Edward D. Zanders

# The Science and Business of Drug Discovery

## Demystifying the Jargon

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ISBN 978-1-4419-9901-6 e-ISBN 978-1-4419-9902-3
DOI 10.1007/978-1-4419-9902-3
Springer New York Dordrecht Heidelberg London

Library of Congress Control Number: 2011931534



Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

*To Rosie*

# Preface

Jargon, according to the *Concise Oxford Dictionary*, can either mean unintelligible words, or gibberish, barbarous or debased language, or else a mode of speech only familiar to a group or profession. Anyone trying to approach the drug discovery industry from the outside might have some sympathy with all of these definitions, particularly if required to deal with industry insiders on a professional basis. The language may indeed seem barbarous or gibberish, but mostly of course, it is the mode of speech familiar to the scientists, clinicians and business people who are responsible for discovering and developing new medicines. All the different professional groups that deal with the pharmaceutical industry will be exposed to the jargon at some point, because the business is highly technical. It is true that a non-scientist, for example, in a technology transfer office, will not be expected to have a detailed knowledge of a product or service being offered to a pharmaceutical company because that is normally left to technical colleagues. On the other hand, he or she should at least be able to recognize where these offerings fit into the bigger picture of drug discovery and why their clients might be interested in taking discussions to another level. In some ways, listening to scientists talking in a business meeting is the same as listening to conversations in a foreign language; just having a sense of the meaning rather than the full detail is enough to avoid feeling excluded. These general principles apply to other professions as well, such as recruiters and translators who, of course, have their own specific issues with jargon. So the need for a guide to the drug discovery industry for non-specialists is clear enough, but what form should it take?

One possibility is a training program like the *How the Drug Discovery Industry Works* course that I run in Cambridge, England. Although it is quite possible to cover the main points about the biopharmaceutical industry in a single day, only a limited amount of information about such a vast subject can be conveyed to delegates without all concerned feeling that they had just finished the New York marathon. My thoughts turned to producing something that could be hosted online. This not only has obvious attractions in terms of distribution and reach, but also runs the risk of being submerged in the vast oceans of information available in cyberspace. Since there is something quite comforting about reading the printed word on

paper (or e-Reader), I resisted the temptations of the new and decided to write a book instead. The aim is to provide a thorough review of the technical and business aspects of drug discovery in a way that can be understood by a reader with little scientific knowledge while still retaining the jargon and terminology that is actually used in the pharmaceutical industry. This jargon and terminology can be daunting even to a trained scientist, so in keeping with the second part of the title *Demystifying the Jargon*, the meanings behind the key terms and phrases are explained in simple terms and placed in the relevant context.

There is no single source of information about all the activities occurring within the pharmaceutical industry, as the sheer number and variety of different processes make this impossible. These activities include such disparate topics as the biology of an infectious microbe, or the leakage of contaminating chemicals from bottle stoppers. Reference material about drug discovery and development is, of course, readily available on the Internet and elsewhere, but this is both a curse and a blessing. When approaching the subject for the first time, it is very difficult to put the information in context, to find authoritative sources and to discriminate between what is important and what is not. On the other hand, once the path through the maze of information has been mapped out, the available resources are incredibly powerful and can provide detail on almost any topic. This book focuses on the most important elements of drug development by laying out a smorgasbord of the topics that underpin discovery, clinical trials, marketing and the pharmaceuticals business, without going into excessive detail about specific points. The vast subject of biochemistry, for example, is covered in fewer than two pages, but the information given is sufficient to give the reader a sense of the essence of the subject, so they are in a position to make an informed (rather than random) search of outside sources.

In writing this book, I have drawn upon experiences gained while working in the pharmaceutical and biotechnology industries for over 20 years since leaving academia. I discuss the technical aspects of chemical and biological research from the perspective of a lab scientist and cover more commercial and strategic issues from a research management background. The great challenge is to convey this knowledge in a way that is intelligible to non-scientists and PhD level scientists alike. I hope that I have been able to achieve this by offering a choice of material that can be used or bypassed according to the reader's experience. Chapter 3, for example, covers the chemistry of small and large molecules in a very basic way and will probably be glossed over by anyone with a science background. However, even in a chapter like this, there will be material that is tailored specifically for some aspect of drug discovery and its jargon, so it will still be useful to those with a more advanced knowledge of chemistry.

Science and business move at such a rapid pace that it is sometimes difficult to keep up with events. Despite this, every effort has been made to keep this book as up to date as possible on both the technical and commercial aspects of drug development. New technical areas (or rebranded old ones), such as systems biology, translational medicine and chemical genomics, are covered in various chapters, as well as the full range of molecular entities that have pharmaceutical potential, including nucleic acids and stem cells. Attention is also given to the major structural upheavals

underway in research-based pharmaceutical companies and how these create both opportunities and barriers to those who deal with the industry.

Finally, to make the demystifying process less arduous, this book intersperses factual information with lighter comments and asides gained from personal observations of the pharmaceutical industry and the behaviour of the participants in this fascinating and important world.

## A Brief Note About Terminology

The names used to describe the drug discovery industry and the companies that form it are used interchangeably according to context:

Drug discovery industry/company
Pharmaceutical industry/company
Pharma industry/company
Biotechnology industry/company
Biotech industry/company
Biopharmaceutical industry/company
Big pharma
Research and development organization
R&D organization

The context should be obvious in most cases. For example, a big pharma company like Pfizer is clearly not the same as a small biotechnology company, although it does use the same technologies. The term "biopharmaceutical company" is a useful term for companies of all sizes that research and develop new medicines, so this term will be used from now on as a generic name for a drug discovery organization. Clearly, a Research and Development organization (or R&D organization) is not restricted to pharmaceuticals, but the term is still used in practice.

Herts, UK Edward D. Zanders

# Acknowledgments

I should firstly like to acknowledge my former employers and colleagues in the biopharmaceutical industry who gave me the opportunity to learn about drug discovery both as a lab scientist and as a manager. In particular, I would like to thank Dr Alan Williamson for opening the doors of large pharma to me and Drs David Bailey and Philip Dean for doing the same with the biotech world.

This book grew out of my drug discovery training courses and it would not have been possible to write it in its present form without helpful discussions and feedback from my delegates, in particular Dr Graham Wagner from Medical Research Council Technology in London. He is an enthusiastic supporter of the approaches I use to explain the complexities of drug development and I am very grateful to him for his encouragement.

I am grateful to Springer Science + Business Media, LLC for agreeing to publish this book and appreciate the editorial assistance of Renata Hutter at their New York office.

I have also had very useful discussions with pharmaceutical translators, who keep me on my toes by picking me up on my use of English. I very much appreciate the assistance of a number of pharmaceutical translators who have helped me with the courses in general and specifically Chap. 20 of the book. They are: Christine Kirkham, Maria Wyborn, Rebekah Fowler, Barbara Patel, also Shelley Nix and some members of her ITI Pharmaceuticals Special Interest Group.

I have been greatly helped by Drs Wendy Snowden and Eddie Blair, who have provided helpful comments and additions to the chapters on clinical trials and diagnostics.

A number of individuals and publishers have kindly supplied figures and data; these include Drs Francesco Falciani, Andrew Filer and Dagmar Scheel-Toellner from the University of Birmingham, Dr Philip Dean from Cambridge, Michael Eckstut from Archstone Consulting and David Campbell from IMS Health in London.

Lastly and by no means least, I am grateful as always to my wife Rosie for her support and encouragement, particularly as she has been experiencing the same ups and downs while writing her own book as I have with mine.

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# Chapter 1
# Introduction

Most people reading this book will be doing so because they want to know how medicines are discovered and developed by the biopharmaceutical industry. They will already know that success and failure in drug development cost money and that there is currently no political or economic will among governments for all the burden of medicines development to be funded by the taxpayer. This means that private drug companies are here to stay for the foreseeable future, despite the less than flattering image that some of them may have acquired over recent years. Whatever the rights and wrongs of the many viewpoints expressed about the pharmaceutical industry, the fact remains that millions of people have first-hand evidence of the power of modern medicines to improve and even save their lives. It is beyond the scope of this book to discuss the different viewpoints in any detail. Having worked in both a major pharmaceutical company and smaller biotechnology start-ups, I can only offer the perspective of a scientist with first-hand experience of what actually goes on inside these organizations and the motivations of the people who work for them. These employees display the range of human personalities found in all walks of life, from the well adjusted, to the perhaps not quite so well adjusted. All of these people have one thing in common: they are enthusiastic about their work and the fact that they might be able to make a positive contribution to human welfare. Sometimes, this last feeling is reinforced when patients write to the company to express their appreciation for a particular medicine used to treat their illness. Despite these fundamentally positive aspects, the challenges facing the biopharmaceutical industry in image and substance are very real. These challenges, and the industry's responses, are discussed further in Chap. 17.

## 1.1 The Benefits of Medicines

Is it possible to measure how much use the biopharmaceutical industry has been to society? One way is to look at the increase in life expectancy at birth that has occurred over the twentieth century. Statistical data from England and Wales combined serve

E.D. Zanders, *The Science and Business of Drug Discovery: Demystifying the Jargon*,
DOI 10.1007/978-1-4419-9902-3_1, © Springer Science+Business Media, LLC 2011

as a representative example of the "developed world" (defined as Europe, North America, Japan, Australia, New Zealand and the former Russian states) (Hicks and Allen 1999). A boy born in 1901 could expect to live for 45 years and a girl for 49 years. By the end of the century, these figures are now 78 and 83 years for boys and girls respectively. Equally striking is the decrease in infant mortality, falling from 140 per thousand live births in 1900 to fewer than 10 at the end of the twentieth century.

How much of this is attributable to better medical intervention? Despite the view held by prominent medical scientists and others that medicines have made the greatest contribution to increased lifespan and decreased mortality, there is considerable debate among historians as to exactly how much of this is due to new medicines and how much is a result of improved nutrition and hygiene. There can be no doubt that the introduction of new medicines in the form of vaccines and antibiotics has contributed to a decline in mortality by controlling infectious diseases. There is, however, a clear distinction between longevity alone and quality of life. There is not much point in extending the lifespan in old age if that means having to put up with chronic disability and suffering. Without wishing to go too much further into this complex subject, it is interesting to note the work of epidemiologists who have studied the contribution of medical intervention to health outcomes. Bunker and colleagues, for example, have made an attempt to quantify these issues, although they recognize that these estimates are based on incomplete data (Bunker 2001). To summarize their results, clinical services, i.e. preventive services and therapeutic interventions, accounted for approximately 17% of the 30-year increase in life expectancy from 1900 to 1950. For the period from 1950 to the turn of the twenty-first century, they estimate that these interventions have contributed to 50% of the 7-year increase in life expectancy. As much as half of this increased medical benefit (post-1950) has been due to the reduction in deaths from heart disease or stroke (cardiovascular diseases); this has been achieved by both antihypertensive (anti-high blood pressure) drugs and cardiac surgery. The remaining 50% increase is due to improved treatments for many other conditions, none of which has individually made such an impact upon life expectancy.

> Everything in life that's any fun, as somebody wisely observed, is either immoral, illegal or fattening.

These words from the humourist P.G. Wodehouse (Wodehouse 1970) have a certain ring of truth to them; leaving out the immoral and illegal bit, this summarizes the dilemma of those with an affluent Western lifestyle who pay for it with a high incidence of chronic disease, such as obesity and diabetes. Major causes of death have changed markedly between 1880 and 1997, most noteworthy being the increase in cancer and cardiovascular disease and the significant reduction in infectious diseases. Respiratory diseases have also been reduced significantly; tuberculosis, for example, killed about 80,000 people in 1880 in England and Wales, but only 440 in 1997 (Hicks and Allen 1999). From a biopharmaceutical industry perspective, there will always be a demand for drugs to treat acute infection, but it is through managing chronic illnesses that the drug discovery industry has the greatest potential to make a positive impact upon human health and wellbeing. This has already been

**Table 1.1** A list of conditions and drug types used to treat them. This is a personalized illustration of the health benefits of modern medicines

| Medicinal product | Benefit |
|---|---|
| Anesthetic | General anesthesia for operations (tonsillectomy, dental abscess) local anesthesia – dentistry |
| Antibiotics | Control of numerous infections, including bronchitis and pleurisy |
| Vaccines | Freedom from polio, smallpox, diphtheria, tetanus, etc. |
| Antipyretics | Aspirin, paracetamol for fever and acute pain relief |
| NSAIDs | Anti-inflammatories for muscle strains and gout |
| Allopurinol | Freedom from gout |
| ACE inhibitors | Normalized high blood pressure |
| Opiates | Pain relief for slipped disk |
| Inhaled steroids | Control of seasonal rhinitis |

*Abbreviations*: *NSAIDs* non-steroidal anti-inflammatory drugs, *ACE inhibitors* angiotensin-converting enzyme inhibitors

illustrated in the case of cardiovascular disease (primarily stroke), where the death rate in USA has fallen threefold between 1950 and 1996.

These statistical data, although informative, are also rather impersonal. Another way of assessing the benefit of medicines is simply to look at one's own life and ask whether it would be significantly different if the treatments were not available. I have been fortunate enough to have enjoyed reasonable health from childhood to middle age without (so far) any serious chronic illness, so the different medical treatments I have required over the years are not very remarkable (Table 1.1).

It is hard to avoid the conclusion that my chances of reaching my present age would have been slim without the vaccines and antibiotics. Furthermore, the control of blood pressure by ACE inhibitors has made it more likely that I can postpone a heart attack or stroke (still the biggest killers) for a few more years at least. Other medicines have enhanced the quality of my life rather than saved it. The anti-inflammatory and analgesic medicines have made it more bearable, as anyone who has suffered an acute attack of gout will understand, and the allopurinol has effectively eliminated this disease, and the accompanying risk of kidney stones, for as long as I take the tablets.

This, of course, is one person's luck of the draw; all of us have lost friends or relatives to cancer, and as we get older, we become more aware of the scourge of dementia. This should focus the mind on what the biopharmaceutical industry is ultimately in business for. The technical and commercial challenges are enormous, but ultimately surmountable, if past experience is anything to go by.

## 1.2 Economic Health

What about the contribution of the biopharmaceutical industry to economic wellbeing? The industry is mainly comprised of individual businesses that have to trade at a profit in order to support their existence through innovation and by attracting investment

from the financial markets. Although its primary role should be to improve human (and animal) health,[1] the economic contribution by pharmaceutical and biotech companies to countries, organizations and individuals can be substantial. One economic indicator is a strong balance of trade in pharmaceutical products. Switzerland, for example, made over $20 billion profit in exported pharmaceuticals during 2007 (Association of the British Pharmaceutical Industry (ABPI) 2010). Other indicators are tax revenues and job creation. The following headline figures for the US economy in 2006 have been published by Archstone Consulting LLC and Professor Lawton Burns of the Wharton School, University of Pennsylvania (Archstone Consulting and Burns L 2009), and are reproduced with the kind permission of Archstone Consulting, a division of The Hackett Group, Inc.

- Jobs
  686,442 direct jobs and 3.2 million jobs
- Ripple effect
  Each direct job in the biopharmaceutical sector supported 3.7 other jobs
- Wages
  Average annual wages of $88,929
- Tax revenues
  Average of $21,858 in federal taxes compared to an average of $7,384 for employees in the rest of the economy
- Macroeconomic Impact
  $88.5 billion direct contribution to GDP, triple the average contribution from sectors in the rest of the economy. On a per-employee basis, the sector's direct contribution to GDP was 71% more than the average contribution from sectors in the rest of the economy. For every dollar that biopharmaceutical companies contributed to GDP in 2006, the ripple effect of that activity supported another $2.33 in contribution to GDP from other sectors
- Investment in R&D
  US biopharmaceutical companies invested $56.1 billion in research and development. This estimate represents an investment in US research of $65,381 per direct employee, approximately eight times the published estimates of R&D spending per employee in all manufacturing industries between 2000 and 2004

Although the US (and global) economy has undergone some major changes since 2006, the strong economic influence of the biopharmaceutical sector is still being felt. There is a feeling in scientific circles that the twenty-first century is the century of biology, just as the twentieth century was dominated by physics. This has caught the attention of governments worldwide, who consider investment in the life sciences to be critical for the future economic wellbeing of their countries.

[1] This book does not cover veterinary medicine and drugs, but the scientific principles are the same for humans and animals.

## 1.3 Third World No Longer

The Westernized "developed" economies are, by a very large margin, the largest markets for prescription medicines. It is, therefore, inevitable that any coverage of the biopharmaceutical industry will assume that its research and development activities are directed almost exclusively at these affluent nations. The problem for millions of people in the developing world is that treatments for tropical diseases such as malaria are not economical to develop and that medicines for "Western" diseases are too expensive. This situation is now changing because of economic, political and social factors, including the rise of "venture philanthropy" and new pricing models. Perhaps most significantly, rapidly growing economies (China, India and Brazil, for example) are sustaining a large number of people with Western lifestyles and the diseases to match. This may be one reason for an increased willingness on the part of multinational pharmaceutical companies to invest heavily in R&D in these countries and to offer generous pricing models for drugs that treat infectious diseases such as malaria. The area of pharmaceutical markets and commercial trends will be covered in Chaps. 16 and 17.

## 1.4 Why Can We Put a Man on the Moon but Still Not Cure Cancer?

The answer to this question is fundamental to understanding the technical challenges that are particular to drug discovery and the life sciences. Put simply, we do not have enough understanding of how living things operate to make precise predictions of what would happen if we perturb them with a drug. Darwinian evolution goes a long way in its explanation of biological phenomena at the population and molecular levels, but this does not really help the pharmaceutical scientist to be more predictive. In fact, evolution throws up a number of obstacles, drug resistance, for example. Physics, in contrast, is underpinned by well-established laws backed up by precise measurements that are often accurate to many decimal places. I have heard a famous physicist state that the subject is actually quite simple. I wouldn't personally go that far (think of quantum theory), but she has a point if a comparison is made with biology. If we look at how physical laws are applied, in electronics for example, the basic idea of digital information being represented by the presence or absence of electrical charge is easy enough to grasp. Combining this with materials science, we get solid state electronics combined with miniaturized power supplies to design computers, mobile phones and the like. The laws of physics create an upper limit to how far these devices can be improved, but it is still possible to say that the limits of present technology have not yet been reached and that better devices will come onto the market. We can almost guarantee that a new electronic device will operate as specified, but we simply cannot do the same for a medicine designed to treat a complex disease. A useful analogy comes in the form of two US

initiatives from the second half of the twentieth century: the Apollo moon landings and the War on Cancer. President Kennedy delivered an address to Congress in 1961 that included the sentence "I believe that this nation should commit itself to achieving the goal, before this decade is out, of landing a man on the moon and returning him safely to the earth". As we know, this was achieved in 1969, through an impressive display of technical skill, project management and bravery on the part of the astronauts. The point here is that the technology was in place to be able to turn a highly ambitious proposal into an achievable objective within a relatively short period of time. Again, the laws of physics were understood and properly exploited. In signing the National Cancer Act in 1971, President Nixon expanded the remit of the National Cancer Institute and enshrined cancer research and prevention into federal law, effectively declaring a "war on cancer". Although it was then understood that the elimination of the disease would take longer to achieve than landing astronauts on the moon, it is now obvious to anyone that 40 years later, despite huge advances in cancer medicine, we are still a long way off the original goal. The blame does not lie with the skilful scientists who have made huge strides in understanding the cellular and molecular biology of cancer and the clinicians who deliver treatments based on drugs, surgery and radiation. Instead, it must lie with the sheer complexity of the disease, with its widespread genetic abnormalities and poorly understood interactions between cancer cells and the cellular environment in the rest of the body.

James Watson is in a good position to comment on the progress in understanding the basic science of cancer since he is co-discoverer of the structure of the DNA molecule. He has written a provocative, but thoughtful, article in the New York Times (Watson 2009) where he recognizes that the 1971 war on cancer has stalled despite the impressive progress that has been made in understanding the molecular details of cancer biology over the last few decades.[2] He also understands that despite the increased number of promising new drug targets for cancer, the drug development process is technically complex, very costly and should be supported in part by government agencies (such as the National Cancer Institute) and the biopharmaceutical industry.

This last sentence neatly encapsulates the themes to be covered in subsequent chapters, namely the technical complexity of drug discovery and the business models that are evolving in industry and academia to support the discovery, development and marketing of these drugs.

[2] Later chapters will cover the technologies (e.g. genetic engineering, DNA sequencing, cell biology and immunology) that have contributed to this knowledge.

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# Part I
# Background to Drug Discovery and Development

# Chapter 2
# Introduction to Drugs and Drug Targets

**Abstract** This chapter lays out some formal definitions of a drug or medicine and introduces the concept of a drug target. It then describes the wide range of drug types that are being produced by the biopharmaceutical industry. These include orally available drugs, proteins, nucleic acids, vaccines and stem cells. Some background on all of these different types of molecule is provided to create a foundation for the remainder of the book.

## 2.1 Introduction

The main focus of this book is the discovery and development of prescription-only medicines (POMS),[1] with some description of the diagnostics being developed to support their use in the clinic. Medical devices, such as metered dose inhalers and osmotic pumps, which are important for delivering drugs to the right places in the body, are only briefly mentioned.

The terms drug and medicine are used interchangeably, although the word "drug" has the connotation of an illegal substance, such as cocaine or heroin (controlled drugs in the UK). The American Food and Drug Administration (FDA) (http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm#D, Accessed 31 Oct 2010) defines a drug as follows:

- A substance recognised by an official pharmacopoeia or formulary
- A substance intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease
- A substance (other than food) intended to affect the structure or any function of the body
- A substance intended for use as a component of a medicine

[1]Once drugs have been approved for use without prescription, they become over-the-counter medicines (OTCs).

E.D. Zanders, *The Science and Business of Drug Discovery*: *Demystifying the Jargon*,
DOI 10.1007/978-1-4419-9902-3_2, © Springer Science+Business Media, LLC 2011

**Fig. 2.1** The dart board analogy of drugs binding to their target. The drugs that bind strongly and selectively to their biological targets are analogous to a dart that sticks firmly to a dart board in a high scoring position. Many drugs bind weakly to a number of targets, giving rise to both desirable and non-desirable side effects

A more scientific definition might be as follows:

> A drug is an agent which modifies a drug target in order to bring about a change in the functionality of that target. Drugs may reduce or accelerate target activity.

A drug target can be thought of as a dart board, where the drug molecules are the darts (Fig. 2.1). Strong, accurate binding of a drug to its target is important for successful activity; by analogy, hitting a high scoring section of the dart board (like the bull's eye in the middle) helps to win the game. The real nature of drug targets and how they are discovered will be covered in the following chapters.

### *2.1.1 Different Types of Medicines*

Many people think of drugs as medicines that are swallowed in the form of pills or capsules. I generally get this answer when I ask my course delegates what comes to their minds when they hear the word drug (leaving aside illegal products). The biopharmaceutical industry was built upon the discovery of orally active medicines and this is still the preferred outcome for any drug development programme. The medicines can be self-administered in a regular way (once or twice daily), with consistent dosing and high patient compliance. Other routes of administration, such as injection, inhalation or topical application, are used to ensure that certain drugs have a chance to enter the circulation without being broken down in the stomach or

liver, but these are simply not as straightforward as oral delivery. While working on drug discovery programmes for asthma, I was told that the ideal drug for a worldwide market would be delivered orally, partly as the result of cultural issues in some countries regarding the use of inhalers. Inhaled drugs are actually very effective in treating asthma, but the point was made that we should always try to develop a pill for this disease if at all possible; indeed this was the desired objective for all our research programmes.

Although orally active small molecules are preferred for new medicines, they are far from the only products being developed by the biopharmaceutical industry, as will become clear in this chapter.

#### 2.1.1.1 Small Molecules

These drugs are usually taken by mouth, although other routes of administration may be required. The chemical definition of a small molecule will be covered in Chap. 3, but drugs of this type are small enough to cross the alimentary canal (stomach and duodenum) after being swallowed. They can then enter the bloodstream and pass into the liver. They are then distributed throughout the body via the circulatory system (Fig. 2.2). The target for the drug is associated with the cells that make up the organs and tissues of the body.

The oral (bio)availability of small molecules that cross the stomach into the liver can be reduced dramatically by a metabolism, which can cause their rapid breakdown and excretion from the body; in addition, drugs can strongly bind to proteins in the blood, thereby reducing the amount available to interact with the drug target. Both metabolism and protein binding contribute to the pharmacokinetic properties of a drug, an important area that is covered in detail in Chap. 11.

If small-molecule drugs are adversely affected by this first-pass metabolism, alternative routes of administration ensure that the drug passes directly into the general circulation. Apart from injection, drugs can be delivered transdermally or subcutaneously (i.e. through, or under the skin respectively). Sometimes drugs are administered rectally in the form of suppositories, particularly if the intended target is associated with gastrointestinal disease. Another route of administration is under the tongue (sublingually), where the drug can reach its target without first passing through the liver. An example of this is the sublingual delivery of nitroglycerine, an important heart medicine in addition to being a high explosive.

#### 2.1.1.2 Proteins

The word protein was first used in 1838 by the Dutch chemist Gerhard Mulder as a result of his studies on biological products such as silk, blood, egg white and gelatin (Vickery 1950). Although not aware of the exact chemical nature of these materials, he reasoned that each source harboured a common “radical” in combination with phosphorus and sulphur. Mulder named this radical “protein” after the Greek word *proteios* meaning “of the first rank or position”.

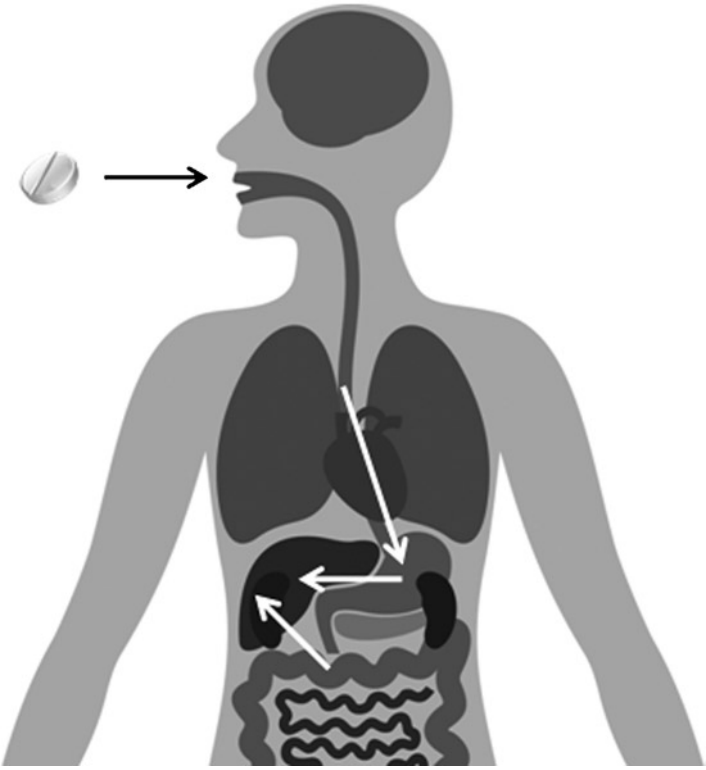

**Fig. 2.2** Passage of orally available drugs into the body. After swallowing a tablet or capsule, the drug is dissolved in the stomach fluids and is passed through the intestines where it is absorbed by the blood vessels entering the liver (hepatic portal system). After the drug has been exposed to metabolic systems in the liver, it passes into the general circulation. Once it reaches the areas where the drug target is expressed, it binds to it and exerts its biological effect

This seems entirely appropriate, as it reflects the central importance of these large molecules in the function of living organisms. From a pharmaceutical perspective, these molecules are both targets for drugs and drugs in their own right. The chemical nature of proteins and their function as drug targets will be extensively covered later in this book.

The first protein drug to be injected into a patient (if we discount vaccines), was insulin. This was purified in 1922 by Banting and Best in Canada who used it to treat a 12-year-old boy with diabetes. After overcoming some initial problems with severe irritation caused by impure samples, the scientists managed to treat the diabetes successfully for several years until the premature death of the patient in a motorcycle accident (Sneader 2005) The success of this, and subsequent trials, led to the introduction of pure forms of porcine insulin (from pigs) and subsequently, human insulin produced using recombinant DNA technology.