1 The biomedical device and drug industry and their markets

1.1 The healthcare industry components and large cycle trends

The healthcare industry and the health markets for services and products differ from the usual free-market industries such as consumer retail or industrial products. For example, while purchasing a retail product or a service in a competitive, free-market economy, the user is the primary customer and makes the purchasing decision from available choices. The user is given all appropriate requested information on the product and the user is then the payer. In the healthcare industry, the end user (patient) usually does not make the purchasing decision (the provider and other intermediary institutions like pharmacy benefit managers make that decision), the patient does not get all the information (the care provider typically gets the detailed briefing and information packages), and the patient is not the direct payer (the payer is the insurance company or government). In many developing countries, while the patient or user is usually the direct payer, the purchasing decision is still made by a more
informed decision maker – usually the caregiver, who could be a doctor or nurse, the pharmacist, or a traditional medicine practitioner. In general, patients do not have the knowledge or training necessary to make an informed decision even if information is provided. The law of averages and pattern recognition built from experience is often the basis for selection and success of the therapy, and the reason why patients are partial to caregivers with the most experience.

Additionally, 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 has a strong influence on payment policies and procedures in the industry. Finally, and most significantly for manufacturers, the government and laws and policies enacted by the legislative bodies play a very important role in shaping the marketplace. Companies must be proactive in monitoring and interacting with legislators (elected representatives) in government and with regulatory agencies to monitor changes in policy that impact the market and to proactively educate and inform the drafting of such policy and regulation. Any commercialization plan for a new biomedical technology must be mindful of the context of this regulated and politically charged healthcare marketplace.

The healthcare marketplace (detailed in Figure 1.1) now must be seen in the broader context of how patients and caregivers make decisions, both for access to and purchase of therapies, whether reactive or proactive, prescriptive (driven by caregiver choice), or over the counter (driven by consumer choice).

The dynamics of power in this industry are now being challenged and changed by the recent increases in computing, making information available to the caregiver and

**Figure 1.1** Regulated human health products and minimally or unregulated human health products

<table>
<thead>
<tr>
<th>Regulated Products</th>
<th>Minimally Regulated or Unregulated Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>(generally regarded as unsafe until proven safe; manufacturer can market with claim to treat disease)</td>
<td>(generally regarded as safe until proven otherwise; manufacturer cannot claim to treat a particular disease)</td>
</tr>
<tr>
<td>Drugs, Biologics</td>
<td>Alternative and Complementary medicine: Dietary supplements, traditional or herbal medicines, homeopathy</td>
</tr>
<tr>
<td>Medical devices used to treat or cure a disease</td>
<td>Mobile apps, fitness trackers, exercise equipment, cosmetics, skincare products</td>
</tr>
<tr>
<td>Diagnostic devices</td>
<td>Devices specifically exempted by FDA in Code of Federal RegisterTitle 21:Parts 862–892</td>
</tr>
<tr>
<td>Veterinary drugs</td>
<td>Veterinary devices</td>
</tr>
</tbody>
</table>
the patient at the point of service. This information is made available as a synthesis or sum of experience and advice from machine learning or artificial intelligence (ML/AI) software that extracts patterns from large pools of “big data.” These same information analysis tools, which are available in more sophisticated and validated form for the caregiver, are making it possible to expand the context for healthcare to be broader than the individual experience, to the community knowledge, and even beyond to bring historical and global knowledge bases to the local point of care.

While social media and internet search engines may have made the patient a “google” doctor, in the end, these new computing methods and technologies may only be shifting some of the decision-power from the caregiver to companies that control the data and analysis. Data are still siloed among providers as a means of control over the patient, and access to potentially useful data is sometimes curbed by legal and business issues.

Advances in computing power are going to continue to impact the healthcare industry at many levels, from the patient to the regulators. In the end, the patient and society have to evaluate whether these and any other new technologies have improved health outcomes, and that will take time.

The rest of this chapter discusses the various product sectors involved in the larger healthcare industry and highlights methods to analyze and better understand their 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 regulatory process (e.g. USA – Food and Drug Administration or FDA, Europe – European Medicines Agency or EMA, China – China Food and Drug Administration or CFDA, India – Central Drugs Standard Control Organization or CDSCO, Japan – Pharmaceuticals and Medical Devices Agency or PMDA) for marketing approval, including therapeutic or prophylactic drugs (the term includes small molecule and biologic drugs), diagnostics, and devices. The term biomedical technology will be used to refer to companies whose products need regulatory approval to get to market. The “technologies” include engineering and various sciences, including natural sciences (e.g. life sciences or biology) and applied sciences (e.g. materials science, computer 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 drugs or biological therapeutics such as cells, DNA, or proteins, and pharmaceutical companies are tying their products to diagnostic or delivery devices. Such products, which are 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 imbedded in a bio-printed matrix, and insulin pumps with blood glucose monitors.
Other examples of the changing technology landscape are the emergence of Software as a Medical Device (SaMD), where stand-alone software programs, apps, and so on are approved as devices for diagnosis or data analysis and decision-support. The following sections in this chapter define the specific product sectors in greater detail.

### 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* (preferred term used in this book) 
   made de novo by synthetic chemistry processes or naturally occurring compounds which have been isolated or resynthesized 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* (preferred term used in this book).

Therefore, the term *drugs* will incorporate both biologics and small molecule pharmaceuticals in common usage and throughout this book. The US Food and Drug Administration (as per section 201(g) of the Federal Food Drug and Cosmetic Act) defines a drug rather broadly as “a substance recognized by an official pharmacopoeia or formulary, intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, and is a substance (other than food) intended to affect the structure or any function of the body [emphasis added].”

The term *biotechnology industry* was used early on to refer to the growing biologics segment of the drug industry, but today is used rather broadly to refer to small-sized bio-pharmaceutical firms that are developing drugs (whether small molecules or biologics) or molecular diagnostics, as most of them are founded based on key inventions or discoveries in the life sciences. It is also important to note that biotechnology companies also develop products for other (non-health related) applications and industries (see Box 1.1). The definition of *biotechnology* (as per the *Encyclopedia Britannica*) 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, immunoglobulins.
**Box 1.1 Diverse applications of biotechnology**

While “biotechnology” in this text focuses on life sciences–based products commercialized in the healthcare industries (needing US 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 also used to loosely 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 important to always understand the specific context in which the term *biotechnology* is being used.

The use of biotechnology processes at the organism, cellular, and molecular levels 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**

Discussed in main text

**Environmental biotechnology**

Engineered microbes and enzymes can efficiently clean up pollution, and application of the life sciences to this process is called *bioremediation*. Environmental applications also include biobleaching, biosulfurization (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, have greater yield, or add new nutritional benefits to 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
Erythropoietin (sold under Epogen and other brand names) was one of the first blockbuster biologic drugs, with over $7 billion of sales in 2015. Biologics are postulated to replace a large portion of the current small molecules due to higher efficacy in many diseases. These biologic 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 quantities. The proteins are then purified and most are formulated for intravenous delivery. For example, the human gene that makes insulin is inserted into yeast cells, which then produce insulin molecules similar to the ones humans make.

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 wave of biologics was driven by mABs like Johnson & Johnson’s Remicade (infliximab); Roche/Genentech’s Avastin (bevacizumab), Herceptin (trastuzumab), and Rituxan/MabThera (rituximab); Bristol-Myers Squibb’s Erbitux (cetuximab); and Abbott’s Humira (adalimumab). In 2006, there were 18 mAB products on the market, and by December 2019 over 79 were approved (Lu et al., 2020), with over $300 billion in global sales projected by 2026 (Fortune Business Insights, 2021). Monoclonal antibodies, like most biologics, cannot be given orally (degraded by digestive enzymes) and hence are infused intravenously. New drug delivery technologies are also in development to allow oral administration.

Next-generation antibodies are already on the market (3 approved) with over 50 in clinical development in 2021. These next-generation antibodies (antibody-drug-conjugates or ADCs) combine the unique targeting capabilities of biologics with the cancer-cell-killing specificity of chemotherapeutics, radioactive isotopes, cytotoxins, or cytokines. The antibodies are directed against antigens that are differentially over-expressed in tumor cells. Potent cancer drugs are chemically linked to these antibodies, giving these antibody-conjugates a superior pharmacological efficiency with minimized side effects.

Cell-based therapies and tissue engineering are used 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 for the truly regenerative potential of stem cells (embryonic and adult). The Japan and Asia-Pacific region is the fastest growing market for regenerative medicine.

Nucleic acid therapy is a particularly interesting and emerging class of drugs that mostly uses synthetic production processes but is usually included under the biologics sector due to the large size of the molecules:

Nucleic acid therapies include gene therapy, which is the introduction of specific genes or segments of nucleic acids appropriately into the body to modify tissues and the production of...
proteins that may be lacking or malfunctioning in the disease state. These therapies lie somewhere between small molecule and biologic drugs in size of molecules, with specific considerations for development driven by their larger size and limited uptake into the targeted tissue. Many different nucleic acid therapies are in development, with antisense therapeutics being the first approved in the USA. Other nucleic acid technologies, such as ribozymes, antisense oligonucleotides, siRNA (short interfering RNA, or ribonucleic acid, molecules), microRNA inhibitors, and triplex and chimeric endonucleases, have tremendous current commercial and scientific interest as seen by the awarding of the 2006 Nobel Prize to the discoverers (Andrew Fire and Craig Mello) of gene silencing by double-stranded RNA. This short interfering RNA (siRNA) interferes with gene expression and uses the cell’s own control mechanism for controlling production of specific proteins. While extremely promising for their targeted approaches, these nucleic technologies have complex development challenges – as seen by Merck’s acquisition of siRNA Therapeutics for over $1 billion in 2006 and subsequent sale a number of years later to Aylaml for $150 million, and Aynlam’s Phase III-level failure in 2016 as a result of seeing more deaths in the drug group than the control population.

Recent discovery of highly specific mechanism for gene editing and repair called CRISPR/Cas-9 [https://en.wikipedia.org/wiki/CRISPR] promises to yield a new class of biologics directed at modifying gene expression using transcription factors (proteins that bind to specific DNA sequences).

The biotechnology/biologics segment of the pharmaceutical industry is about 40 years old (since early 1980s) and has seen its revenues grow at an average of 16% per year over the past two decades, to reach over $132 billion in global revenues in 2015 (Ernst & Young Annual Biotechnology Industry Reports, 2015–2020).

Biologics are a rapidly growing portion of the overall pharmaceutical industry, accounting for over 30% of the total pharmaceutical sales compared to 23% in 2014 (www.statistica.com, “Evaluate Biotech and Medtech 2020 in Review” report, 2021). The growth rate and strong product pipeline of the biologic drugs have attracted interest from investors and from the traditional pharmaceutical companies themselves. In particular, the biotech impact on the pharmaceutical industry has led to the industry naming itself the “biopharmaceutical industry,” as more large pharmaceutical firms (e.g. J&J, Novartis, Wyeth) have adopted biotechnology manufacturing platforms to make drugs.

The interest in the biotechnology sector lies in the future impact of this technology, as more and more biologic drugs are coming through the pipeline, with over 2,500 biotechnology drugs in the clinical development pipeline in 2021, for a variety of human diseases (www.bio.org/fda-approvals-clinical-development-pipeline). Another component of the interest in biotechnology (life sciences as a more general science platform) today is in the promise of forthcoming new discoveries, like the recent CRISPR mechanism discovery, which 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 these new tools and discoveries will lead to new therapies that will truly aim to 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 nonregulated 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, and financial and investment profiles of these companies are very different from most of the companies discussed here. Examples of providers of tools and technologies are Thermo Fisher Scientific (Invitrogen, Applied Biosystems), Qiagen, Perkin Elmer, and Illumina.

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” [emphasis added] (www.fda.gov/medical-devices/classify-your-medical-device/how-determine-if-your-product-medical-device), i.e. achieve their purpose by mechanical action or placement, or now by data analysis if software. Medical device companies use traditional materials such as metals, plastics, or ceramic and advanced materials such as composites to produce devices that work by providing electrical, mechanical, or physical (not chemical) support and interaction with the human body. Some of these devices are implanted (defibrillators), some noninvasive (e.g. EKG monitors) and others minimally invasive (e.g. 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 like Johnson and Johnson, Becton Dickson, Welch Allyn, and others and feature a broad portfolio of 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.

Conversely, 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 (bought by 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 grew to $371 billion in 2017. The industry is composed of a few large players that hold market access and brand name, and many small companies (80% have fewer than 50 employees) that have found
niche markets in the device industry. The industry sales, broken into the various therapeutic and clinical areas, are summarized in Figure 1.2. Orthopedics and cardiovascular are the two largest device application areas, but others are growing too, as the population demographics shift.

1.4.2 Diagnostics – IVD industry

The diagnostics market is segmented broadly into the in vitro diagnostics (IVD) (in \textit{vitro} means in the test tube, laboratory, or outside the organism) and in vivo diagnostics businesses (in \textit{vivo} means within a living organism). This book will focus mainly on IVD, which are classified and regulated as medical devices by the US FDA.

In vivo diagnostics is a specialty market, with the key players being large instrument manufacturers of imaging or other instrumentation technology (GE, Phillips, Siemens). Examples of in vivo diagnostics are blood pressure screening, magnetic resonance imaging (MRI), thermometer, ultrasound, x-ray, and computed tomography (CT) scan. The development, sales cycles, and regulatory issues (e.g. radiation safety 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 all launched 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 diagnostics products are largely regulated as devices by the US FDA. There are two types of IVD products: devices (analyzers for samples such as blood, serum, urine, tissue) 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.
Immunochemistry – matching antibody-antigen to indicate the presence or level of a protein, e.g. testing for allergen reactions, prostate-specific antigen (PSA) tests, HIV antibody tests.

Hematology/cytology – study of blood, blood-producing organs, and blood cells, e.g. CD4 cell counts, complete blood count, preoperative coagulation tests.

Microbiology/infectious disease – detection of disease-causing agents, e.g. streptococcal testing, urine culture/bacterial urine testing, West Nile virus blood screening.

Molecular, nucleic acid tests (NAT), proteomic, metabolomic testing – 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.

In vitro diagnostics companies are primarily one of four types:

1. Large pharma with diagnostic divisions
2. Diagnostic companies, which focus on manufacture, distribution, and marketing of diagnostic test kits (reagents) and devices
3. Biotechnology (smaller startup) companies, which focus on discovery of technology devices/reagents for novel diagnostic methods or tests for specific diseases (e.g. a marker for cervical cancer)
4. Clinical sample analysis laboratory services companies

In vitro diagnostics is a mature market with a high volume of clinical tests using immunoassays and simple blood tests that have not changed in decades. More than 20 billion blood tests are performed annually worldwide. The overall estimated IVD market was $65 billion in 2017. Industry segments by sales are shown in Figure 1.3.

A rapidly growing segment of IVD markets is in vitro molecular diagnostics, or nucleic acid testing (NAT, or genetic testing), which analyzes DNA or RNA from a patient to identify a pathogen, a disease, or the predisposition of a disease. These genetic tests also have applications in the area of in vivo diagnostics in the emerging applications of molecular imaging and in the development of new drugs. Biotechnology processes are used to make NAT diagnostic reagents such as nucleic acid probes.

The lab testing industry in the USA has larger companies such as Quintiles, LabCorp, Covance, Roche, J&J, 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% market share and 10% is with physician offices. 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. Product sales are dominated by industry-leading companies such as Roche, Illumina, Thermo-Fisher, and Danaher.