CLINICAL TRIALS AND TRANSLATIONAL MEDICINE COMMENTARY

Drug Delivery Trends in Clinical Trials and Translational Medicine: Growth in Biologic Molecule Development and Impact on Rheumatoid Arthritis, Crohn's Disease, and Colitis

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Received 28 March 2012; accepted 28 March 2012

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.23154

ABSTRACT: There are 94,709 clinical trials across 179 countries. Approximately half (47,467) are related to the three categories within the scope of the free online resource "Drug Delivery Trends in Clinical Trials and Translational Medicine," which are (1) drug delivery technology and systems, (2) biological molecule platforms, and (3) pharmacokinetic and pharmacodynamic interactions. In this commentary, trends in biological molecule platforms and their impacts are discussed. The sales of top 15 biologic drugs have reached over $63 billion in 2010. In the past 10 years, major pharmaceutical companies have acquired biological molecule platforms and have become integrated biopharmaceutical companies, highlighting the role of biotechnology in driving new therapeutic product development. The top three products—Remicade, Enbrel, and Humira—indicated for arthritis and colitis and targeted to tumor necrosis factor-alpha (TNF-α), each generated over $6 billion in annual sales. In addition to TNF-α, biologic candidates targeted to other inflammatory molecules are in clinical development, partly driven by commercial interests and medical need. Although clinical experience indicates that all the anti-TNF-α molecular platforms are effective for rheumatoid arthritis, Crohn's disease, and colitis, whether the new agents can provide additional relief or cures remains to be seen. © 2012 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci

Keywords: pharmacokinetics; proteins; biotechnology; macromolecular drug delivery; targeted drug delivery; physicochemical properties; drug interaction; pharmacodynamics; formulation; prodrugs

INTRODUCTION

Since the introduction of this series of commentaries, the registered number of clinical trials around the world has grown significantly. To date there are 121,201 human trials, of which 94,709 are intended to evaluate some form of treatment. These numbers have more than doubled compared with our first report.[1] Following the implementation of the 1997 US Food and Drug Administration (FDA) Modernization Act and the 2007 Food and Drug Amendments Act, all drugs, biologics, and devices undergoing clinical evaluation for marketing approval must be registered. In addition, all registered clinical trial information must be filed at ClinicalTrials.gov, which is now a centralized resource. Registration is required regardless of the geographic location of clinical trials if any of the data are to be submitted to the FDA for marketing approval. Therefore, the participating countries have expanded from 154 (in 2008) to 179 around the globe.[2]

Our commentaries are intended to inform pharmaceutical scientists about the translational trends in drug delivery technologies and biotechnology innovations based on the insights and analysis of up-to-date clinical trial data. These commentaries as well as data

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Journal of Pharmaceutical Sciences

Table 1. Categorical Organization of Descriptors Found in ClinicalTrials.gov

I. Drug Delivery Technology, System, and Device	II. Biological Molecule Platform/Technology	III. Drug Metabolism and PK–PD Interactions
Device	Antibody	Drug metabolism inhibitor
Drug delivery system	Biologics and vaccines	Drug transport modulator
Dosage form	Peptide	Drug interactions
Formulation	Recombinant proteins	Drug metabolic induction
Formulation comparison	Anitbody conjugates	Active metabolite
Transdermal	Antisense	
Aerosol or inhalation	Oligonucleotide	
Route	siRNA	
Sustained release	Aptamer	
Lipid formulation		
Liposome		
Nanoparticles		
Microparticles or microcarriers		
Prodrugs		
Colloid		

summarized in the tables and graphs are also available online at the *Journal of Pharmaceutical Sciences* web site: http://www3.interscience.wiley.com/journal/117935713/grouphome/home.html. We have also provided readers with online access to expert commentaries on various aspects of trends in translational research related to drug delivery, pharmaceutical research, and product development.[3–9]

Although the number of clinical trials has continued to grow, corresponding growth in product approval by the FDA should not be anticipated anytime soon. We continue to face late-stage failures of large clinical trials because of lack of efficacy or toxicity. The drug recalls, blackbox warnings, and ensuing class action lawsuits epitomize the public's demand for a higher standard of safety.[10] Although the FDA regulatory review intends to balance risks and benefits, in the current risk-averse climate, the FDA has repeatedly emphasized safety as the top priority for regulatory review of all new drug applications and biologic licensing applications.[11]

OVERVIEW OF DRUG DELIVERY TECHNOLOGY IN CLINICAL DEVELOPMENT

Clearly, drug delivery platforms and strategies, including the design and choice of target and biological molecule platforms, are intended to improve drug efficacy and safety to enhance the overall therapeutic index of new or existing drugs. Thus, for the Clinical Trials and Translational Medicine Commentaries, drug delivery is broadly defined into three categories. The three categories, shown in Table 1, are (1) drug delivery technology, system, and device; (2) biological molecule platform or technology; and (3) drug metabolism and pharmacokinetic and pharmacodynamic (PK–PD) interactions. The first category covers all the known drug delivery devices and systems, including biopolymers, drug carriers, as well as pro-drug platforms. The second category highlights biological and molecular approaches, including recombinant proteins, antibody derivatives, peptides, and oligonucleotide platforms including small interfering RNA and aptamer technologies. Each of these technology platforms has unique development issues. For instance, development strategies and issues for conjugated antibodies are different from antibodies because of their molecular and chemical modification. The third category, drug metabolism and PK–PD interaction strategies, pertains to metabolic drug-drug interaction-mediated enhancement or reduction in overall drug exposure. Although novel therapies based on the knowledge of drug metabolism and PK–PD interaction are not traditionally considered as drug delivery approaches, such strategies often lead to dose recommendations and dose adjustments in patients to achieve targeted exposure to the parent drug or its active metabolites as a new drug. The safer replacement of the active carboxylate metabolite of now defunct terfenadine (Seldane) with fexofenadine (Allegra), a popular over-the-counter allergy medication, is a good example.[12] Sequence modification of insulin, such as Insulin-lispro and Insulin-asp, to provide faster therapeutic onset is a good example of a biological molecule platform.[13]

The total number of clinical trials and intervention trials associated with drug delivery systems, devices, or select molecular technology or platform descriptors are summarized in Table 2 according to respective clinical progression. Interestingly, 5788 clinical trials (59% in the biological molecule platform) are associated with antibody technology. The majority of the antibody trials are listed in the early stage (i.e., Phase II) of development with only a small percentage (6%) of trials conducted in Phase IV. Although the total number of antibody drug candidates continues to increase, the fraction of trials in each phase remained similar over the past few years. On the contrary,