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On the Development of Medicines and Innovation



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Drug discovery is the process by which new medications are discovered.

Historically, drugs were discovered through identifying the active ingredient from traditional remedies or by serendipitous discovery. Later chemical libraries of synthetic small molecules, natural products or extracts were screened in intact cells or whole organisms to identify substances that may have a desirable therapeutic effect. The advent of the sequencing of the human genome allowed a speedier process.

Modern drug discovery involves the identification of screening hits. Once a compound that fulfills all of these requirements has been identified, it will begin the process of drug development prior to clinical trials. One or more of these steps may, but not necessarily, involve computer-aided drug design.

Despite advances in technology and understanding of biological systems, drug discovery is still a lengthy, “expensive, difficult, and inefficient process” with low

rate of new therapeutic discovery². In 2010, the research and development cost of each new molecular entity (NME) was approximately US\$1.8 billion³. Drug discovery is done by pharmaceutical companies, with research assistance from universities. The “final product” of drug discovery is a patent on the potential drug. The drug requires very expensive Phase I, II and III clinical trials, and most of them fail. Small companies have a critical role, often then selling the rights to larger companies that have the resources to run the clinical trials.

Drug development is a blanket term used to define the process of bringing a new drug to the market once a lead compound has been identified through the process of drug discovery. It includes pre-clinical research (microorganisms/animals) and clinical trials (on humans) and may include the step of obtaining regulatory approval to market the drug.

Governments have been heavily involved in the regulation of drug development and drug sales. In the U.S., the Elixir Sulfanilamide disaster led to the establishment of the Food and Drug Administration, and the 1938 Federal Food, Drug, and Cosmetic Act required manufacturers to file new drugs with the FDA. The 1951 Humphrey-Durham Amendment required certain drugs to be sold by prescription. In 1962 a subsequent amendment required new drugs to be tested for efficacy and safety in clinical trials⁴.

The regulation of drugs varies by jurisdiction. In some countries, such as the United States, they are regulated at the national level by a single agency. In other jurisdictions they are regulated at the state level, or at both state and national levels by various bodies, as is the case in Australia. The

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² Anson, Blake D.; Ma, Junyi; He, Jia-Qiang (1 May 2009). “Identifying Cardiotoxic Compounds”. *Genetic Engineering & Biotechnology News*. TechNote 29 (9) (Mary Ann Liebert). pp. 34–35. ISSN 1935-472X. OCLC 77706455

³ Steven M. Paul, Daniel S. Mytelka, Christopher T. Dunwiddie, Charles C. Persinger, Bernard H. Munos, Stacy R. Lindborg & Aaron L. Schacht (2010). “How to improve R&D productivity: the pharmaceutical industry’s grand challenge”. *Nature Reviews Drug Discovery* 9 (3): 203–214. doi:10.1038/nrd3078. PMID 20168317

⁴ Ibid

role of therapeutic goods regulation is designed mainly to protect the health and safety of the population. **Regulation is aimed at ensuring the safety, quality, and efficacy of the therapeutic goods which are covered under the scope of the regulation.** In most jurisdictions, therapeutic goods must be registered before they are allowed to be marketed. There is usually some degree of restriction of the availability of certain therapeutic goods depending on their risk to consumers.

Depending upon the jurisdiction, medications may be divided into over-the-counter drugs (OTC) which may be available without special restrictions, and prescription only medicine (POM), which must be prescribed by a licensed medical practitioner. The precise distinction between OTC and prescription depends on the legal jurisdiction. A third category, behind-the-counter medications (BTMs), is implemented in some jurisdictions. BTMs do not require a prescription, but must be kept in the dispensary, not visible to the public, and only be sold by a pharmacist or pharmacy technician. The Classification of Pharmacotherapeutic Referrals helps guide the referral process between pharmacists and doctors.

The International Narcotics Control Board of the United Nations imposes a world law of prohibition of certain medications. They publish a lengthy list of chemicals and plants whose trade and consumption (where applicable) is forbidden.

In 2000 U.S. based firms developed 29 of the 75 top-selling drugs; firms from the second-largest market, Japan, developed eight, and the United Kingdom contributed 10. France, which imposes price controls, developed three. Throughout the 1990s outcomes were similar.

Within the United States, pre-approval demand is generally met through treatment IND (investigational new drug) applications (INDs), or single-patient INDs. These mechanisms provide access to drugs for groups of patients or individuals. Through these programs, patients are able to access drugs in late-stage clinical trials or approved in other countries for a genuine, unmet medical need, before those drugs have been licensed in the patient's home country. Patients who have not been able to get access to drugs in development have organized and advocated for greater access (ACT UP, Treatment Action Group, the Abigail Alliance)

World Trade Organization negotiations in the 1990s, including the TRIPS Agreement and the Doha Declaration, have centered on issues at the intersection of international trade in pharmaceuticals and intellectual property rights, with developed world nations seeking strong intellectual property rights to protect investments made to develop new drugs, and developing world nations seeking to promote their generic pharmaceuticals industries and their ability to make medicine available to their people via compulsory licenses.

Some have raised ethical objections specifically with respect to pharmaceutical patents and the high prices for medication that they enable their proprietors to charge, which poor people in the developed world, and developing world, cannot afford⁵. Critics also question the rationale that exclusive patent rights and the resulting high prices are required for pharmaceutical companies to recoup the large investments needed for research and development. One study concluded that marketing expenditures for new drugs often doubled the amount that was allocated for research and development. Other critics claim that patents reward and abet misplaced pharmaceutical R&D priorities, which they describe as being directed to creating incremental improved treatments for diseases prevalent in wealthy countries and away from diseases that cause devastation in the developing world.

Until the 1970s, drug prices were not a major concern for doctors and patients. As more drugs became prescribed for chronic illnesses, however, costs became burdensome, and by the 1970s nearly every U.S. state required or encouraged the substitution of generic drugs for higher-priced brand names. This also led to the 2006 U.S. law, Medicare Part D, which offers Medicare coverage for drugs.

In many jurisdictions drug prices are regulated. For example, in the UK the Pharmaceutical Price Regulation Scheme is intended to ensure that the National Health Service is able to purchase drugs at "reasonable prices." In Canada (as in Lebanon), the Patented Medicine Prices Review Board examines drug pricing, compares the proposed Canadian price to that of seven other countries and determines if a price is "excessive" or not. In these circumstances, drug manufacturers must submit a proposed price to the appropriate regulatory agency. In other jurisdictions, such as the United States, drug costs are unregulated.

⁵ Novartis fought a protracted battle with the government of India over the patenting of its drug, Gleevec, in India (Novartis v. Union of India & Others).



A blockbuster drug is a drug generating more than \$1 billion of revenue for the pharmaceutical company that sells it each year. Cimetidine was the first drug ever to reach more than \$1 billion a year in sales.

Box I: Historical Developments

Using plants and plant substances to treat all kinds of diseases and medical conditions is believed to date back to prehistoric medicine. The Kahun Gynaecological Papyrus, the oldest known medical text of any kind, dates to about 1800 BC and represents the first documented use of any kind of medication⁶. It and other medical papyri describe Ancient Egyptian medical practices, such as using honey to treat infections.

Ancient Babylonian medicine demonstrates the use of prescriptions in the first half of the 2nd millennium BC. Medicinal creams and pills were employed as treatments⁷. On the Indian subcontinent, the Atharvaveda, a sacred text of Hinduism whose core dates from the 2nd millennium BC, although the hymns recorded in it are believed to

be older, is the first Indic text dealing with medicine. It describes plant-based medications to counter diseases⁸. The earliest foundations of ayurveda were built on a synthesis of selected ancient herbal practices, together with a massive addition of theoretical conceptualizations, new nosologies and new therapies dating from about 400 BC onwards⁹. The Hippocratic Oath for physicians, attributed to 5th century BC Greece, refers to the existence of "deadly drugs", and ancient Greek physicians imported medications from Egypt and elsewhere¹⁰.

Al-Kindi's 9th century AD book, De Gradibus and Ibn Sina (Avicenna)'s *The Canon of Medicine* cover a range of drugs known to Medicine in the medieval Islamic world. Medieval medicine saw advances in surgery, but few truly effective drugs existed, beyond opium and quinine. Folklore cures and potentially poisonous metal-based compounds were popular treatments. Theodoric Borgognoni, (1205–1296), one of the most significant surgeons of the medieval period, responsible for introducing and promoting important surgical advances including basic antiseptic practice and the use of anaesthetics. Garcia de Orta described some

⁶ Griffith, F. LI. The Petrie Papyri: Hieratic Papyri from Kahun and Gurob
⁷ H. F. J. Horstmanshoff, Marten Stol, Cornelis Tilburg (2004), Magic and Rationality in Ancient Near Eastern and Graeco-Roman Medicine, p. 99, Brill Publishers, ISBN 90-04-13666-5.
⁸ Atharvaveda XIX.34.9
⁹ Kenneth G. Zysk, Asceticism and Healing in Ancient India: Medicine in the Buddhist Monastery, Oxford University Press, rev. ed. (1998) ISBN 0-19-505956-5
¹⁰ Heinrich Von Staden, Herophilus: The Art of Medicine in Early Alexandria (Cambridge: Cambridge University Press, 1989), pp. 1-26.

herbal treatments that were used.

For most of the 19th century, drugs were not highly effective, leading Oliver Wendell Holmes, Sr. to famously comment in 1842 that “if all medicines in the world were thrown into the sea, it would be all the better for mankind and all the worse for the fishes”¹¹. During the First World War, Alexis Carrel and Henry Dakin developed the Carrel-Dakin method of treating wounds with irrigation with Dakin’s solution, a germicide which helped prevent gangrene.

In the inter-war period, the first anti-bacterial agents such as the sulpha antibiotics were developed. Antibiotics first arrived on the medical scene in 1932; coined the “wonder drugs.” The Second World War saw the introduction of widespread and effective antimicrobial therapy with the development and mass production of penicillin antibiotics, made possible by the pressures of the war and the collaboration of British scientists with the American pharmaceutical industry. The introduction of the sulfa drugs led to a decline in the U.S. mortality rate from pneumonia to drop from 0.2% each year to 0.05% by 1939. Streptomycin found in 1942, proved to be the first drug effective against the cause of tuberculosis and also came to be the best known of a long series of important antibiotics. A second generation of antibiotics were introduced in the 1940s: aureomycin and chloramphenicol.

Medicines commonly used by the late 1920s included aspirin, codeine, and morphine for pain; digitalis, nitroglycerin, and quinine for heart disorders, and insulin for diabetes. Other drugs included antitoxins, a few biological vaccines, and a few synthetic drugs. Drugs increasingly became “the center of medical practice”¹². In the 1950s other drugs emerged including corticosteroids for inflammation, rauwolfia alkaloids as tranquilizers and antihypertensives, antihistamines for nasal allergies, xanthines for asthma, and typical antipsychotics for psychosis. In the 1950s new psychiatric drugs, notably the antipsychotic chlorpromazine, were designed in laboratories and slowly came into preferred use. As of 2007, thousands of approved drugs have been developed. Increasingly, biotechnology is used to discover biopharmaceuticals. Recently, multi-disciplinary approaches have yielded a wealth of new data on the development of novel antibiotics

and antibacterials and on the use of biological agents for antibacterial therapy¹³.

Box II: PhRMA

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country’s leading biopharmaceutical researchers and biotechnology companies. PhRMA is devoted to advancing public policies in the U.S. and around the world that support innovative medical research, yield progress for patients today and provide hope for the treatments and cures of tomorrow.

The Pharmaceutical Research and Manufacturers of America (PhRMA) was formed in 1958 to represent America’s biopharmaceutical research companies and seek essential alignment between public policy and medical research to address patient needs.

Prior to the introduction of a generic to the market, an innovator biopharmaceutical research company has taken a brand-name medicine through the long journey from idea to discovery, early-stage research and development to clinical trials, regulatory review and finally to patients. Over time, these innovative new medicines lead to generic copies that patients use at low cost for many years. Generics currently account for 84 percent of all prescriptions filled in America—and that is part of the lifecycle at work¹⁴.

It is estimated that more than 5,000 innovative drugs are in development worldwide by biopharmaceutical companies and over \$500 billion invested in R&D since 2000. Biopharmaceutical research companies and their partners in the scientific arena forge alliances. There is however a need for a regulatory and public policy environment that fosters medical advancements.

Key Facts

- PhRMA companies spent an estimated 51.1 billion in 2013 to discover and develop new medicines.
- More than 300 new medicines were approved by the Food and Drug Administration in the last decade.
- Roughly 2,900 compounds are currently being studied in the United States alone—more than in any other region.

¹¹ Finkelstein S, Temin P (2008). Reasonable Rx: Solving the drug price crisis. FT Press.

¹² Miller, AA; Miller, PF (editor) (2011). Emerging Trends in Antibacterial Discovery: Answering the Call to Arms. Caister Academic Press. ISBN 978-1-904455-89-9.

¹³ Ibid

¹⁴ <http://www.phrma.org/access#sthash.SDqefcTr.dpuf>



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