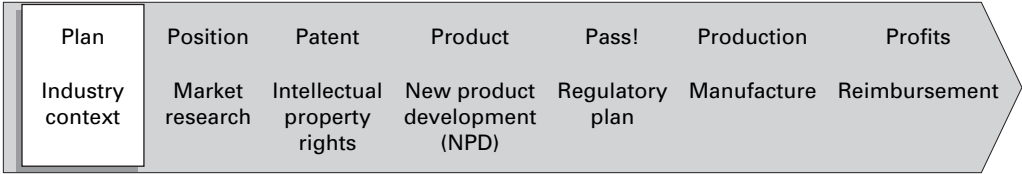


1 The biomedical drug, diagnostic, and devices industries and their markets



Roadmap of a product commercialization plan. Stage 1

- Learning points:
- Description of types of FDA-regulated products covered in this book,
 - Understand the technological base and application for each product type,
 - Description of functions and processes involved in commercialization activities for each product type,
 - Analysis of industry sector competitiveness by value chain model and Porter’s five forces analysis,
 - Understand the technology trajectories for the biomedical industry.

1.1 The healthcare industry

The healthcare industry and the markets for healthcare services and biomedical products have one significant difference from the rest of the free-market industries in the US – the healthcare market is heavily regulated. But several other differences are also notable. For example, while purchasing a retail item or a service in a competitive market, the user is the primary customer and makes the purchasing decision, the user is given all appropriate requested information on the product, and the user is then the payer. In the healthcare marketplace, the user (patient) usually does not make the purchasing decision (the provider and other intermediary institutions, such as pharmacy benefit managers make that decision), the patient does not get all the information (the provider typically gets the detailed briefing and information packages) and the patient is not the payer (the patient usually does not know the true price of services and products; the payer is the insurance company or government). This marketplace is highly regulated, starting from the early product development stages to the preparation and

dissemination of marketing information, and including the flow of payments, goods, and information. The government is also the largest single payer organization in the healthcare industry and, thus, politics influence payment policies and procedures in the industry. Laws and policies enacted by the legislative bodies play a very important role in shaping the healthcare marketplace. Manufacturers or product developers, therefore, need to pay attention to laws and policies as changes could affect their product development process. In fact, as noted here in Box 1.1 by the heads of two major biomedical technology company associations, companies must be proactive in monitoring and interacting with legislators (elected representatives) in government and with regulatory agencies. The manufacturers must monitor changes in policy that impact the market and take an active role to educate and inform the drafting of such policy and regulation. Any commercialization plan for a new biomedical technology must be carried out mindful of the context of this regulated and politically charged healthcare marketplace.

The rest of this chapter discusses the various product development sectors involved in the larger healthcare industry and highlights methods to analyze and understand better the functional structures from a product development perspective.

1.2 Biomedical technology – definition and scope; applications

This book covers regulated biomedical products that go through the FDA (Food and Drug Administration, USA) for marketing approval, including therapeutic or prophylactic drugs (the term includes small molecule and biologic drugs), diagnostics, and devices. The term **biomedical technology companies** will be used to refer to companies whose products need FDA approval to get to market. The “technologies” include engineering and various sciences, including natural (e.g., life sciences or biology) and applied sciences (e.g., materials science).

Proceeding through these first few chapters, it will become apparent that the terms “biotechnology” and “device” have blurred boundaries today, as an increasing number of leading medical device companies are incorporating biological therapeutics such as cells, DNA, or proteins, and pharmaceutical companies are increasingly tying their products to diagnostic or delivery devices. Such products, codependent or intermingled with other technologies are called combination products. Some examples of combination products are the drug Herceptin (used to treat breast cancer), which has to be prescribed based on a diagnostic test for the gene HER2, drug-eluting stents, bioresorbable sponges with growth factors, skin grafts containing live cells embedded in a matrix and insulin pumps with glucose monitors. The following sections in this chapter define specific product areas in greater detail.

Box 1.1 Policy matters

Building a successful biotechnology company is a risky business. The science is challenging, the endeavor is expensive, and the time horizons from discovery to sales revenue are long. Drugs often fail in clinical trials and investors can be fickle.

But even the most skilled research and development teams backed with the brightest management and supported with hundreds of millions of investment dollars can fail in a policy environment that is not conducive to success.

If patent law doesn't adequately protect intellectual property; if the FDA takes too long or demands unrealistic submissions; if CMS refuses to adequately reimburse; if Congress inadequately funds the NIH or the FDA or imposes irrational requirements on drug approvals; if state, federal, or foreign governments impose price controls or ban technologies, the most competent biotech enterprises cannot succeed.

Every biotech company employee must add his or her voice to our effort. The future depends upon our success.

James C. Greenwood
President and CEO
Biotechnology Industry Organization (BIO)

The importance of medical technology companies engaging in the policy debate and dialogue in Washington, DC has never been greater.

Although most start-up companies are primarily concerned with raising money or moving products towards commercialization, the decisions made by policy makers in Washington often have a greater impact on a company's ability to succeed in the long term. For example, in the past year alone, MDMA and its member companies worked on issues impacting intellectual property, FDA regulations, CMS reimbursement, and barriers to market access.

In the past, advocacy efforts were primarily discussed and driven by large companies. However, increasingly, small to mid-size companies are joining associations and organizations in Washington to ensure that their voice is heard on critical issues. Furthermore, there is a growing appreciation in Washington that the majority of innovation is developed by smaller companies. Therefore, the health of the industry requires policies that foster innovation and competition, not hinder it.

Mark B. Leahey
Executive Director
Medical Device Manufacturers Association

1.3 Drugs and biotechnology – definition and scope

Today, drugs are developed from one of two distinct technological platforms –

- (1) Synthetic organic molecules – *small molecules* (the preferred term used here) made de novo by synthetic chemistry processes or naturally occurring compounds, which have been isolated or re-synthesized in the lab. These are interchangeably called small molecules, drugs, or pharmaceuticals. Oligonucleotide-based drugs (RNA or DNA; composed of nucleic acids) made using synthetic processes are also included in this classification of small molecule drugs as they have more in common with small molecule drugs than the large molecule biologic proteins.
- (2) Biological molecules made by living organisms – using cells or other living organisms to produce therapeutic proteins or biological molecules. These are interchangeably called drugs, biotech drugs, biopharmaceuticals, large-molecule drugs or *biologics* (the preferred term used here).

Therefore, the term *drugs* includes both biologics and small molecule pharmaceuticals. The US Food and Drug Administration defines a drug rather broadly as a substance (other than food) recognized by an official pharmacopoeia or formulary, that is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, and that is intended to affect the structure or any function of the body.

The term *biotechnology industry* was intended to refer to the biologics segment of the drug industry, where core life sciences technologies (and living organisms) are used to make products. However, the term biotechnology industry is currently often used to refer to small or start-up pharmaceutical firms that are developing drugs (whether small molecules or biologics), as most of them are founded based on key inventions in the life sciences. It is important to note that biotechnology companies also develop products for other (non-health related) applications and industries (see Box 1.2). The definition of biotechnology is, in fact, “the use of cellular and molecular processes to solve problems or make products.”

Among the therapies produced by biological production processes (produced in cells or bacteria), the various classes of biotech human therapeutics (biologics) being developed for a large variety of diseases are:

Vaccines, another class of human therapeutics and prophylactics, are produced in biological systems, such as chicken eggs, or engineered cell lines.

Biologic drugs are based on large-molecular proteins or complex biological molecules, such as growth hormones, enzymes, etc. Examples are insulin, growth hormone, enzymes, and immunoglobulins. Erythropoietin (sold as Epogen and other brand names) is a blockbuster drug, with over \$10 billion of sales in 2005. These biological drugs are most efficiently produced by cells or within other living organisms. Biopharmaceutical companies use bioreactors where cells, engineered to produce a specific type of protein, are grown in large

Box 1.2 Diverse applications of biotechnology

While “biotechnology” in this text focuses on life-sciences-based products commercialized in the healthcare industries (needing FDA approval), it is important to remember that many other applications of biotechnology also have great commercial value. In the popular media, the term “biotechnology industry” is used loosely to refer to activities that may be based on a range of technologies unrelated to the life sciences, such as laboratory equipment manufacture, device manufacture, lab automation, reagent production, and synthetic chemistry with small molecules. Therefore, it is always important to understand the specific context in which the term biotechnology is being used.

The use of biotechnology processes at the organism, cellular, and molecular level has many diverse applications, some of which are described briefly below but not covered any further in this book (e.g., even though biotechnology food products are regulated, they are not in the same market and approval paths as other biomedical products discussed here). A common technology base of tools and processes for manipulation and analysis of cells, DNA, and proteins ties all these diverse applications together across these different industries.

Healthcare

This is discussed in the main text.

Environmental biotechnology

Engineered microbes and enzymes can efficiently clean up pollution, and the application of the life sciences to this process is called bioremediation. Environmental applications also include biobleaching, biodesulfurization (removal of sulfur from oil and gas), biofiltration, biopulping, etc.

Industrial biotechnology

Engineered microbes and enzymes can be used as highly efficient components in many industrial chemical synthesis processes. Various industrial applications of biotechnology include the efficient use of enzymes to convert sugars to ethanol (transportation fuel), to make polymers such as polylactic acid (PLA) for consumer plastics production, and to improve processes in the production of fine chemicals, bulk chemicals, and commodity chemicals. Currently efforts are underway to convert cellulose to sugars (and ethanol) on a large scale, thus harnessing biomass that would otherwise be discarded as waste products of food and grain processing.

Agriculture

Biotechnology has been used to engineer new plant and crop varieties that are pathogen-resistant or have greater yield, or add new nutritional benefits to

Box 1.2 (cont.)

existing crops. Some specific applications are in the development of new genetically modified plant and seed varieties, improved processing of grain products and the development of biofertilizers. Basic biotechnologies are also used to improve livestock for food production and to provide new treatments for veterinary medicine. Genetically modified foods are already in widespread use in the US food supply. Agricultural biotechnology is arguably the oldest continuing application of life sciences and includes the manipulation of plants and micro-organisms to enhance yield, add new characteristics, such as increased nutrition or taste, and reduce the use of toxic pesticides or fertilizers; these are all key goals of biotechnology in agriculture and in the food-processing industry.

quantities. The proteins are then purified and most are formulated for intravenous delivery.

A *monoclonal antibody* (*mAb*), a particularly significant type of biologic drug, is a highly specific, purified antibody (protein) that is derived from only one clone of cells and recognizes only one antigen. Monoclonal antibodies (one class of biologics) are an ideally targeted therapy that will only affect the specific protein target against which this antibody is made. The current wave of biologics is driven by mAbs: e.g., Johnson & Johnson's Remicade (infliximab), Roche/Genentech's Avastin (bevacizumab) and Herceptin (trastuzumab) and Rituxan/MabThera (rituximab), Bristol-Myers Squibb's Erbitux (cetuximab) and Abbott's Humira (adalimumab). With 18 mAb products already on the market (as of June 2006) and over 70 in clinical trials, billions of dollars of revenue are projected to be generated by these mAb therapies in the next decade. Like most biologics, mAbs cannot be given orally (they are degraded by digestive enzymes) and hence are infused intravenously. New drug-delivery technologies are also being developed to allow oral administration.

Cell based therapies and tissue engineering – for tissue and organ replacement or functional augmentation. The market for regenerative medicine worldwide is in the billions of dollars, primarily using autologous cells. Gene therapy holds many promises but has been hampered by limitations in delivery vehicles and side effects in some patients. In particular, cell-based therapies are attracting a great deal of attention because of the promise shown by stem cells (embryonic and adult) to become truly regenerative therapies.

Nucleic acids therapy is a particularly interesting, emerging class of drugs that uses synthetic production processes.

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Shreefal S. Mehta

Excerpt

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1.3 Drugs and biotechnology – definition and scope

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Nucleic acid therapies include gene therapy, which is the introduction of specific genes appropriately into the body to enable tissues to produce proteins currently lacking or malfunctioning in the diseased state. Many different gene therapies are being developed, with antisense therapeutics being the first approved in the US. Among other nucleic acid technologies, such as ribozymes, antisense oligonucleotides, and triplex and chimeric endonucleases, siRNA (short interfering RNA, ribonucleic acid molecules) has tremendous current commercial and scientific interest, as seen by the awarding of the 2006 Nobel Prize for Medicine to the discoverers of gene silencing by double-stranded RNA (Andrew Fire and Craig Mello) and Merck's acquisition of siRNA Therapeutics for over US \$1 billion in December 2006. Short interfering RNA interferes with gene expression and uses the cell's own mechanism to control the production of specific proteins.

The biotechnology and biologics segment of the pharmaceutical industry is only 25–30 years old and has seen its revenues grow at an average of 16% per year over the last decade, to reach over \$48 billion in global revenues in 2004 (data from Ernst and Young *Annual Biotechnology Industry Reports*). For the sake of comparison, it is worth noting that small molecule drugs had global sales of over \$400 billion in 2004 (data from annual reports, IMS Health). Although still a small segment of the overall pharmaceutical industry, the growth rate and strong product pipeline of biologic drugs has attracted interest from investors and from the traditional pharmaceutical companies themselves. In particular, the recent biotech impact on the pharmaceutical industry has led to the industry naming itself the “biopharmaceutical industry,” as more large pharmaceutical firms (e.g., Johnson & Johnson, Novartis, Wyeth) adopt biotechnology manufacturing platforms to make drugs. The drug industry thus includes not only large conglomerates with tens of thousands of employees in globally distributed offices, but also includes many small start-up companies formed out of university inventions in the life sciences. Smaller and mid-sized companies are increasingly seeking out niche markets to commercialize their innovations, building focused sales forces and taking their own products to market (for more discussion on business models in the biotechnology sector, see Section 3.9).

The interest in the biotechnology sector lies in the future impact of this technology, as more and more biologic drugs appear, with over 350 biotechnology drugs in the clinical development pipeline in 2004, for a variety of human diseases. An indicator of this rising wave of biologic drugs is that for the first time in 2004, over half of the new drugs approved by the US FDA were biotechnology-based drugs. Another component of the interest in biotechnology (life sciences as a more general science platform) today is in the promise of forthcoming discoveries that will lead to an even better understanding of normal and pathological (disease) processes in the human body, as discussed later in this chapter. The hope is that discoveries will be followed in time with new therapies that will cure disease instead of merely offering palliative treatment or temporary symptomatic relief.

It is important to mention that a significant portion of the biotechnology industry is composed of companies that provide services or make non-regulated products, such as research tools, reagents, bioinformatics programs or services, biomaterials,

etc., that are sold to the drug or diagnostic companies or to the research community in general. The business models, product development cycles, financial, and investment profiles of these companies are quite different from most of the companies discussed in this book. An example of a large company of this type is Invitrogen.

1.4 Devices and diagnostics – definition and scope

1.4.1 Medical devices industry

Devices are defined by the US FDA as an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, . . . , which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals, and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes. Medical device companies use traditional materials like metals or ceramic and advanced materials like composites to produce devices that work by providing mechanical or physical (not chemical) support and interaction with the human body. Some of these devices are implanted (defibrillators), some are non-invasive (EKG monitors) and others are called minimally invasive (catheters). These companies have shorter product cycles and thus are more dynamic in product introductions than biotechnology companies.

Medical device products can be classified by two distinct types of markets – commodity products and innovative medical device products. The former are typically made by large mature companies, such as Johnson and Johnson, Becton Dickson, Welch Allyn, and feature a broad portfolio of commonly used products sold to clinics and hospitals. These products have a long life cycle in the market and their development is marked by incremental innovations that do not change the product mix, merely adding specific features to the design. Profit margins for these products are typically low as customers have high price sensitivity.

On the other hand, innovative medical products such as implantable devices, minimally invasive surgical devices, and new imaging devices are made by both large and small companies, such as Medtronic, Guidant (now part of Boston Scientific and Abbott), Bard, Stryker, and many others. These innovative devices have a short product life cycle, with the next generation entering advanced development even as the first generation enters the market. Innovative medical devices command high profit margins by delivering greater life-saving benefits directly to the patient, but also require high investment in research and development (R&D) for continued improvement and incorporation of new technologies. The medical device industry’s gross revenues for 2005 in the US were greater than \$35 billion. The industry is composed of a few large players, which hold market access and brand name, and many small companies, which have found niche markets in the device industry. The industry sales, broken into the various therapeutic and clinical areas, are summarized in Figure 1.1. Orthopedics and cardiovascular are the two largest device market areas, but others are growing too, as the population demographics shift.

1.4 Devices and diagnostics – definition and scope

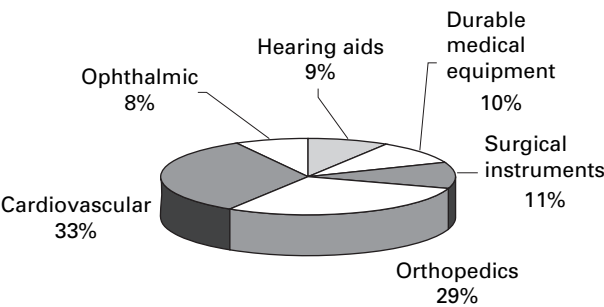


Figure 1.1 US medical device sales by clinical category (\$ 63.9 billion, 2004). Data from Frost and Sullivan, as reported in Standard & Poor’s Industry Survey. For current data and graph, visit www.cambridge.org/9780521870986.

1.4.2 Diagnostics – IVD industry

The diagnostics market is segmented broadly into the *in vitro* diagnostics (IVD; *in vitro* means in the test tube, in the laboratory, or outside the organism) and *in vivo* diagnostics businesses (*in vivo* means within a living organism). *In vivo* diagnostics is a specialty market, with the key players being large instrument manufacturers of imaging or instrumentation technology (GE, Phillips, Seimens). Examples of *in vivo* diagnostics are blood pressure screening, MRI, thermometry, and ultrasound, X-ray, and computed tomography (CT) scanning.

This book will focus mainly on *in vitro diagnostics (IVD)*. The imaging machines that make up the bulk of *in vivo* diagnostic products are made and sold by a handful of large companies and represent a specialized market segment of the device and diagnostics industry. Additionally, the development, sales cycles, and regulatory issues (e.g., radiation issues) are quite different from most of the products discussed here. However, it is important to keep in mind that most of these large companies, GE, Siemens and Phillips, have announced initiatives in molecular imaging diagnostics (which will be regulated as imaging agents or drugs). Thus, this exclusion (from the book) is on the basis of a specialty market segment, not an exclusion of specific companies.

In vitro diagnostic products are largely regulated as devices by the US FDA. There are two types of IVD products: devices (analyzers for samples like blood, serum, urine, tissue, etc.) and reagents (chemicals used to mark or recognize specific components in the samples). All devices and reagents perform tests on samples taken from the body and the applications can be divided into five broad types of IVD testing:

- (1) *General clinical chemistry* – measurements of base compounds in the body, e.g., blood chemistry, cholesterol tests, serum iron tests, fasting glucose tests, urinalysis, etc.
- (2) *Immunochemistry* – matching antibody–antigen pairs to indicate the presence or level of a protein, e.g., testing for allergen reactions, prostate-specific antigen (PSA) tests, HIV antibody tests, etc.

- (3) *Hematology and cytology* – the study of blood, blood producing organs, and blood cells – e.g., CD4 cell counts, complete blood count, preoperative coagulation tests, etc.
- (4) *Microbiology and infectious disease* – detection of disease-causing agents, e.g., streptococcal testing, urine culture or bacterial urine testing, West Nile virus blood screening.
- (5) *Molecular, nucleic acid tests (NAT), and proteomic and metabolomic testing* – the study of DNA and RNA to detect genetic sequences that may indicate presence or susceptibility to disease, e.g. HER2/neu overexpression testing in breast cancer, fluorescence in situ hybridization (FISH) tests for prenatal abnormality testing, HIV viral load assays, etc.

In vitro diagnostics companies are primarily one of three types:

- (1) Large pharma with diagnostic divisions,
- (2) Diagnostic companies, which focus on the manufacture, distribution, and marketing of diagnostic test kits (reagents) and devices,
- (3) Biotechnology (smaller start-up) companies, which focus on the discovery of technology devices and reagents for novel diagnostic methods or tests for specific diseases (e.g., a marker for cervical cancer).

In vitro diagnostics is a mature market (estimated US\$28.6 billion world-wide in sales in 2005) with the highest volume being clinical tests using immunoassays and simple blood tests. More than 20 billion blood tests are performed annually world-wide. However, a rapidly growing segment of IVD markets is in vitro molecular diagnostics or nucleic acid testing (NAT), which analyzes DNA or RNA from a patient to identify a disease or the predisposition of a disease. These nucleic acid tests also have applications in the area of in vivo diagnostics in the emerging molecular imaging techniques and in the development of pharmaceuticals. Biotechnology processes are used to make NAT diagnostic reagents, such as nucleic acid probes.

The industry is fragmented, with larger companies like Quintiles, LabCorp, Covance, Roche, Johnson & Johnson, Abbott, Bayer, and others dominating market access, along with large independent companies such as Bio-Rad, Guerbert, bioMerieux, and Idexx. In terms of lab service revenues, the largest market share, of about 60%, is captured by hospital labs, while independent labs (also called reference labs) hold about 30% of the market share and physician offices cover the rest. Most small private companies either find a niche or get acquired as they are typically unable to attain the market reach of the big players to sustain growth.

1.5 Industry analysis

There are many ways to analyze an industry, with some of the more common methods discussed here. The questions addressed in the following sections are:

Where are the biomedical industry clusters and what are their key characteristics?