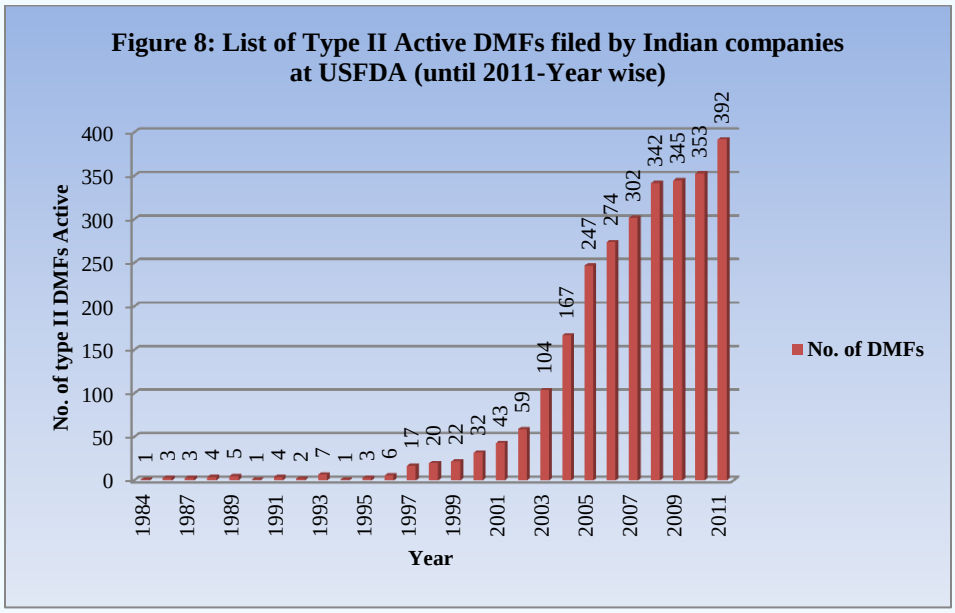
Table 4: List indicative No. of DMF filings & % yoy growth at USFDA (2007-2011)-Top 10 Countries based on cumulative DMFs until 2011

Rank (as a whole-cumulative -2011)	Year/ Country (Rank 2011)	2007	%yoy 2007	2008	%yoy 2008	2009	%yoy 2009	2010	%yoy 2010	2011	%yoy 2011	Grand Total (as a whole cumulative)	%yoy Grand Total
1	India (I)	302	46.5	342	53.6	345	48.3	353	48.0	392	51.2	2759	35.0
2	USA (II)	52	8.0	45	7.1	66	9.2	67	9.1	50	6.5	1323	16.8
3	China (III)	104	16.0	75	11.8	113	15.8	142	19.3	137	17.9	870	11.0
4	Italy (IV)	44	6.8	42	6.6	54	7.6	33	4.5	43	5.6	644	8.2
5	Japan (V)	18	2.8	16	2.5	21	2.9	9	1.2	17	2.2	270	3.4
6	Spain (VI)	15	2.3	15	2.4	13	1.8	17	2.3	20	2.6	268	3.4
7	Germany (VII)	20	3.1	20	3.1	14	2.0	13	1.8	9	1.2	266	3.4
8	France (VIII)	14	2.2	6	0.9	7	1.0	11	1.5	12	1.6	170	2.2
9	Israel (IX)	12	1.8	8	1.3	9	1.3	9	1.2	3	0.4	170	2.2
10	Switzerland (X)	7	1.1	8	1.3	8	1.1	2	0.3	11	1.4	136	1.7
	Grand Total	649		638		714		736		766		7886	



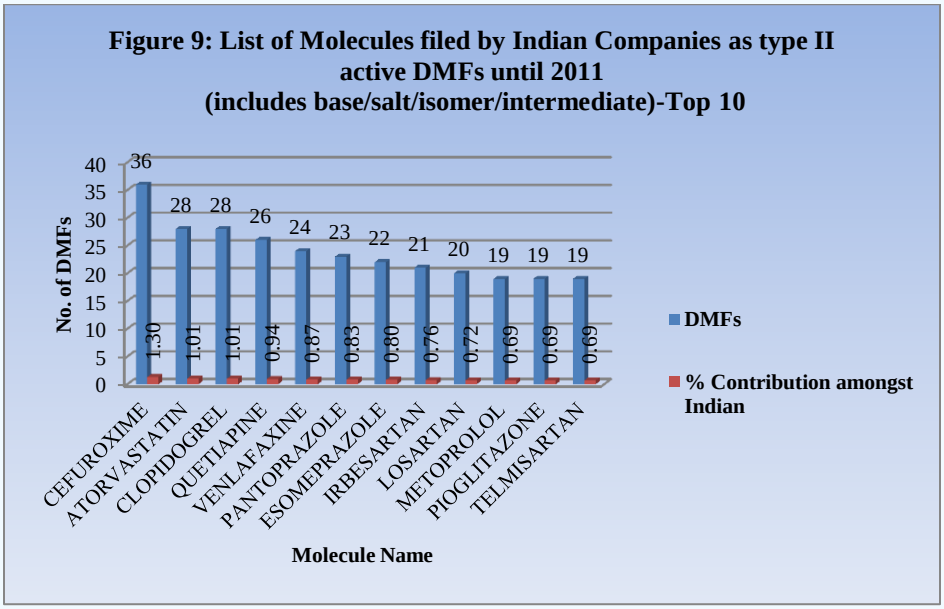
Type II DMFs Active-India's contribution year wise

Studies reveal that a total of 2759 type II DMFs are active until 4th quarter 2011. Figure 8 reveals that type II DMFs are filed and active from India since 1984. The figure clearly indicates an uptrend in filing type II DMFs which clearly indicates strength of Indian pharmaceutical industry pioneering in manufacture of pharmaceuticals that comply to global standards.



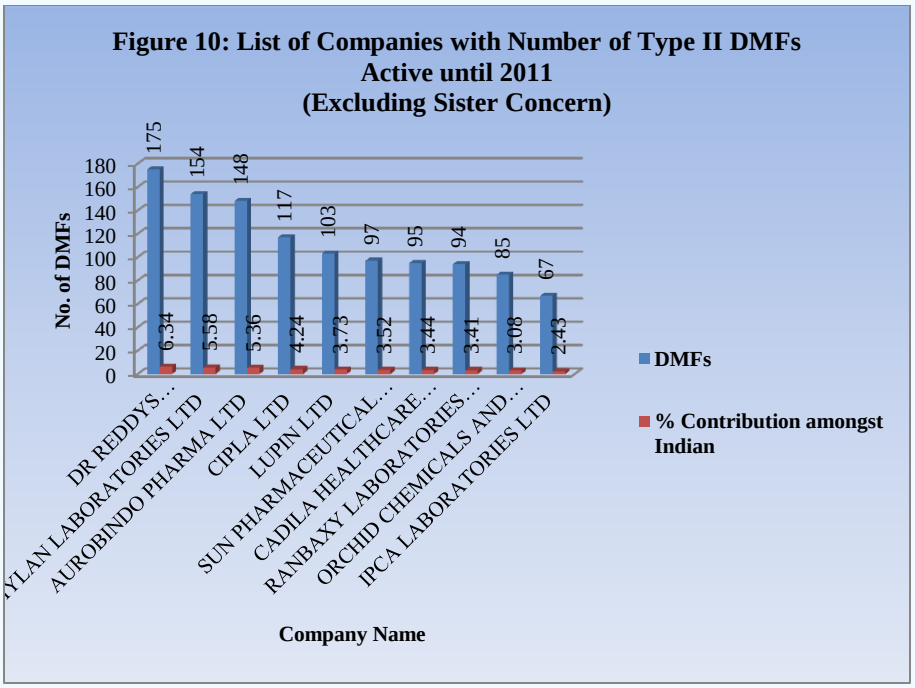
Type II DMFs Active-India's contribution Molecule wise-Top 10

It is observed that about 721 molecules either as base, salt, isomer, or intermediates are filed for Drug master files from India as type II DMFs and are active. Figure 9, reveals that Cefuroxime being filed maximum with 36 DMFs and Metoprolol, Pioglitazone, Telmisartan with 19 filings each standing top 10th among India filings. Among the 721 molecules that were filed, the contribution of top 10 molecules is 10.3 percent.



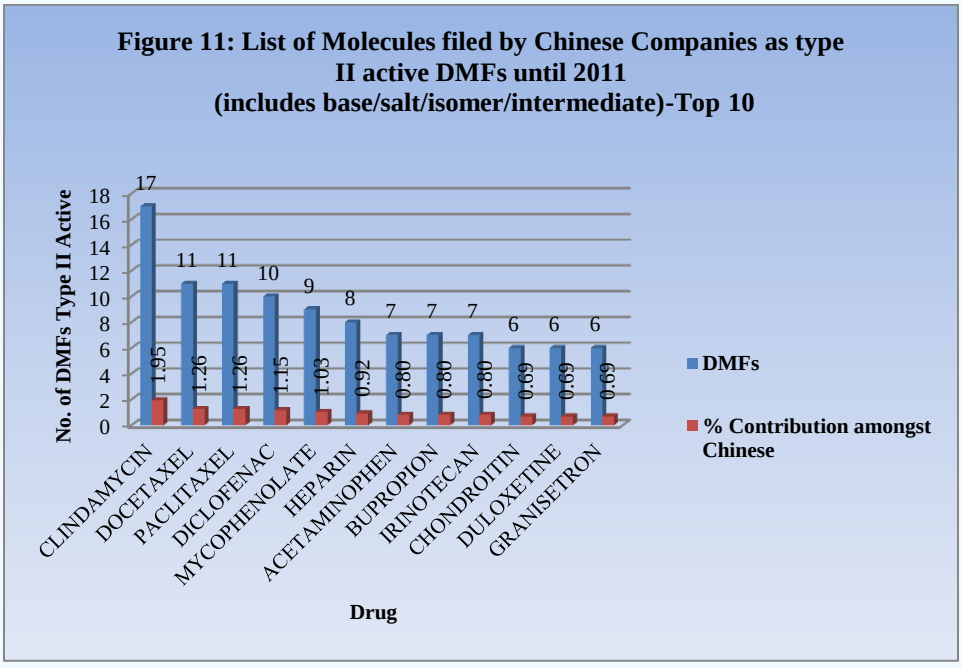
Type II DMFs Active-India's contribution Company wise-Top 10

When a study is made with relating to number of type II DMFs active with respect to company wise, it has been observed that a total 225 companies have filed DMFs and are active. Figure 10, reveals that Dr. Reddy's Laboratories Limited with a maximum of 175 active DMFs while Ipca Laboratories Limited with 10th position of 67 active DMFs. It has been observed that 41 percent contribution in type II DMFs active is by the top 10 companies.



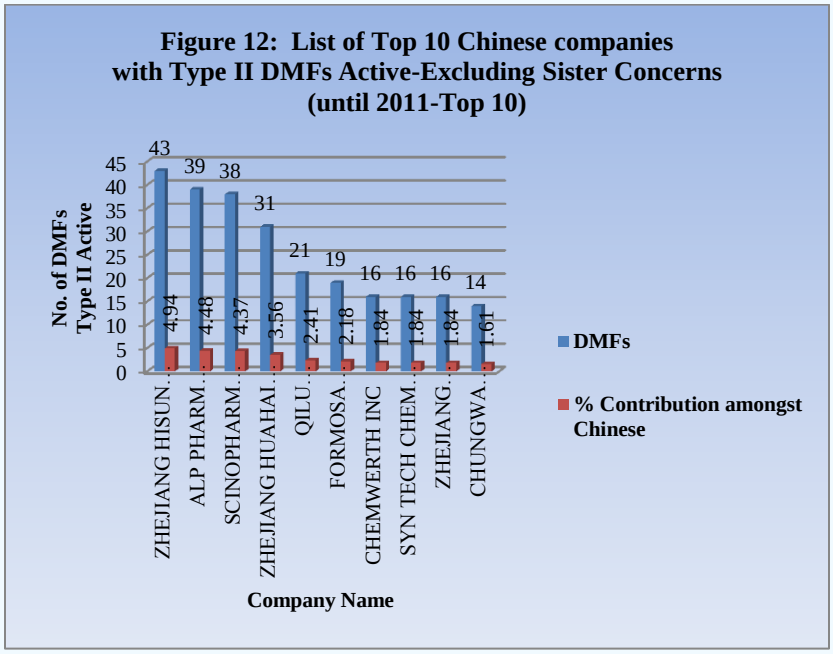
Type II DMFs Active-China's contribution Molecule wise-Top 10

It is believed that China is the immediate competitor to Indian pharmaceutical industry and it is observed that about 471 molecules either as base, salt, isomer, or intermediates are filed by China as type II DMFs and are active. Figure 11, reveals that Clindamycin being filed maximum with 17 DMFs and Chondroitin, Duloxetine, Granisetron with 6 filings each standing top 10th among Chinese filings. Among the 471 molecules that were filed, the contribution of top 10 molecules is 12 percent.



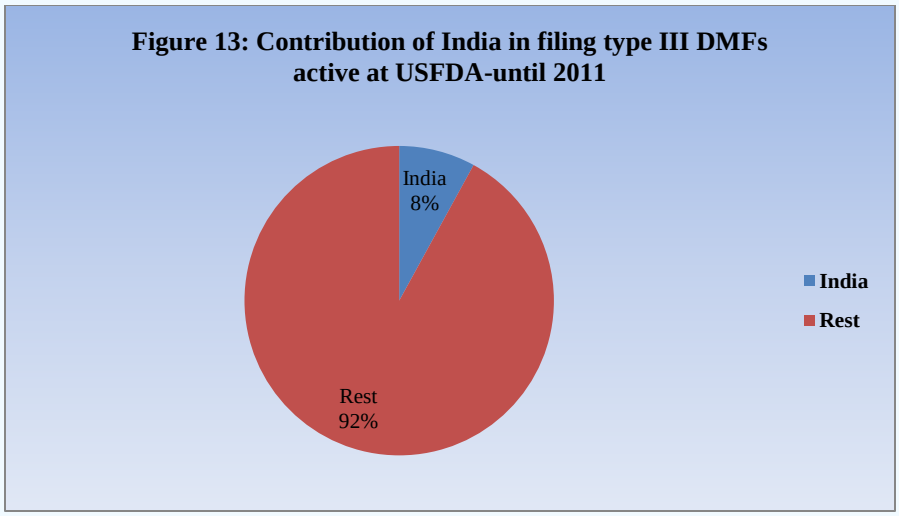
Type II DMFs Active-China's contribution Company wise-Top 10

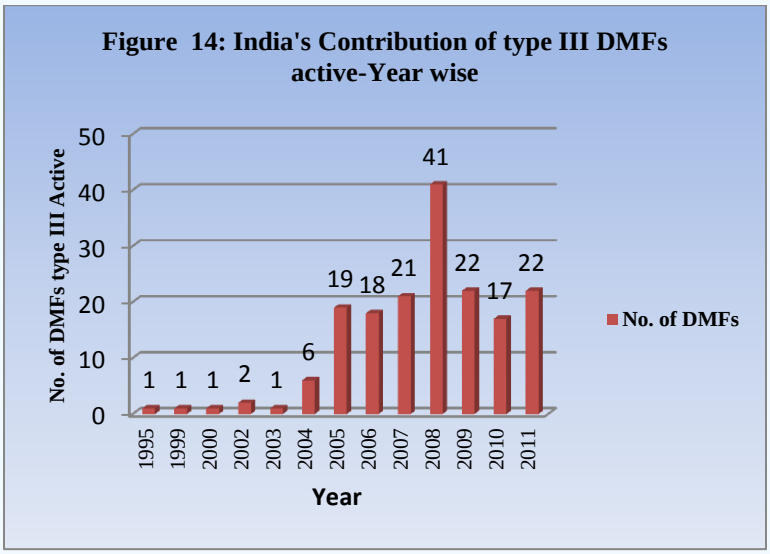
When a study is made with relating to number of type II DMFs active with respect to company wise, it has been observed that a total 277 companies have filed DMFs and are active. Figure 12, reveals that Zhejiang Hisun Pharmaceutical Co Ltd., with a maximum of 43 active DMFs while Chungwa Chemical Synthesis & Biotech Co Ltd., with 14 active DMFs. It has been observed that 29 percent contribution in type II DMFs active is by the top 10 companies among Chinese filings.



Type III DMFs Active-India's contribution year wise

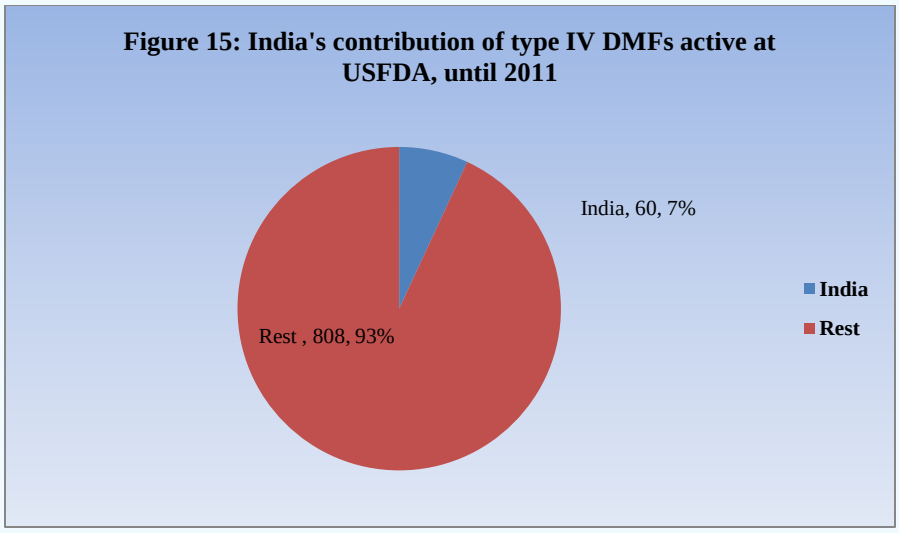
Out of a total of 2154 type III DMFs active, figure 13 reveals India's contribution of 8 percent which is very low. Figure 14, is a plot of number of type III DMFs that are active year wise and it reveals that a maximum number of filings were made in the year 2008.

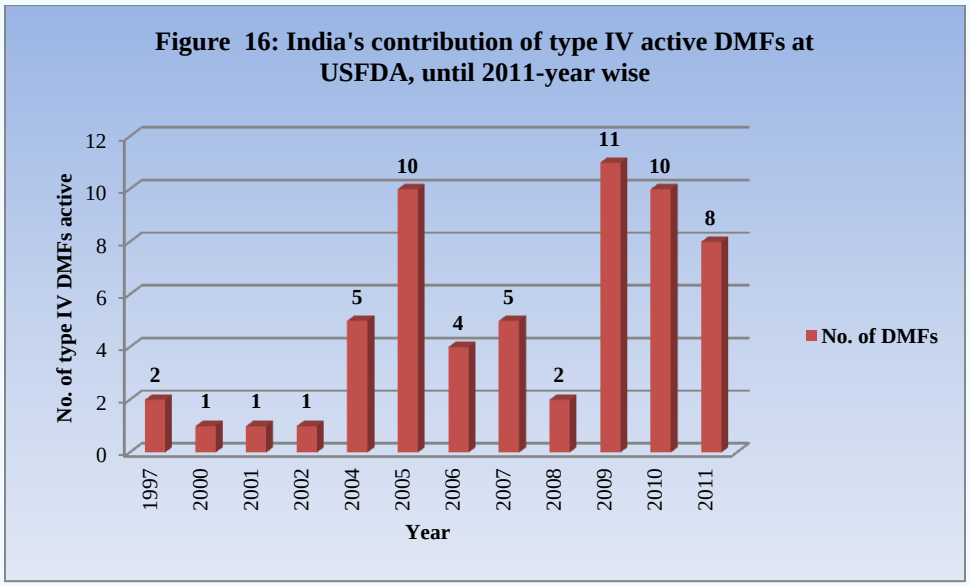




Type IV DMFs Active-India's contribution year wise

Out of a total of 868 type IV DMFs that are active, figure 15 reveals that India has filed 60 DMFs contributing to 7% which is very low. Figure 16 indicates year wise the number of type IV DMFs that are active and it reveals that a maximum of 11 DMFs were filed in the year 2009. Our studies reveal that USFDA has approved 3017 inactive ingredients for 11100 permutation/combination products specifying clearly for a particular dosage form with a specified route of administration (419). Even though certain inactive ingredients come under the category of fine chemicals, filings DMFs is very poor and Indian industry should emphasize on such filings under the category.

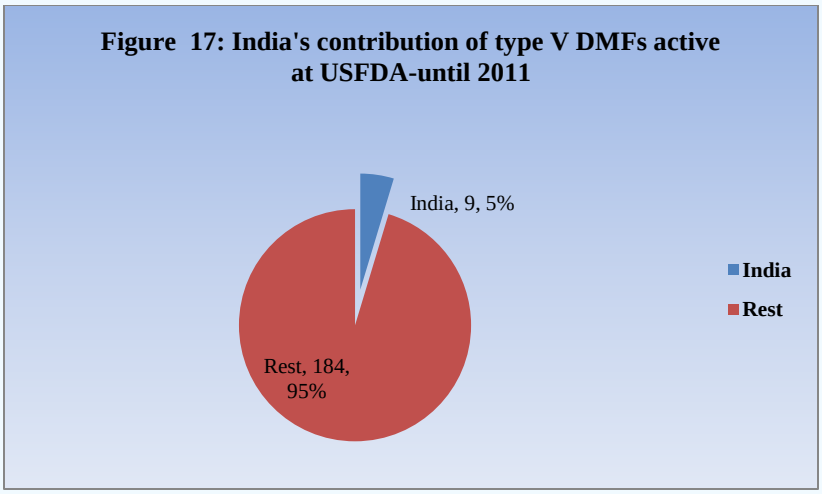


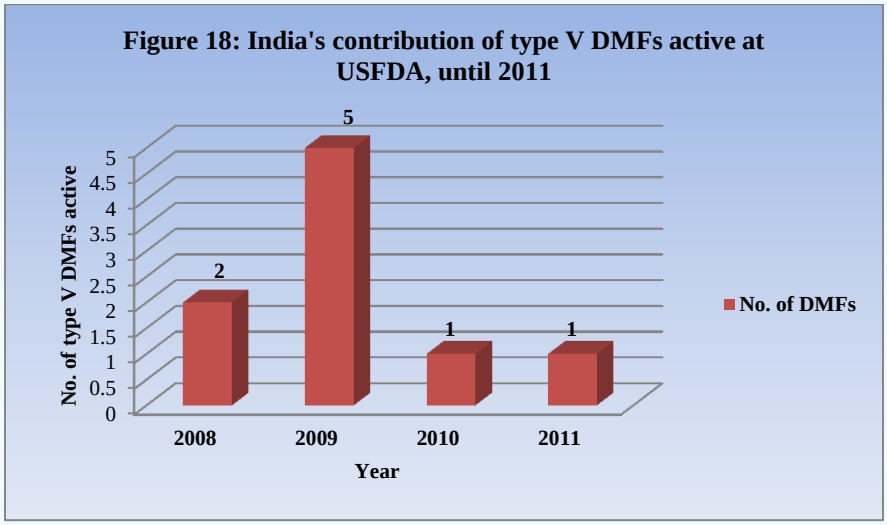


Among the type IV DMF filings, Associated Capsules Group has a major contribution of 24 DMFs.

Type V DMFs Active-India's contribution year wise

Out of a total of 193 active DMFs, figure 17 reveals that India's contribution is 5 percent. Among the Indian filings, figure 18 indicates a maximum filing of 5 DMFs in the year 2009.





Conclusion

Pharmexcil believes that drug master filing at USFDA by companies is one selected key strategy in identifying molecules interested by companies. Such molecules developed by companies can be assumed are of demand both in terms of volume and economic viability of the product in marketing in United States. It is necessary to understand by the industries to regularly monitor drug master files at USFDA so as to develop forecast strategies. It is also necessary to understand several of the drug master files are under administrative review. Accepting a drug master file by USFDA under administrative grounds leads to inspections by the authorities both at the facility and the production levels when required.

References

1. United States Food and Drug Administration