

1 Introduction to Pharmaceutical Sciences

1.1 ORIGINS

a. Ancient Civilizations – World

When humans evolved as a society and started experimenting with food gathering, identifying and eventually growing their own food, especially grains, they also started experimenting with treatments for their ailments. Perhaps the earliest ailments may have a lot to do with injuries – during hunting and fighting – the quest for treatments kept on increasing as they must have realized that many ailments could be treated with simple herbs etc. It is imagined that such treatments must have evolved localized in their original places and subsequently transferred to other places with development of trade.

According to ancient legend, Chinese emperor Shennong is credited as founder of Chinese herbal medicine when he composed the *Shennong Bencao Jing* or The Divine Farmer's Herb-Root Classic in about 2700 BCE. While this composition is lost in time, a copy of this made in 500 CE survives and it details about 365 herbs. It was compiled during the Han dynasty. Around 168 BCE a manuscript described as "Recipes for 52 Ailments" was sealed into a tomb in Mawangdui that included prescriptions for specific ailments (discovered in 1973).

Similarly, ancient Egyptians had the Papyrus Ebers, one of the earliest known herbals dating to 1550 BCE and based on sources, dating back a further 500 to 2000 years. The earliest Sumerian cuneiform clay tablets dated about 2500 BCE give descriptions of various medicines. Inscribed Assyrian tablets dated 668–626 BCE list about 250 vegetable drugs.

A little later, around 400 BCE, Hippocrates was a renowned physician who learned his craft from his father and grandfather (who were also physicians), used about 400 drugs, most being of plant origin. It is claimed by many that the ancient Greeks obtained a large part of their corpus of knowledge from Egypt and Mesopotamia, which they supplemented further with their own experimentation. Aristotle's pupil Theophrastus (371–287 BCE) in his *Historia Plantarum*, (Enquiry into Plants) which was based primarily on Aristotle's notes, deals specifically with medicinal herbs and their uses in the Ninth Book (chapter). In 4th century BCE another Greek physician called Diocles of Carystus studied medicinal properties of plants and wrote a composition detailing medicinal properties of plants. In fact the period around 330 BCE could be considered as golden era of Greek medicine when written herbals were introduced by the physicians Herophilus, Mantias, Andreas of Karystos, Apollonius Mys, and Nicander.

The Greek physician Pedanius Dioscorides wrote a five volume book detailing about 500 medicinal plants in his native Greek in the 1st century CE. The Latin translation *De Materia Medica* was used a basis for many medieval texts. Similarly, Pliny the Elder's (23–79 CE) *Naturalis Historia* (c. 77–79 CE) is a collection of the information contained in about 2000 scrolls detailing, among other things, medicinal plants. Aelius Galenus or Claudius Galenus (Galen) (129- 217 CE) wrote the work *De Simplicibus* which is considered a milestone in medical literature. Later Apuleius also wrote extensively

and his texts also contained the alternative names for plants in several languages. It dates to about 400 CE and a surviving copy dates to about 600 CE.



Fig 1.1 An apothecary publically preparing the drug theriac, under the supervision of a physician
Source: Wikimedia Commons (Library reference: ICV No 11019, Photo number: V0010760)

Galen in fact was a Greek physician who was born in Pergamon which was earlier part of the Greek empire and had now come under the Roman Byzantine Empire (in present day Turkey). By the end of his lifetime, the Western Roman Empire had crumbled and the eastern Byzantine Empire was close to being under Islam in a few hundred years and therefore his works particularly and of other earlier Greek physicians had a great influence in the later Islamic world. The Arabic translations of these works formed the basis of Islamic medicine which was then further developed along scientific lines of research. Such system of medicine is therefore still known as Unani medicine (Unani means Greek in

Arabic). It was also heavily influenced by Ayurveda from the Indian subcontinent whose knowledge had percolated westwards into Middle East.

Muhammad ibn Zakariya Razi (865–915) promoted the medical uses of chemical compounds. Abu al-Qasim al-Zahrawi (936–1013) developed medicines by sublimation and distillation. His *Liber servitoris* provides recipes and explains how to prepare the ‘simples’ from which complex drugs were compounded. Sabur Ibn Sahl (d 869), initiated the pharmacopoeia, describing a large number of treatments for ailments. Al-Biruni (973–1050) wrote one of the most valuable Islamic works on pharmacology, entitled *Kitab al-Saydanah fi al-Tibb* (Book of Pharmacy in the Healing Art), in which he detailed the properties of drugs and outlined the role of pharmacy and the functions and duties of the pharmacist. It lists synonyms for drug names in Syriac, Persian, Greek, Baluchi, Afghan, Kurdi, and some Indian languages. Avicenna, too, described no less than 700 preparations, their properties, modes of action, and their indications. He devoted in fact a whole volume to simple drugs in The Canon of Medicine. Al-Biruni was a contemporary of Ibn Sina (Avicenna) and they corresponded with each other frequently. Of great impact were also the works by al-Maridini of Baghdad and Cairo, and Ibn al-Wafid (1008–1074). Al-Muwaffaq in the 10th century wrote The Foundations of the True Properties of Remedies, amongst others describing arsenious oxide, and being acquainted with silicic acid.

b. Ancient Civilization - India

Perhaps the earliest system of medicine in the world was Ayurveda, which was already highly codified and scientifically developed at the time of its inception, thought to be around 1500 BCE. Ayurveda is a Sanskrit word meaning knowledge of life. The uniqueness of Ayurveda is that it is inexorably linked with Hindu religious texts which imparts it, both an advantage and a disadvantage. The advantage is that it is approved as genuine source of information with the faith of the Hindu masses firmly behind it. The disadvantage is that it is a part of Hindu religious tradition that is part of oral history (*Shruti*) rather than written or composed (*Smriti*) and hence to ascribe a date to such system is difficult.

The oldest Ayurvedic text can be said to be from Charak called Charaka Samhita and it was followed by the Sushruta Samhita around 1500 BCE. It is claimed that the book by Charak was first taught by Atreya, and then subsequently codified by Agnivesh, revised by Charak, and the manuscripts that survive into the modern era are based on one edited by Dridhabala. In *Sushruta Samhita*, the source of all such medical knowledge is claimed to be from Dhanvantari, Hindu god of Ayurveda, who incarnated himself as a king of Varanasi and taught medicine to a group of physicians, including Sushruta. Sushruta was a physician who taught in a school in Kashi (Varanasi) in parallel to another medical school in Taxila (on Jhelum river). Except for some topics, both discuss similar subjects such as General Principles, Pathology, Diagnosis, Anatomy, Sensorial Prognosis, Therapeutics, Pharmaceutics and Toxicology. The Sushruta and Charaka texts differ in one major aspect, with Sushruta Samhita providing the foundation of surgery, while Charaka Samhita being primarily a foundation of medicine.

Ayurveda classifies seven basic tissues (*dhatu*), which are plasma (*rasa*), blood (*rakta*), muscles (*māmsa*), fat (*meda*), bone (*asthi*), marrow (*majja*), and semen (*shukra*). Like the medicine of classical antiquity, Ayurveda has historically divided bodily substances into five classical elements (Sanskrit *panchabhuta*), viz. earth, water, fire, air and ether. There are also twenty *gunas* (qualities or characteristics) which are considered to be inherent in all substances. These are organized in ten pairs: heavy/light, cold/hot, unctuous/dry, dull/sharp, stable/mobile, soft/hard, non-slimy/slimy, smooth/coarse, minute/gross, and viscous/liquid.

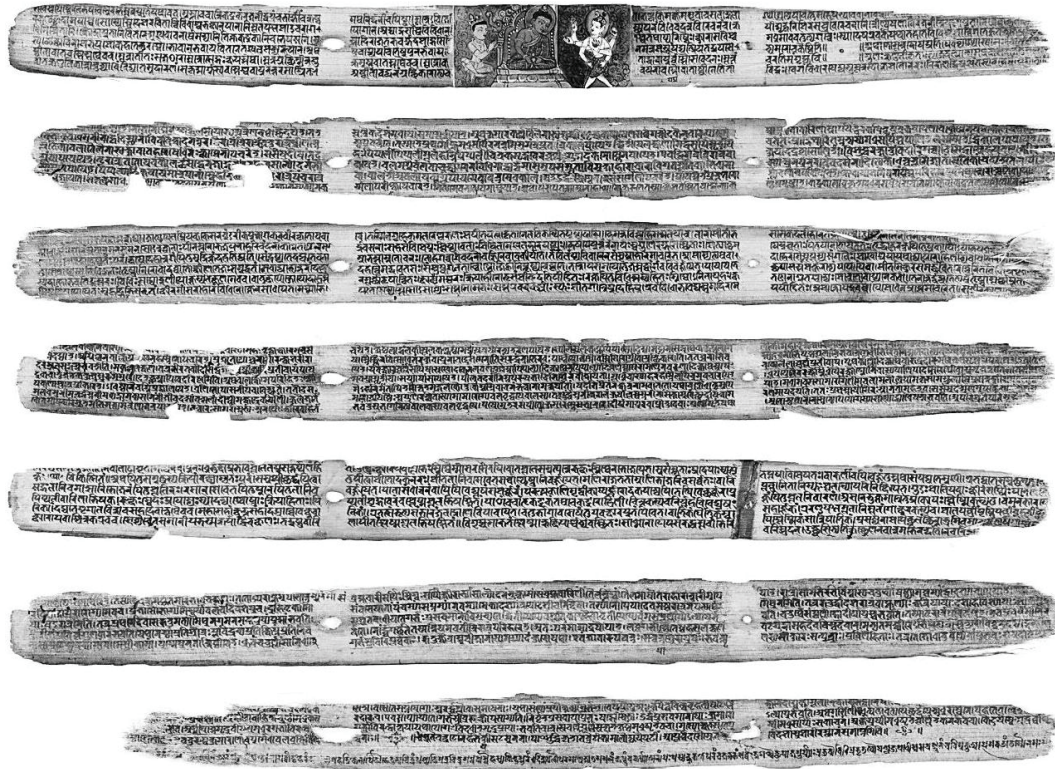


Fig 1.2: The Susruta-Samhita, 12th-13th century (Source: Wikimedia Commons)

Ayurveda also names three elemental substances, the *doshas* (called *Vata*, *Pitta* and *Kapha*), and states that a balance of the *doshas* results in health, while imbalance results in disease. One Ayurvedic view is that the *doshas* are balanced when they are equal to each other, while another view is that each human possesses a unique combination of the *doshas* which define this person's temperament and characteristics. In either case, it says that each person should modulate their behavior or environment to increase or decrease the *doshas* and maintain their natural state.

1.2 EVOLUTION OF MODERN PHARMACEUTICAL INDUSTRY

a. World

With passage of time, such islands of information that were formed initially, started developing into small enterprises that made the medicines and prescribed them to patients and came to be known as pharmacies. The ones who could expand their business, did so and started making larger batches of medicines, to be stored in containers, ready to dispense to patients when they needed them.

In 1240 Roman emperor Frederic II issued a decree by which the physician's and the apothecary's professions were separated. The first pharmacy in Europe (still working) was opened in 1241 in Trier,

Germany. There are old pharmacies still operating in Dubrovnik, Croatia, located inside the Franciscan monastery, opened in 1317; and in the Town Hall Square of Tallinn, Estonia, dating from at least 1422.

In order to improve quality of medicines that were being made at that time in the 16th and 17th centuries, certain minimum standards were drawn up for the manufacturers to follow. In 1546 the first pharmacopoeia, or collected list of pharmaceutical items with directions for making those preparations, appeared in Nürnberg, Germany. Other pharmacopoeias followed in Basel (1561), Augsburg (1564), and London (1618). The London Pharmacopoeia became mandatory for the whole of England and thus became the first example of a national pharmacopoeia.

In London the Society of Apothecaries (pharmacists) was founded in 1617. King James I authorized the separation of apothecaries from grocers also mandated that only a member of the society could keep an apothecary's shop and make or sell pharmaceutical preparations. In 1841 the Pharmaceutical Society of Great Britain was founded. This society oversaw the education and training of pharmacists to assure a scientific basis for the profession.

Merck began as a small apothecary shop in Darmstadt, Germany by Heinrich Emanuel Merck in 1668 and started larger sizes of production, especially alkaloids around 1827. Similarly, Schering in Germany; Hoffmann-La Roche in Switzerland; Burroughs Wellcome in England; Etienne Poulenc in France; and Abbott, Smith Kline, Parke-Davis, Eli Lilly, Squibb, and Upjohn in the US all started as apothecaries and pharmaceutical suppliers between the early 1830s and late 1890s.

In the same time period, synthetic chemistry was also evolving, especially dyestuffs derived from coal tar. It was only soon discovered that these dyes (and their by-products) had ability to act as medicines, especially as antiseptics initially and later against a wide range of diseases. Researchers soon modified the dyestuffs and their by-products to make them more effective as medicines.

Therefore at the end of the nineteenth century and beginning of twentieth century, when both these groups of businesses came together, that resulted in explosive growth rate of the pharmaceutical industry and we can trace the larger and wider operations of these companies from this time period.

This period also saw developments of biologicals in the form of vaccines etc. that were also a part of the large developing pharmaceutical operations in various countries. Englishman Edward Jenner introduced the first vaccine, against smallpox in 1796. He was followed in 1881 by French microbiologist Louis Pasteur who demonstrated immunization against anthrax. Four years later he also developed a vaccine against rabies. More such preparations followed over the years.

The pharmaceutical research from here onwards, the beginning of the twentieth century, marked a future trajectory away from the historical sources of medicines from plants to more closely rely on synthetic chemistry. Since the by-product of sudden development of large towns and its associated antiquated sanitary standards, infections were widespread and were the main cause of health concerns at that time. Necessarily therefore, the initial efforts for new medicines were directed in this direction and was rewarded by the invention of first anti-infective called Arsphenamine (trade name Salvarsan) in 1910 by Paul Ehrlich, a German scientist. This invention was also significant that it was derived using a scientific approach of synthesizing many chemicals and tested each of them until he found the effective one, incidentally Arsphenamine was 606th compound to be tested.

This was followed later by more such significant discoveries like Penicillin in 1929 by Sir Alexander Fleming. Later many more were introduced including other antibiotics (Streptomycin by Merck, Chlorotetracycline by Lederle, Chloramphenicol by Parke-Davis, Erythromycin by Abbott and Lilly, and tetracycline by Pfizer), hormones, vitamins and insulin. Cardiovascular, neurological, and anti-asthmatic diseases also had a fair share of such new medicines.

b. India

In India, the advent of western allopathic medicines came with the coming of western physicians into India. Perhaps the earliest example could be the Portuguese Mestre Joham, accompanying the expedition of Pedro Alvares Carbral in 1500 as the earliest European physician not only in Goa but in all India. Mestre Joham settled in Goa and married a local girl. He was followed by others like Father Joham, Gaspar Pires, Tome Pires, Mestre Jeronimo Dias, Mestre Gil Oria, Cosme Saraiva and Dimas Bosque. The most famous Portuguese physician of the time was Garcia d'Orta who came to India in 1534 when the Portuguese first came to Goa and remained here till his death.

He had already acquired a house and an extensive garden full of medicinal plants when in 1554 he was granted a long lease of a part of an island (Bombay) which he also sublet to other people for additional income. He also supplemented his previous medical knowledge with many more medicinal plants that were new to him in India and was fond of acquiring such knowledge from interactions with Deccanis, Gujaratis, Bengalis, Singalese (Ceylon), Persians, Arabs and Malays when he was assisted by an intelligent Konkani servant girl Antonia. In 1563, Orta wrote his influential book in Portuguese whose title translates as *Colloquies on the Simples, Drugs and Materia Medica of India*.

A hundred years after Orta, a Dutchman Hendrik Adriaan van Reede tot Drakenstein (1636–1691), became the governor of Dutch territories in Malabar, and himself the son of a chief forester in the Netherlands. van Reede consulted the Vaidyars, the traditional Ayurvedic physicians with an extensive, time-tested knowledge of the medicinal value of plants. His chief helper was a Vaidyar named Itti Achuden. Van Reede's magnum opus, the 12-volume *Hortus Malabaricus*, was published from Amsterdam during the period 1686–1703. It described about 780 species of plants, supported by 794 illustrations.

John Fryer (c. 1650–1733) comes across as the next physician of some prominence who after graduation from Cambridge, joined the East India Company and first came to Iran for two years (1677–1679) and from there came to India, landing up at Surat and Bombay.

Nicholas Manucci (1639 – 1717) from Venice was perhaps the most well-known European doctor who came in direct contact with Mughal royalty. In 1656 Manucci came to Delhi and worked as the Mughal Emperor Shahjahan's son Dara Shikoh's artilleryman. After Dara's murder in 1659, he decided to become a doctor, apparently without any training or knowledge. During 1671–78, Manucci practiced medicine in Lahore and then, during 1678–82, served as physician to Shah Alam, the eldest son of Aurungzeb. While in Bidar during this period, he was also sent by the emperor to treat the wounds of the last living Guru of the Sikhs, Guru Gobind Singh which he had acquired after being attacked by assassins. Along similar lines was the story of Francois Bernier (1620–1688) who had a formal degree, an M.D. from Montpellier. Arriving in India in 1658 or 1659, he served for a while as a surgeon to Dara Shikoh and then to his brother Aurungzeb.

Many other European surgeons came to India like:

Armenian	Sikandar Beg	Suleiman Shikoh, Dara's eldest son in 1658
Dutch	Jacob Minues	Agra in 1663
Dutch	Gelmer Vorburg	Assam
Portuguese	Luis Beicao	Mirza Raja Jai Singh in the Deccan (1664)
Venetian	Angello Legrenzi	Shah Alam at Aurungabad (1679)
Venetian	D'Estremon	Sultan of Golconda (1684)
Frenchman	Cattem	Bengal (1700)
Frenchman	Francois de la Palisse	Mughal court
Frenchman	Claudius Malle	Governor of Allahabad 1666
Armenian	Johannes Petuliet	Nawab of Carnatic 1693

By late 1700 to early 1800s, the practice of western medicine slowly got established as the primary health provider service and it had developed to an extent that the physicians were increasingly finding it difficult to collect and prepare their prescribed medicines. Therefore the time was ripe for opening of slightly larger scale apothecaries (pharmacy shops). The first one was opened in Calcutta in 1811, by a Scottish chemist and druggist called Bathgate. He started dispensing prescriptions and toileteries, later adding photographic department and began manufacturing products such as aerated waters, galenicals and biologicals. The company later opened several branches, including one in Calcutta in 1900 and another in Ballygunge in 1910.

Around 1815 a small apothecary's shop was opened in Calcutta by two British surgeons, John Robinson and James Williamson. A third partner, John Smith, joined them in 1826, and a fourth, Thomson Dowson Stanistreet in 1844. The firm changed its name to Smith, Stanistreet & Co. and gradually built up a substantial pharmaceutical trade. By 1869 it was acquired by Charles Noyce Kernot who was so successful that Silas Burroughs (of Burroughs Wellcome), on his travels through India in 1883, noted that Kernot had made "a very large fortune" from it.

E. J. Lazarus, a Welshman from Carmethen arrived in India around 1839, initially gaining experience in a British pharmacy and in a few years moved to Benares, starting his own firm, the first such firm in Benares. William Treacher established the business of Treacher & Co in Bombay in 1864 (manufacturing and wholesale chemist business), opening a branch in Poona in 1879, and another in the popular hill station of Mahabaleshwar in 1889. Similarly Thomson & Taylor opened English pharmacies in Bombay and Poona in 1872 and David Skinner Kemp came to India in 1855 and, within 10 years, had set up his own business in Bombay. He took on two local partners, and in 1882, the business was converted into a limited company.

A British man, Edward Plomer came to India with the East India Company in the early 1860s and sensing a good business opportunity, decided to open a pharmacy shop to mostly cater to the British population in Shimla and also sold stationary, tobacco and set up a photography studio. In 1869 a Scotsman Tom Bliss joined the firm and four years later in 1873 when the owner offered to sell the business, with the assistance of friends, he acquired the firm. Four years later, in 1877, Bliss bought another pharmacy business in Lahore, again trading under the title E. Plomer & Co. He later opened other branches, in Amritsar and Delhi. J. L. Lyell set up the first British pharmacy business in Mussoorie in 1862. He had earlier founded his first British pharmacy in Allahabad in 1858.

Many enterprising Indians were able to develop their apothecaries (or as they called them 'Medical Halls'). One such was Butto Kristo Paul. Starting in the 1860s in a tiny shop in a small one-storeyed building it had moved to a busy side lane in 1896, and occupied two upper floors of the building, with

an elegant sign board. B. K. Paul & Co. It carried out wholesale as well as retail business, and dealt in a wide range of drugs, chemicals and related articles. Many such chemists opened up all over India in late 1800s and early 1900s like Jagat Singh and Brothers in Lahore and Murree, Harnam Das Thakur Das and Sons in Nowshera etc.

The earliest Indian pharmaceutical manufacturing company was Bengal Chemical and Pharmaceutical Works started in 1901 in Calcutta. Later, Alembic Chemical Works was established in 1907 at Baroda where it started manufacturing tincture and alcohol. Sometime later in 1935, Cipla was established in Bombay.

A Pharmaceutical Society of India was formed in 1913 and, in 1920, a new publication — the Indian and Eastern Druggist — for British pharmacists in India was launched. It remained in existence until 1941.

Government of India on 11th August 1930, appointed a committee under the chairmanship of Late Col. R. N. Chopra to see into the problems of Pharmacy in India and recommend measures to be taken. This committee published its report in 1931 stating that there was no recognized specialized profession of Pharmacy. No quality standards existed that included Indian medicinal products as well, in addition to European ones. A little while later Prof. Mahadeva Lal Schroff initiated pharmaceutical education at the university level in the Banaras Hindu University. In 1935 United Province Pharmaceutical Association was established which later converted into Indian Pharmaceutical Association. The Indian Journal of Pharmacy was started by Prof. M. L. Schroff in 1939.

From this report, we find the following categories of pharmaceuticals being used at that time:

- Tincture and other Spirit Preparations
- Liquid Extracts
- Solid Extracts
- Alkaloids
- Organic Antimony and Arsenic Compounds
- Vaccines and Sera
- Organic Therapeutic Products
- Proprietary Liquid Preparations
- Proprietary Solid Preparations
- Oleums, Syrups and Oxymels
- Confections, Emplastrum, Glycerine, Pulveres (powders), Unguentums (Ointments)

In 1940 Government brought ‘Drugs Bill’ to regulate the import, manufacture, sale and distribution of drugs and was finally adopted as ‘Drugs Act of 1940’. Next year the first Drugs Technical Advisory Board (D.T.A.B.) under this act was constituted, as was Central Drugs Laboratory in Calcutta.

In 1945 a milestone was created when Drugs Rule under the Drugs Act of 1940 was established, which is still in force although after numerous additions and deletions as per requirement of the times. In the same year Government brought the Pharmacy Bill to standardize the Pharmacy Education in India. In 1948 Pharmacy Act was published, followed by establishment of Pharmacy Council of India next year. Last major milestone was the publication of the First Edition of Indian Pharmacopoeia in 1955.

1.3 CURRENT STATUS

Indian pharmaceutical industry has an annual turnover of about Rs. 2.2 lac crores, out of which little less than half is contributed by exports. Pharmaceutical exports go to all corners of the world with the majority (about half) going to EU and USA. Around 12,000 manufacturers are actively producing APIs (Active Pharmaceutical Ingredient) or Bulk Drugs as well formulations (dosage forms like tablets, capsules, injections etc.). India is producing a wide range of pharmaceuticals like (in order of market share):

- Anti-Infective
- Cardiovascular
- Gastro Intestinal
- Vitamins and Minerals
- Respiratory
- Pain/Analgesic
- Anti-Diabetic

Top ten Indian pharmaceutical companies:

- Sun Pharmaceuticals
- Lupin
- Dr. Reddy's
- Cipla
- Aurobindo
- Cadila
- Glenmark
- Glaxo Smithkline
- Divis Labs
- Torrent

Top ten Indian biotechnology companies:

- Serum Institute of India
- Biocon
- Jubilant Life Sciences
- Syngene International
- Biological E
- Nuziveedu Seeds
- AstraZeneca Pharma India
- Mahyco
- Bharat Biotech International
- GSK India

While India is recognized internationally for its well-developed infrastructure with respect to pharmaceutical industry, (as demonstrated by fast growing exports of pharmaceuticals, medical devices, pharmaceutical machines, biotechnology products etc.), there are various factors that will be having an impact on future growth. Chief among these include:

- Healthcare spending by government
- Number of hospitals and beds
- Healthcare spending by population
- Health insurance penetration
- Affordability and accessibility of medicines
- Penetration into Tier 2 and rural markets
- Development of Generics market
- Development of biotech segment etc.

1.4 FUTURE

The world pharmaceutical industry had total sales in 2017, of USD 1.11 trillion. Out of this USD 150 billion was spent by pharmaceutical companies on research and development. The top pharmaceutical companies in 2018 include:

- Pfizer
- Roche
- Sanofi
- Johnson & Johnson
- Merck
- Novartis
- Abb Vie
- Gilead
- GSK
- Amgen

Pharmaceutical sciences are by themselves quite specialized and involve a very high level of technology in biologicals, sciences and engineering. Still, efforts are ceaseless to improve in various fields within the industry. Some of the areas attracting special attention from researchers and technologists include:

- Discovering new and better molecules to treat various diseases
- Research methods to minimize or replace animal testing
- Increasing use of supercomputers for molecular modelling for research
- Introducing newer and better drug delivery systems to enhance therapeutic effect
- Researching for green chemistry to minimize generation of waste materials and conservation of energy
- Researching for green engineering for better efficiencies
- Adopting automated manufacturing to a greater extent than at present
- Improving manufacturing efficiency using computerized manufacturing execution systems and ERP
- Increasing use of biotechnology to manufacture complex molecules in cost efficient manner