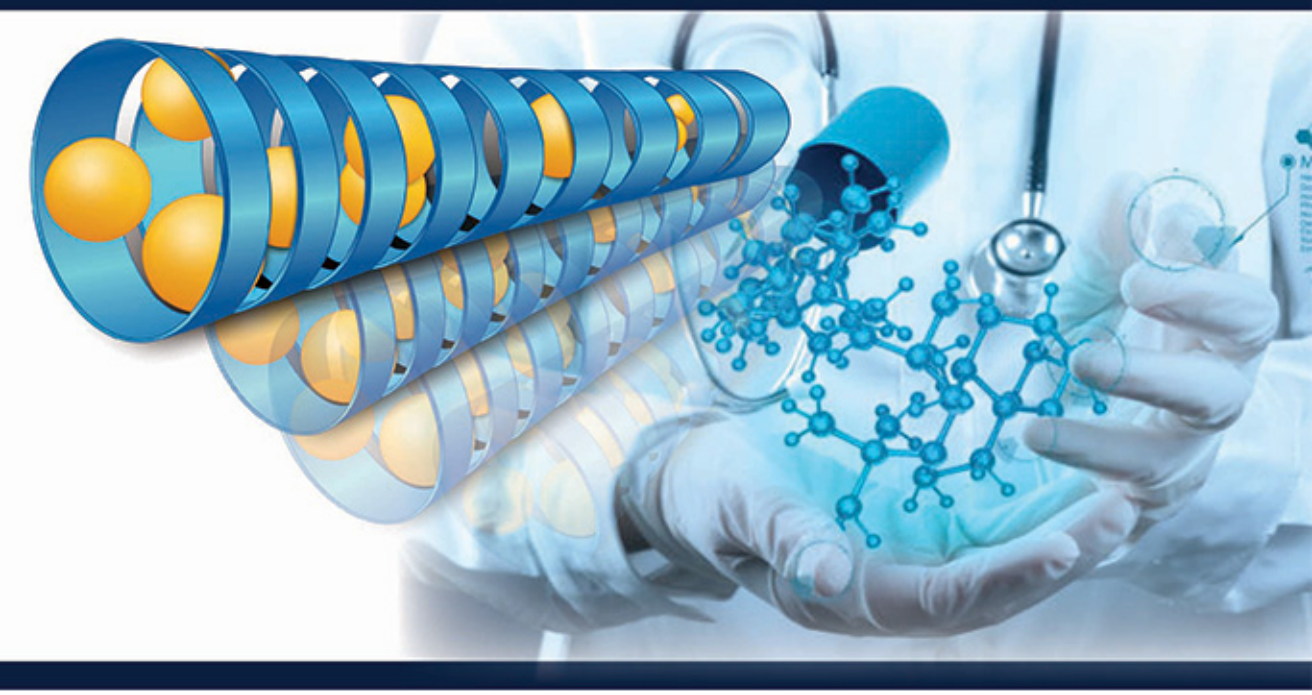
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Drug Discovery & Clinical Research



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2nd Edition

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4

Chapter

Drug Discovery and Development of Biologics

Rajani Mathur, Prateek Sharma

SCIENCE OF DRUG HUNTING

The aim of drug discovery program has always been to use the right science and technology to develop the right products, for the right patients, at the right cost, thereby posing a huge challenge in front of the academia and industry (Lundberg and Reilly, 2009). The drug discovery program has many facets including understanding disease condition, target identification, lead generation, lead optimization and clinical testing.

The task is complicated by looming patent expiries in front of major pharma companies, potentially reducing funds for future investment into R & D and existence of number of good medicines already in the market which shrink the window of opportunity for new discoveries. In addition, the regulatory agencies have set the bar very high and now, require extensive data with proof of safety and efficacy. Even after a new drug has cleared all hurdles for approval, its pricing remains a crucial decision that may be taken only after considering numerous factors such as rise of emerging markets, aging demographics, better disease detection, emergence of new diseases ('diabesity' in the younger population, antibiotic resistance, bacterial and viral infections etc) and co-morbidities of diseases etc.

The amalgam of these factors convert the science behind drug discovery program into a drug hunting program, the success-rate of which is as probable as that when looking for a needle in the haystack. The fact is borne out by the low numbers of new molecular entities approved by regulators in recent years.

Till recently, the scientists in the drug discovery program have been either tapping natural products (medicinal plants, microorganisms, marine source etc.) or synthesizing newer chemical entities. Both the approaches have produced their share of successful molecules. However, the scenario of drug discovery has phenomenally changed with the advent of genomics-based technologies, integrated ultra-high throughput screening based techniques. The emphasis is now on speedy results, and there is immense pressure on traditional approaches to keep pace.

"Biologics" offer solution to the deadlock in the drug discovery program and may help to make it an efficient operation.

DEFINING BIOLOGICS

Biologicals or "Biologics" can be defined as products of which, the active substance is produced by or extracted from a biological source. This is an all-encompassing definition which includes substances that are the product of living organisms, and target a specific biologic molecule (Tandon et al, 2006). Biologics encompass vaccines, blood and blood components, allergenic, somatic cells, genes, tissues, therapeutic serum, toxin, antitoxin, and recombinant therapeutic proteins (RNAi, alternate scaffolds, antisense

nucleotides, aptamers, vaccines, monoclonal antibodies, recombinant proteins and peptides, prophylactic vaccines) that are meant for the prevention, treatment or cure of disease in human beings.

Biologics have been broadly classified into-gene and cell-based products. Chemically, biologics can be sugars, proteins, nucleic acids or complex combinations of these substances, or may even be living entities such as cells and tissues. The product-based classification of biologic preparations and products available in market is cited in **Table 4.1**. The biotherapeutic modalities have undergone a sea-change and evolved to a higher platform. They are projected for phenomenal future growth, with biggest players being recombinant proteins and monoclonal antibodies.

Biologics are further classified into three broad categories depending on the basis of their mechanism of action, namely—monoclonal antibodies, enzyme modulators and receptor modulators.

Structurally, monoclonal antibodies consist of two major domains—FAb arms and Fc domain. The former binds to the antigens and the latter interacts with the immune moieties. The binding strength, binding site and Fc activity decides the potency of the monoclonal antibody. Monoclonal antibodies against HER2/neu receptor in HER2 positive breast cancer, cytokines (interferon) in multiple sclerosis are some of the therapeutically used biologics.

The source of biologics is primarily natural vis-à-vis, human, animal, or microorganism. These may be later modified large scale production by biotechnology based techniques. Research on biologics is gaining momentum and they are being tapped to treat a variety of medical conditions for which no other treatments are available. At the US-FDA, Center for Biologics Evaluation and Research (CBER) regulates the development and approval process of biologics and biologic devices under various heads including Biologics License Applications (BLAs), Premarket Approvals (PMAs), New Drug Applications (NDAs). Nearly 15 biologic products were approved over eight months in the year 2015 in the US alone (http://www.fda.gov). Biologicals are also being developed for unique targets like interleukin IL-17 (brodalumab, ixekizumab, and secukinumab), IL-23 (guselkumab and tildrakizumab), psoriasis,

Table 4.1 Class and examples of the currently marketed biologics

Class	*Product type*	*Example*
Allergenics	Allergen extracts, allergen patch tests, antigen skin test	GRASTEK®, Oralair
Blood and blood products	Blood, blood components, blood bank devices, blood donor screening tests	Albumin alpha1-proteinase inhibitor Antihemophilic factor (recombinant) Antihemophilic factor/von Willebrand factor complex Anti-inhibitor coagulant complex Antithrombin (Recombinant) C1 esterase inhibitor coagulation factors
Cellular and gene therapy products	Gene-based treatments, cell-based treatments, cloning	ALLOCORD®, Laviv®, Carticel®, Gintuit®, PROVENGE®
Tissue and tissue products	Bone, skin, corneas, ligaments, tendons, stem cells, sperm, heart valves	Bone (including demineralized bone, ligaments, tendons, fascia Cartilage, ocular tissues (corneas and sclera), skin, encapsulated pancreatic islet cells
Vaccines	Vaccines for use in children and adults, tuberculin testing	Hepatitis B vaccine, influenza A vaccine, HPV vaccine, BCG Live
Xenotransplantation	Transplantation of non-human cells, tissues or organs into a human	NA

alpha toxin (MEDI4893) and pneumonia (Sause et al, 2015; Leonardi et al 2015).

Interestingly, biologics are also facing recalls and discontinuation. Recall may be initiated by the firm for removal or correction of the marketed product in order to avoid legal action. The other problem faced by biologic products is that of shortages and discontinuation. This can delay and in some cases even deny critically ill patients of therapy and pose a significant public health threat. On an average, there may be 5–6 such instances that are dealt by FDA per annum.

MAKING BUSINESS SENSE OUT OF BIOLOGICS

In the United States, the first biological, recombinant insulin, was approved in October 1982. Since then, more than 250 biologics, including recombinant (blood) products, monoclonal antibody–based products, and recombinant vaccines have been approved by regulatory authorities. In 2010, the market of biologics was 137 billion US dollar and it has been forecasted that by the year 2020 it will reach 319 billion US dollar. Worldwide biologics account for about 25% of all new drugs in the market and contributing 16% of the total sales. It has been forecasted that by the year 2025, 70% of the pharmaceutical market would be taken up by biotechnology-based products. According to IMS, by 2016, approximately 17% of total global spending are expected to be on biologics and reach an overall market value of $200 billion to $210 billion way ahead from $157 billion 2011. Considering the fact that the amount of money spent on the development of biologics is a mere 3% of the total spending, the returns are encouraging and there is scope for tremendous evolution **(Fig. 4.1)**.

The biological products are bringing golden reaps for the pharmaceutical industry and many mutually beneficial deals are being materialized. To cite the case of Sanofi Pasteur which announced that it had acquired the worldwide rights for KB-001, a monoclonal antibody (mAb) fragment of KaloBios Pharmaceuticals. The product is in Phase I/II development to treat and prevent *Pseudomonas aeruginosa* infections. The agreement involves an upfront payment of US$35 million and potential milestones of up to $255 million. In addition, KaloBios has retained the development and marketing rights for cystic fibrosis and bronchiectasis indications.

In another case, MassBiologics and Medarex published positive Phase II results showing that two mAbs targeting *Clostridium difficile* toxins A and B (called CDA1 and CDB1, respectively) significantly reduced the recurrence of *C. difficile* infection when administered together. Merck had licensed the development and commercialization rights for these mAbs in April 2009 for a $60 million upfront fee. MassBiologics and Medarex could also be eligible for additional cash payments of up to $165 million, if certain milestones are met (Lowry et al, 2010). Biologicals that have been approved recently are enlisted in **Table 4.2**.

WHY A HALO AROUND BIOLOGICS?

Biologics are being heralded as the "gold standard" for the future. Extensive and sophisticated research is being carried out to identify the best molecule in terms of potency, affinity and half-life against a target. Such biologics are capable of delivering

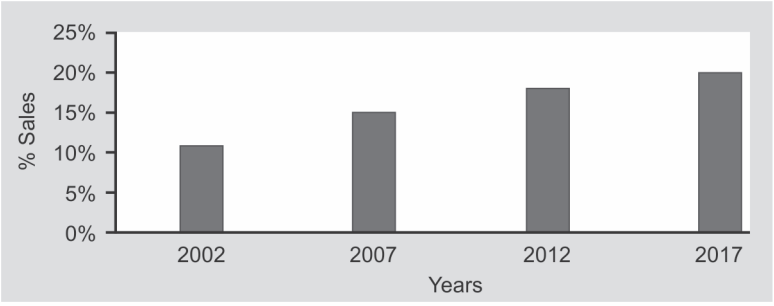


Fig. 4.1 Projected sales (%) of biologics between 2002 and 2017

Table 4.2 Recently Approved Biologicals

Trade name/Proper name	*Manufacturer*	*Approval date*
FLUAD Influenza Vaccine, Adjuvanted	Novartis Vaccines and Diagnostics, Inc.	11/24/2015
ADYNOVATE Antihemophilic Factor (Recombinant), PEGylated	Baxalta US Inc.	11/13/2015
IMLYGIC Talimogene laherparepvec	Amgen, Inc	10/27/2015
COAGADEX Coagulation Factor X (Human)	Bio Products Laboratory	10/20/2015
Source Plasma	Hemarus LLC	9/11/2015
Nuwiq Antihemophilic Factor (Recombinant), rAHF	Octapharma Pharmazeutika	9/4/2015
Anavip Crotalidae Immune F(ab')2 (Equine)	Instituto Bioclon, SA de C.V.	5/06/2015
RAPLIXA Fibrin Sealant (Human)	ProFibrix, BV	4/30/2015
IXINITY Coagulation Factor IX (Recombinant)	Cangene Corporation	4/29/2015
QUADRACEL Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus Vaccine	Sanofi Pasteur Limited	3/24/2015
ANTHRASIL Anthrax Immune Globulin Intravenous (Human)	Cangene Corporation	3/24/2015
BEXSERO Meningococcal Group B Vaccine	Novartis Vaccines and Diagnostics	1/23/2015

great value for the patients due to the following points:

Unique Target Space

Broadly classifying from the pharmacology point-of-view, the intervention sites of most of the drugs can be identified as:

(i) Ligand-receptor interactions
(ii) Intracellular pathways
(iii) Cell-cell talk
(iv) Cell-matrix talk

Traditionally, the drugs in the form of small molecule have acted by affecting intervention sites (i) and (ii), while nominally targeting (iii) and (iv). However, with the advent of biologics, the target space available has expanded manifold. They are being successfully used to target any of the intervention sites. In fact, a novel approach is being developed wherein the two therapies will be used together. They will affect different intervention sites to expand the target space, thereby yielding better results.

Good R & D Survival Rate

Drug discovery and development program requires that any novel molecule should be sequentially analysed for various paradigms in preclinical and clinical stages. This helps to remove chaff and bring out successful molecule. However, it makes the process cumbersome and costly with high attrition rates. It has been recorded that traditional small molecules have had a low survival rate, with only 1 in 51 molecules making it to the market. In contrast, the overall R & D survival rate of novel biologics is as high as 1 in 21. The higher success

rate of biologics can be attributed to their higher survival rate of almost 90% in preclinical studies.

BIOMARKER-BASED-STRATEGY IN THE DISCOVERY AND DEVELOPMENT OF BIOLOGICS

Recent advances in drug discovery have been in a core area namely, structure-based design. This involves developing the design of typically small molecules that bind to a biomolecular target and inhibit its function. In contrast, the strategy in developing biomarker protein as biologics target site involves in designing process features that build three-dimensional structures of complexes of the small molecules with the target. Structure-based design can be carried out with nothing more than the target structure, which most often comes from X-ray crystallography, and graphics tools for placing small molecules in the proposed binding site. Many such molecules are now in the clinical phase of development. The following are cases in point.

- Identification of molecular alterations in key proteins involved in breast cancer cell proliferation and survival resulted in the development of a new treatment strategy with target-based agents. The anti-ErbB-2 monoclonal antibody (mAb) Trastuzumab and the dual epidermal growth factor receptor/ErbB-2 tyrosine kinase inhibitor Lapatinib are effective in patients with breast cancer that overexpresses ErbB-2. The anti-vascular endothelial growth factor-A mAb Bevacizumab is approved in combination with taxanes for treatment of unselected patients with metastatic breast cancer. In addition, preclinical data suggest that signaling inhibitors can prevent or overcome resistance to endocrine therapy in estrogen receptor positive (ER+) breast cancer (Normanno, 2009).
- Sepsis is currently the 10th leading cause of death overall and accounts for significant healthcare expenditures in the developed world. Incidence of deaths attributable to sepsis are rising and unfortunately, to date, there are very few successful therapeutic agents available in the clinical setting. Several novel therapeutic adjuncts for the management of critically ill patients with sepsis are being developed which largely focus on therapies that directly target the host inflammatory response, specifically those that result in activation of the transcription factor, nuclear factor (NF)-κB. Activated protein C (Drotrecogin alfa, Xigris®, Eli Lilly and Co), and Afelimomab, a monoclonal antibody F(ab′)2 fragment directed against tumor necrosis factor (TNF)-α are biomarker-based-biologics that are currently being investigated in clinical trials (Wheeler et al. 2009).
- CD4 cell has been identified as the 'primary receptor' for the AIDS virus. Recently, role of additional molecules such as CXCR4 have been identified as the co-receptor for X4 HIV-1 isolates. In addition, it has been demonstrated that CCR5 is the co-receptor along with CD4 that allows entry of R5 HIV-1. The discovery of the HIV co-receptors provided a logical target in the management of HIV-1 infection. Recently, orally bioavailable CCR5 blocking agent, Maraviroc, is the first such therapeutic to be approved by the U.S. Food and Drug Administration. CXCR4-based blocking agents are less attractive due to the crucial role of CXCR4 in many other biological processes. However, agents that are aimed at down modulating CXCR4 expression are also being explored as they might provide some benefits for HIV-positive patients (Alkhatib, 2009).
- Monoclonal antibodies are a promising new class of therapeutic agents that can be employed to target specific molecules of the immune system or any tissue. They are currently being tested in a number of clinical trials in autoimmune diseases such as multiple sclerosis (MS). One of these, the humanized monoclonal anti-CD25 antibody Daclizumab (Zenapax), is directed against the interleukin-2 (IL-2) receptor alpha chain (CD25) that is involved in clonal expansion of autoreactive T-cells by binding of its ligand IL- 2.
- Many orphan conditions are being successfully treated by biosimilars. The discovery that clinically unrelated conditions, such as rheumatoid arthritis and Crohn's disease, share similar immune dysregulation has led to a shift in the management of these conditions

(Kuek et al. 2007). They have been collectively named as immune-mediated inflammatory diseases (IMIDs) and the management has shifted from one of organ-based to symptom relief to mechanism-based treatment. To cite an example, anticytokine therapy has been effective in treating IMID due to its widespread role in pathogenesis of multiple inflammatory conditions **(Table 4.3)**.

The use of biomarkers presents an opportunity in understanding target engagement and disease impact while accelerating drug development. For effective integration in drug development, it is essential for biomarkers to aid in the elucidation of mechanisms of action and disease progression. The recent years have witnessed significant progress in biomarker selection, validation, and qualification, while enabling surrogate

Table 4.3 Immune-mediated inflammatory diseases (IMIDs) in which biologic therapy appears promising

Infliximab	*Etanercept*	*Adalimumab*	*Rituximab*
Sjögren's	Sjögren's	Crohn's disease	Polymyositis/dermatomyositis
Polymyositis/ dermatomyositis	Polymyositis/dermatomyositis	UC	Wegener's granulomatosis
Wegener's vasculitis	Wegener's vasculitis	Psoriasis	GCA/PMR
Behçet's	Behçet's	JIA	Polyarteritis nodosa
GCA/PMR	GCA	Behçet's	JIA
Takayasu's arteritis	Takayasu's arteritis	Takayasu's arteritis	Graft versus host disease
Polyarteritis nodosa	Polyarteritis nodosa	Sarcoidosis	Cryoglobulinaemic vasculitis
Sarcoidosis	Sarcoidosis	Adult onset Still's disease	ITP
Adult onset Still's disease	Adult onset Still's disease	Hydradenitis suppurativa	TTP
JIA	Cryoglobulinemic vasculitis	Pyoderma gangrenosum	AIHA
Kawasaki disease	Relapsing polychondritis	Pemphigus	Antiphospholipid syndrome
Cryoglobulinemic vasculitis	Hydradenitis suppurativa		Idiopathic membranous GN
Relapsing polychondritis	Pyoderma gangrenosum		Hep C associated GN
Hydradenitis suppurativa	Graft versus host disease		Multiple sclerosis
Coeliac disease	Chronic hepatitis C		Myasthenia gravis
Myelodysplastic syndrome	ITP		Pemphigus
Pyoderma gangrenosum	Refractory asthma		Grave's disease
Erythema nodosum	Amyloidosis		CIDP
SAPHO syndrome	Multicentric reticulohistiocytosis		
Graft versus host disease	Pemphigus		
Chronic hepatitis B/C	Grave's disease		
TTP	CIDP		

Abbreviations: AIHA, autoimmune hemolytic anemia; CIDP, chronic inflammatory demyelinating polyneuropathy; GCA, giant cell arteritis; GN, glomerulonephritis; JIA, juvenile idiopathic arthritis; PMR, polymyalgia rheumatica; SAPHO, synovitis, acne, pustulosis, hyperostosis, osteitis; SLE, systemic lupus erythematosus.
Source: Adapted from Kuek et al. 2007.

and clinical endpoint qualification and application. Biomarkers play a central role in target validation for novel mechanisms. They also play a central role in the learning/confirming paradigm, particularly when utilized in concert with pharmacokinetic/pharmacodynamic modeling. Clearly, these attributes make biomarker integration attractive for scientific and regulatory applications to new drug development (Krishna, 2008).

The rapidly increasing availability of genomic data for numerous biological entities presents exciting possibilities for understanding human health and disease. Biomarkers are playing a pivotal role in diagnosis of disease condition. Etiopathological studies have brought fore ideal biomarker, or panel of biomarkers associated with each disease condition that can be used in its early detection. This when coupled with biotechnology techniques such as microarray, can help to screen large number of samples in a cost-effectivel manner using minimum time and labor. In contrast to traditional serological/microbiological assay based diagnosis, biomarker based-system of diagnosis can accurately analyse low quantity of samples and delineate complicated cases of resistance or relapse etc. in a single test. This mode of high-throughput diagnosis has revolutionized diagnostic sciences and is being widely used for many viral diseases (AIDS, HCV, influenza etc.), cancer, tuberculosis (Pai et al, 2006; Besson and Kazanji, 2009).

CHALLENGES IN THE DISCOVERY AND DEVELOPMENT OF BIOLOGICS

The discovery and development of biologics is fraught with numerous challenges, some of which are critically discussed below:

- *Complex process:* The production and purification process of biologics is complex, as it involves numerous steps. Minor alterations at any of the step in the production cascade can lead to drastic changes in the characteristics of the end product.
- *Safety implications:* Small differences and changes in the production process can therefore have major implications on the safety profile of biologics. For example, pure red cell aplasia is an extremely rare complication recorded in patients treated with recombinant human epoetin. The incidence was observed to be unexplainably elevated in patients. The reason provided was that these patients were administered one particular formulation of recombinant human epoetin in which human serum albumin had been replaced with polysorbate 80 and glycine.
- *Contamination:* The risk of contamination with pathogens by the donor is another problem related to the production process (e.g. for products extracted from human blood or plasma).
- *Chances of withdrawal:* As the knowledge of a new drug is incomplete at the time of approval, due to a variety of factors including constraints in the sample size and the design of randomized controlled trials. Therefore a huge risk is attached with the use of biologicals especially with regards to their safety profile. Identification of important safety problems, has led to the withdrawal of drugs from the market.
- *Immunogenicity:* Biologicals are specifically prone to the induction of immunogenicity. In many cases, immunogenicity can lead to loss of efficacy of the drug or, even worse, lead to autoimmunity to endogenous molecules.
- *Limited information:* The predictability of preclinical data to humans is limited for biologicals due to the species-specific action and immunogenic properties in animals. To cite a recent example, healthy volunteers participating in a phase 1 clinical study of a CD28 agonist monoclonal antibody (TGN1412; TeGenero Inc.), recorded a serious adverse event. The observed cytokine storm following infusion had not been observed in the preclinical studies. Thus, in order to obtain valuable results from the preclinical studies, the battery of tests should not only be selected based on pharmacological and pharmacokinetic properties but its potential for immunogenicity should also be taken into account.
- *Complicated pharmacokinetic and Pharmacodynamic (PK-PD) properties:* In some cases, the preclinical program has been complicated by a complex pharmacodynamic-pharmacokinetic relationship.

- *Limited safety information:* Limited information is available on the safety-related actions of biologics. It is difficult to extrapolate the actions, kinetics and adverse effects of drugs belonging to the same mechanistic classes. This complicates the associated regulatory actions.
- *Patient compliance:* From the patients' perspective, biologics pose a challenge because majority of them have to be administered from the parentral route. This is inconvenient in long-term therapy and affects compliance. In addition, trained healthcare staff may be required to administer the drug, which translates into frequent hospital visits and additional cost burden on the patient.
- *Biosimilars:* How biosimilars might be developed is a burning question that is doing the rounds. It is quite evident that the skills that are required to develop biosimilars are quite different from typical generics. In case of biosimilars, the new drug has to go through the complete rigors of preclinical, manufacturing and clinical studies, as data from class biologic cannot be extrapolated. This means additional cost burden on the pharmaceutical industry and time lapses.
- *Storage and shelf life:* Most of the biologics are temperature and humidity-sensitive, susceptible to microbial contamination products with short shelf-lives. These products have to be stored under appropriate conditions, as use of improperly stored products can prove to be hazardous. Thus they require cold chain storage during transportation. Therefore, their use may be limited amongst developing nations, which are often the biggest markets of pharmaceuticals.
- *Shortage of useful products:* A shortage situation occurs when the total supply of all licensed or approved product available at the market level will not meet the current demand and there is no adequate alternative therapy available that is judged by appropriate medical staff to be a suitable alternative. Many of the launched products face shortages due to many reasons including manufacturing issues, corporate decisions to discontinue the product, distribution disruptions, regulatory actions, or natural disasters **(Table 4.4)**. The goal of Center for Biologics Evaluation and Research (CBER) is to help prevent or alleviate shortages of biological products, and to work with all parties involved to make certain medically necessary products are available within the United States.
- *Patent and commercial issues:* Many of the commercially successful therapeutic biologics will go off patent between 2013 and 2019. This will lead to drop in inventors' market share, unless a follow-on-biologic is developed before the deadline. Consequently, there has been a surge in investments on follow-on biologics. Products whose patents are likely to expire are tabulated **(Table 4.5)**.
- *Adjuvant therapy:* Monoclonal antibodies (mAbs) and immune-based therapies prove to be useful as adjunctive and not mainline therapy. They may be given in addition to antibiotics, antivirals, anticancer and antiallergic drugs.
- *Aseptic environment:* Most biologics are complex mixtures that are not easily identified, purified or characterized. Their manufacture requires elaborate biotechnology-based techniques that have to be carried out on aseptic principles.
- *Inherent limitations:* There are diverse application areas of drugs that include diagnosis, prevention and cure. Their use may be intended for exploring or modifying both physiological and pathological states. Due to their inherent limitations, biologics cannot be used in all areas.

BIOLOGICS VS SMALL MOLECULES: WHAT IS THE SCORECARD?

It has been estimated that all the known small molecules taken together, target around 14% of the druggable genes, 50% of disease modifying genes and over 1,500 potential targets. In contrast, the biologics mainly act on 31% of the known extracellular targets, 12% of disease modifying genes and approximately 900 potential targets. There are 375 unique targets for small molecules as compared to 225 targets available for biologics with an overlap of 75–80% targets between small molecules and

Table 4.4 Biological products facing shortage

Product	*Shortage status*
Immune Globulin (Human) GamaSTAN® S/D Talecris Biotherapeutics, Inc.	Jan 2010–Ongoing
Antivenin (Latrodectus Mactans) Antivenin (Black Widow Spider Antivenin) Merck and Co., Inc.	Jan 2009–Ongoing
Hepatitis B Vaccine Recombivax HB® Merck and Co., Inc.	Jan 2009–Ongoing
Pediatric and Adult Hepatitis A Vaccine VAQTA® Merck and Co., Inc.	Feb 2008– Being monitored
Haemophilus influenza Type b (Hib) Conjugate PedvaxHIB® and Comvax® Merck and Co., Inc.	Dec 2007–Ongoing
Rubella Virus Vaccine Live Meruvax II® Merck and Co., Inc.	2008– Ongoing
Zoster Vaccine Live Zostavax® Merck and Co., Inc.	July 2008– Ongoing
Measles, Mumps, Rubella and Varicella Virus Vaccine Live ProQuad® Merck and Co., Inc.	June 2007– Being monitored

biologics. Thus, from the scorecard it is evident that the two classes of drugs run head-to-head, as far as their feasible applications are concerned. In such a condition the real determinants are the efficacy and safety profiles.

To cite a case in the point, breast cancer is the most common female malignancy in many industrialized countries. Approximately one fourth of all women diagnosed with early breast cancer present with tumors that are characterized by erbB2 amplification. While the associated Her-2/neu receptor overexpression results in a high risk of relapse and poor prognosis, these tumors also represent a target for a selective monoclonal antibody therapy with trastuzumab (Herceptin®). The combination of trastuzumab with chemotherapy has led to a considerable reduction of recurrences and to a significant reduction in breast cancer mortality both in the adjuvant and metastatic setting. Unfortunately, despite Her-2/neu overexpression, not all patients equally benefit from trastuzumab treatment, and almost all women with metastatic breast cancer eventually progress during antibody therapy. Moreover, trastuzumab is burdened with cardiotoxicity, thus increasing the risk of symptomatic congestive heart failure. In addition, the marginal costs for a 1 year therapy of trastuzumab-based therapy,

Table 4.5 Products whose patents are likely to expire

		Approval date		*Expiry date*	
	Biologicals	*US*	*EU*	*US*	*EU*
Humanized antibody	Avastin (bevacizumab)	26-02-2004	12-01-2005	04-07-2019	21-01-2022
	Herceptin (trastuzumab)	25-09-1998	28-08-2000	18-06-2019	Expired
	Humira(adalimumab)	31-12-2002	08-09-2003	31-12-2016	16-4-2018
	Synagis(palivizumab)	19-06-1998	13-08-1999	Expired	Expired
Non-humanized antibody	Erbitux (cetuximab)	12-02-2004	29-06-2004	13-02-2016	Expired
	Remicade (infliximab)	24-08-1998	13-08-1999	04-09-2018	Expired
	Rituxan/MabThera (rituximab)	26-11-1997	02-06-1998	22-09- 2016	Expired
Others	Aranesp (darbepoetin alfa)	17-09-2001	06-08-2001	15-05-2024	06-07-2016
	Avonex/ Rebif (Interferon Beta-1a)	07-02-2003	19-03-2009	Expired	Expired
	Enbrel (etanercept)	2-11-1998	03-02-2000	22 -11-2028	Expired

which is currently considered to be the most effective treatment regimen in the adjuvant setting, may amount for up to US$ 40.000 (Fischer et al 2003).

Thus it becomes clear that even "star drugs" have their limitations and contentious issues in terms of efficacy and safety need to be resolved.

SAFETY BIOLOGICS

Drug safety has always been a key aspect of drug development. Recently, the Vioxx case and several cases of serious adverse events being linked to high-profile products have increased the importance of drug safety, especially in the eyes of drug development companies and global regulatory agencies. Safety biomarkers are increasingly being seen as helping to provide the clarity, predictability, and certainty needed to gain confidence in decision making: early-stage projects can be stopped quicker, late-stage projects become less risky. Public and private organizations are investing heavily in terms of time, money and manpower on safety biomarker development. An illustrative and "door opening" safety biomarker success story is the recent recognition of kidney safety biomarkers for pre-clinical and limited translational contexts by FDA and EMEA. This milestone achieved for kidney biomarkers and the "know how" acquired is being transferred to other organ toxicities, namely liver, heart, vascular system. New technologies and molecular-based approaches, i.e., molecular pathology as a complement to the classical toolbox, allow promising discoveries in the safety biomarker field.

CONCLUDING REMARKS

When targeting new disease areas with the objective of drug discovery, 'target validation' is the first approach that is adopted, which is nothing but extensive biologic studies. The crux lies in knowing for certain that the target pathway plays an important role in the pathogenesis of the disease and developing appropriate modality that targets the same. Target engagement, and disease-related, biomarkers have significantly accelerated drug development. The use of biomarkers as tools facilitated design of clinical efficacy trials while streamlining dose focus and optimization, the net impact of which reduced overall cycle time to filing as compared to the industry average (Krishna, 2008).

Biologics and small molecules complement each other. They are the two faces of the same coin and are complementary to each other as they are developed with the same objective of ameliorating the disease. Based on the validated target, suitable approach either in the form of small molecule or biologic, either singly or in combination has to be pursued.

Very high stakes have been placed on the drug discovery program, world over. A portfolio based complementary approach in tapping small molecule and biologics will yield better results. It will help in making the program efficient, and will help to evenly spread the overall risk in the discovery and development phases.

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