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Midyear Commentary on Trends in Drug Delivery and Clinical Translational Medicine: Growth in Biosimilar (Complex Injectable Drug Formulation) Products Within Evolving Collaborative Regulatory Interagency (FDA, FTC, and DOJ) Practices and Enforcement

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Abstract

Before the 2009 Biologics Price Competition and Innovation Act that enabled the U.S. Federal Drug Administration (FDA) to create the 351(k) Biologic License Application–an abbreviated biosimilar approval process, FDA approved follow-on biomolecule products such as beta-interferon, glucagon, hyaluronidase, and somatropin (human growth hormone) under varying and evolving rules. With the 351(k) Biologic License Application biosimilar approval process in place, currently, there are 4 (licensed in 2015–2016) biosimilars available, namely Neupogen (filgrastim; $1 B/y), Humira (adalumumab; $14.2 B/y), Enbrel (etanercept; $8.7 B/y), and Remicade (infliximab; $6.5 B/y). With well-established product market capitalization of these and other top income producers—such as Rituxan (rituximab; $6.8 B/y), Herceptin (trastuzumab; $6.5 B/y), and Avastin (bevacizumab; $5.8 B/y), and a price differential of 15%–30% compared to branded products, there is an intense interest in development of biosimilars by established pharmaceutical companies. Currently, there are 160 biosimilar candidates in clinical studies, many of which are sponsored by large pharmaceutical companies known for product innovation. This trend will likely continue. Additional information on a biomolecule platform is presented in the *Journal of Pharmaceutical Sciences* Drug Delivery Clinical Trials Database (jpharmscidatabase.org). There are 44,789, 18,456, and 12,897 clinical trials registered to evaluate (1) drug delivery technology, (2) biomolecule platform, and (3) drug metabolism and pharmacokinetic-pharmacodynamic interactions; representing 19%–60% increase over the last 3 years.

Keywords

drug delivery systems; follow-on biologics; biocompatibility; bioequivalence; monoclonal antibody; regulatory approval and enforcement; biosimilar; BLA; BPCI

The *Journal of Pharmaceutical Sciences* has developed a Web-based tool called the Drug Delivery and Clinical Trials Database (curated information derived from ClinicalTrials.gov, see Text Box 1 for details) to provide readers with a periodic update on emerging trends and

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to accompany expert commentaries with respect to the translational prospects of drug delivery and pharmaceutical research and related technological advancements in pharmaceutical sciences. The interactive access to clinical information and understanding the translation trends provided through this user interface allows scientists in the pharmaceutical science community to stay up-to-date on state-of-the-art drug delivery technologies and formulate innovative strategies in developing safe and effective treatments for a wide range of diseases.

Text box 1

ClinicalTrials.gov—A Centralized Resource

Through the US FDA Modernization Act, the National Library of Medicine and the NIH (National Institutes of Health) the clinical trial registry, called ClinicalTrials.gov, has been developed to collect data from federally and privately supported clinical trials. In addition to information about disease states, patient and interventional criteria, and sponsor information, the descriptor of this international database includes key words related to drug delivery technologies and platforms. The initial goal was to seek voluntary data sharing and validation for published work. According to the 2007 Food and Drug Amendments Act, deposits of clinical outcome data pertaining to adverse events from any trial are now mandatory (since September 2009). Thus, registration and publication of results for all clinical trials of drugs, biologics, and devices under FDA regulation are now required within 30 days of product approval. In essence, ClinicalTrails.gov has become the central resource for researchers engaged in clinical research, drug discovery, and development.

This commentary will first discuss the impact of the progressive implementation of laws, policies, and database improvements over the past few years. The progression in regulatory requirements has driven growth in the number of registered clinical trials within the database and an increase in access to the trials' outcomes. Comments are based on the trends of scientific and commercial areas of growth, as well as the emerging issues related to overall clinical drug development and regulatory enforcement. This commentary will conclude with highlights on biosimilars which are parts of complex biologic injectable drug delivery platforms. The evolving, favorable regulatory climates and well-defined market capitalization have attracted renewed interest in developing biosimilars by generic and established pharmaceutical companies.

Evolution of ClinicalTrials.gov as the Central Source of Drug Development and Approval

Since inception of a centralized clinical trial database in 2000 (Text Box 1), the introduction of ClinicalTrials.gov as an open access database with a federal mandate immediately attracts the attention of sponsors (and drug manufacturers) to register their ongoing human trials. With a number of professional organizations and journal editors requiring clinical trial registration for publication of data in all their submitted manuscripts, most, if not all, human clinical trials can be accessed in ClincalTrials.gov. The 2007 U.S. Food and Drug

Administration (FDA) amendment act,[1] requiring all interventional human trials to be registered, has prompted an increase in the number of clinical trials currently in the database. Final rules were published in 2016 requiring the sponsor to post their clinical trial results. The sponsor must post their study outcomes, regardless of whether they are positive or negative.[2] Therefore, one would expect a steady growth of clinical trial results available to the public and scientists alike. The *Journal of Pharmaceutical Sciences* has created an online interface for readers to study distribution and trends related to biopharmaceutical technologies, drug formulation and delivery, and pharmacokinetic and drug–drug interaction platforms to transform new and existing drugs into safer and more effective therapeutic products.

Midyear Review of Clinical Translation of Pharmaceuticals and Regulatory Progress

Top Selling Drugs and Drug Pricing

There is no question that the high cost of drug therapy becomes the key topic of public interest and probed by a number of US news agencies. The 2015 top 10 selling drugs are commanding $144 billion in aggregates, and Humira leads the list with $14.2 billion in annual sales (Table 1). In the public eye, one can justify and appreciate the high manufacturing costs of biologics such as Humira, Enbrel, Remicade, Rituxan, Avastin, Herceptin, and even Lantus. Even if proven to have a high cure rate, the price of hepatitis C treatments Harvoni and Januvia is unimaginably expensive. This public sentiment is based on much lower manufacturing or production costs of small synthetic drugs and public awareness of much higher costs to produce biologics or macro molecules. Although some have considered approximately $80–$95,000 listed for each (12–24 weeks) treatment of these hepatitis C drug combination products (equivalent to about $1100 per oral dose) too expensive, they are justified based on cost-effectiveness and the life quality gained from being cured of the hepatitis C disease (which progresses to liver failure requiring organ transplantation). A majority of the lay public and law makers felt that small molecule drug combinations are produced with substantially lower cost than macromolecule platforms.

Thus, most people expect lower cost per treatment than biologic drug pricing. The public expects these small molecules to be priced much lower than they currently are. Drug pricing, which includes consideration of drug development cost and overall impact on treatment outcomes (based on cost-effectiveness analysis), is a complex integration of science and business decision-making. This current drug pricing strategy is called into question by the lay public and US congress.[3] The debates on ethics and what constitute a reasonable return on the investment of a curative treatment will likely continue. However, public and private positions on drug priorities could improve through (1) reassessment of current drug development strategies with a balanced approach to recoup research and development costs, (2) some degree of transparency, and (3) public and private discussions on drug access and business sustainability.

Perspective and Trends in Clinical Translation

As discussed previously, data in Table 1 indicate that, with the exception of the 2 small molecule antiviral products for hepatitis C and asthma (Seretide), the other top 10 products are biologics or macromolecules that capture as much as $14 billion in annual sales. This annual sale data continue to drive the growth of biomolecules tested in humans. Data in Table 2 summarize the number of clinical trials listed on ClinicalTrials.gov. From the perspective of pharmaceutical sciences and drug delivery, we organized the data in 3 major drug delivery categories.[4] They are (1) drug delivery technology system and device, (2) biomolecule platform and technology, and (3) drug metabolism and pharmacokinetic-pharmacodynamic (PK-PD) interactions. Biomolecules are proteins and peptides, which are distinctively different from that of small chemical molecules in molecular weights (>1500 vs. <1000 Da) and complexities. Perhaps because of its versatility of molecular platform and target selectivity, large biomolecules—mainly antibody and well-defined protein peptides—continue to dominate and capture the market share.

As of August 2016, there are 44,780, 18,456, and 12,897 clinical trials registered for interventional studies in the mentioned 3 categories (Table 2). These numbers reflect an increase of 18.6%, 30.9%, and 60.0%, respectively, since our last update.[5] Although a substantial 60% increase in clinical train focusing on drug metabolism and PK-PD interactions studies may relate to regulatory requirements to ensure drug safety mandated by the FDA, compared to 18.6% increase in clinical trials related to small molecules, a higher 30.9% increase in clinical trials related to biological molecules is likely to reflect the general perception of higher clinical success rates that favor the biological molecular option, if possible for developing the clinical lead, despite a higher cost of goods.

With the biological molecule platform, clinical trials evaluating antibody drug candidates continue to dominate the majority of biomolecular platforms with about 52% (9521 of 18,456 = 51.6%) of the antibody candidates, in which most of the antibodies are in phase II followed by phase I and less so in phase III pivotal trials (Table 3). These figures compared to antibody conjugates where most of them are in phase III and phase II testing and a fewer number of them are entering a phase I study. Whether the few number of antibody conjugates entering phase I human testing is a temporary slowdown in general interest in antibody conjugates as a targeted drug delivery platform or if there are challenges in developing antibody conjugates as a drug delivery platform is not clear. However, it is clear that many more recombinant proteins are entering phase I clinical testing, whereas the overall fraction of recombinant proteins in biological molecules only constitute about 3% (605/18.456). It is also interesting to note that more nucleic acid–based compounds—antisense, oligonucleotide, siRNA, and aptamers—are entering phase I testing and at least 1 of the siRNA is under a phase III pivotal trial. Any success in delivery of siRNA into target cells for a therapeutically meaningful clinical outcome could open up more opportunities to use this platform to address many gaps in diseases which are linked to variation or defect in gene expression.

Evolving Role of Collaborative Interregulatory Agency Practice and Enforcement

According to an annual FDA report, the agency recalls about 100–200 prescription drug products per year.[6] The citations could include not meeting respective specifications or product contamination and other possible defects. Depending on the citation, a manufacturing facility that has failed FDA inspection could be shut down, and in some cases, the product in circulation will be recalled. In fact, some facility failures and upgrade requirements of old facilities may have caused a number of drug shortages. Some of these issues have also contributed to recent exponential price increases of old drug products with low sale volume. In light of the increasing complexity in rationales for product recall, the agency is considering classifying a recall notice into I, II, or III according to the degree of severity.

What is clear, however, is that the US Department of Justice (DOJ) is now implementing regulatory enforcement authority shared by the Federal Trade Commission (FTC) and FDA. Although the FDA is chartered to regulate manufacturing, approval, use, and advertising of prescription drugs, the FTC is charged to enforce interstate advertising and marketing of nonprescription products. In practice and for many years, the FDA and FTC have operated under a memorandum of understanding that charges the FDA with product labeling (specification for which a drug is approved for use) and the FTC with advertising (for additional details on the link between product labels and market positon, see Text Box 2).[7] Over the years, the FDA has broadened the interpretation of product labeling to include dissemination of information relating to the sales of products, including those provided in written or oral form and those posted on Web sites. When sponsors are not in compliance and not responsive to requests to stop production, sales, or advertising, the FDA and FTC have limited tools to enforce them. Traditionally, the FDA and FTC operate independently with limited interactions in sharing data over cases under investigation. An increased collaboration between the FDA and FTC is notable as integrated investigation and joint agency or sequentially timed letters of violation notices are sent to marketers.

Text Box 2

The link between product indications and product sales potential

The FDA tightly regulates the text of the product label for each approved drug in the United States. The product label forms the basis of the company’s literature, advertising, and promotional materials (CFR Title 21, part 201). Although some product labels may contain 17 subject headings, all include the following 11 key subjects: (1) description of the product, (2) clinical pharmacology, (3) indications and usage, (4) contraindications, (5) warning, (6) precautions, (7) adverse reactions, (8) drug abuse and dependence, (9) overdosage, (10) dosage and administration, and (11) how it is supplied.

Within the product label, “Indications and Usage” or product indication approved by the FDA for marketing is pivotal in the commercial success of pharmaceutical companies. Proposed text for indications are reviewed and approved by the FDA in the treatment, prevention, or diagnosis of diseases or conditions. The final text is granted based on

evidence of effectiveness and safety data collected in controlled clinical trials. The indications thus directly impact the potential patient population that will benefit from the drug. The larger the patient population the higher the market potential.

Although the final language of a product indication is negotiated at the time of FDA approval, the clinical hypothesis in an investigational new drug (IND) application at initiation of human studies sets the direction for a product. Even for the same drug molecule, the company must submit a separate IND application for different indication or intended uses and evaluate the efficacy and safety before progressing into expanded product indication.

Adopted from Ho 2013: Biotechnology and Biopharmaceutics. Box 3.1: Significance of product validation and therapeutic targets in drug development (p. 27) Chapter 3.[7]

The interagency collaboration, along with policing or active enforcement, which is now led by the DOJ, has built cases against noncompliant drug companies. A combination of these enforcement approaches have begun to make significant impact. The enforcement cases, which take longer time to build and process through the US judicial system, often involve off-label promotion and failure to perform a postmarketing safety study (or filing of phase IV results after New Drug Application [NDA] approval). The cases with sufficient merits often lead to significant sums of settlements. As provided in Table 4, over the past 10 years, the DOJ has taken the lead in enforcing the regulations on marketing and product safety. Inter-agency collaborations and concerted efforts have led to settlements as high as $3 billion. In fact, many major pharmaceutical companies are named as defendants (Table 4). It is clear from these data that all—small and large—pharmaceutical companies are equally susceptible to be on the DOJ's list of investigation if they are non-compliant. In fact, it is interesting to note that Google, a well-known information provider, is not immune to the DOJ's enforcement when the company's targeted drug advertising is noncompliant.

Biosimilars—a Generic Equivalent of Biologics Coming of Age

Although a regulatory path for a biosimilar or a generic version of well-characterized macromolecules was implemented in 2006 by the European Medicines Agency, it has taken another 3 years for the US FDA to develop a set of provisions.[8] These statutory provisions are referred to as the *Biologics Price Competition and Innovation Act of 2009* (BPCI Act). These provisions were signed into law by President Obama on March 2010 under the Patient Protection and Affordable Care Act (sometimes referred to as the Affordable Care Act). The BPCI Act amends the US Public Health Service Act to create an abbreviated regulatory [designated as 351(k)] biologics license application (BLA) pathway for protein and antibody products that are "biosimilar" to or "interchangeable" with an FDA-licensed innovator's biological product.[9]

When compared to small molecule drug products, the purity and trace amount of contaminant in recombinant macromolecule products are more difficult to analyze in regards to determining the similarities between the innovator and competitor's biological products. Therefore, the existing "Drug price competition and patent term restoration act of 1984"

(typically used for approving small molecule generic drugs) is not suitable for regulatory review of the generic version of biological products. One of the contentious issues in developing the BPCI Act is the generic manufacturer's ability to access reference data submitted in confidence to the FDA (by the innovator) as part of the original NDA (or BLA). Because these confidential data are protected, generic manufacturers could not use it as a basis for a 351(k) BLA submission. The time from the original approval of the innovator's BLA and their filing of a biosimilar for an abbreviated approval is generally referred to as the data exclusivity period. This period is intended to encourage innovation and allow sponsors to recognize the risk, cost, and time investments in gaining licensing approval of the innovator's product. Although the 14-year data exclusivity period was originally proposed, the final, compromised version in the BPCI Act lists 12 years of data exclusivity.[9]

Under the BPCI Act, the FDA will review a biosimilar or interchangeable product candidate submitted as a 351(k) BLA. These applications must include (1) a high degree of similarity (with acceptable differences that are clinically inactive), (2) toxicology data collected in animal studies, and (3) limited clinical studies to access safety, purity, and potency (immunogenicity, PK, or in some cases PD drug effects) in ≥1 conditions for which the reference product is indicated for.[9] Product indication is an important consideration for pharmaceutical companies as it has significant influence on the population that would benefit from the drug (for additional details on product indications please refer to Text Box 2). The FDA has reached out to biosimilar sponsors to address whether any study elements listed in the innovator's NDA is unnecessary for a respective 351(k) BLA for a specific biosimilar candidate.

Previously, a number of follow-on or similar recombinant products such as β-interferon, glucagon, hyaluronidase, and somatropin (human growth hormone) have been approved by the FDA under different sets of rules and circumstances. Most of these products may require some variation of therapeutic or toxicity evaluation to demonstrate equivalency. In fact, there are ≥5 versions of follow-on somatropin products available to compete with the recombinant human growth hormone (originally introduced as Humatrope and Nutropin which were jointly developed by Lilly and Genentech in 1987). The follow-on somatropin includes Omnitrope (Sandoz), Genotropin (Upjohn), Saizen (Serono), Norditropin (Nova Nordisk), and Zomacton (Teva/Ferring).

Five years after implementation of the BPCI Act, a number of "generic" versions of biological products have been approved under the biosimilar 351(k) pathway, instead of a follow-on pathway for which most of the similar somatropin (human growth hormone) products are licensed. Currently, only 4 products are approved as biosimilars under the 351(k) pathway and 3 of 4 which were approved in 2016 (Table 5).[10] It is interesting to note that all 4 bio-similar products, adalimumabatto, infliximab-dyyb, filgrastim-sndz, and etanercept-szzs are sponsored by Amgen, Pfizer, and Sandoz (sndz and szzs), respectively. Some may be surprised to learn the trend of major pharmaceutical companies leading the development of biosimilar products. In fact, Amgen, Pfizer, and Sandoz are companies known to focus on new and innovative products rather than efforts in developing generic drugs.

With over 160 biosimilar candidates registered for interventional studies in ClinicalTrials.gov, clinical development of biosimilars, which are often more complex injectable formulations, has grown and begun to take center stage. In comparison to the development of small molecule generic drugs, a significantly higher investment in resources, technology, and time is required for biosimilar products. Regardless of the pharmaceutical company's status, (1) competitive pricing of biosimilar to innovator products, (2) well-proven market capitalization of innovator product, and (3) a validated product where disease states and outcomes are well defined are attractive attributes for significant interests in developing a biosimilar product. For example, Humira's (which is indicated for rheumatoid arthritis) market capitalization is proven for many years to be $7–$14 billon (Table 1). Also, the price differential between innovator and biosimilar somatropin products is small being within 15%–30% (as compared to 1/100 or less for small molecule generics).[11] Unlike low cost, small molecule generic products, the profit margin for a bio-similar is likely to be much higher. For these reasons, most major pharmaceutical companies have a number of biosimilar products in clinical development. For example, Pfizer, a major pharmaceutical company, has biosimilar infliximab-dyyb approved for marketing; plus, a number of its PF biosimilar compounds in phase 3 clinical trials to compete with Rituxan, Herceptin, Avastin, and Humira (Table 5). It is interesting to note that Avastin, Herceptin, and Rituxan are the top 3 income producers listed on the 2015 Roche Genentech annual sales report.[12] This trend is likely to continue for the foreseeable future. As a result, we can expect continued growth in bio-similar products as many are in late-stage clinical development for approval through an abbreviated 351(k) pathway. The effort to develop biosimilar versions of competitors' innovative products is often referred to as the "Biosimilar War." It will be interesting to see the eventual victors of this long and drawn-out war.

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Table 1

Top 10 Pharmaceutical Products With Highest Sales in 2015 According to the Molecular Platform, Treatment Indications, and Manufacturer/Sponsor

Product	Indication	Molecular Platform	Sponsor	2015 Sales[a] (US$ Billions)
Humira	Inflammation	Antibody and derivative	AbbVie/Eisai	14.2
Harvoni	Infection/HepC	Small molecule	Gilead Sciences	13.9
Enbrel	Inflammation	Antibody and derivatives	Amgen/Pfizer/Takeda	8.7
Remicade	Inflammation	Antibody and derivatives	Janssen/Merck	8.3
Rituxan	Cancer	Antibody and derivatives	Roche	7
Lantus	Diabetes	Insulin-peptide derivatives	Sanofi	6.9
Avastin	Cancer	Antibody and derivatives	Roche/Chugai	6.6
Herceptin	Cancer	Antibody and derivatives	Roche	6.5
Januvia/Janumet	Infection/HepC	Small molecule	Merck	6.2
Seretide (Serevent)	Asthma	Small molecule	GlaxoSmithKline	5.7

[a]Annual sales data were collected from each respective company's annual reports and 10-K filing with the US Security and Exchange Commission.

Table 2

Summary of the Number of Clinical Trials Listed on ClinicalTrials.gov Organized as the 3 Major Drug Delivery categories (Updated on August 2, 2016)

Category	All	Intervention	Phase I	Phase II	Phase III	Phase IV
I. Drug delivery technology and system						
Device	9740	9459	2010	3002	2478	2946
Dosage form	16,655	16,542	5049	5824	4604	2295
Drug delivery system	7591	7520	1567	2562	2105	1901
Formulation	4338	4316	2205	1118	842	408
Liposome	1696	1693	407	921	430	115
Transdermal	614	607	134	158	182	152
Formulation comparison	1830	1820	983	363	384	180
Route	1564	1550	550	527	362	243
Sustained release	440	436	82	120	169	84
Lipid formulation	149	148	80	41	18	25
Nanoparticles	199	198	88	125	16	3
Aerosol and inhalation	188	187	48	53	72	25
Prodrugs	179	178	89	73	20	14
Colloid	129	126	12	43	31	46
Drug delivery technology and system	**Subtotal**	**44,780**				
II. Biological molecule platform/technologies						
Antibody	9596	9521	3298	4359	2149	728
Biologics and vaccines	4931	4900	1943	1836	1127	552
Peptide	2249	2222	843	950	368	329
Recombinant proteins	760	755	332	310	165	43
Antibody conjugates	609	605	147	203	220	75
Antisense	132	131	77	70	13	0
Oligonucleotide	114	112	65	58	10	2
siRNA	36	36	25	18	1	0
Aptamer	29	29	12	13	8	1
Biological molecule platform	**Subtotal**	**18,456**				
III. PK-PD interactions						

Category	All	Intervention	Phase I	Phase II	Phase III	Phase IV
Metabolic inhibitor	2919	2890	610	710	879	829
Drug transport modulator	6378	6321	1114	1682	1905	1961
Drug interactions	2246	2220	1368	478	197	287
Metabolic induction	641	629	139	229	140	169
Active metabolite	839	837	498	230	69	81
PK/PD interactions	**Subtotal**	**12,897**				

Table 3

The Increase in the Number of Drug Delivery–Related Clinical Trials Between September 2013 and August 2016

Categories	September 2013[a]	August 2016	Net Change (%)
I. Drug delivery technology, system, and device	37,738	44,780	7042 (18.6%)
II. Biological molecule platform/technology	14,104	18,456	4352 (30.9%)
III. Drug metabolism and PK-PD interactions	8060	12,897	4837 (60.0%)
Subtotal	**59,902**	**76,133**	**16,231 (27.1%)**

[a]Chien and Ho.[5]

Table 4

Partial List of Settlements Involving Off-Label Promotion and Drug Safety

Date	Company	Drug Name	Approval Indication	Alleged Off-Label Promotion	Settlement Amount[a] (Millions)
May 2004	Pfizer	*Neurontin*	Adjunctive or supplemental antiseizure use by epilepsy patients	Bipolar disorder, various pain disorders, amyotrophic lateral sclerosis, attention deficit disorder, migraines, etc.	$430
October 2005	Serono, S.A.	*Serostim*	AIDS wasting (involuntary loss of >10% body weight, plus >30 days of either diarrhea or weakness and fever)	Lipodystrophy and body cell mass wasting	$704
August 2006	Schering-Plough	*Temodar and Intron A*	Certain types of brain tumors, specific types of cancer, and chronic hepatitis B and C	Other types of brain tumors and metastases and superficial bladder cancer	$435
October 2006	InterMune	*Actimmune*	Disorders of the immune system caused by defects in immune cells and severe malignant osteoporosis	Lung scarring	$36.9
April 2007	Pfizer	*Genotropin*	Certain growth failure and related diseases in children and adults	Antiaging, cosmetic use, and athletic performance enhancement	$34.7
April 2007	Cell Therapeutics	*Trisenox*	A specific and rare type of leukemia	Various forms of cancer	$10.5
May 2007	The Purdue Frederick	*OxyContin*	Management of moderate to severe pain in specific instances	Wider pool of patients and conditions	$635.5
September 2007	Bristol-Myers Squibb	*Abilify*	Treatment of adult schizophrenia and bipolar disorder	Pediatric use and dementia-related psychosis	$515
September 2008	Cephalon	*Gabitril Provigil*	Treatment of partial seizures Daytime sleepiness associated with narcolepsy	Anxiety, insomnia and pain Sleepiness, tiredness, decreased activity, lack of energy and fatigue	$425
January 2009	Eli Lilly	*Zyprexa*	Treatment of psychotic disorders; bipolar; schizophrenia	Aggression, Alzheimer, anger hostility, dementia, depression + other	$1415
April 2010	AstraZeneca	*Seroquel*	Schizophrenia, bipolar	Aggression, Alzheimer, anger ADD, mood, dementia, depression	$520
September 2010	Allegan	*Botox*	Strabismus and blepharospasm; cervical dystonia and 1° axillary hyperhidrosis	Pain and headache	$600
September 2010	Novartis	*Trileptal*	Epilepsy	Off-label promotion	$420
February 2011	Elan	*Zonegran*	Epilepsy	Off-label promotion	$204
June 2011	Novo Nordisk	*Novoseven*	Hemophilia A or B with factor VII or VIII or IX deficiency	Coagulation agent for general, liver and heart surgery, trauma and brain hemorrhage	$25
August 2011	Google	*Prescription drugs*	Ads placement of unlawful drug marketing from Canada	Targeting US consumers for prescriptions based on non-US regulation	$500
May 2012	Abbot Laboratory	*Depakote*	Epileptic seizures, bipolar mania and migraines prevention	Control agitation and aggression in dementia	$1500

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Date	Company	Drug Name	Approval Indication	Alleged Off-Label Promotion	Settlement Amount[a] (Millions)
July 2012	GlaxoSmithKline	*Paxil, Wellbutrin Avandia*	Depression and diabetes	Promotion of outside indication and age range (Paxil & Wellbutrin); failure to file postmarketing data (Avandia)	$3000
December 2012	Amgen	*Aranesp*	Anemia caused by cancer	Off-label promotion	$762
January 2013	Janssen	*Risperdal*	Antipsychotic, schizophrenia	Misbranded	$344
July 2013	Wyeth	*Rapamune*	Immune suppression in kidney transplant patients	Off-label promotion	$491
February 2014	Endo	*Lidoderm*	Postherpetic pain	Misbranded	$192
November 2015	Novartis	*Exjade Myfortic*		Kickback promotion through	$370

Compiled from DOJ's Web site (www.usdoj.gov), HHS Web sites (www.cancer.gov and www.fda.gov), and FDA's OCC and 2008 GAO report.

For the purposes of this report, an off-label settlement is defined as any civil and criminal settlement or disposition of a matter where a sponsor's promotion of a drug for a use not contained in FDA-approved labeling was investigated, regardless of whether that alleged conduct was the basis for the ultimate disposition.

[a]Settlement amounts may include penalties for offenses not involving off-label promotion.

Table 5

Current Status of Approved Biosimilar Products Those in Late-State Clinical Trials Organized According to the Innovator Products With Respective Annual Market Capitalization of Each Biological Macromolecule

Product and Innovator	Innovator (Market in USD)[a]	Biosimilar		Status[c] (Date Approved)
		Name[b]	Manufacturer	
Approved products				
Neupogen (Filgrastim)	Amgen ($1049 M/y)	Filgrastim-sndz	Sandoz	March 6, 2015
Remicade (Infliximab)	Centocor/Janssen ($6500 M/y)	Infliximab-dyyb	Celltrion/Pfizer	April 5, 2016
Enbrel (Etanercept)	Immunex/Amgen/Pfizer/Takeda ($8700 M/y)	Etanercept-szzs	Sandoz/Novartis	August 30, 2016
Humira (Adalimumab)	Abbott/AbbVie ($14,200 M/y)	Adalimumab-atto	Amgen	September 23, 2016
Candidates in development				
Rituxan (Rituximab)	Genentech/Roche ($6885 M/y)	PF-05280586	Pfizer	Phase 3
		CT-P10	Celltrion	Phase 3
		Gp2013	Sandoz	Phase 3
		ABP-798	Amgen	Phase 3
Herceptin (trastuzumab)	Genentech/Roche ($6534 M/y)	PF-05280014	Pfizer	Phase 3 (C)[d]
		ABP-980	Amgen	Phase 3
		SB3	Samsung	Phase 3
Avastin (bevacizumab)	Genentech/Roche ($5809 M/y)	PF-06439535	Pfizer	Phase 3 (C)
		ABP-215	Amgen	Phase 3 (C)
		BI 695502	Boehringer-Ing	Phase 3
Humira (adalimumab)	Abbott/AbbVie ($14,200 M/y)	PF-06410293	Pfizer	Phase 3
		GP2017	Sandoz	Phase 3 (C)

[a]Market capitalization in annual sales of each biological molecule is presented as US dollars reported in 2015. For Genentech/Roche products, the Swiss France is converted to USD by a factor of 1.03.

[b]Name of the biosimilar is designated with a common name (e.g., Humira's common name is adalimumab) plus the abbreviated manufacturer of biosimilar (in this case dyyb) adalimumab-dyyb to signify a biosimilar produced by Celltrion/Pfizer.

[c]Status of each biosimilar molecule is derived from the FDA purple book and the ClinicalTrials.gov database.

[d](C) indicates the clinical phase 3 trial listed has been reported as completed.