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Clinical Trials and Translational Medicine Commentary

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/yr). 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.

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 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.

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.

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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.

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

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.