discoveries and technological advancements have enabled the development of new drugs and therapies that have enhanced the lives of countless millions worldwide. Today, the scientific exploration of *disease mechanisms* is leading to the discovery and development of agents that specifically impact these mechanisms, resulting in new therapeutic modalities. There is a dramatic advance in the development of *biologic drugs*, including monoclonal antibodies, therapeutic proteins, immunotherapies, and vaccines, which is transforming the treatment of many diseases. Presently, biologics is the fastest growing segment within the new prescription drug market and is expected to continue as such in the years ahead. Annually, approximately 40 new molecular entities receive FDA approval for marketing. In addition, many new dosage strengths and dosage forms of previously approved drugs, new generic products, and new biologics are approved each year.

Not all drugs are discovered, developed, and first approved in the United States. Many pharmaceutical companies do drug R&D in other countries, and many drugs are first marketed abroad. Many of the world's largest pharmaceutical companies are multinational firms with facilities for R&D, manufacturing, and distribution in countries around the world. Irrespective of the country of origin, a drug may be proposed by its sponsor for regulatory approval for marketing in the United States and/or in other countries. These approvals do not occur simultaneously, as they are subject to the laws, regulations, and requirements peculiar to each country's governing authority. However, the international effort to harmonize the regulations through the work of the International Conference on Harmonization (ICH) as described at the end of this chapter fosters multinational drug approvals.

Sources of New Drugs

New drugs may be discovered from a variety of natural sources (e.g., plants), synthesized in the laboratory, or created through processes of biotechnology. Historically, some drugs were found by accident, others by serendipity, but most through years of largely random but tireless pursuit by the synthetic organic chemist. Nowadays, new drugs are the chemical or engineered biologic material resulting from research that is more targeted; that is, directed specifically toward the identified physiologic/metabolic process or biomolecular target of a disease. Current methods of drug discovery are discussed later in this chapter.

Throughout history, plant materials have served as a reservoir of potential new drugs. Yet, only a small portion of the approximately 270,000 known plants thus far have been investigated for medicinal activity. Certain major contributions to modern drug therapy may be attributed to the successful conversion of botanic folklore remedies into modern wonder drugs. The chemical reserpine, a tranquilizer and a hypotensive agent, is an example of a medicinal chemical isolated by design from the folklore remedy *Rauwolfia serpentina*. Another plant drug, periwinkle, or *Vinca rosea*, was first scientifically investigated as a result of its reputation in folklore as an agent useful in the treatment of diabetes mellitus. Plant extracts from *V. rosea* yield two potent drugs that, when screened for pharmacologic activity, surprisingly exhibited antitumor capabilities. These two materials, vinblastine and vincristine, since have been used successfully in the treatment of certain types of cancer, including acute leukemia, Hodgkin disease, lymphocytic lymphoma, and other malignancies. Another example, paclitaxel (Taxol), prepared from an extract of the Pacific yew tree, is used in the treatment of ovarian cancer.

After the isolation and structural identification of active plant constituents, organic chemists may recreate them by total synthesis in the laboratory or, more importantly, use the natural chemical as the starting material in the creation of slightly different chemical structures through molecular manipulation. The new structures, termed semisynthetic drugs, may have a slightly or vastly different pharmacologic activity from that of the starting substance, depending on the nature and extent of chemical alteration. Other plant constituents that in themselves may be inactive or rather unimportant therapeutically may