ANDA Filing Dynamics and the Paragraph IV Market

-Part I: The Impact of Increased ANDA Activity on First Filings-

by Gregory Glass

Abstract: In 2014, the Paragraph IV Market witnessed a dramatic -- and record -- number of Paragraph IV patent cases. With over 350 cases filed, the record number represents a 50% increase in cases filed above the average number of PIV cases filed during the prior three years. The increase in PIV cases raises the obvious questions regarding its impact on the Paragraph IV Market: what are the driving forces behind the increased number of filings and do they change the dynamics of the market? To answer these questions, it makes sense to break the market dynamics into several parts. Part I researches and answers the questions: what are some of the driving forces behind the record number of PIV cases and how do these cases impact first-filing dynamics? Papers to be researched, written, and published at a later date will cover Part II, examining PIV cases and products as they advance through the litigation process and through to the emergence of the generic markets.

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Background

2014 set a record in terms of number of Paragraph IV cases filed. By the end of 2014, there were 359 Paragraph IV cases filed.[1] This figure represents a dramatic increase in PIV cases filed from the three prior years which are represented in Figure 1.

The record number of cases raises the obvious questions of what are the driving forces behind the increase (and the Abbreviated New Drug Application (ANDA) filings they represent) and how do they impact the Paragraph IV Market?

To explain the increase in filings, market participants can develop rationales to account for the 119 additional cases filed in 2014 compared to 2013. For example, there are several simple, plausible explanations:

(1) there are more companies entering the PIV Market;
(2) the companies already in the PIV Market are filing more ANDA's;
(3) as more ANDA's are filed, there is a broader array of brand products receiving filings than in the past.

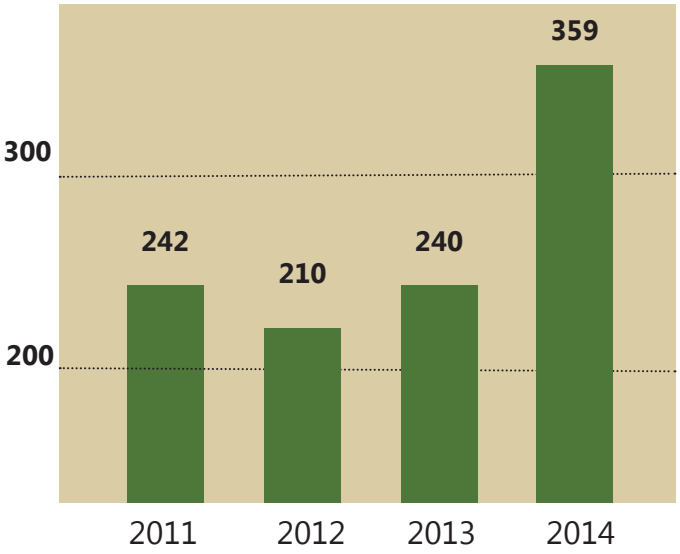

Figure 1: Lawsuits involving ANDAs with PIV Certifications

Of course, research and data can test these plausible explanations and provide some insight as to which are the most significant driving forces behind the number of cases and the filings they represent.

Moreover, regardless of the explanations behind why there are so many ANDA filings, the simple fact that there were so many cases filed in 2014 -- a 50% increase than the average annual number from the three prior years -- might lead to plausible conclusions as well:

(1) there are many ANDA filers present at the time the first ANDA is filed (or shortly thereafter);
(2) during the course of the first ANDA filer(s) litigation, there are many additional ANDA filers who enter the market;
(3) when the first ANDA filer(s) launches its product, there are many other ANDA filers present or waiting to launch as soon as an exclusivity period expires.

This paper -- Part I -- analyzes the plausible explanations of the driving forces behind the record number of ANDA filings in 2014 and then analyzes the first plausible conclusion: when the first ANDA is filed, there must be many other ANDA filers present.

Testing the Plausible Explanations

The PIV data can offer a quick analysis of the plausible explanations.

(1) There are more companies entering the PIV Market

The first plausible explanation for so many new ANDA filings and PIV cases is that there are new entrants into the PIV Market. Certainly in 2014, the PIV Market saw 20 new market entrants -- that is, 20 ANDA filers were involved in a PIV case for the first time in 2014.

While more entrants is a factor driving the case activity, it does not appear to be a significant factor. These 20 filers account for 26 cases of the 119 additional ones filed in 2014, accounting for only 22% of the new cases filed. In addition, the Paragraph IV Market has new ANDA filers enter the market every year (12 new entrants in 2013, for example) adding to the number of annual cases so is not a new phenomena.

Moreover, the PIV Market has ANDA filers leave every year as well. While difficult to define and quantify how many leave each year, there are many examples of ANDA filers that file only one or two PIV-ANDA's and then appear to leave the Paragraph IV Market. So, while the number of new entrants to the PIV Market is a factor, it can best be considered a slight factor.

(2) The companies already in the PIV Market are filing more ANDA's

Answering this question could entail an entire paper by itself. However, a quick pull of data can answer it with sufficiency here. First, consider that not all PIV cases are equal. For example, most PIV cases are associated

with one or more **new** ANDA filings. In other words, a typical PIV case involves an ANDA (or more than one) and is the first PIV case filed on the unique ANDA.

Second, then, are all of the other types of PIV cases. These include subsequent cases over amendments to ANDA filings on new dosage strengths or recently-listed Orange Book patents. While still classified as PIV cases, these new cases involve the same ANDA's already in litigation.

By identifying PIV cases that are associated with unique ANDA's, a simple comparison between 2014 and 2013 can be made. Figure 2 below covers these data and others involving the "plausible explanations."

While there were more ANDA's filed in 2014, the ANDA's alone do not account for the increase in cases. The data indicate that there were proportionately more PIV cases filed in 2014 that did not involve a new ANDA but instead involved an amendment to an existing ANDA (that is, a "subsequent PIV case" involving an ANDA already in litigation.)

	2013	2014
(1) New market entrants	**12**	**20**
(2) PIV cases filed =	**240**	**359**
(a) with "new" ANDA's +	191	262
(b) "subsequent" cases	49	97
(3) Total ANDA's in PIV cases	**214**	**292**
(4) Brands with first PIV case	**36**	**45**

Figure 2: Data Comparisons 2013-2014[2]

Row 2 shows that in 2013, there were 240 total PIV cases filed which is the sum of the 191 cases involving an ANDA for first time and 49 "subsequent PIV cases." The 191 "new ANDA PIV cases" represent 79% of the total cases filed in 2013. If the additional ANDA's were the key driving factor behind the increase in cases for 2014, we would then expect this figure to be **higher** than it was in 2013. But is actually lower at 73%. Hence, while additional ANDA's were filed in 2014, they alone do not account for the increase in cases.

Considered another way, if there were 214 total ANDA's in 2013 and an increase in 50% more cases in 2014, we would then expect about 321 ANDA's litigated in 2014. But the 2014 total number is a quite a bit less at 292.

This leads to the bottom line. While indeed there were more ANDA's filed by those already in the market, these do not entirely account for the increase in cases. Hence, while companies already in the PIV Market filed more ANDA's, their contribution to the total number of cases filed is not a dominant driving force.

(3) As more ANDA's are filed, there is a broader array of brand products receiving filings than in the past.

The data do not suggest that a broader group of brand products are receiving PIV certifications to any degree of significance. Each year, a certain number of brand products are the subjects of PIV cases for the first time. In 2014, 45 brand products were involved in their first PIV cases. By comparison, in 2013, 36 brand products were involved in their first PIV cases.

If 36 brand products received their first PIV cases in 2013, that would suggest, if there were 50% more cases filed, then we might expect about 54 brand products to receive their first PIV cases in 2014. However, the actual number of 45 falls well short of what we might expect. These figures suggest that while ANDA filers are likely broadening their scope of brand products, this explanation, like the others, is a contributing, and not a dominating factor.

While the three plausible explanations play a factor in driving the number of PIV cases in 2014, it appears that none of them are a leading force. However, they clearly do contribute to the increased number of cases. Of course, there is one other factor, discussed in the Quarterly Note (October 2014),[3] and that is the FDA change in operations.

While all three plausible explanations factor into the increase in PIV cases, it appears that none of them is the dominant force

From the timing of case filings -- that is, the time between the ANDA filing to its PIV case -- it appears that FDA changed its operational processes sometime in 2011 and was taking longer to process its initial review of ANDA's. It appears that in 2014, FDA was returning to its prior timelines of review. So, the number of cases filed in 2014 could also be a function of its "catching up" to past ANDA filings. In other words, cases that would have been filed in 2013 under normal FDA processing of ANDA's were filed in 2014 as it returned to normal processing times. Thus, while difficult to measure its impact, it is likely a factor as well.

Testing the Plausible Conclusion

While it is reasonable to conclude that all of the plausible explanations, as well as the FDA operational issues, play their roles in increasing the number of ANDA filings and PIV cases, they provide little insight as to their impact on the PIV Market dynamics.

However, if the data reflect more cases filed -- and ANDA's -- it might just be reasonable to conclude that there are many filers at time of first-filing. In other words, while in, say 2008, there might have been one ANDA first-filer on a product, it might be logical to conclude that in 2014, a product might have multiple first-filers. At the very least, after the first-filed ANDA files, several ANDA filers may follow shortly thereafter.

Anecdotal data support this plausible conclusion. For example, in 2013, the PIV cases over Vimpat®(lacosamide) surfaced which included one case filed against a record-breaking 15 ANDA filers, the timing of which suggests that all 16 filers submitted their ANDA's on the first-filing date or within a month or two after the first filing.

More multiple-filer PIV cases soon followed including Treanda®(bendamustine) which began with 8 ANDA filers and increased to 18 over the months following and Effient®(prasugrel) which started with 12 ANDA filers and increased to 16 over the months following.

So, the compiled data and anecdotal data lead to the first plausible conclusion:

(1) There are many ANDA filers at the time the first ANDA is filed (or soon thereafter)

For the definition of "many", practitioners in the Paragraph IV Market would likely agree that "more than 4 ANDA's" would be a reasonable definition for "many". Moreover, we can define "first-filer dynamics" as the time period when the first filer(s) files its ANDA to a short time period after (as better defined below.)

As any ANDA filer really wants to know: when we file our ANDA, will there be a bunch of other ANDA filers waiting in the FDA parking lot to file as well? If we get sued by the brand, will we be the only one? If we start PIV litigation, will we be followed by other cases before the first witness is examined?

Two data sets can provide the answer to the question of "how many ANDA filers are present at first filing or soon therafter?" While the question can be answered using either data set, both data sets are simple to compile and act as a check on the other to help eliminate any issues that could possibly mislead analysis:

Data Set (1): List the products that received their first PIV Certifications in 2013, then count how many ANDA filers are present in the PIV cases the brand company filed by December 31, 2014. In other words, if FDA reports that Brand A received its first PIV certification on March 7, 2013, simply record the PIV cases the brand company filed over Brand A by December 31, 2014 and compile the number of ANDA's involved.

Data Set (2): List all of the brand products that filed their first PIV cases in 2012 and 2013, then analyze the PIV cases the brand company filed over the next 12 months and compile the number of ANDA filers. In other words, if Brand B files its first PIV case on May 5, 2013, record the PIV cases the brand company filed through May 4, 2014, and compile the number of ANDA's involved.

	Data Set (1): Products Receiving First PIV Certification in 2013 (through 2014)		Data Set (2): Products With First PIV Case in 2012-13 (through One Year after Filing)	
	NME Products (n=15)	NF Products (n=19)	2012 Products (n=36)	2013 Products (n=36)
1-4 ANDA Filers	9	18	30	30
5-9 ANDA Filers	2	0	5	1
10+ ANDA Filers	4	1	1	5

Table 1: Distribution of Products with Paragraph IV Cases and their Numbers of PIV Filers

While the data sets overlap ten products, the two enable the analysis of more products than one set alone. Moreover, while Data Set (2) covers exactly one year's worth of PIV cases over particular products, Data Set (1) covers a longer time period (between 1-2 years) depending on when the brand received its certification.

Data Set (1) was further segmented by brand product type -- either a New Molecular Entity (NME) (also known as a New Chemical Entity, or NCE) or a New Dosage Form (NF).[3] Data Set (2) included any type of product (and thus not limited to NME's/NF's) which helps reduce error presented by any phenomena regarding product classification. Table 1 summarizes the data from both data sets,[5] and the raw data are included in Appendix 1.

Findings and Discussion

As the data from Table 1 suggest, the vast majority of PIV products only have a small number of ANDA filers when these cases begin and thus when the first-filer submits its ANDA. So, the answer to the question, "how many PIV cases begin with many ANDA filers?" is very few indeed, only a small fraction of them.

Consider Data Set (1): 27 of the 34 products (79%) started with 1-4 ANDA filers. In other words, for those products receiving their first PIV certifications in 2013, 79% of them had only 1-4 ANDA filers from the time the first-filer certified to the end of 2014 (1-2 years later.) Only 21% of them started with more than 4 ANDA filers. That is, only 1 in 5 products had 4 or more ANDA filers certify at the same time as the first-filer (or between 1-2 years later.)

Per Appendix 1, Data Set (1) also shows that 38% (13 of the 34 products) had only one ANDA filer from the time the first-filer certfied to the end of 2014.

A vast majority of PIV products will only have 1-4 ANDA filers at the time of first-filing with many products having only a single filer

Though a different measure, Data Set (2) shows similar results. For Data Set (2), 83% of the products had between 1-4 filers from the first PIV case to one year later. Moreover, 55% (39 of the 72 products) had only one ANDA filer from the time the first PIV case was filed to one year later. Data Set (2) also reveals that only 12 of the products (17%) had more than 4 ANDA filers.

So, while there are a few products that have many filers at time of first-filing, a vast majority of them do not. Both data sets show that about 4 out of 5 products will only have 1-4 filers. Moreover, about half of all products will only have one filer.

Appendix 1 also reveals one important observation which alludes to the driving forces behind the increase in PIV cases in 2014.

Data Set (1) shows that 6 NME products had more than 5 ANDA filers at the time of the first-filing (or 1-2 years later.) All 6 of these products received their first PIV Certifications at 48 months after approval.[6] In other words, all 6 of these products would be considered "NCE-1" products by practitioners in the industry.

For these six NCE-1 products, there were 64 ANDA's filed, or about an average of 11 ANDA's per product. While these data alone do not account for the increase in PIV cases, they nonetheless suggest a key market dynamic accounting for the increase in PIV cases.

A small number of NCE-1 products will be hyper-competitive, inviting 10 or more ANDA filers who file and certify on or around the NCE-1 date.

While certain NCE-1 products are hyper-competitive, not every NCE-1 product is hyper-competitive: 5 of the 11 NCE-1 products from Data Set (1) had fewer than 5 ANDA filers with 2 having only 1 or 2 filers. Of course, discerning which NCE-1 products will attract a hyper-competitive market is the key management question.

Conclusion

Over the past year, there has been a dramatic increase in Paragraph IV ANDA's and cases filed. From these data, there are a few conclusions that can be drawn.

First, three plausible explanations for this increase -- more market entrants, filers filing more ANDA's, and a broader array of brands receiving PIV certifications -- have some merit. While they play supporting roles, none appear to be the leading, significant driving force.

Second, in spite of the sheer number of PIV cases and ANDA's filed, a vast majority of brand products will only have a few ANDA filers with more than half having only one filer during the period of first-filing.

Third, the key market dynamic is that a select few NCE-1 products receive a high concentration of ANDA filers.

Footnotes

[1] For counting, ParagraphFour.com takes the total number of Paragraph IV cases filed each year and backs out certain types of cases including duplicate cases (when brands file the same case in two jurisdictions), transferred cases, those involving BLA applications, and declaratory actions added to current PIV cases. In 2014, there were a total number of 435 cases, less 67 duplicates, less 3 transfers, less 4 BLA cases, less 2 declaratory actions, yielding a total number of 359 PIV cases.

[2] Figure 2 includes the following data. Row 1 is the number of new ANDA filers that have received their first PIV lawsuit. Row 2 is total number of PIV cases which is the sum of (a) the PIV cases that are the first over an ANDA and (b) subsequent PIV cases (that is, a PIV case filed over an ANDA already in litigation.) For counting, 2(a) and (b) -- PIV case involves one or more ANDA's counts as one case. Row 3 is the total number of litigated ANDA's represented by all cases (PIV case involves 3 ANDA's counts as 3 ANDA's). Row 4 is the number of brand products receiving their first PIV case.

[3] Gregory Glass publishes the Quarterly Note which is available at ParagraphFour.com.

[4] When approving a product, FDA classifies it. Here, the New Molecular Entities are classified by FDA as a "1" product and the New Dosage Forms as a "3." The author uses the term "New Formulation" as interchangeable with New Dosage Form consistent with industry parlance.

[5] While the sets certainly answer the question "how many PIV cases begin with many ANDA filers?" and provide insight into the market dynamics of first-filings, they do make one assumption: they assume that, if a brand company files a PIV case against one ANDA filer, it files PIV cases against all of them. As ANDA's are confidential, it is difficult to determine the exact answer to this assumption. However, the 10+ years of research compiled and analyzed at ParagraphFour.com suggests that while at times brand companies do not file PIV cases against every ANDA filer, this practice is indeed infrequent, and the two data sets should help reduce error this assumption presents.

[6] The Hatch-Waxman Act does not allow an ANDA with a Paragraph IV certfication to be filed before 48 months after a New Molecular Entity (more commonly referred to as a New Chemical Entity) was approved. FDA also allows for a five year exclusivity for NCE products. Hence, practitioners often refer to these products as "NCE-1" products as they receive their first PIV certfication one year before its exclusivity expires. There are no such restrictions for PIV Certfications for any other type of classification (New Formulations, for example) and thus may receive their first PIV certifications any time after approval.

Appendix 1 -- Data Set #1
Products Receiving First PIV Certifications in 2013
and Number of PIV ANDA Filers through December 31, 2014

Product -- New Molecular Entities	Date of First PIV Certification	Number of ANDA Filers	NCE-1 Product?
Fanapt®(iloperidone)	May 6, 2013	1	Yes
Neupro®(rotigotine)	November 26, 2013	1	
Nuvaring®(ethinyl estradiol....)	June 17, 2013	1	
Invanz®(ertapenem)	June 20, 2013	2	
Istodax®(romidepsin)	November 5, 2013	2	Yes
Samsca®(tolvaptan)	September 23, 2013	2	
Saphris®(asenapine)	August 13, 2013	3	Yes
Bepreve®(bepotastine)	September 9, 2013	4	Yes
Folotyn®(pralatrexate)	September 24, 2013	4	Yes
Livalo®(pitivastatin)	August 5, 2013	7	Yes
Multaq®(dronedarone)	July 1, 2013	9	Yes
Onglyza®(saxagliptan)	July 31, 2013	10	Yes
Savella®(milnacipran)	January 14, 2013	10	Yes
Uloric®(febuxostat)	February 13, 2013	12	Yes
Effient®(prasugrel)	July 10, 2013	16	Yes
Product -- New Formulations	**Date of First PIV Certification**	**Number of ANDA Filers**	**Not Applicable**
Astagraf XL®(tacrolimus)	November 15, 2013	1	
Butrans®(buprenorphine)	June 6, 2013	1	
Diclegis®(doxylamine....)	August 1, 2013	1	
Forfivo XL®(buproprion)	February 28, 2013	1	
Nucynta OS®(tapentadol)	December 30, 2013	1	
Oxtellar XR®(oxcarbazepine)	March 20, 2013	1	
Quillivant XR®(methylphenidate)	August 2, 2013	1	
Topicort®(desoximetasone)	December 18, 2013	1	
Zomig NS®(zolmitriptan)	November 14, 2013	1	
Zubsolv®(buprenorphine....)	October 22, 2013	1	
Canasa®(mesalamine)	May 24, 2013	2	
Giazo®(balsalazide)	November 5, 2013	2	
Vagifem®(estradiol)	January 2, 2013	2	
Axiron®(testosterone)	January 29, 2013	3	
Phoslyra®(calcium acetate)	December 5, 2013	3	
Prolensa®(bromfenac)	July 26, 2013	3	
Quartette®(levonorgestrel....)	July 10, 2013	3	
Zortress®(everolimus)	September 30, 2013	3	
Namenda XR®(memantine)	June 10, 2013	13	

Appendix 1 -- Data Set #2
Products with First PIV Cases Filed in 2012 and 2013 and
Number of PIV ANDA Filers One Year Later (One Year After First Case Filed)

Product (2012)	Date of First PIV Case	Number of ANDA Filers (One Year after First Case)
ActoPlus Met XR®(pioglitazone...)	January 3, 2012	1
Apriso®(mesalamine)	September 7, 2012	1
Argatroban®(argatroban)	March 30, 2012	1
Carac®(fluorouracil)	January 26, 2012	1
Clolar®(clofarabine)	July 27, 2012	1
Cuvoposa®(glycopyrrolate)	December 17, 2012	1
Duexis®(ibuprofen...)	March 28, 2012	1
Emtriva®(emtricitabine)	August 20, 2012	1
Exjade®(deferasirox)	March 21, 2012	1
Ganirelix®(ganirelex)	August 27, 2012	1
Ixempra Kit®(ixabepilon)	December 21, 2012	1
Lexiva®(fosamprenavir)	August 22, 2012	1
Moxeza®(moxifloxacin)	July 24, 2012	1
Norvir Tabs®(ritonavir)	April 10, 2012	1
Oleptro®(trazodone)	August 21, 2012	1
Omnaris®(ciclesonide)	August 2, 2012	1
Pro-Air HFA®(albuterol)	September 5, 2012	1
Remodulin®(treprostinil)	March 14, 2012	1
Sprix®(ketorolac)	August 10, 2012	1
Staxyn®(vardenafil) ODT	April 25, 2012	1
Xopenex HFA®(levalbuterol)	July 27, 2012	1
Zyclara®(imiquimod)	August 31, 2012	1
Emend®(fosaprepitant)	March 31, 2012	2
Epiduo®(adapalene...)	June 26, 2012	2
Fusilev®(levoleucovorin)	January 20, 2012	2
Natazia®(estradiol...)	November 28, 2012	2
Astepro®(azelastine)	January 19, 2012	3
Diovan HCT®(valsartan)	July 20, 2012	3
Pennsaid®(diclofenac)	August 30, 2012	3
Exforge HCT®(amlodipine)	May 14, 2012	4
Acetadote®(acetylcysteine)	May 17, 2012	5
Oxecta®(oxycodone)	October 31, 2012	5
Gralise®(gabapentin)	March 2, 2012	6
Intermezzo®(zolpidem)	August 23, 2012	6
Bystolic®(nebivolol)	March 13, 2012	7
Pristiq®(desvenlafaxine)	June 22, 2012	12

Appendix 1 -- Data Set #2 (continued)
Products with First PIV Cases Filed in 2012 and 2013 and
Number of PIV ANDA Filers One Year Later (One Year After First Case Filed)

Product (2013)	Date of First PIV Case	Number of ANDA Filers (One Year after First Case)
Absorica®(isotretinoin)	October 29, 2013	1
Amitiza®(lubiprostone)	Feburary 7, 2013	1
Bactroban®(mupirocin)	January 24, 2013	1
Brevibloc®(esmolol)	October 18, 2013	1
Busulfex®(busulfan)	September 27, 2013	1
Fanapt®(iloperidone)	November 25, 2013	1
Finacea®(azelaic)	March 14, 2013	1
Forfivo XL®(buproprion)	August 23, 2013	1
Fortesta®(testosterone)	February 28, 2013	1
Norvir Caps®(ritonavir)	June 14, 2013	1
Nuvaring®(ethinyl estradiol....)	December 24, 2013	1
Oxtellar XR®(oxcarbazepine)	August 7, 2013	1
Safyral®(drospirenone)	June 4, 2013	1
Suprenza®(pentermine)	June 26, 2013	1
Valcyte OS®(valganciclovir)	September 4, 2013	1
Zipsor®(diclofenac)	July 26, 2013	1
Axiron®(testosterone)	May 24, 2013	2
Canasa®(mesalamine)	July 5, 2013	2
Rapaflo®(silodosin)	June 17, 2013	2
Rayos®(prednisone)	August 26, 2013	2
Samsca®(tolvaptan)	November 26, 2013	2
Vagifem®(estradiol...)	July 25, 2013	2
Acanya®(clindamycin...)	October 24, 2013	3
Istalol®(timolol)	June 14, 2013	3
Mozobil®(plerixafor)	August 29, 2013	3
Nucynta ER®(tapentadol)	July 25, 2013	3
Nucynta®(tapentadol)	July 25, 2013	4
Suboxone®(buprenorphine...)	August 20, 2013	4
Vimpat OS®(lacosamide)	July 10, 2013	4
Zyvox®(linezold)	March 20, 2013	4
Banzel®(rufinamide)	July 24, 2013	5
Savella®(milnacipran)	September 23, 2013	10
Toviaz®(fesoterodine)	June 21, 2013	11
Uloric®(febuxostat)	October 30, 2013	11
Vimpat Tab®(lacosamide)	June 28, 2013	16
Treanda®(bendamustine)	October 21, 2013	18