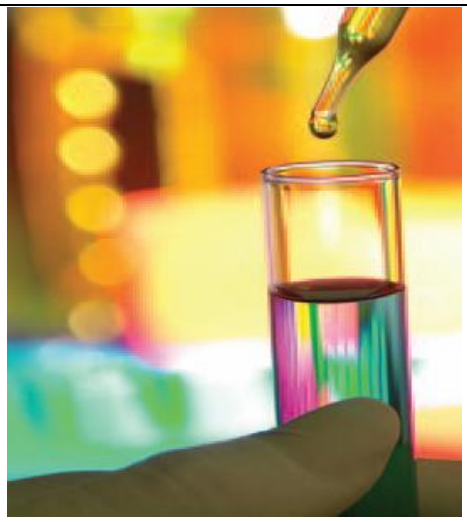

The US Biotechnology Industry

A Market Report

June 2017

Wallonia.be
EXPORT
INVESTMENT

Bureau AWEX – New York

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I. The US Biotech Landscape

The US biotech industry remains the benchmark in international terms. It is considered to be the most successful in the world and it is likely to maintain this leading position for the foreseeable future.

According to *"Beyond Borders Biotechnology Industry Report 2016"* released by Ernst & Young, most of the US biotech companies are privately owned, only 436 are publicly traded. Their cumulative market cap rose only 4% in 2015, versus 34% the prior year. The report also states that American companies spent US$33.9 billion on R&D, 18% more than the previous year and that their revenues increased 16% to US$107.7 billion.

US biotechnology at a glance, 2014-15 (US$b)

	2015	2014	% change
Public company data			
Revenues	107.7	93.0	16%
R&D expense	33.9	28.8	18%
Net Income	15.6	10.8	45%
Market capitalization	889.3	854.6	4%
Number of employees	131,690	109,450	20%
Financing			
Capital raised by public companies	51.5	37.8	36%
Number of IPOs	45	63	-29%
Capital raised by private companies	9.6	7.3	32%
Number of companies			
Public companies	436	409	7%
Private companies	2,336	2,354	5%
Public and private companies	2,772	2,763	0%

Source: **http://www.ey.com**
Numbers may appear inconsistent because of rounding

Revenues and net income experienced highly concentrated growth. With seven drugs generating greater than US$1 billion in 2015 sales, Gilead again led the way in the US and globally. In all, Gilead accounted for about 30% of all US biotech revenue, and its revenue growth accounted for 44% of the total US industry growth. Big biotechs Amgen, Biogen, Celgene and Regeneron Pharmaceuticals combined with Gilead to account for nearly three-quarters of all revenue from US biotechs, and well over half of all biotech revenue worldwide. Gilead also led the way in net income growth with US$18.11 billion and R&D spending totaling USD$3.01 billion.

US commercial leaders by revenue, R&D and net income, 2015 vs. 2014 (US$m)

Company	2015 revenue	% change in revenue vs. 2014	2015 R&D	% change in R&D vs. 2014	2015 net income (loss)	% change in net income vs. 2014
Vertex Pharmaceuticals	1,032	78%	996	16%	(556)	-25%
Incyte Corporation	754	47%	481	37%	7	113%
Regeneron Pharmaceutical	4,104	46%	1,621	27%	636	83%
Medivation	943	33%	293	16%	245	-11%
Gilead Sciences	32,639	31%	3,014	6%	18,108	50%
Celgene	9,256	21%	3,697	61%	1,602	-20%
Illumina	2,220	19%	402	3%	462	31%
BioMarin Pharmaceutical	890	18%	635	38%	(172)	28%
Alexion Pharmaceutical	2,604	17%	709	38%	144	-78%
Emergent BioSolutions	523	16%	154	2%	63	71%
Cepheid	539	15%	116	20%	(49)	-3%
United Therapeutics	1,466	14%	245	1%	652	92%
Biogen	10,764	11%	2,013	6%	3,547	21%
Amgen	21,662	8%	4,191	-7%	6,939	35%
IDEXX Laboratories	1,602	8%	108	10%	192	6%
Myriad Genetics	723	-7%	76	12%	80	-54%
Bio-Rad Laboratories	2,019	-7%	193	-12%	113	27%

Source: **http://www.ey.com**

Top 10 Biotech Co's in the United States (as of May 18, 2016)

Rank	Company	Market Value 2015
1	Gilead Sciences	$113.9 billion
2	Amgen	$110.4 billion
3	Celgene	$78.3 billion
4	Biogen Idec Inc.	$57.9 billion
5	Regeneron Pharmaceuticals Inc.	$40.3 billion
6	CSL Limited	$37.9 billion
7	Alexion Pharmaceuticals Inc.	$31.9 billion
8	Baxalta	$29.7 billion
9	Illumina, Inc.	$20.6 billion
10	Vertex Pharmaceuticals	$20.2 billion

Source: **https://www.forbes.com**

II. Research & Development

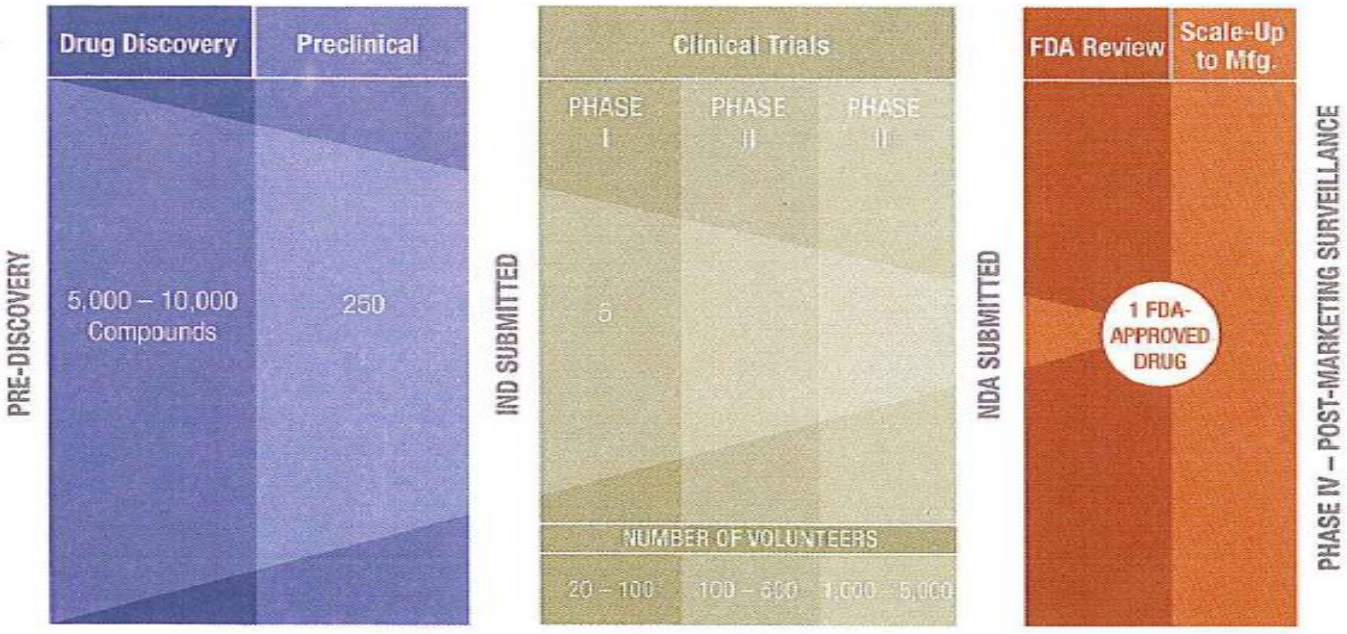
Scientific and technological advances and growing understanding of the underlying mechanisms of disease are fueling the development of new treatments and cures for patients. At the same time, the costs, time, and complexities of biopharmaceutical research have also increased, introducing additional challenges in the research and development process.

The drug development process begins with the identification and investigation of disease targets and often includes the screening of thousands of compounds. From the time a potentially promising candidate medicine is identified and optimized, on average it takes 10 to 15 years for a medicine to make its way through the entire R&D process to US Food and Drug Administration (FDA) approval. And only 12% of investigative medicines entering clinical trials are ultimately approved by the FDA. The average cost to develop a new medicine is estimated at $2.6 billion dollars, including the cost of failure.

Overview of the R&D Process

Although millions of potential drug candidates may be screened and assessed early in the R&D process, many compounds ultimately fail to make it through the R&D pipeline. Candidate medicines must navigate a lengthy, complicated, multi-step process before being approved by the FDA and delivered to patients. And the journey does not end with FDA approval; ongoing research and data collection, as the medicine is used in a clinical setting and examined in any required post-approval studies, will continue to provide important insights.

The chart below highlights the US drug development and approval process, illustrating the activities that occur during the estimated 10 to 15 years needed for a new drug to reach the market.



Source: ***http://www.innovation.org***

There are a number of stages involved in the drug development and approval process and they are the following:

● **Preclinical Testing -** A pharmaceutical company conducts laboratory and animal studies to show biological activity of the compound against the targeted disease, and the compound is evaluated for safety.

● **Investigational New Drug Application (IND) -** After completing preclinical testing, a company files an IND with the U.S. Food and Drug Administration (FDA) to begin to test the drug in people. The IND becomes effective if FDA does not disapprove it within 30 days.

The IND shows results of previous experiments; how, where and by whom the new studies will be conducted; the chemical structure of the compound; how it is thought to work in the body; any toxic effects found in the animal studies; and how the compound is manufactured. All clinical trials must be reviewed and approved by the Institutional Review Board (IRB) where the trials will be conducted. Progress reports on clinical trials must be submitted at least annually to FDA and the IRB.

- **Clinical Trials, Phase I -** These tests involve about 20 to 100 normal, healthy volunteers. The tests study a drug's safety profile, including the safe dosage range. The studies also determine how a drug is absorbed, distributed, metabolized, and excreted as well as the duration of its action.

- **Clinical Trials, Phase II -** In this phase, controlled trials of approximately 100 to 500 volunteer patients (people with the disease) assess a drug's effectiveness.

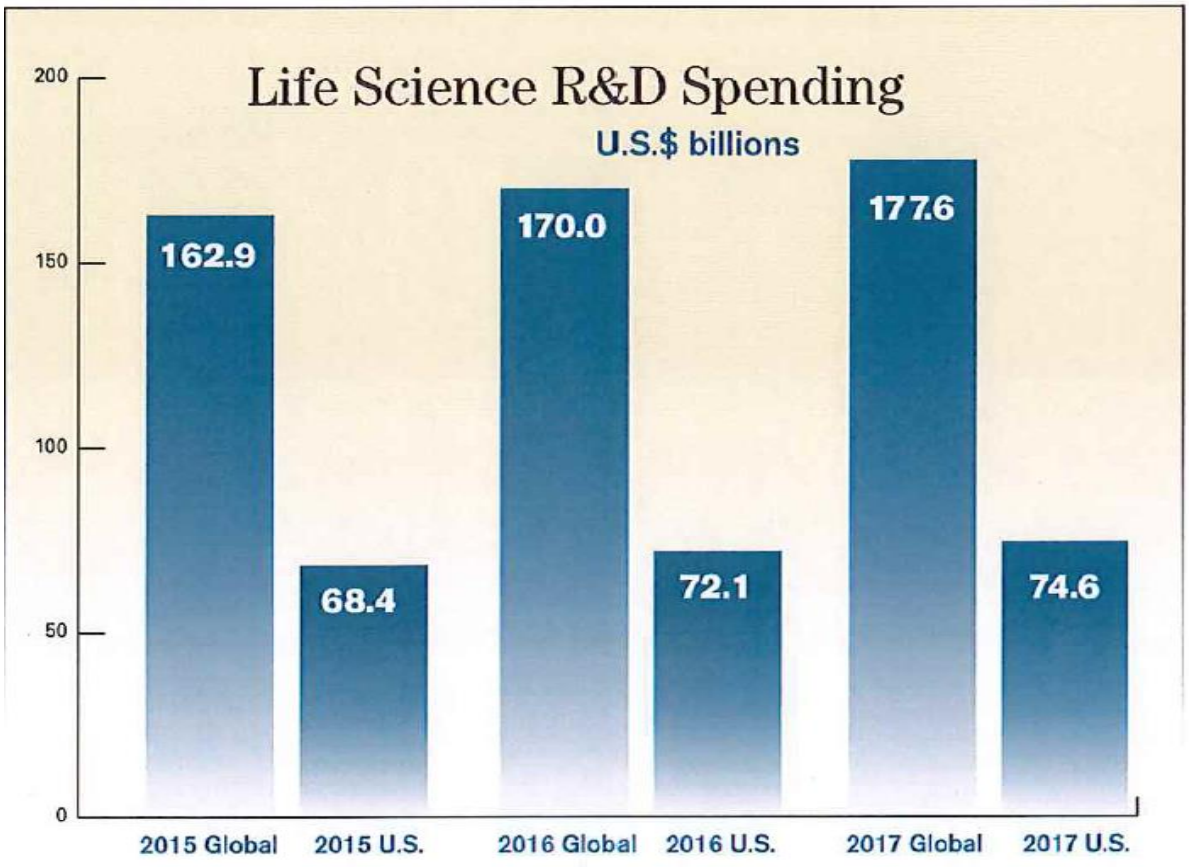
- **Clinical Trials, Phase III -** This phase usually involves 1,000 to 5,000 patients in clinics and hospitals. Physicians monitor patients closely to confirm efficacy and identify adverse events.

- **New Drug Application (NDA)/Biologic License Application (BLA) -** Following the completion of all three phases of clinical trials, a company analyzes all of the data and files an NDA or BLA with FDA if the data successfully demonstrate both safety and effectiveness. The applications contain all of the scientific information that the company has gathered. Applications typically run 100,000 pages or more. The average review time for the 26 new therapeutics approved by the FDA in 2007 was 11.1 months.

- **Approval -** Once FDA approves an NDA or BLA, the new medicine becomes available for physicians to prescribe. A company must continue to submit periodic reports to FDA, including any cases of adverse reactions and appropriate quality-control records. For some medicines, FDA requires additional trials (Phase IV) to evaluate long-term effects.

R&D Spending

According to the "***2017 Global R&D Funding Forecast***" published by R&D Magazine, the life science R&D investments are driven by the expansive biopharmaceutical sector which accounts for about 80% of the industry's total R&D spending. The companies involved in this sector are well-known and well-established. Over the years, they have acquired numerous smaller life science enterprises and smaller start-ups and integrated them into the larger bio-pharm entity. The report says that for the year 2016 U.S. R&D spending was up over 5% to $72.1 billion and it is forecasted to increase another 3.5% in 2017 to reach $74.6 billion.



Source: http://www.rdmag.com

A number of challenges were reported by R&D Magazine in their 2017 global R&D funding forecast which are said to threaten the life science industry's funding resources. One, of course, is that there is significant backlash in government and public circles to biopharmaceutical pricing. President-elect Donald Trump has stated that he doesn't like what has happened to drug prices and he is going to bring them down. Two of the vehicles mentioned in the Trump campaign for lowering drug prices were to allow Medicare to negotiate drug prices or import drugs from outside the U.S. The transition team also mentioned that the new administration would "reform the U.S. Food and Drug Administration (FDA) to put a greater focus on the need of patients for new and innovative medical products."

Another aspect of the drug pricing concerns was voiced by the FDA in that this agency would prioritize and expedite their review of applications for first generics, making sure that the first

applicants for generic alternatives to high-priced drugs are moved to the head of the queue and given priority reviews. The same is holding true for the development of biosimilars.

The more traditional challenge which has reared its head in 2016 was the failure in clinical trials of a widely anticipated Alzheimer drug. Patients using Lilly's solanezumab did not experience a statistically slowing in cognitive decline compared to patients treated with a placebo. Lilly's clinical failure was a bellwether for other drug developers who were working on similar drugs.

Additionally, some drug developers, such as Allergan, are scaling back on the number of drugs they are developing to focus on those drugs they have the most experience in and fit better into their overall drug pipeline.

TOP 20 BIOPHARMACEUTICAL COMPANIES BY R&D SPENDING

Company	Ticker	R&D expenses 2016 ($M)	R&D expenses 2015 ($M)	% Change
Gilead Sciences	GILD	5098	3014	69.1
Celgene	CELG	4470	3697	20.9
Amgen	AMGN	3840	4070	-5.6
Regeneron Pharmaceuticals	REGN	2052	1620	26.6
Biogen	BIIB	1973	2143	-8.0
Shire	SHPG	1440	1564	-8.0
Vertex Pharmaceuticals	VRTX	1048	996	5.2
Alexion Pharmaceuticals	ALXN	757	709	6.8
BioMarin Pharmaceutical	B MRN	662	635	4.3
Incyte	INCY	582	479	21.3
Alkermes	ALKS	387	344	12.4
Alnylam Pharmaceuticals	ALNY	382	276	38.3
Seattle Genetics	SGEN	379	294	28.8
Ionis Pharmaceuticals	IONS	344	322	6.8
Juno Therapeutics	JUNO	264	205	28.8
Coherus Biosciences	CHRS	254	213	19.4
Clovis Oncology	CLVS	251	269	-6.7
Portola Pharmaceuticals	PTLA	247	200	23.2
Puma Biotechnology	PBYI	223	208	6.9
Agios Pharmaceuticals	AGIO	220	142	55.2

Source: http://clarivate.com

Drugs in Clinical Development

The rapid pace of scientific advances is giving patients unprecedented hope. Researchers are leveraging growing knowledge of the biological basis of disease and harnessing technological advances across the biopharmaceutical ecosystem to usher in a new era of treatment possibilities. This commitment to bringing new medicines to patients is evidenced by the robust pipeline of medicines currently in development.

According to *"**Biopharmaceutical Industry 2016 Profile**"*, a report issued by the Pharmaceutical Research and Manufacturers of America (PhRMA), there are currently more than 7,000 medicines targeting a broad array of disease areas and conditions which are in clinical development around the world. Many of these

medicines have the potential to meet substantial unmet patient need. In fact, experts estimate 70% are potential first-in-class medicines with a mechanism of action distinct from any other marketed drug.

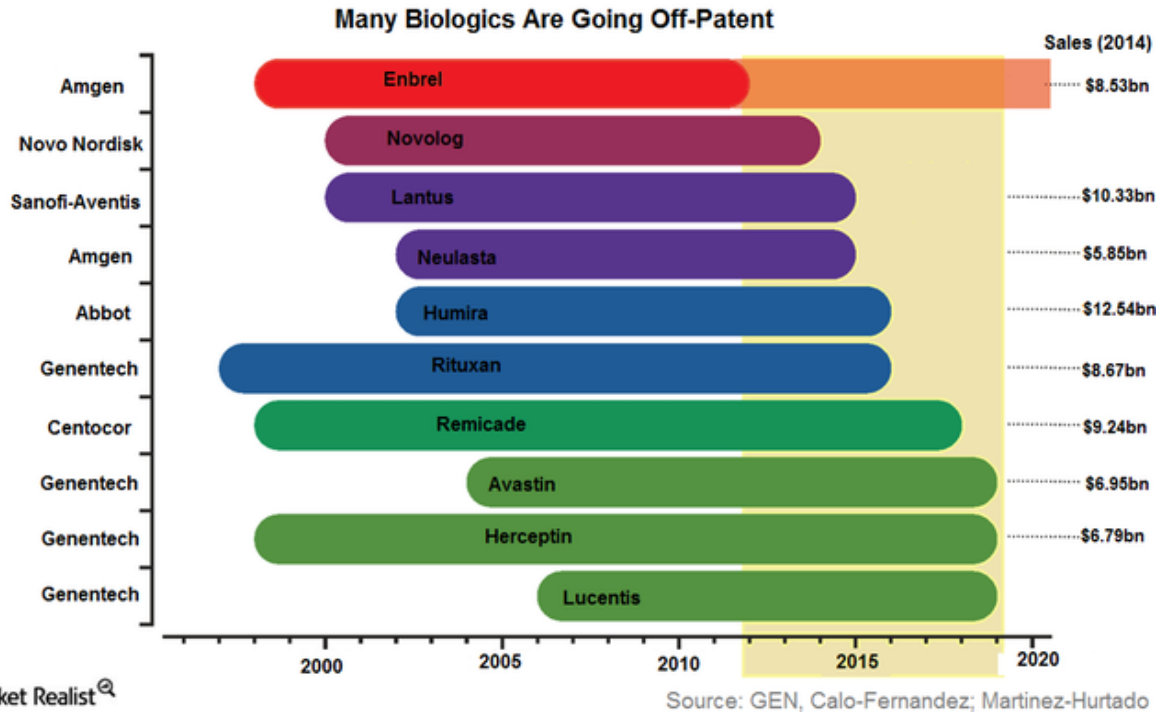
Today, 42% of medicines in development have the potential to be personalized medicines, and 73% of cancer medicines have the potential to be personalized medicines.

Selected Diseases	Medicines in Development*
Cancers	1,919
Neurological disorders	1,308
Infectious diseases	1,261
Immunological disorders	1,123
Cardiovascular disorders	563
Mental health disorders	510
Diabetes	401
HIV/AIDS	208

Defined as single products which are counted exactly once regardless of the number of indications pursued
Source: ***http://phrma.org***

III. The Biologic Medicines Market

According to "***Winning with biosimilars: Opportunities in global markets***", a report issued by Deloitte, global sales of biologics totaled $150 billion in 2013. The report also states that biologics are likely to make up 27% of the pharmaceutical market and $290 billion in sales by 2020. But 48% of these sales would come from 11 biologics that face patent expirations and loss of exclusivity in the next few years, as noted in the graph below. This change could mean an exciting opportunity for the generic drugs market—specifically for biosimilars.



According to the "***2016 Drug Trend Report***" released by Express Scripts, spending on prescription drugs for the year increased 3.8% per person for those who have health insurance coverage, 26.9% less than the 5.2% increase the prior year. Furthermore, specialty drug spending increased only 13.3% in 2016 compared to 17.8% in 2015, which was the lowest trend in 14 years. Specialty drugs accounted for more than a third of total spending in 2016.

Five specialty therapy classes ranked in the top 15 in 2016, due to their high per-member-per-year (PMPY) spend. Hepatitis C, the only top specialty therapy class with negative trend, declined in spend by 34.0% in 2016, due to lower utilization and unit cost. Three other specialty therapy classes – inflammatory conditions, oncology and HIV – all had large increases in both utilization and unit cost; this resulted in positive trends greater than 20% for each class in 2016.

COMPONENTS OF TREND FOR TOP 15 THERAPY CLASSES

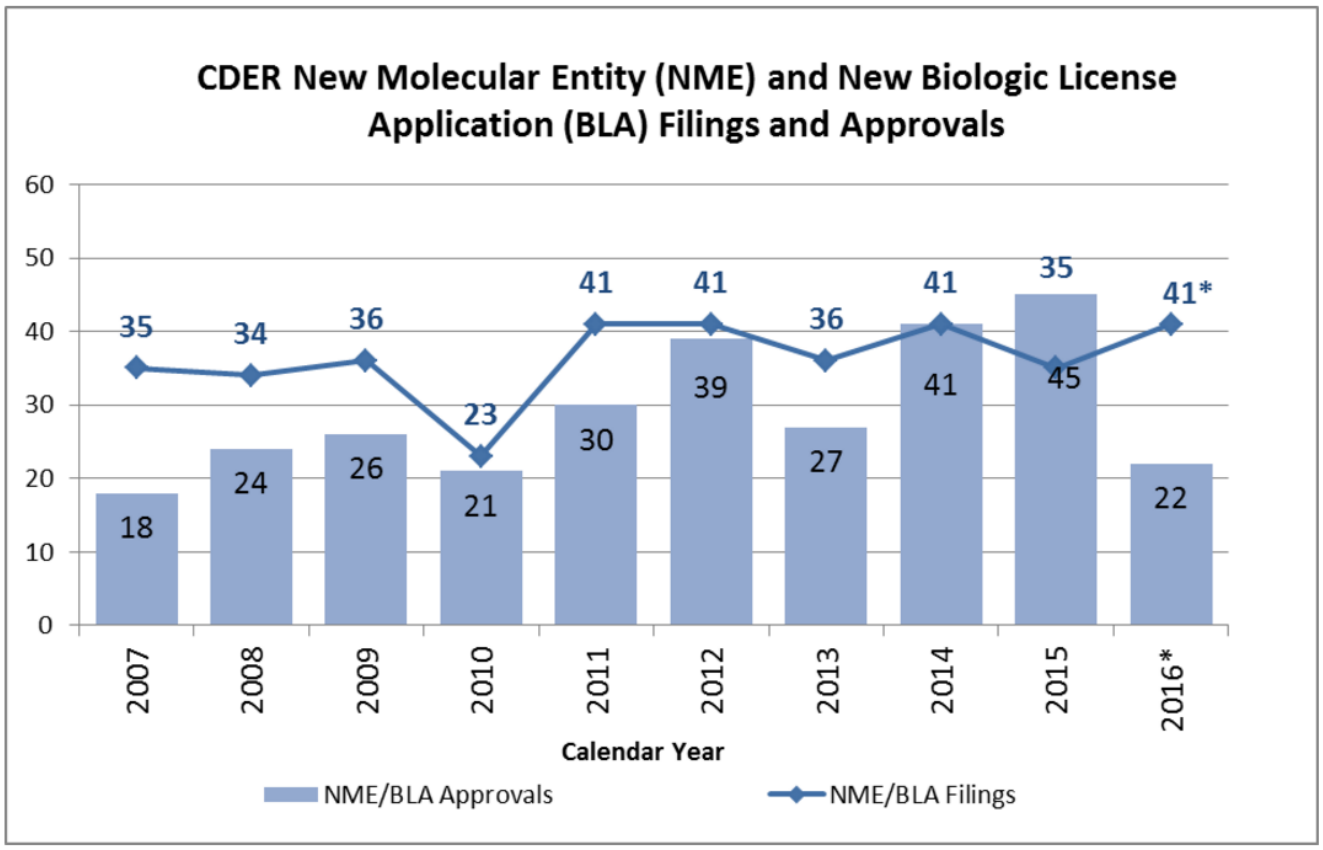
RANKED BY 2016 PMPY* SPEND

				TREND		
RANK	TYPE	THERAPY CLASS	PMPY SPEND	UTILIZATION	UNIT COST	TOTAL
1	S	Inflammatory conditions	$118.21	11.3%	15.1%	26.4%
2	T	Diabetes	$108.80	5.3%	14.1%	19.4%
3	S	Oncology	$60.70	11.9%	9.6%	21.5%
4	S	Multiple sclerosis	$58.63	-1.3%	7.4%	6.1%
5	T	Pain/inflammation	$51.64	0.6%	0.9%	1.5%
6	S	HIV	$39.92	5.5%	16.2%	21.7%
7	T	High blood cholesterol	$38.45	-0.9%	-6.5%	-7.4%
8	T	Attention disorders	$36.30	5.6%	-5.5%	0.1%
9	T	High blood pressure/heart disease	$34.52	1.5%	-10.6%	-9.1%
10	T	Asthma	$30.42	3.3%	-2.6%	0.7%
11	S	Hepatitis C	$25.26	-27.3%	-6.7%	-34.0%
12	T	Depression	$23.46	4.8%	-6.4%	-1.6%
13	T	Contraceptives	$20.97	3.0%	-2.8%	0.2%
14	T	Heartburn/ulcer disease	$20.93	-1.3%	-22.7%	-24.0%
15	T	Skin conditions	$20.76	1.2%	0.4%	1.6%
		Other therapy classes	$389.07	0.0%	0.3%	0.3%
		TOTAL	$1,078.04	1.3%	2.5%	3.8%

S = Specialty, T = Traditional *Per member per year

2016 New Drug Approvals

In 2016, the FDA approved only 22 new molecular entities (NMEs) and novel new biologics license applications (BLAs), its fewest since 2010 and down considerably from its recent highs in 2014 and 2015. And while FDA's former Office of New Drugs Director John Jenkins attributed the decline in part due to fewer applications from industry, more rejections and a handful of drugs approved in 2015 ahead of their 2016 goal dates, many questioned whether 2016 was a sign of a slowdown at the agency.



Some of the highlights from the FDA's report entitled *"Novel New Drugs 2016 Summary"* include:

- 8 of the 22 NMEs were considered "first in class" which means that they utilize a novel or unique mechanism of action over existing therapies.

- 9 of the 22 NMEs were approved to treat orphan diseases. Orphan diseases are considered rare diseases that affect 200,000 or fewer Americans. This is more approvals for orphan drugs than in any previous year.

- 16 of the 22 NMEs were designated in one or more expedited pathway categories – Fast Track, Breakthrough, Priority Review, and Accelerated Approval.

    - **Fast Track** designation is identified by FDA as drugs with the potential to address unmet medical needs. "Fast Track speeds new drug development and review, for instance, by increasing the level of communication FDA allocates to developers and by enabling developers to use a "rolling review" process such that CDER can review portions of an application ahead of the submission of the full application." (8 NMEs had this designation)

    - **Breakthrough** designation is identified by FDA as drugs with preliminary clinical evidence that shows the potential of substantial improvement over at least one clinically significant endpoint compared with current therapy. "A breakthrough therapy designation conveys all

of the fast track program features as well as more intensive FDA guidance on an efficient drug development program." (7 NMEs had this designation)

- **Priority Review** is determined by FDA that the drug has the potential to provide a significant advance on medical care. With priority review, FDA sets a target to review the drug within six months instead of the standard that is 10 months. (15 NMEs had this designation)

- **Accelerated Approval** allows early approval of a drug for a serious or life-threatening illness that offers benefits over current treatments. "This approval is based on a "surrogate endpoint" (e.g., a laboratory measure) or other clinical measure that FDA considers reasonable likely to predict clinical benefit. After this approval, the drug must undergo additional testing to confirm that benefit; this speeds the availability of the drug." (6 NMEs had this designation)

- 21 of the 22 were approved on the first cycle, which means that they were approved without the need for additional information that would delay approval.

- 19 of the 22 were approved first in the United States before any other country.

The Personalized Medicine Coalition (PMC) recently reported in the *"**Personalized Medicine at FDA: 2016 Progress Report**"* that personalized medicines accounted for more than 20% of all new molecular entities (NMEs) approved by the U.S. Food and Drug Administration (FDA) in 2016. Of the 22, the Personalized Medicine Coalition (PMC) classified six of them — more than 25% — as personalized medicines, continuing a trend that PMC first documented in 2014 when it pointed out that nine of 41 NMEs approved that year are personalized medicines. The analysis underlines that nearly one of every four drugs the agency approved from 2014 to 2016 is a personalized medicine. That ratio is a sharp increase from 2005, when personalized medicines accounted for just 5% of NME approvals.

As expected, oncology indications dominated the list of newly approved precision medicines. Of the 6 approved new precision medicines, 3 were in oncology.

The six personalized medicines approved in 2016 include:

1. Rubraca (rucaparib) for the treatment of advanced ovarian cancer. The decision to use this product is informed by the BRCA1/2 biomarker status in patients.

2. Exondys 51 (eteplirsen) for the treatment of Duchenne muscular dystrophy. The decision to use this product is informed by the DMD mutation biomarker status in patients.

3. Epclusa (sofosbuvir and velpatasvir) for the treatment of chronic hepatitis C infection. The decision to use this product is informed by the HCV genotype status of the viral infection in patients.

4. Tecentriq (atezolizumab) for the treatment of advanced or metastatic urothelial cancer and metastatic non-small cell lung cancer. The decision to use this product is informed by PD-L1 expression levels in the tumors of patients.

5. Venclexta (venetoclax) for the treatment of chronic lymphocytic leukemia. The decision to use this product is informed by the chromosome 17p deletion biomarker status in patients.

6. Zepatier (elbasvir and grazoprevir) for the treatment of chronic hepatitis C infection. The decision to use this product is informed by the HCV genotype 1 and 4 biomarker status of the viral infection in patients.

Novel Biologic Drugs Approved by CDER in 2016

Included in the report were 7 biotech drugs or biologics that were approved by CDER. This number was down from last year where there were 13 approved. In addition, 5 of the 7 approved biologics participated in at least one expedited pathway designation.

2016 biologics approvals, *in order of approval date (latest to earliest)*

Drug Name	Active Ingredients	FDA Expedited Pathway	Expression System	Company	Indications
Zinplava	bezlotoxumab	First in Class, Fast Track, Priority Review	Not provided	Merck	To reduce the recurrence of Clostridium difficile infection in patients aged 18 years or older
Lartruvo	olaratumab	Orphan, Fast Track, Priority Review, Accelerated Approval	Olaratumab is a recombinant human IgG1 monoclonal blocking antibody that binds specifically to human platelet-derived growth factor receptor alpha (PDGFR-α) produced in genetically engineered mammalian NS0 cells.	Eli Lilly and Company	To treat adults with certain types of soft tissue sarcoma
Zinbryta	daclizumab	First in class	Not provided	Biogen and AbbVie	To treat multiple sclerosis
Tecentriq	atezolizumab	Breakthrough, Priority Review, Accelerated Approval	Not provided	Genentech	To treat urothelial carcinoma, the most common type of bladder cancer

2016 biologics approvals, *in order of approval date (latest to earliest)*

Drug Name	Active Ingredients	FDA Expedited Pathway	Expression System	Company	Indications
Cinqair	reslizumab	n/a	CINQAIR (reslizumab) is a humanized interleukin-5 antagonist monoclonal anti-body (IgG4k). Reslizumab is produced by recombinant DNA technology in murine myeloma non-secreting 0 (NS0) cells.	Teva Respiratory	To treat severe asthma
Taltz	ixekizumab	n/a	Ixekizumab is a humanized immunoglobulin G subclass 4 (IgG4) monoclonal antibody (mAb) with neutralizing activity against IL-17A. Ixekizumab is produced by recombinant DNA technology in a recombinant mammalian cell line and purified using standard technology for bioprocessing.	Eli Lilly and Company	To treat adults with moderate-to-severe plaque psoriasis.
Anthim	obiltoxaximab	Orphan, Fast Track	Not provided	Elusys Therapeutics	To treat inhalational anthrax in combination with appropriate antibacterial drugs.

Source: FDA and Prescribing Information

10 Best-Selling Biologics for 2016

Among the top 10 pharmaceutical products in 2016, biologics beat out small molecules, and treatments for cancer and inflammation dominated the field. Holding the lead again was Humira, a monoclonal antibody targeting inflammatory and autoimmune diseases. At $16.1 billion in sales, Humira outpaced the next-best-selling drug by more than $6 billion.

In second place is Gilead Sciences' hepatitis C drug Harvoni, which grew rapidly after launching in late 2014. Sales cooled considerably—but not unexpectedly—this year as successful treatment has led to a decline in the patient population.

Among the firms behind the top products, Roche stands out for having three. But its leading cancer biologics—as well as Humira, Remicade, and Enbrel— will face biosimilar competition.

Top 10 products

AbbVie's Humira retained the top spot while Gilead's sales of Harvoni faded

DRUG NAME	TYPE	MARKETER	INDICATION	2016 SALES ($ BILLIONS)	% CHANGE FROM 2015
Humira	Antibody	AbbVie, Eisai	Inflammation	16.1	13
Harvoni	Small molecule	Gilead Sciences	Hepatitis C	9.9	-29
Enbrel	Protein	Amgen, Pfizer	Inflammation	8.7	0
Remicade	Antibody	Janssen, Merck & Co.	Inflammation	8.5	1
Rituxan	Antibody	Roche	Cancer	7.4	4
Revlimid	Small molecule	Celgene	Cancer	7.0	21
Herceptin	Antibody	Roche	Cancer	6.9	5
Avastin	Antibody	Roche, Chugai	Cancer	6.9	1
Lantus	Peptide	Sanofi	Diabetes	6.2	-11

DRUG NAME	TYPE	MARKETER	INDICATION	2016 SALES ($ BILLIONS)	% CHANGE FROM 2015
Januvia/Janumet	Small molecule	Merck & Co.	Diabetes	6.1	2

Note: Estimated sales are based on company statements and C&EN calculations.

Source: **http://cen.acs.org**

The Outlook for Biologic Drugs

With many best-selling products recently losing market exclusivity and advances in biotechnology undercutting the entire concept of a drug, pharma is being pushed to fill product pipelines faster than individual R&D departments can develop new compounds or transform them for commercialization. For example, a drug used to be conceived as a small molecule, chemically-manufactured product. These pharmaceuticals were made more effective during the late 20th century, and now the current market for their development is concentrated in finding novel doses, administrations or uses for existing drugs. Today, large molecule biologics are the real center of drug innovation, and medical devices are even competing with traditional drug therapies. In 2017 a fresh wave of biologics is expected to be approved for use by general practitioners (see the Table below).

Novel Drug Approvals for 2017

No.	Drug Name	Active Ingredient	Approval Date	FDA-approved use on approval date
20.	Radicava	edaravone	5/5/20017	To treat patients with amyotrophic lateral sclerosis (ALS)
19.	Imfinzi	durvalumab	5/1/20017	To treat patients with locally advanced or metastatic urothelial carcinoma
18.	Tymlos	abaloparatide	4/28/2017	To treat osteoporosis in postmenopausal women at high risk of fracture or those who have failed other therapies
17.	Rydapt	midostaurin	4/28/2017	To treat acute myeloid leukemia
16.	Alunbrig	brigatinib	4/28/2017	To treat patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib
15.	Brineura	cerliponase alfa	4/27/2017	To treat a specific form of Batten disease
14.	Ingrezza	valbenazine	4/11/2017	To treat adults with tardive dyskinesia
13.	Austedo	deutetrabenazine	4/3/2017	For the treatment of chorea associated with Huntington's disease
12.	Ocrevus	ocrelizumab	3/28/2017	To treat patients with relapsing and primary progressive forms of multiple sclerosis
11.	Dupixent	dupilumab	3/28/2017	To treat adults with moderate-to-severe eczema (atopic dermatitis)
10.	Zejula	niraparib	3/27/2017	For the maintenance treatment for recurrent epithelial ovarian, fallopian tube or primary peritoneal cancers
9.	Symproic	naldemedine	3/23/2017	For the treatment of opioid-induced constipation
8.	Bavencio	avelumab	3/23/2017	To treat metastatic Merkel cell carcinoma
7.	Xadago	safinamide	3/21/2017	To treat Parkinson's disease
6.	Kisqali	ribociclib	3/13/2017	To treat postmenopausal women with a type of advanced breast cancer

5.	Xermelo	telotristat ethyl	2/28/2017	To treat carcinoid syndrome diarrhea
4.	Siliq	brodalumab	2/15/2017	To treat adults with moderate-to-severe plaque psoriasis
3.	Emflaza	deflazacort	2/9/2017	To treat patients age 5 years and older with Duchenne muscular dystrophy (DMD)
2.	Parsabiv	etelcalcetide	2/8/2017	To treat secondary hyperparathyroidism in adult patients with chronic kidney disease undergoing dialysis
1.	Trulance	plecanatide	1/19/2017	To treat Chronic Idiopathic Constipation (CIC) in adult patients

* This information is currently accurate. In rare instances, it may be necessary for FDA to change a drug's new molecular entity (NME) designation or the status of its application as a novel new biologics license application (BLA). For instance, new information may become available which could lead to a reconsideration of the original designation or status. If changes must be made to a drug's designation or the status of an application as a novel BLA, the Agency intends to communicate the nature of, and the reason for, any revisions as appropriate.
Source: ***https://www.fda.gov***

IV. The US In-Vitro Diagnostic Tests Market

According to Millennium Research Group (MRG), the global authority on medical technology market intelligence, the introduction of the Patient Protection and Affordable Care Act (PPACA) in 2014 will significantly affect the United States in vitro diagnostics (IVD) market landscape which is expected to grow nearly $8.6 billion by 2017 in the United States. Most notably, the implementation of this Act will increase the percentage of people covered by insurance, which will drive test volumes, especially as the US population ages and the demand for IVD increases.

The PPACA will also lead to increased centralization of IVD testing as more laboratories, hospitals and care facilities consolidate as a result of the health care reform. Although the rise of centralized labs will leave manufacturers with fewer potential sites for capital sales, these facilities will see high testing volumes and ultimately have the resources to purchase a broader array of diagnostic tests.

High testing volumes at centralized sites will mean that these labs will look for vendors that can offer a broad range of instrumentation and automation equipment.

"As the trend of centralization continues, these high-throughput laboratories will look to purchase from large, cross-segment vendors that can equip them with a full array of instrumentation," said MRG Analyst Mickel Phung. "The labs will prefer to purchase all of their equipment from one vendor to improve workflow logistics and reduce costs."

As a result, the majority of market share is held by a few key multi-segment players, including Siemens Healthcare, Roche and Abbott Laboratories. Large multinational companies will likely continue to dominate the market through 2017—especially those players with a finger in molecular diagnostics technologies. This market segment will grow rapidly through 2017, cannibalizing sales from more mature segments such as immunoassay and microbiology testing.

Top 5 Trends in IVD Testing for 2017

In a report titled, *"**Five IVD Market Trends to Watch for in 2017**,"* Kalorama published its picks for the top five trends in IVD testing for 2017. The five most prominent trends recognized by the healthcare research marketer are as follows:

1. Core Labs a Focus Amid Consolidation – As healthcare organizations consolidate, IVD companies are looking at core lab markets and automation systems that target big accounts. There is increasing demand among integrated health networks for greater centralization of diagnostic testing to streamline workflows and steer better healthcare information to professionals. Major IVD companies launched products this year to enhance workstation. Siemens Healthineers used the AACC Annual Meeting this year to unveil its Atellica Solution for automated core lab testing. Abbott Diagnostics unveiled its Alinity line of "harmonized systems" across the core lab (clinical chemistry and immunoassays), hematology, point-of-care (POC) diagnostics, blood screening, and molecular diagnostics.

2. Ascent of China's Food and Drug Administration (CFDA): In the past five years, China has solidified its place as an IVD market just behind the United States, European Union, and Japan. Outside of U.S. Food and Drug Administration (FDA) approval or European CE marking, China FDA (CFDA) approval has been the next most heralded product development for many IVD companies. Roche issued a 2016 press release for the CFDA approval of its CINtec PLUS Cytology test or immunocytochemistry assay for the detection of human papillomavirus (HPV). Roche also markets a molecular HPV assay that may find greater usage in emerging markets in the coming years after being approved by the U.S. FDA as a first-line HPV screening tool. Qiagen has also targeted the Chinese HPV test market with its CFDA-approved careHPV platform for low-resource settings.

"Most surprising in the Chinese market's ascent has been the prominence of its cancer diagnostics space. Advanced cancer testing is not associated with middle-income countries, but China's research prowess in sequencing, and globally significant patient populations in urban markets, have created considerable opportunities for overseas IVD companies," noted the Kalorama researchers, who added that next-generation sequencing is the highest area of activity in Chinese cancer diagnostics.

3. US Developers of Laboratory Developed Tests (LDTs) Penetrate the European Union (EU) Market: Kalorama researchers labeled the penetration of the EU market by cancer-focused American LDT companies as an "emerging dynamic." Among those companies introducing LDTs to the EU are: Myriad Genetics; Foundation Medicine; and Genomic Health.

Kalorama's research notes that Genomic Health has a substantial European LDT business, and that 14% of the company's 2015 revenue came from international markets.

4. Growth in Urgent Care Center and Retail Clinic Markets: About 7,100 urgent care centers operate in the US, according to the Urgent Care Association of America (UCAOA), which defines urgent care centers as those that include full-service urgent care medicine, clinical laboratory, and X-ray services.

Urgent care centers, along with 1,200 retail clinics (generally installed in retail settings, smaller than urgent care centers, and offer fewer services), have led IVD companies to prioritize services specific to the centers' workflows, according to Kalorama.

For example, Kalorama researchers noted Roche's cobas Liat System is designed specifically for the centers. According to Roche, the system:

• Automates the testing process;
• Simplifies workflow; and
• Enables healthcare workers to quickly offer molecular testing in a variety of settings.

5. More Companies Seek to Acquire Technology through Partnerships, Mergers, and Acquisitions: In addition to the ongoing consolidation of hospitals and healthcare systems, merger and acquisition activity involving IVD companies is "brisk," Kalorama found.

Here are deals sealed and launched in 2016, according to Kalorama research:

• LabCorp purchased Sequenom, an American molecular and genetic testing technology company based in San Diego;

• Abbott announced its intent to buy Alere, a developer of point-of-care (POC) rapid diagnostics technologies. However, this acquisition did not succeed and resulted in Abbott declaring "full-scale war" on Alere, according to a *New York Times* article;

• Danaher purchased molecular diagnostics developer Cepheid;

• Bio-Techne acquired ACD, a developer of molecular pathology and diagnostic tests for personalized medicine;

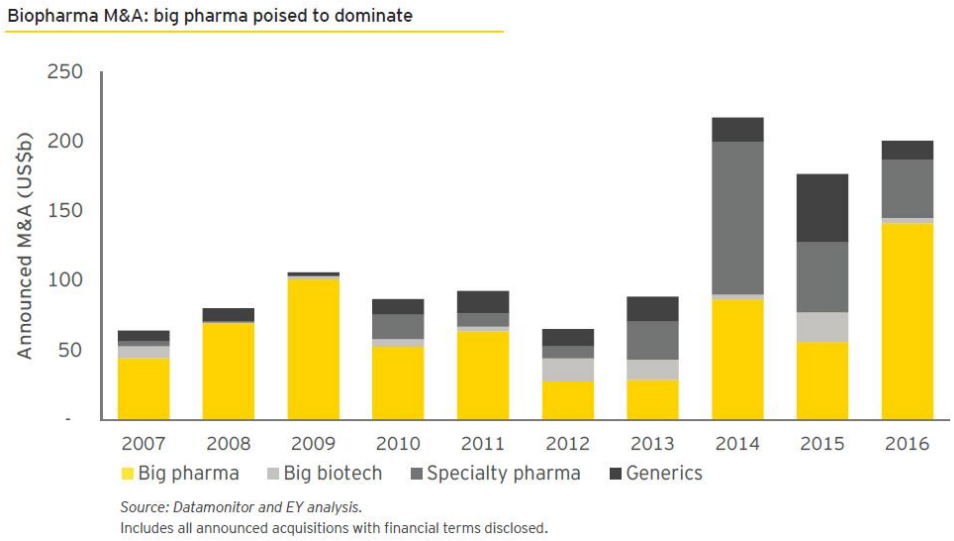
• Oxford Immunotec acquired most of the assets of Imugen, a clinical laboratory located in Norwood, Mass., that specializes in the testing of clinical specimens for tick-borne diseases; and

• Luminex acquired Nanosphere, a developer of molecular microbiology and molecular diagnostics.

V. Current Trends

Mergers & Acquisitions

After 2015 turned out to be a strong year for biopharma mergers and acquisitions (M&A), several industry watchers expected 2016 to reach the stratosphere, and with good reason. The largest-ever deal in industry history was in the works, Pfizer's planned $160 billion acquisition of Allergan, and the industry had seen the market for biopharma stocks recover from the near standstill of the 2007–09 recession.



Instead, an Obama administration crackdown on tax-slicing "inversion" mergers derailed the Pfizer-Allergan deal, while fears of price curbs on prescription drugs—concerns that President Trump has continued to stoke by railing against drug developers on Twitter—rattled investors enough to deflate stock prices, dampening company valuations enough to slow down the pace of deal-making. The overall value of biopharma M&A climbed, while the number of deals declined.

10 Biggest Pharma and Biotech M&A Deals Announced in 2016

Source: EvaluatePharma® January 2017

Date Announced	Acquirer	Target	Value ($bn)
Jan 2016	Shire	Baxalta	32.0
Aug 2016	Pfizer	Medivation	14.0
Apr 2016	AbbVie	Stemcentrx	9.8
Feb 2016	Mylan	Meda	7.2
May 2016	Pfizer	Anacor Pharmaceuticals	5.2
Dec 2016	Lonza	Capsugel	3.5
Sep 2016	Allergan	Tobira Therapeutics	1.7
Aug 2016	Pfizer	AstraZeneca's ex-US anti-Infectives	1.6
Jul 2016	Galenica	Relypsa	1.5
May 2016	Jazz Pharmaceuticals	Celator Pharmaceuticals	1.5

The biopharmaceutical industry's desire for inorganic growth is expected to intensify an already heated mergers and acquisitions (M&A) environment in 2017. This is according to the "***EY M&A Outlook and Firepower Report 2017***". With new regulatory and tax environments expected following the changing geopolitical landscape, most notably in the post-election U.S., expectations are that the industry may roar past the $200 billion in global M&A deal volume seen in the last three years.

The EY report finds the industry's need to engage in M&A has become amplified as payers continue to push back forcefully on price increases for older drugs while dampening the growth trajectory of newer drugs, creating a potentially daunting payer-driven revenue growth gap. As the probability of revenue shortfalls increases across the global industry, even companies with solid growth prospects may look to pursue M&A in 2017 as a defensive safeguard.

Key findings highlighted in this year's EY Firepower Index report include:

- "New normal" $200 billion deal environment persists in 2016: Total M&A volume across the biopharmaceutical industry exceeded US$200b in 2016, a level unheard of prior to 2014 but in line with the deal volume of the previous two years. Big pharma was responsible for the lion's share of this deal activity with over 70%.

- Finding growth in traditional strongholds is becoming increasingly difficult: Yesterday's breakthrough innovations in disease areas, such as autoimmune disease and oncology, have become today's crowded therapeutic battlefields, forcing the industry to seek therapeutic "white spaces" in underserved areas. For example, Alzheimer's disease remains high-risk, but pharmaceuticals represent only about 1% of the US$250b in related global health care costs.

- Overall firepower on the decline: Falling equity valuations and debt raised to fuel previous years' M&A have resulted in roughly a 20% decline in firepower across the industry. Specialty pharma and big biotech companies have experienced the largest declines, down 62% and 24%, respectively, while big pharma dropped only 17%.

- But plenty of firepower remains: Even with falling firepower levels, there are many companies with the ability to make large and potentially transformative deals. Notably, big pharma and big biotech companies have spent only about 10% of their firepower on M&A annually over the past several years.

The report identifies several industry challenges and considerations likely to drive M&A in 2017 and beyond.

- U.S. political climate could drive deals: Potential regulatory and tax reform in the U.S. could create an even more heated global deal environment. Of particular significance is the potential repatriation to the US of roughly US$100b in cash, which would provide U.S. companies with considerable firepower to complete deals.

- Big pharma likely to dominate deal making in 2017: Now in possession of nearly 70%, or US$600b, of the total industry firepower, big pharma is in the driver's seat for acquiring the most desirable M&A targets.

- Specialty pharma may sit one out: Specialty pharma will likely find it difficult to compete in M&A in 2017 due to both falling valuations and its three-year marathon of M&A transactions. On average, specialty pharma valuations have fallen 34% during 2016, and no fewer than six of the largest 10 specialty pharma companies have exhausted their firepower.

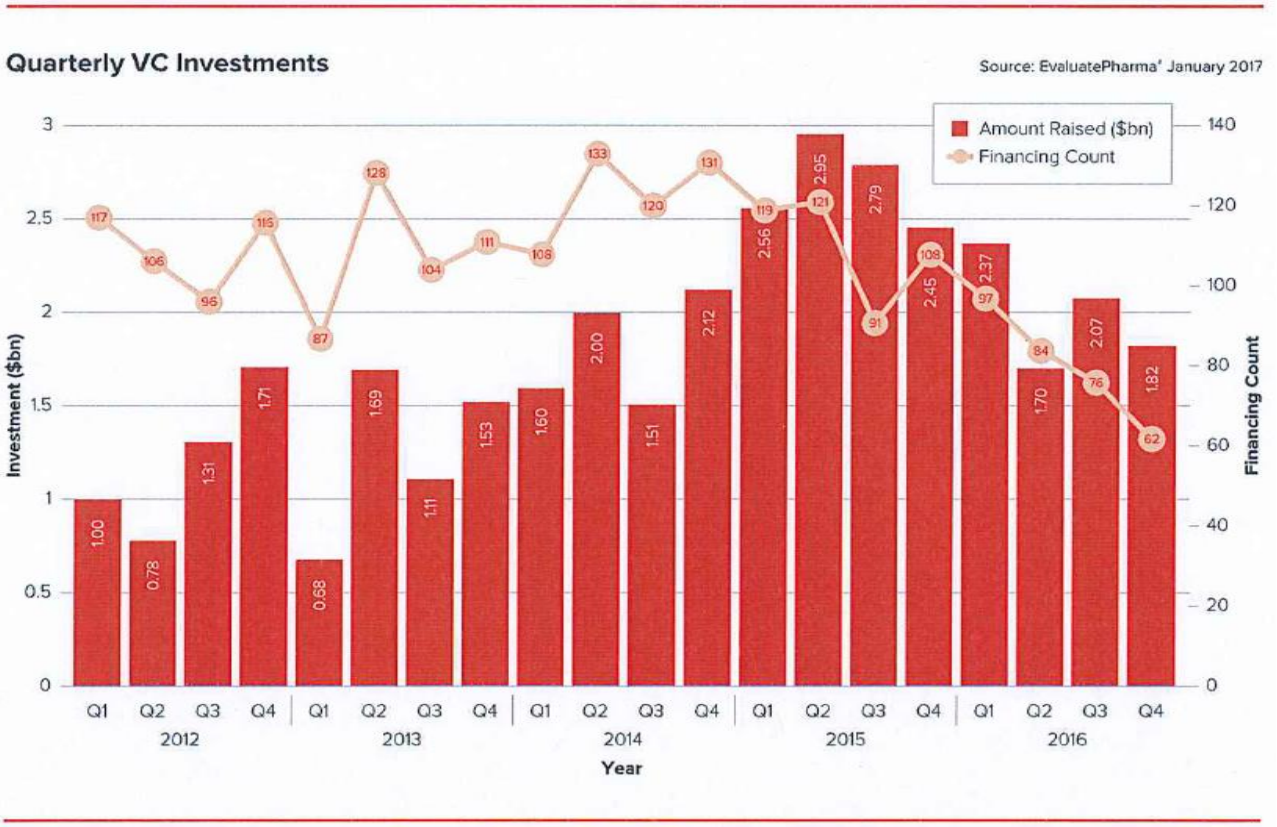
- Ex-US advantages could wane: U.S. tax policy reform could also lessen or erase the dealmaking advantages that companies with ex-U.S. tax domiciles have enjoyed. It may also spur global pharma companies seeking U.S. market growth to accelerate their M&A plans.

Venture Capital

According to EP Vantage's *"**Pharma & Biotech 2016 in Review report**"*, 2016 was an active year for fund-raisings. While the totals might have dropped off from 2015, this was largely down to the exit of crossover funds from the sector. These investors, who help fund large pre-IPO rounds, were in less demand as the rate of new issues also declined last year.

Some of the biggest beneficiaries of the takeovers that did happen last year were venture firms, which have pumped huge amounts of cash into private start-ups in the past few years. These firms wasted no time raising new funds while the biotech bull run charged ahead, and many remain well stocked and willing to make new investments.

A remarkable fourth quarter saw three rounds breaking the $200m barrier, and included four of the 10 biggest of the year. The big prize of 2016 went to Moderna Therapeutics, which has been a master showman in exceeding the mythical $1bn mark before revealing more of itself to the world at the JP Morgan conference this year.



The downside to this analysis is perhaps the continuing slide in the number of fund-raisings, particularly for groups trying to raise their first round of investment. The fourth quarter of 2016 saw the fewest rounds, 62, of any three-month period since 2008. This broke the previous low of 76 in the third quarter of 2016. The annual number, 319, is also the lowest recorded in this time period.

Annual VC Investments

Source: EvaluatePharma® January 2017

Date	Investment ($bn)	Financing Count	Avg per Financing ($m)	No. of Rounds ≥$50m	No. of Rounds ≥$100m
2016	8.0	319	25	43	11
2015	10.7	439	24	57	14
2014	7.2	492	15	35	4
2013	5.0	433	12	12	3
2012	4.8	437	11	16	2
2011	4.4	408	11	11	3
2010	5.0	452	11	13	3

Still, the $8bn that came in in 2016 is second only to 2015 in terms of amount raised, showing that there are substantial funds to be tapped. The lesson here is that private biotechs need to have a more compelling story than ever to earn venture backing. And, if they succeed, the rewards will be rich.

This thesis is confirmed by the $25m average raise last year, the highest since at least 2010 and likely to be a record. And the number of companies raising bumper $50m+ and $100m+ rounds remains high, even with the exit of crossover funds.

Few expect 2017 to witness any notable slowing in the venture capital environment. With well-stocked investors and plenty of enthusiastic acquirers, this section of the drug development world should remain a bright spot this year.

Top 10 Rounds of 2016

Source: EvaluatePharma® January 2017

Company	Investment ($m)	Round	Date
Moderna Therapeutics	451	Series Undisclosed	Aug
Innovent Biologics	260	Series D	Nov
BlueRock Therapeutics	225	Series A	Dec
Intarcia Therapeutics	206	Series Undisclosed	Dec
Intarcia Therapeutics	215	Series I	Sep
Denali Therapeutics	130	Series B	Aug
UNITY Biotechnology	116	Series B	Oct
Zai Lab	100	Series B	Jan
DelCor Pharmaceuticals	100	Series B	Apr
Hengrui Therapeutics	100	Series Undisclosed	Jun

Despite another big showing for the Bay Area in the roster of VC deals that delivered in 2016, Cambridge/Boston was the clear leader in the US last year, according to the latest tally of 2016 numbers by Thomson Reuters.

There's long been a rivalry between the two coasts when it comes to investing in the life sciences. And if you include the three key hub cities in California, adding number 3 player San Diego, the West Coast continues to dominate the field. But the confluence of academia, VC cash, big pharma migrations and big science has made Cambridge the epicenter of new biotech investments globally.

Top Cities for Biotech VC Investment (2016)

CITY	TOTAL $M	DEALS	CO.S	AVG/CO. $M
Boston	3,111.76	117	98	31.75
San Jose	1,791.29	98	81	22.11
San Fran/Berkeley	1,123.49	54	45	24.97
San Diego Metro	648.43	39	30	21.61
New York Metro	564.35	56	48	11.76
Great Lakes	394.00	54	42	9.38
Other US	352.14	76	60	5.87
Orange County	339.41	27	18	18.86
Twin Cities	205.70	8	7	29.39
Philadelphia	181.06	35	28	6.47
Research Triangle	169.80	18	13	13.06
Seattle	154.74	14	14	11.05
Los Angeles	153.27	15	11	13.93
Austin	96.63	8	7	13.80
Washington Metroplex	88.38	25	22	4.02
Atlanta	84.95	9	7	12.14
South NJ/West Pa	81.60	8	6	13.60
Nashville	79.72	11	8	9.96
Dallas	68.95	5	4	17.24
Chicago	47.95	3	3	15.98
Houston	35.29	8	5	7.06
Denver	25.87	9	8	3.23
San Antonio/S.Texas	16.66	3	3	5.55
Pittsburgh/Tristate	8.38	13	13	0.64
Portland	5.10	1	1	5.10
Total	**9,828.91**	**714**	**582**	**16.89**

ENDPOINTS NEWS / DATA: THOMSON REUTERS

Top Regions for Biotech VC Investment (2016)				
REGION	TOTAL $M	DEALS	COMPANIES	AVG/CO. $M
New England	3,238.36	133	111	29.17
Silicon Valley	2,915.28	154	127	22.95
San Diego	648.43	39	30	21.61
NY Metro	564.35	56	48	11.76
LA/Orange County	492.68	42	29	16.99
Midwest	434.29	68	56	7.76
Southeast	404.56	62	45	8.99
North Central	278.39	20	19	14.65
Philadelphia Metro	262.66	43	34	7.73
Texas	217.54	24	19	11.45
Northwest	159.84	15	15	10.66
DC/Metroplex	88.38	25	22	4.02
SouthWest	67.41	7	6	11.23
Colorado	26.40	11	9	2.93
Upstate NY	14.90	5	4	3.72
Sacramento/N.Cal	14.53	6	4	3.63
AK/HI/PR	0.50	1	1	0.50
South Central	0.42	3	3	0.14
Total	9,828.91	714	582	16.89

ENDPOINTS NEWS / DATA: THOMSON REUTERS

Top 100 VC firms investing in U.S. biotech companies

Based on all known 2016 deals

	Firm	# Deals	# of Companies	Avg Equity/Deal ($M)	Avg Equity/Company ($M)	Total Equity Invested
1	Flagship Pioneering	12	9	21.82	29.09	261.83
2	Third Rock Ventures LLC	14	11	12.18	15.51	170.57
3	New Enterprise Associates, Inc.	22	21	6.64	6.96	146.11
4	Arch Venture Partners LLC	17	15	7.72	8.75	131.18
5	Venrock Inc	10	8	11.88	14.85	118.78
6	Deerfield Management Company LP	14	14	8.25	8.25	115.51
7	OrbiMed Advisors LLC	15	14	6.99	7.48	104.79
8	Atlas Venture Advisors Inc	13	13	7.11	7.11	92.42
9	Gurnet Point Capital LLC	1	1	92.00	92.00	92.00
10	5AM Ventures LLC	21	15	4.31	6.03	90.47
11	Celgene Corp	5	5	16.79	16.79	83.95
12	F-Prime Capital Partners	8	7	10.33	11.80	82.63
13	GE Ventures Inc	4	4	19.98	19.98	79.93
14	Canaan Partners	20	17	4.00	4.70	79.90
15	Polaris Venture Partners	23	21	3.30	3.61	75.82

	Firm	# Deals	# of Companies	Avg Equity/Deal ($M)	Avg Equity/Company ($M)	Total Equity Invested
16	Frazier Management LLC	14	12	4.83	5.63	67.56
17	KKR & Co LP	3	3	22.14	22.14	66.42
18	Essex Woodlands Management Inc	5	4	12.40	15.50	62.01
19	Luxin Venture Capital Group Co Ltd	1	1	61.45	61.45	61.45
20	Illuminate Ventures	1	1	55.00	55.00	55.00
21	Google Ventures	7	7	7.60	7.60	53.19
22	Kleiner Perkins Caufield & Byers LLC	10	10	5.17	5.17	51.68
23	Domain Associates LLC	13	11	3.86	4.57	50.23
24	Novartis Venture Funds	7	7	7.17	7.17	50.17
25	Khosla Ventures LLC	6	6	8.30	8.30	49.81
26	Altitude Funds LLC	4	4	12.23	12.23	48.91
27	Fidelity Investment Funds II	1	1	48.00	48.00	48.00
28	Pfizer Venture Investments	9	8	5.21	5.86	46.90
29	Sofinnova Ventures Inc	7	6	6.54	7.63	45.80
30	Amzak Capital Management LLC	2	2	21.95	21.95	43.91
31	Alexandria Venture Investments	12	12	3.53	3.53	42.33
32	Column Group	4	4	10.38	10.38	41.51
33	S.R. One, Limited	7	7	5.66	5.66	39.61
34	Bezos Expeditions	2	2	19.75	19.75	39.50
35	Vivo Capital LLC	9	8	4.21	4.74	37.93
36	MPM Capital LLC	8	7	4.72	5.40	37.77
37	HealthQuest Capital	3	3	12.18	12.18	36.53
38	Aisling Capital LLC	8	8	4.34	4.34	34.72
39	Apple Tree Partners	6	5	5.55	6.66	33.31
40	ORI Capital	2	2	16.50	16.50	33.00
41	Johnson & Johnson Innovation-JJDC	7	7	4.67	4.67	32.72
42	Alaska Permanent Fund Corp	1	1	32.33	32.33	32.33
43	Sofinnova Partners SAS	4	4	7.93	7.93	31.71
44	Novo A/S	8	8	3.90	3.90	31.21
45	Clarus Ventures LLC	10	9	3.01	3.34	30.05
46	Foresite Capital Management LLC	4	4	7.44	7.44	29.75
47	SV Life Sciences Advisers, LLC	10	9	2.97	3.30	29.66
48	Osage Partners	9	9	3.25	3.25	29.28
49	Lundbeckfond Ventures	5	5	5.54	5.54	27.70
50	WuXi Healthcare Ventures	5	4	5.54	6.93	27.70
51	Y Combinator Inc	2	2	13.46	13.46	26.92
52	Boston Scientific Corp	2	2	13.40	13.40	26.80
53	Sutter Hill Ventures	2	2	13.04	13.04	26.07
54	Topspin Partners LP	3	3	8.17	8.17	24.51
55	Arboretum Ventures Inc	4	4	6.11	6.11	24.45
56	RA Capital Management LLC	6	6	3.86	3.86	23.19
57	Rock Springs Capital Management LP	4	4	5.70	5.70	22.79
58	NanoDimension Management Ltd	6	5	3.78	4.54	22.69
59	U.S. Venture Partners	10	9	2.20	2.44	21.98
60	Kraft Group LLC	3	3	7.27	7.27	21.80
61	F Hoffmann La Roche AG	5	5	4.35	4.35	21.73
62	Mayo Medical Ventures	4	3	5.17	6.89	20.68
63	Sectoral Asset Management Inc	2	2	10.31	10.31	20.63
64	Oak Investment Partners	2	2	10.06	10.06	20.13
65	Lightstone Ventures LP	3	3	6.71	6.71	20.12

	Firm	# Deals	# of Companies	Avg Equity/Deal ($M)	Avg Equity/Company ($M)	Total Equity Invested
66	**Morgenthaler Ventures**	7	5	2.85	3.99	19.96
67	**RiverVest Venture Partners LLC**	6	6	3.27	3.27	19.63
68	**Versant Venture Management, LLC**	4	4	4.82	4.82	19.28
69	**Mission Bay Capital LLC**	6	6	3.13	3.13	18.76
70	**Alta Partners**	2	2	9.31	9.31	18.61
71	**InterWest Partners LLC**	6	6	3.08	3.08	18.47
72	**Temasek Holdings (Private) Ltd**	3	3	6.15	6.15	18.46
73	**Merieux Developpement SAS**	2	2	9.21	9.21	18.42
74	**Salem Capital Partners, L.P.**	1	1	18.31	18.31	18.31
75	**Lux Capital**	5	5	3.53	3.53	17.64
76	**HBM Healthcare Investments AG**	3	3	5.66	5.66	16.98
77	**Xeraya Capital Sdn Bhd**	3	3	5.66	5.66	16.98
78	**North Bridge Venture Partners LP**	4	3	4.04	5.39	16.16
79	**Meritech Capital Partners**	2	1	8.04	16.09	16.09
80	**Trinnovate Ventures Inc**	2	2	7.95	7.95	15.90
81	**Abingworth Management Ltd**	2	2	7.94	7.94	15.88
82	**Venbio Partners LLC**	2	2	7.86	7.86	15.72
83	**Newspring Capital**	2	2	7.84	7.84	15.68
84	**Partisan Management Group, Inc.**	2	2	7.63	7.63	15.25
85	**Longitude Capital Management Co**	3	3	4.95	4.95	14.85
86	**Windham Venture Partners**	2	2	7.23	7.23	14.46
87	**Shire Pharmaceuticals, Inc.**	1	1	14.35	14.35	14.35
88	**Merck Global Health Innovation Fund**	3	3	4.72	4.72	14.16
89	**Heritage Group LLC**	2	2	7.06	7.06	14.11
90	**Advent Venture Partners LLP**	2	2	6.92	6.92	13.83
91	**Beijing Bencao Investment Advisor Co**	1	1	13.75	13.75	13.75
92	**Gimpo Ind Invest Fund Mgmt Co**	1	1	13.75	13.75	13.75
93	**Kaiser Permanente Ventures LLC**	4	4	3.42	3.42	13.68
94	**Biostar Ventures II LLC**	2	2	6.79	6.79	13.57
95	**Lightspeed Management Company LLC**	3	3	4.52	4.52	13.55
96	**AbbVie Biotech Ventures, Inc.**	2	2	6.65	6.65	13.30
97	**Aperture Venture Partners LLC**	3	3	4.43	4.43	13.29
98	**Paladin Capital Management LLC**	2	2	6.62	6.62	13.24
99	**Third Point Ventures LP**	1	1	13.05	13.05	13.05
100	**Partners Innovation Fund LLC**	4	3	3.23	4.31	12.93

Source: ***Thomson Reuters***

Top U.S. life sciences clusters

Life sciences companies continue to cluster around universities, particularly leading research institutions, and capital sources. As a result, it should be no surprise that JLL's fifth annual ***Life Sciences Outlook Report*** reveals Greater Boston is the top cluster in the US. In fact, the region possesses the largest concentration of life science researchers in the country and has more than 3.75 million square feet of requirements. To top it off, the Boston area has accounted for more than 1/3 of the nation's life science funding over the past year.

Along with Greater Boston, the other U.S. top life science clusters continue to thrive, even as high-volume mergers, business swaps and divestitures reshape the industry's U.S. footprint. Continuing patent expirations, the high cost of R&D and the diminished availability of strategic tax inversions have increased company shareholder pressure to maximize efficiency and generate profits.

High costs and a shortage of laboratory space in infill locations are pushing life sciences developments and operations to the suburbs—but access to leading research institutions and top talent limits how far companies will go beyond the core clusters. The top U.S. life sciences clusters in 2016 include:

Rank	2016 *Outlook Report*(current)	2015 *Outlook Report*
1	Greater Boston	Greater Boston
2	San Francisco Bay Area (+1)	Raleigh-Durham
3	Raleigh-Durham (-1)	San Francisco Bay Area
4	San Diego	San Diego
5	Seattle-Bellevue (+6)	New York City
6	Maryland Suburbs/DC Metro (+7)	Los Angeles/Orange County
7	Philadelphia	Philadelphia
8	Los Angeles/Orange County (-2)	Long Island
9	Westchester County, NY (+5)	Minneapolis
10	New Jersey (+2)	Seattle

· Year-Over-Year Trends

· Life sciences real estate vacancy rates remain below 1 percent in Boston's East Cambridge and the Bay Area's North County. Rents have increased accordingly, reaching a high of $70.12 per square foot in East Cambridge.

· Resource-rich U.S. cities are developing new life sciences facilities, such as New York's Alexandria Center for Life Science, a $2 billion commercial campus in Houston and a 320,000-square-foot lab and office tower in downtown Philadelphia.

· Office-to-lab conversions are helping meet demand for lab space in tight markets.

· Fierce competition for space and labor has led to greater emphasis on site selection and amenities to attract talent and capital.

Source: ***JLL 2016 Global Life Sciences Outlook Report***

Biosimilars Finally Reach the U.S. Market

Although the United States has been behind the rest of the world in providing a clear approval pathway for biosimilars, two developments are now driving a push forward:

1. President Obama incorporated the Biosimilar Price Competition and Innovation Act (BPCIA) into the Affordable Care Act in 2010, thus facilitating a large number of FDA approvals expected in the coming months and years.

2. Second, biologic products with aggregate sales of approximately $60 billion are expected to be off patent in the U.S. by 2016.

Under the Biologics Price Competition and Innovation Act (BPCIA), enacted in 2009, the FDA will approve a biosimilar if there is a showing of high similarity to an FDA-approved biologic, known as a reference product. The biosimilar cannot have any clinically meaningful differences in safety or effectiveness. It must use the same action mechanism, administration route, dosages, and strengths,

and can only be used to treat the same conditions. The increased complexity of biologics necessitates a more thorough development, testing, and review process than that utilized for other generics. Additionally, biosimilars require a doctor's involvement in the prescription process.

To date, only 4 biosimilars have been approved in the United States. In March of 2015, Zarxio (filgrastim-sndz), a biosimilar for of Neupogen, was the first biosimilar approved. Zarxio was followed by Inflectra (infliximab-dyyb) in April 2016, Erelzi (etanercept-szzs) in August 2016, and Amjevita (adalimumab-atto) in September 2016. Europe on the other hand has 22 approved products. The large gap may be explained by comparatively strict rules governing interchangeability in the US: only 1 of its 4 products is "interchangeable," meaning it can be substituted for another treatment, so the other 3 cannot truly fulfil their roles as biosimilars.

In January 2017, the FDA made a big move and released new interchangeability guidelines for biosimilars, opening up opportunities to existing and future drugs as more products can be substituted for a reference by a pharmacist without the approval of a health care provider. The United States did have an "interchangeable" designation for biologic medicines prior to this move, but it was wholly separate from the "biosimilar" designation. The new guidelines synchronize these two tracks through three main avenues: switching, presentation and discussion.

Switching refers to a necessary study by manufacturers in which patients alternate between the reference and biosimilar products with no loss in efficacy or safety, compared to the continued use of the reference product. The reference product needs to be licensed in the United States to be considered appropriate for the switching study.

Regarding **Product Presentation**, the FDA suggests that biosimilar manufacturers keep the same presentation of the drug as its original in order to simplify substitution. The manufacturers of the original products will also have to redefine their positioning strategies in the face of the biosimilars onslaught.

Finally, early and close **discussion** with the FDA is suggested to support the accuracy and completeness of data. Moreover, requirements regarding information sharing are not the same for all products, so sorting out what is necessary will save a lot of time for new biosimilars in the application process.

On March 6, 2015, the FDA approved the first biosimilar called ZarxioTM (filgrastim-sndz), which will compete with Neupogen® (filgrastim) – a blockbuster treatment used to decrease rates of infection in certain cancer patients during chemotherapy. Neupogen accounted for $1.2 billion in U.S. drug spend last year.

The next in line to gain approval as early as June is InflectraTM (infliximab), the first monoclonal antibody biosimilar. It could be indicated in all uses approved for Remicade, including rheumatoid arthritis, psoriasis, psoriatic arthritis, Crohn's disease, ulcerative colitis and ankylosing spondylitis. Remicade U.S. sales totaled $4.5 billion last year.

Biosimilars are likely to revolutionize the pharmaceutical industry. A large number of biosimilars currently used in Europe or under development will attempt to follow Zarxio onto the market as the corresponding biologic's exclusivity period ends. Competition with biosimilars will drive down the price of biologics, according to a Congressional Budget Office prediction, saving the U.S. health system $25 billion over the next ten years.

Pricing Controversies

High prices for pharmaceutical products, with biopharmaceuticals the most expensive, are a growing concern, including in the U.S., the largest market lacking price controls. Focus on the cost of biologics may affect the investment climate. Related to pricing, the US insurance situation may be affected if the Affordable Care Act (ACA, or Obamacare) is repealed by the new administration; this could include repeal of the BPCIA (Biologics Price Competition and Innovation Act), which is part of ACA.

Plummeting drug approvals

In 2015, the Food and Drug Administration approved 45 new drugs. In 2016, that number had dropped to 22.

So why such a sharp drop from a record year of new therapies? For one, several of 2015's approvals weren't slated to come until this year, but were granted early green lights; and the FDA issued more rejections in 2016 than usual.

But the most worrisome reason might be that the industry generally filed fewer new drug applications in 2016, highlighting the struggles that traditional drugmakers have had in successfully developing new therapies (especially outside of the cancer drug space) and bringing them to market.

The passage of the 21st Century Cures Act

One unequivocal victory for biopharma was the **passage of the 21st Century Cures Act** in December 2016—a sweeping health reform bill that contains a grab bag of provisions long sought by drugmakers.

The bill easily passed Congress in the wake of an intense lobbying push from seemingly every major health care interest group, from patient advocates to the biopharma industry. It funds medical research through appropriations for the National Institutes of Health (NIH) and could help speed up the drug approval process by allowing drug makers to use "real-world" data on medicines (instead of just randomized clinical trials).

But Cures has its share of critics, too. Some argue that it will weaken the FDA's regulatory standards and knock it from its perch as one of the more discerning medical regulatory bodies in the world. Others point out that the NIH funding must be reauthorized every year, and might come under fire in a new Congress.

Advances in next-gen genomic science and technology

Remarkable advances in genomics technologies, including pharmacogenomics, direct-to-consumer genomics, and wearable data-collection devices are leading to large pools of stored data.
Using in-memory computing technology, researchers are able to analyze and use this genomic data in innovative ways, leading to extraordinary changes in the way healthcare is delivered today. Some

of these advancements are happening now, as liquid biopsy DNA tests emerge as noninvasive screening options for early cancer detection.

And then there's the groundbreaking new methods of manipulating and re-engineering the body's cells to fight diseases. Chinese scientists launched the first **CRISPR gene-editing trial in humans** to treat cancer; immunotherapy companies like Kite, Juno, and Novartis made progress on their experimental treatments that train the body's immune cells to target cancer; digital health continued

to change the face of drug delivery, with device maker Medtronic winning approval for the **first "artificial pancreas"** to treat type 1 diabetes; and the U.K. made three-parent babies **an officially sanctioned tool** for fighting devastating genetic disorders passed on through the mitochondria.

VI. FDA Regulations

Biological Products

Both the FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) have regulatory responsibility for therapeutic biological products, including premarket review and oversight. The categories of therapeutic biological products regulated by CDER (under the *FDC Act* and/or the *PHS Act*, as appropriate) are the following:

- Monoclonal antibodies for in vivo use.
- Most proteins intended for therapeutic use, including cytokines (e.g., interferons), enzymes (e.g. thrombolytics), and other novel proteins, except for those that are specifically assigned to the Center for Biologics Evaluation and Research (CBER) (e.g., vaccines and blood products). This category includes therapeutic proteins derived from plants, animals, humans, or microorganisms, and recombinant versions of these products. Exceptions to this rule are coagulation factors (both recombinant and human-plasma derived).
- Immunomodulators (non-vaccine and non-allergenic products intended to treat disease by inhibiting or down-regulating a pre-existing, pathological immune response).
- Growth factors, cytokines, and monoclonal antibodies intended to mobilize, stimulate, decrease or otherwise alter the production of hematopoietic cells in vivo.

Categories of Therapeutic Biological Products Remaining in CBER

- Cellular products, including products composed of human, bacterial or animal cells (such as pancreatic islet cells for transplantation), or from physical parts of those cells (such as whole cells, cell fragments, or other components intended for use as preventative or therapeutic vaccines).
- Gene therapy products. Human gene therapy/gene transfer is the administration of nucleic acids, viruses, or genetically engineered microorganisms that mediate their effect by transcription and/or translation of the transferred genetic material, and/or by integrating into the host genome. Cells may be modified in these ways ex vivo for subsequent administration to the recipient, or altered in vivo by gene therapy products administered directly to the recipient.
- Vaccines (products intended to induce or increase an antigen specific immune response for prophylactic or therapeutic immunization, regardless of the composition or method of manufacture).
- Allergenic extracts used for the diagnosis and treatment of allergic diseases and allergen patch tests.
- Antitoxins, antivenins, and venoms

- Blood, blood components, plasma derived products (for example, albumin, immunoglobulins, clotting factors, fibrin sealants, proteinase inhibitors), including recombinant and transgenic versions of plasma derivatives, (for example clotting factors), blood substitutes, plasma volume expanders, human or animal polyclonal antibody preparations including radiolabeled or conjugated forms, and certain fibrinolytics such as plasma-derived plasmin, and red cell reagents.

Please refer to the Transfer of Therapeutic Biological Products to the Center for Drug Evaluation and Research at http://www.fda.gov/oc/combination/transfer.html for updates that further define the categories of biological products that are regulated by CDER and CBER.

- ***Establishment Registration***

  Blood Establishments - All owners or operators of establishments that manufacture blood products are required to register with the FDA, pursuant to section 510 of the Federal Food, Drug, and Cosmetic Act, unless they are exempt under **21 CFR 607.65**. A list of every blood product manufactured, prepared, or processed for commercial distribution must also be submitted. Products must be registered and listed within 5 days of beginning operation, and annually between November 15 and December 31. Blood product listings must be updated every June and December.
  Human Cells, Tissues and Cellular and Tissue-Based Products (HCT/Ps) Establishments - Establishments that manufacture HCT/Ps that are regulated solely under section 361 of the PHS Act and the regulations in part 1270 are required to register and list under 21 CFR Part 1271 in 2001. Establishment that manufacture HCT/Ps that are: 1) Drug, 2) Medical Devices, 3) Biological Products, 4) Hematopoietic stem cells from peripheral and cord blood, 5) Reproductive cells and tissues; or 6) Human heart valves and human dura mater, are required to register with FDA and list HCT/Ps using the registration and listing procedures in 21 CFR part 1271, subpart B. HCT/P establishments that only manufacture HCT/Ps currently under IND or IDE do not need to register and list their HCT/Ps until the investigational HCT/P is approved through a Biologics License Application (BLA), a New Drug Application (NDA), or a Premarket Approval Application (PMA); or cleared through a Premarket Notification Submission 510(k).

- ***Investigational New Drug Application*** - A drug that passes animal safety studies may move into human testing following the submission of an investigational new drug (**IND**) application to the FDA. Most studies, or trials, of new products may begin 30 days after the agency receives the IND. During this time, FDA has an opportunity to review the IND for safety to assure that research subjects will not be subjected to unreasonable risk.

  Almost every new drug goes through multiple clinical trials, beginning with early studies (Phase I) in small groups of patients to test safety. Larger mid-stage trials (Phase II) examine safety and obtain preliminary efficacy data. The final stage of pre-market testing (Phase III) seeks to gather convincing efficacy data in the specific patient population the drug's developer hopes to treat.

There are three IND types:

- An Investigator IND is submitted by a physician who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. A physician might submit a research IND to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population.

- Emergency Use IND allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND in accordance with 21CFR , Sec. 312.23 or Sec. 312.34. It is also used for patients who do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist.

- Treatment IND is submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place.

There are two IND categories:

- Commercial
- Research (non-commercial)

The IND application must contain information in three broad areas:

- Animal Pharmacology and Toxicology Studies - Preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans. Also included are any previous experience with the drug in humans (often foreign use).

- Manufacturing Information - Information pertaining to the composition, manufacturer, stability, and controls used for manufacturing the drug substance and the drug product. This information is assessed to ensure that the company can adequately produce and supply consistent batches of the drug.

- Clinical Protocols and Investigator Information - Detailed protocols for proposed clinical studies to assess whether the initial-phase trials will expose subjects to unnecessary risks. Also, information on the qualifications of clinical investigators--professionals (generally physicians) who oversee the administration of the experimental compound--to assess whether they are qualified to fulfill their clinical trial duties. Finally, commitments to obtain informed consent from the research subjects, to obtain review of the study by an institutional review board (IRB), and to adhere to the investigational new drug regulations.

The initial IND submission and each subsequent submission to the IND should be accompanied by a **Form FDA 1571** and must be submitted in triplicate (the original and two photocopies are acceptable).

Mailing addresses for initial IND submissions are:

For a Drug:
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Rd.
Beltsville, Md. 20705-1266

For a Therapeutic Biological Product:
Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

- ***Biologics License Application*** - Biological products are approved for marketing under the provisions of the Public Health Service (PHS) Act. The Act requires a firm who manufactures a biologic for sale in interstate commerce to hold a license for the product. A biologics license application is a submission that contains specific information on the manufacturing processes, chemistry, pharmacology, clinical pharmacology and the medical affects of the biologic product. If the information provided meets FDA requirements and the establishment passes the inspection, the application is approved and a license is issued allowing the firm to market the product. **Form356h** specifies the requirements for a BLA. This includes:

    - Applicant information
    - Product/Manufacturing information
    - Pre-clinical studies
    - Clinical studies
    - Labeling

  Some responsibilities of a licensed biologics manufacturer include:

    - complying with the appropriate laws and regulations relevant to their biologics license and identifying any changes needed to help ensure product quality
    - reporting certain problems to FDA's Biological Product Deviation Reporting System
    - reporting and correcting product problems within established timeframes
    - recalling or stopping the manufacture of a product if a significant problem is detected

- ***Post-Approval*** - Every approved drug comes with an official product label, in a standardized format, whose contents are developed by the FDA and the company marketing the drug. The label contents include the approved indication, as well as a description of the drug, its side effects, dosage, clinical trial summaries and other information useful to physicians. Although doctors may prescribe a therapy "off-label" for indications not expressly approved by the FDA, manufacturers are prohibited from marketing off-label indications, and insurance does not always cover such uses.

  The story does not end with approval and labeling. Companies often conduct additional Phase II and III trials in other indications and may apply for approval through a supplemental BLA. If approved, the new indication is added to the product label.

  Companies also conduct Phase IV trials to refine knowledge about the drug. In addition, drug makers are required by law to report adverse events to the FDA, and they are subject to ongoing manufacturing and marketing rules.

General Biological Product Standards

- ***Potency*** - Tests for potency shall consist of either in vitro or in vivo tests, or both, which have been specifically designed for each product so as to indicate its potency in a manner adequate to satisfy the interpretation of potency given by the definition in 600.3(s) of this chapter.

- ***General Safety Test*** - A general safety test for the detection of extraneous toxic contaminants shall be performed on biological products intended for administration to humans. The general safety test shall be conducted upon a representative sample of the product in the final container from every final filling of each lot of the product. If any product is processed further after filling, such as by freeze-drying, sterilization, or heat treatment, the test shall be conducted upon a sample from each filling of each drying chamber run, sterilization chamber, or heat treatment bath.

- ***Sterility Test***

- ***Purity*** - Products shall be free of extraneous material except that which is unavoidable in the manufacturing process described in the approved biologics license application. In addition, products shall be tested as provided in **paragraphs (a) and (b) of this section**.

- ***Identity*** - The contents of a final container of each filling of each lot shall be tested for identity after all labeling operations shall have been completed. The identity test shall be specific for each product in a manner that will adequately identify it as the product designated on final container and package labels and circulars, and distinguish it from any other product being processed in the same laboratory.

  Identity may be established either through the physical or chemical characteristics of the product, inspection by macroscopic or microscopic methods, specific cultural tests, or in vitro or in vivo immunological tests.

- ***Constituent Materials***

- ***Total Solids in Serums*** - Except as otherwise provided by regulation, no liquid serum or antitoxin shall contain more than 20 percent total solids.

- ***Permissible Combinations*** - Licensed products may not be combined with other licensed products either therapeutic, prophylactic or diagnostic, except as a license is obtained for the combined product. Licensed products may not be combined with non-licensable therapeutic, prophylactic, or diagnostic substances except as a license is obtained for such combination.

- ***Cultures***

- ***Labeling Standards***

  - ***Container Label***

(a) *Full label* - The following items shall appear on the label affixed to each container of a product capable of bearing a full label:

(1) The proper name of the product;
(2) The name, address, and license number of manufacturer;
(3) The lot number or other lot identification;
(4) The expiration date;
(5) The recommended individual dose, for multiple dose containers.
(6) The statement: "`Rx only'" for prescription biologicals.
(7) If a Medication Guide is required under part 208 of this chapter, the statement required under 208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label.

(b) *Package label information* - If the container is not enclosed in a package, all the items required for a package label shall appear on the container label.

(c) *Partial label* - If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label.

(d) *No container label* - If the container is incapable of bearing any label, the items required for a container label may be omitted, provided the container is placed in a package which bears all the items required for a package label.

(e) *Visual inspection* - When the label has been affixed to the container a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents.

- ***Package Label***

The following items shall appear on the label affixed to each package containing a product:

(a) The proper name of the product;

(b) The name, address, and license number of manufacturer;

(c) The lot number or other lot identification;

(d) The expiration date;

(e) The preservative used and its concentration, or if no preservative is used and the absence of a preservative is a safety factor, the words "no preservative";

(f) The number of containers, if more than one;

(g) The amount of product in the container expressed as (1) the number of doses, (2) volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable;

(h) The recommended storage temperature;

(i) The words "Shake Well", "Do not Freeze" or the equivalent, as well as other instructions, when indicated by the character of the product;

(j) The recommended individual dose if the enclosed container(s) is a multiple-dose container;

(k) The route of administration recommended, or reference to such directions in an enclosed circular;

(l) Known sensitizing substances, or reference to an enclosed circular containing appropriate information;

(m) The type and calculated amount of antibiotics added during manufacture;

(n) The inactive ingredients when a safety factor, or reference to an enclosed circular containing appropriate information;

(o) The adjuvant, if present;

(p) The source of the product when a factor in safe administration;

(q) The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information;

(r) Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words "No U.S. standard of potency."

(s) The statement: "`Rx only'" for prescription biologicals.

- ***Proper name; package label; legible type***

(a) *Position* - The proper name of the product on the package label shall be placed above any trademark or trade name identifying the product and symmetrically arranged with respect to other printing on the label.

(b) *Prominence* - The point size and typeface of the proper name shall be at least as prominent as the point size and typeface used in designating the trademark and trade name. The contrast in color value between the proper name and the background shall be at least as great as the color value between the trademark and trade name and the background. Typography, layout, contrast, and other printing features shall not be used in a manner that will affect adversely the prominence of the proper name.

(c) Legible type - All items required to be on the container label and package label shall be in legible type. "Legible type" is type of a size and character which can be read with ease when held in a good light and with normal vision.

- ***Divided manufacturing responsibility to be shown***

If two or more licensed manufacturers participate in the manufacture of a biological product, the name, address, and license number of each must appear on the package label, and on the label of the container if capable of bearing a full label.

- ***Name and address of distributor***

The name and address of the distributor of a product may appear on the label provided that the name, address, and license number of the manufacturer also appears on the label and the name of the distributor is qualified by one of the following phrases: "Manufactured for _____", "Distributed by _____", "Manufactured by _____ for _____", "Manufactured for _____ by ____", "Distributor: _____", or "Marketed by _____". The qualifying phrases may be abbreviated.

- ***Bar code label requirements***

Biological products must comply with the bar code requirements at 201.25 of this chapter. However, the bar code requirements do not apply to devices regulated by the Center for Biologics Evaluation and Research or to blood and blood components

intended for transfusion. For blood and blood components intended for transfusion, the requirements at 606.121(c)(13) of this chapter apply instead.

In-vitro Diagnostic (IVD) Products Regulation

- ***Establishment Registration*** - Manufacturers (both domestic and foreign) and initial distributors (importers) of medical devices must register their establishments with the FDA. All establishment registrations must be submitted electronically unless a waiver has been granted by FDA. All registration information must be verified annually between October 1st and December 31st of each year. In addition to registration, foreign manufacturers must also designate a U.S. Agent. Beginning October 1, 2007, most establishments are required to pay an establishment registration fee. Please find below the schedule of registration fees for fiscal years 2013 through 2017.

Year	FY 2013	FY 2014	FY 2015	FY 2016	FY 2017
Fee	$2,575	$3,313	$3,636	$3,872	$3,382

More information about FDA establishment registration can be found at: **http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/default.htm#reg**.

- ***Classification of IVD Products*** - FDA classifies IVD products into Class I, II, or III according to the level of regulatory control that is necessary to assure safety and effectiveness. The classification of an IVD (or other medical device) determines the appropriate premarket process.

Class I Devices: include commodity products such as stethoscopes, scalpels, and other commodity products that pose relatively little patient risk. Makers of these products need only register their establishment, conform to Good Manufacturing Practices (GMP) and notify the FDA at least 90 days before they start marketing the devices. GMP's are standards set by the FDA for ensuring manufacturing quality. More information about GMP requirements can be found at: **http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/QualitySystemsRegulations/default.htm**.

Class II Devices: include devices that present a moderate degree of risk to the patient. Examples include x-ray machines, endoscopes, and surgical lasers. Manufacturers have to provide the FDA with some evidence of safety and efficacy and meet certain performance standards. In addition, they are responsible for post-market surveillance and maintenance of patient registries.

Class III Devices: these are sophisticated products that present significant risk to patients and must go through extensive clinical trials before undergoing FDA reviews. Included in this category are life supporting devices, such as implantable cardiac pacemakers, angioplasty catheters, stents, and similar devices that prevent potentially dangerous medical conditions such as heart attacks and cardiac arrhythmias.

- ***Premarket Notifications*** - Premarket notifications are also known as 510(K). This is a more commonly used filing and applies to devices that are Substantially Equivalent (SE) to approved products already on the market. Many Class I devices are exempt from the 510(K) process, although other regulations apply. Once the device is determined to be SE, it can then be marketed in the U.S. The SE determination is usually made within 90 days and is made based on the information submitted by the submitter.

  In many cases, descriptive data and a labeling review are sufficient, though some devices may require further clinical studies to support a 510(K). Before marketing a device, each submitter must receive an order, in the form of a letter, from FDA which finds the device to be substantially equivalent and states that the device can be marketed in the U.S. This order "clears" the device for commercial distribution. The submitter may market the device immediately after 510(K) clearance is granted.

- ***Premarket Approval*** - Premarket approval (PMA) apply to most Class III devices due to the level of risk. PMA is the most stringent type of device marketing application required by FDA. The applicant must receive FDA approval of its PMA application prior to marketing the device. PMA approval is based on a determination by FDA that the PMA contains sufficient valid scientific evidence to assure that the device is safe and effective for its intended use(s). An approved PMA is, in effect, a private license granting the applicant (or owner) permission to market the device. The PMA owner, however, can authorize use of its data by another.

  FDA regulations provide 180 days to review the PMA and make a determination. In reality, the review time is normally longer. Before approving or denying a PMA, the appropriate FDA advisory committee may review the PMA at a public meeting and provide FDA with the committee's recommendation on whether FDA should approve the submission. After FDA notifies the applicant that the PMA has been approved or denied, a notice is published on the Internet (1) announcing the data on which the decision is based, and (2) providing interested persons an opportunity to petition FDA within 30 days for reconsideration of the decision.

  On October 26, 2002 the Medical Device User Fee and Modernization Act of 2002 was signed into law. This law authorizes FDA to charge a fee for medical device product reviews. These fees apply to Premarket Approvals (PMAs), Product Development Protocols (PDPs), Biologics Licensing Applications (BLAs for certain medical devices reviewed by FDA's Center for Biologics Evaluation and Research), certain supplements, and Premarket Notification 510(k)s.

  The fee must be paid for the above listed applications, unless the applicant is eligible for a waiver or exemption. Small businesses may qualify for a reduced fee. Payment must be received on or before the time the application is submitted. If the applicant has not paid all fees owed, FDA will consider the application incomplete and will not accept it for filing.

The Fees for Fiscal Year 2017 (October 1, 2016 through September 30, 2017) are as follows:

FY17 User Fees (in U.S. Dollars)

Application Type	Standard Fee	Small Business Fee†
510(k)‡	***$4,690***	***$2,345***
513(g)	***$3,166***	***$1,583***
PMA, PDP, PMR, BLA	***$234,495***	***$58,624***
panel-track supplement	***$175,871***	***$43,968***
180-day supplement	***$35,174***	***$8,794***
real-time supplement	***$16,415***	***$4,104***
BLA efficacy supplement	***$234,495***	***$58,624***
PMA annual report	***$8,207***	***$2,052***
30-day notice	***$3,752***	***$1,876***

† For small businesses with an approved SBD.
‡ Note: all types of 510(k)s (Traditional, Abbreviated, and Special) are subject to the user fee. However, there is no user fee for 510(k)s submitted to the FDA on behalf of an FDA-accredited third-party reviewer.
Small businesses with an approved SBD with gross receipts or sales of $30 million or less are eligible to have the fee waived on their **first** PMA, PDP, PMR, or BLA.
Annual Establishment Registration Fee: $3,382
There are no waivers or reductions for small establishments, businesses, or groups – all establishments must pay the establishment registration fee.

Source: ***www.fda.gov***

- ***Labeling Requirements*** - The label for IVD's must state the following information, except in cases where it is not applicable. In addition, all information must appear on the outside container or wrapper, or be easily legible through the outside container or wrapper. If the presence of any label information will interfere with the test, the information may appear on the outside wrapper or container instead of the label. If the immediate containers are too small, or otherwise unable to bear labels with sufficient space, then the required labeling as listed below annotated with an asterisk (*) may appear on the outer container labeling only.

  Label requirements for the immediate container:

  - o The established and proprietary names of the product, e.g., cholestrolometers;

  * o The intended use or uses, e.g., pregnancy detection, diabetes screening, etc.;

  * o A statement of warnings or precautions for users listed in 16 CFR part 1500 (hazardous substances) and any other warnings appropriate to user hazards, and a statement "For In Vitro Diagnostic Use";

- Name and place of business of the manufacturer, packer, or distributor;

  - o Lot or control number traceable to the production history
    - Multiple unit products must have traceability of the individual units;
    - Instrument lot numbers must allow for traceability of subassemblies; and
    - A multiple unit product that requires use of its components as a system should have the same lot number, or other suitable uniform identification, on all units.

  For Reagents:

  - o Established (common or usual) name;

  - o Quantity, proportion, or concentration of all active ingredients: e.&., mg., weight per unit volume, mg./dl etc., and for reagents derived from biological materials the source and measure of its activity, e.g., bovine, I.U., etc.;

  - o Storage instructions, i.e., temperature, humidity, etc.;

  - o Instructions for manipulation of products requiring mixing or reconstitution;

  - o Means to assure that the product meets appropriate standards of purity, quality, etc., at the time of use, including one or more of the following:
    1. expiration date (date beyond which the product is not to be used);
    * 2. statement of any visual indication of alteration;
    * 3. instructions for a simple check to assure product usefulness;

    * - The net quantity of contents.

  Label requirements for inserts and outer packaging:

Labeling must contain in one place the following information in the format and order listed below, except where information is not applicable, or as specified in a standard for a particular product class. If the device is a reagent intended as a replacement in a diagnostic system, labeling may be limited to that information necessary to adequately identify the reagent and to describe its use in the system. If the device is a multiple purpose instrument used for diagnostic purposes, and not committed to specific diagnostic procedures or systems, labeling can be restricted to those points annotated by an asterisk (*).

* o The proprietary and established product name;

* o The intended use of the product and whether it is a qualitative or quantitative type of procedure, e. g., screening, physician's office, home use, etc. ;

o Summary and explanation of the test, including a short history containing methodology and the special merits and limitations of the test;

o The chemical, physical, physiological, or biological principles of the procedure.

For Reagents:

o The common name, if any, and quantity, proportion, or concentration or each reactive ingredient; and for biological material, the source and measure of its activity;

o Appropriate cautions or warnings listed in 16 CFR Part 1500; the statement: "For In Vitro Diagnostic Use;" and any other limiting statements appropriate to the intended use of the product;

o Adequate directions for reconstitution, mixing, dilution, etc.;

o Appropriate storage instructions;

o A statement of purification or treatment required for use; and

o Physical, biological, or chemical indications of instability or deterioration.

- ***Exemptions from Labeling Requirements*** - Shipments or other deliveries of IVD devices are exempt from label and labeling requirements in the above headings and from standards listed under Part 861 provided the following conditions are met:

o A shipment or delivery for an investigation subject to Part 812, Investigational Device Exemption (IDE), if the device is in compliance with the subject IDE; or

o A shipment or delivery for an investigation that is not in compliance with Part 812 most IVD are exempt from the IDE because of the following labeling) if the following conditions are met:
- A product in the laboratory research phase, not represented as an IVD, that is prominently labeled: "For Research Use Only. Not for use in diagnostic

procedures;" and

- A product that is being shipped or delivered for product testing prior to full commercial marketing that is prominently labeled: "For Investigational Use Only. The performance characteristics of this product have not been established.

- ***Investigational Device Exemption (IDE)*** - An investigational device exemption (IDE) allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data required to support a Premarket Approval (PMA) application or a Premarket Notification [510(K)] submission to the FDA. Clinical studies are most often conducted to support a PMA. Only a small percentage of 510(K)'s require clinical data to support the application. Investigational use also includes clinical evaluation of certain modifications or new intended uses of legally marketed devices. All clinical evaluations of investigational devices, unless exempt, must have an approved IDE before the study is initiated. Many IVDs are exempt from IDE requirements.