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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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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.

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 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/group/home/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 prodrug 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-aspartate, 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, one would expect the fraction of trials in Phases III and IV to grow if there was an increase in the rate of maturation and clinical success. However, analysis of the clinical trials database related to device, dosage form, and drug delivery indicates a larger fraction of clinical trials in later Phase II and III stages of clinical testing, suggesting the maturation of science in this area. A majority of formulation and liposome-related studies are found in Phase I clinical evaluation. In the PK–PD interaction category, the majority of clinical trials are related to metabolic inhibitors, drug transport modulators, and drug interactions (Table 2).

Analysis of therapeutic area or disease based on terminologies for organ systems or disease category for drug delivery systems is summarized in Table 3. The cardiovascular system remained the most common organ system evaluated in clinical trials associated with drug delivery systems, accounting for 29% of the trials in the disease category (Fig. 1). Cancer (18%), diabetes (11%), and immune system (10%) are the second, third, and fourth most common disease categories, respectively. These are followed by digestive system and central nervous system at 9% each. We found the fraction of remaining clinical trials related to disease organ and disease distribution to be as follows: infection (8%) and AIDS and behavioral/mental diseases (3% each) (Fig. 1).

Even with the narrow definition of drug delivery as formulation and drug carriers, the US market is projected to be \$57 billion to \$82 billion with a 6%–9% annual growth rate. Regardless of one's definition, novel drug delivery platforms and strategies intended to improve the therapeutic index continue to play a pivotal role in the global effort to improve safety, efficacy, and cost-effectiveness of new or existing medicinal products. Our analysis indicates that since 2008, there was approximately a 120.8% increase in documented drug-delivery-related clinical trials (Table 4). The delivery technology/system and category contributed 133.3%, whereas the PK–PD interaction category recorded a 114.6% increase for the same period (Table 4). A lower number of growth in clinical trials related to the biological molecule platform recorded a 97.7% increase. It is important to note, however, that these numbers reflect only drug delivery technologies that advanced to clinical trials. In the following section, we will update the readers with biological molecule technologies

currently in development and discuss emerging trends in the translation of drug delivery concepts into pharmaceutical products.

EMERGING TRENDS IN BIOLOGIC DRUG DEVELOPMENT

Biological molecules are the platforms that continue to drive new therapeutic product development. The annual sales for 2008–2010 presented in Table 5 reveal that all of the 15 top-selling biologic drugs reach beyond \$1 billion in sales. This is phenomenal growth compared with our first analysis in 1999 wherein only four products reached the \$1 billion milestone and none were above \$2 billion.¹² In contrast, four of the top 15 products generated income over \$6 billion in 2010 for their respective sponsors. The 2010 annual revenue for the top six antibody and derivatives products—Remicade, Enbrel, Humira, Avastin, Rituxan, and Herceptin—reached more than \$5 billion each. Remicade, indicated for Crohn's disease, rheumatoid arthritis (RA), and colitis, reached annual worldwide sales of more than \$7.3 billion. This sales figure is equivalent to \$20 million per day.

Table 5 also highlights a change in the landscape of the sponsors for biologic medicines. For the past 10 years, most of the large pharmaceutical companies such as Pfizer, Johnson and Johnson, Wyeth, Merck, and Roche, with low-level biologic drug development programs, have become central players in the development of biotechnology products by acquiring and merging with successful biotechnology and startup companies. As a result, although there are hundreds of startup biotechnology and technology-driven pharmaceutical companies, the number of independent biotechnology-based companies is diminishing. The major pharmaceutical companies, which are now referred to as integrated biopharmaceutical companies, showcase biotechnology products as their top 10 revenue generators in their respective annual reports. Eli Lilly, for example, has 40% of their portfolio invested in biological molecule platforms. In essence, biotechnology drugs not only make significant impacts on health care, but have also become pivotal to the commercial vitality and success of the pharmaceutical industry. In total, the top 15 biotechnology products generated over \$63 billion in the health care economy in 2010.

It is also interesting to note that the top three products—Remicade, Enbrel, and Humira (common names: infliximab, etanercept, and adalimumab, respectively)—in Table 5 are indicated for treating RA, Crohn's disease, colitis, or psoriatic arthritis. These products affect immune regulation by inhibiting tumor necrosis factor- α (TNF- α) with antibodies (infliximab and adalimumab) or TNF- α -receptor-antibody fusion protein (etanercept). With two additional products, Cimzia and Simponi, added in 2008 and 2009, there are five biologic drugs that neutralize TNF- α inflammation factor (Table 6). Data in Table 6 indicate that depending on the specific anti-TNF- α therapeutic molecule, the dosing frequency differs from weekly to every other month. Dosing frequency differences are due to pharmacokinetic variations—half-life, clearance, and volume of distribution. Also, side-effect profiles may be different (Table 6). However, a recent meta-analysis indicates that these therapeutic agents are effective for RA, Crohn's disease, colitis, and psoriatic arthritis.¹⁴ Clearly, these agents are making an impact on public health and overall health care.

With improved understanding of inflammation and immune regulation related to RA, Crohn's disease, colitis, and psoriatic arthritis, as well as expanding market potential, therapeutic candidates targeted to a wide range of inflammation molecules are now in various stages of clinical testing. A summary of these candidate products, their molecule platforms, and molecular targets, along with the stage of clinical testing, is presented in Table 7. Some of the immune targets include inflammatory cytokines, interleukin (IL)-6, IL-13, IL-17, integrins, and chemokine (C-C chemokine receptor type 9 or CCR9). Because of the intense medical interests and financial support to find better treatments and cures for patients suffering from RA and Crohn's disease as well as colitis, there are nearly a thousand clinical trials distributed around the world addressing these inflammatory diseases (Fig. 2). Although it is clear from clinical experience that all the anti-TNF- α molecular platforms with or without an immunosuppressive regimen have made an impact on RA, Crohn's disease, colitis, and psoriatic arthritis, whether the additional agents targeted to other immune regulatory pathways could provide additional relief or cures remains to be seen. Finally, it is interesting to note that most of these drug candidates are based on monoclonal antibodies or antibody derivative platforms, highlighting the role of biotechnology in driving new therapeutic product development.

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Figure 1. Distribution of clinical trials associated with drug delivery systems or devices according to diseases and expressed in percentage.

Figure 2.
The distribution of clinical trials around the globe to evaluate drug candidates to treat rheumatoid arthritis and associated inflammatory diseases. The number in each region indicates the registered human clinical trial number out of a total of 944 registered. The color bar indicates the trial density from least (green) to the most (red) in specific regions.

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		

Table 2

Summary of the Number of Clinical Trials Listed on ClinicalTrials.gov Organized as the Three Major Drug Delivery Categories (Updated on February 16, 2012)*

	All	Intervention	Phase I	Phase II	Phase III	Phase IV
I. Drug delivery technology, system, and device						
Device	11,055	10,498	2880	3528	3074	1200
Dosage form	11,303	9203	1021	1581	1471	1763
Drug delivery system	3151	2924	611	927	661	401
Formulation	2727	2647	1144	686	578	228
Liposome	1154	1129	509	219	280	100
Transdermal	937	888	264	265	190	133
Formulation comparison	536	526	168	274	100	24
Route	501	479	81	108	151	100
Sustained release	317	301	47	78	111	48
Lipid formulation	134	118	4	21	21	24
Nanoparticles	118	113	27	27	31	15
Aerosol and inhalation	113	110	38	26	14	22
Prodrugs	111	104	43	47	16	10
Colloid	105	98	37	63	8	2
<i>Subtotal</i>		29,138				
II. Biological molecule platform/technology						
Antibody	6256	5788	1676	2731	1296	380
Biologics and vaccines	3498	3409	1223	1268	810	324
Peptide	1741	1533	518	564	230	173
Recombinant proteins	570	530	223	195	106	30
Antibody conjugates	337	325	57	104	140	33
Antisense	95	93	54	45	12	0
Oligonucleotide	99	84	45	39	12	2
siRNA	56	41	15	13	12	4
Aptamer	21	20	10	9	4	1
<i>Subtotal</i>		11,823				

	All	Intervention	Phase I	Phase II	Phase III	Phase IV
III. Drug metabolism and PK-PD interactions						
Metabolic inhibitor	2310	2136	317	464	644	535
Drug transport modulator	1584	1511	251	315	450	380
Drug interactions	2169	1795	726	295	127	192
Metabolic induction	690	575	80	133	88	96
Active metabolite	508	489	236	124	44	41
	<i>Subtotal</i>	6506				

* All the clinical trial data filed with the [ClinicalTrials.gov](https://clinicaltrials.gov) database were sorted according to the delivery platform listed under the three major categories. All clinical trials include observation and intervention studies.

Table 3

Summary of the Number of Clinical Trials Related to Device, Drug Delivery System, Formulation, or Dosage Form that are Listed According to the Disease Target or Organ Systems (Updated on February 16, 2012)*

Disease	All	Intervention	Phase I	Phase II	Phase III	Phase IV
Cardiovascular	3581	3089	308	571	677	836
Cancer and neoplasm	2106	1891	524	808	276	101
Central nervous system	1164	1006	236	286	187	122
Immune system	1269	1127	214	370	212	141
Diabetes, endocrine, and metabolism	1449	1238	199	273	198	252
Digestive system	1046	931	175	284	175	94
Infection	936	833	156	163	169	125
Behavioral and mental disorders	341	318	44	90	60	38
AIDS	307	278	69	53	52	24
<i>Subtotal</i>		10,711				

* All clinical trials include observation and intervention studies.

Table 4

The Increase in the Number of Drug-Delivery-Related Clinical Trials Between October 2008 and February 2012

Categories	October 2008	February 2012	Net change (%)
I. Drug delivery technology, system, and device	12,492	29,138	16,646 (133.3)
II. Biological molecule platform/technology	5979	11,823	5844 (97.7)
III. Drug metabolism and PK–PD interactions	3031	6506	3475 (114.6)
<i>Subtotal</i>	21,502	47,467	25,965 (120.8)

Annual Sales of the Top 15 Selling Products of Biological Molecule Platforms and Technologies, Their Indications, Sponsors, and Sale Figures for 2008–2010

Table 5

Product ^a	Common Name	Sponsor(s) ^b	Indication(s)	Annual Sales (in Million) ^c		
				2008	2009	2010
Remicade	Infliximab	J & J; Centocor>Merck	Crohn's disease, rheumatoid arthritis (RA), colitis	5856	6631	7324
Enbrel	Etanercept	Amgen; Wyeth>Pfizer	RA and psoriasis	6191	5916	6808
Humira	Adalimumab	Abbott	RA and psoriatic arthritis	4500	5500	6500
Avastin	Bevacizumab	Genentech>Roche	Colorectal, lung, breast, renal, and brain cancers	2908	5837	6061
Rituxan	Rituximab	Genentech>Roche	Non-Hodgkin's lymphoma, leukemia (CLL), RA	2852	5710	5962
Herceptin	Trastuzumab	Genentech>Roche	Breast and gastric cancer	1819	4940	5093
Novolog	Insulin-asp	Nova Nordisk	Diabetes	2503	3020	3666
Lantus	Insulin-glargine	Sanofi-Aventis	Diabetes mellitus	3259	4096	4668
Epogen; Procrit/Epex	Epoetin alfa	Amgen; J & J	Anemia	4,916	4814	4458
Neulasta (Peg-G-CSF)	Pegfilgrastim	Amgen	Febrile neutropenia	3318	3,355	3558
Aranesp	Darbepoetin alfa	Amgen	Anemia	3137	2652	2486
Novolin	rh-Insulin	Nova Nordisk	Diabetes	2194	2103	2198
Humalog	Insulin-lispro	Eli Lilly	Diabetes mellitus	1736	1959	2054
Pegasys	Peginterferon α-2a	Roche	Hepatitis C	1534	1553	1543
NovoSeven	rh-Factor VIIa	Nova Nordisk	Hemophilia A and B	1189	1314	1493
Total annual sales				47,911	59,401	63,873

CLL, chronic lymphocytic leukemia; J & J, Johnson and Johnson; RA, rheumatoid arthritis; rh, recombinant human product.

^aProducts of the same common name and original source were combined regardless of sponsor or marketing company for US and international sales.

^bThe semicolon indicates that there are more than one sponsor for the same product with an identical common name. The arrow ">" symbol indicates the recent merger/acquisition of two company sponsors.

^cData were collected from annual reports and sponsor's filing documents including those reported in the Securities and Exchange Commission form F-20 or 10-K. The data reported in foreign currency were converted as follows; 1€= 1.33 US\$; 1CHF = 1.066 US\$.

Table 6
Comparison of Molecular Platforms, Pharmacokinetics, Dosing Frequency, and Major Side Effects of anti-TNF Therapeutics and Their Approval Dates

Anti-TNF Biomolecule	Description	Pharmacokinetics			Major Side Effects		Dosing		
		Half-life (Day)	Clearance (mL/h)	Volume (L)	Description	Frequency (%)	First Approved	Route	Frequency
Remicade [infliximab]	anti-TNF- α -chimeric antibody	7.7–9.5	5.4	~5	Infusion Infection	18 11	August 1998	i.v.	q 6 or 8 weeks
Enbrel [etanercept]	TNFR–Fc fusion protein	4.25	6.7	6–18	Injection site Upper respiratory	37 8	November 2005	s.c.	Weekly
Humira [adalimumab]	anti-TNF- α -human antibody	14(10–20)	12	4.7–6.0	Injection site Upper respiratory	20 8	December 2002	s.c.	q 2 weeks
Cimzia [certolizumab-pegol]	anti-TNF- α -humanized antibody-Fab'-fragment-PEG conjugate	14	17	6.4	Upper respiratory	7	April 2008	s.c.	q 2 weeks
Simponi [golimumab]	anti-TNF- α -human antibody	14	4.9–6.7	~5	Injection site Upper respiratory	6 6	April 2009	s.c.	q 1 month

Table 7

Therapeutic Candidates in Clinical Development for Crohn's Disease, Colitis, and Rheumatoid Arthritis (RA)

Drug Candidate	Description	Molecular Target	Indication	Clinical Status (Phase)
Golimumab	Antibody	TNF- α	Colitis	II–IV
AMG 827	Antibody	IL-17	Crohn's	II
AIN 457	Antibody	IL-17A	Crohn's	II
PF-04236921	Antibody	IL-6	RA, Crohn's	I and II
Ustekinumab	Antibody	IL-12/23p4	Crohn's	III
Anrakinumab	Antibody	IL-13	Colitis	II
ATN 103	Nanobody (antibody derivative)	TNF- α	RA	II
Vedolizumab	Antibody	$\alpha 4\beta 7$ integrin	Crohn's, colitis	III
CCX282-B	Small molecule	CCR9	Crohn's	II
rhuMAb $\beta 7$	Antibody	$\beta 7$ integrin	Colitis	I
PF-00547659	Antibody	MAdCAM	Crohn's, colitis	I and II