Pharmaceutical drug discovery & development

by

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Introduction

Pharmaceutical drugs tend to vary greatly in their structure. The main groups of pharmaceutical drugs today are small molecules and biopharmaceuticals, which are mainly proteins. A main subgroup of biopharmaceuticals is monoclonal antibodies. Future pharmaceuticals may be more diverse in structures and include RNA based drugs and vaccines such as corona vaccines.

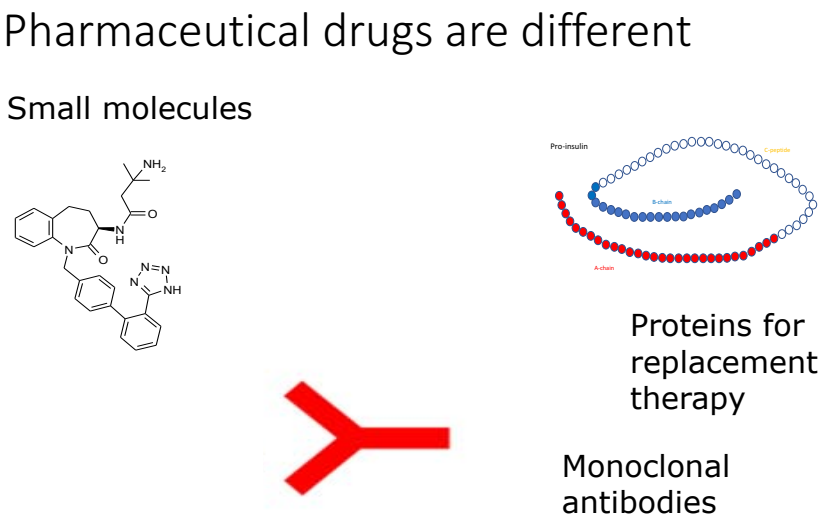

Figure. Different types of pharmaceutical drugs.

The different types of pharmaceutical drugs are administered to patients in different ways. Small molecules can be administrated orally as tablets or

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capsules. Biopharmaceuticals are administrated by injections, in order to avoid their degradation in the gastrointestinal tract.

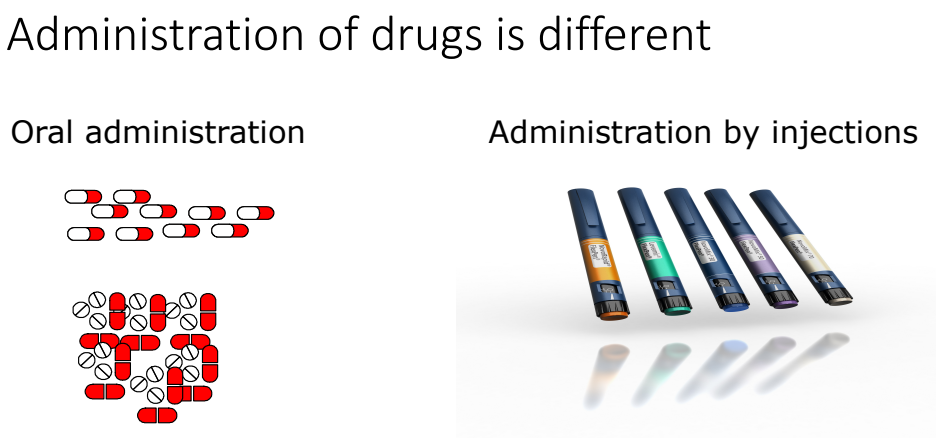

Figure. Different administrations of pharmaceutical drugs.

Drug Discovery & Development Process

Pharmaceutical products need to undergo a long research (drug discovery) and development process successfully in order to be used for the treatment of diseases. The process of drug discovery and drug development is briefly summarized below.

Drug discovery.

Drug discovery for small molecules involves different activities, including:

- basic exploratory biology on target identification and validation;
- assay development;
- chemical lead identification, which usually requires access to high-throughput screening;
- pharmaceutical lead optimization by medicinal chemistry and
- selection of a drug candidate with pharmacological validation from a disease model and/or from biomarker studies.

Optimization of the pharmaceutical properties of the drug candidate with good absorption, distribution, metabolism and excretion (ADME) characteristics, lack of overt toxicity of the drug candidate, and clear efficacy of the drug candidate

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are all crucial factors for a successful outcome of drug discovery activities for a pharmaceutical drug candidate.

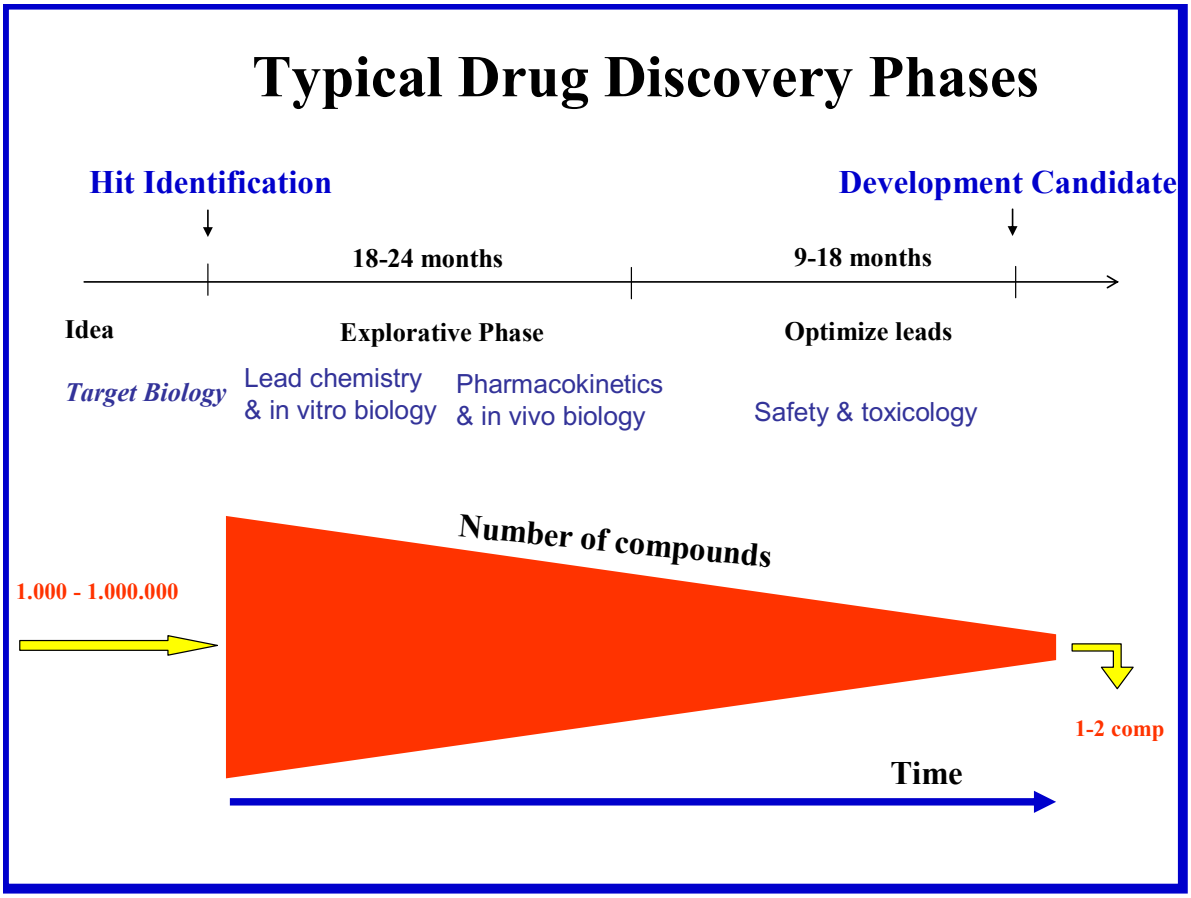

Figure. A typical drug discovery process for a small molecule.

Drug discovery for monoclonal antibodies also requires initial target identification and validation. Thereafter follows the selection of high-affinity antibodies against the target from a large pool of antibodies. Selected antibodies may then be modified in different ways. A drug candidate is selected based on the candidate's antibody profile, including the affinity of the antibody to its target antigen.

For other biopharmaceuticals, like insulin and erythropoietin, there are no target identification or traditional screening activities for leads, but the protein may be modified to optimise its pharmaceutical properties. Optimisation of the manufacturing of the peptide/protein may be complicated depending on the size and complexity of the protein.

Biotech and pharmaceutical companies work with a number of technologies in the discovery phase.

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We can classify technologies within biotechnology in two categories, the technologies generating pharmaceutical drug candidates and the technologies serving as a tool in the drug discovery process like technologies for the characterisation of the drug candidates.

Drug development.

The development process starts with a pharmaceutical drug candidate entering preclinical development. The drug candidate undergoes preclinical animal safety studies using Good Laboratory Practice (GLP).
Process chemistry or biomanufacturing is also initiated to generate sufficient amounts of the drug candidate to enable clinical testing of the drug candidate and subsequently the manufacturing process is optimised for commercial production. The manufacturing process is divided into upstream processes (for biopharmaceutical proteins the development of producer cell lines and master cell banking and then production in bioreactors) and downstream processes (harvesting of protein, purification, formulation and filling). The early work with the manufacturing processes allows for an assessment of drug scalability and drug stability under Good Manufacturing Practice (GMP) conditions. Cost of goods may be estimated, when the optimal manufacturing process has been identified. There is a huge variation of drug candidates in size ranging from the small molecules, like aspirin of 180 Daltons, to peptides like insulin of 5.700 Daltons to proteins such as antibodies of app. 150.000 Daltons. Proteins are more heterogeneous than small molecule because of their size and that they may be modified differently, such as having different glycosylation patterns. Small molecules are produced by chemical methods, while most peptides and proteins are produced by recombinant DNA technologies.

The clinical testing processes are more generic for the different groups of pharmaceutical drug candidates.

Following an approved Investigational New Drug application (often abbreviated to "IND"), the drug candidate can be administered to humans for the first time (Phase I) for safety studies. The next stage is Phase II, which focuses on determining the optimal dosage of the drug, followed by the pivotal Phase III study to analyse efficacy of the drug in patients. Upon completion of clinical studies, sponsors can submit a Marketing Authorisation Application (often abbreviated to "MAA") to regulatory agencies in different countries. The MAA for small molecules is called a New Drug Application (often abbreviated to "NDA") in the United States.

Regulatory applications are handled by the Food and Drug Administration (FDA) in USA. FDA is a federal agency of the United States Department of Health and Human Services. FDA´s goal is to protect the public health by assuring the safety and effectiveness of the products under its supervision and FDA approves or rejects company applications for approval of new

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pharmaceutical drugs. Regulatory authorities similar to FDA (such as the European Medicines Agency in Europe) are responsible for the approval process in other countries.

The below table illustrates the most important characteristics of the discovery and development phases for pharmaceutical drugs.

	Discovery & preclinical studies	Clinical phase 1 studies	Clinical phase 2 studies	Clinical phase 3 studies	Regulatory phase
Duration (years)	2-4	1	2	2-3	1
Success rates	2-5% increasing to >50% over the process	70%	30%	70%	90%
Test population	Laboratory & animal studies	20 – 100 healthy subjects	100-300 patient subjects	> 1.000 patient subjects	
Purpose	Assess biological effect & toxicity	Investigate safety and determine dose	Evaluate optimal dose for efficacy and safety	Show efficacy and safety in significant number of patients	Review
Outcome	Regulatory application (IND for FDA)			Regulatory application (NDA for FDA)	Regulatory approval or decline

Table. The most important characteristics of the discovery and development phases for pharmaceutical drugs.

It will normally take about 8-12 years to take a new compound through the development process, from pre-clinical development to regulatory approval, and the costs will often amount to several hundreds of millions of dollars, (Dickson M. et. al. 2004, Grabowski H. 2008, Wehling M. 2009). Only large well-consolidated companies have the resources to take a drug candidate through this process and bring it to the market. Small biotech companies typically take part in the early research and development process, which is less resource demanding, and then seek a partner among the bigger pharmaceutical companies, which has the capability to continue the development and commercialisation of the potential drug candidate (Munos B. 2009).

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Drug discovery & development costs and timelines

In a previous study on the cost of drug development, DiMasi et.al. estimated that it costs US$ 802 mio (year 2000 dollars, capitalised costs) to bring a new drug to the market (DiMasi J.A. et.al. 2003). This number was later adjusted to US $ 1,241 mio (DiMasi J.A. et.al. 2007).
Drug discovery and development activities are often conducted differently in smaller biotech companies compared to big pharmaceutical companies (Bogdan B. et.al. 2010).
It has been suggested, that the drug development costs overall for biotech are a factor five smaller compared to the development costs of big pharmaceutical companies.
Costs depends in general on the disease indication targeted by the pharmaceutical drug, the complexity of the clinical trials & the clinical endpoints selected in the trial.

Phase	Cost (US$ mio)
Lead optimisation	2-3
Preclinical phase	2-3
Phase 1	1-5
Phase 2	3-11
Phase 3	10-60
approval	2-4

Table. Drug development costs for a small to medium-size biotech/pharma company for an individual project (Bogdan B. et.al. 2010).

The normal timelines for the drug discovery and development phases are outlined in more detail in the table below.

Phase	Length (months)
Lead optimisation	20-40
Preclinical	10-12
Phase 1	18-22
Phase 2	24-28
Phase 3	28-32
Approval	16-20

Table. Duration of drug development (Bogdan B. et.al. 2010).

As an example, Lundbeck recently developed a new anti-depressant molecule Vortioxetine. The drug was developed in drug discovery in 2001. Phase 1 trials were started in 2003 and phase II trials were started in 2006. Positive phase II data were reported in 2007 and phase III trials were started at the end of 2007. Positive phase III data were announced in 2012 and applications for regulatory approval were submitted later in 2012. October 1st 2013 FDA approved Vortioxetine for treatment of depression in USA. The drug had been tested in

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app 5.000 patients over 10 years and development costs were more than 500 mio US dollars.

Pharmaceutical drug attrition

It has been estimated that out of 10,000 small chemical molecule compounds, that might be assessed as potential drug development candidates, only about 10 compounds will be tested in humans to assess effect and safety. Only one of these 10 compounds will subsequently be approved for use in patients. Drug candidates fail to achieve registration for several reasons, and the attrition percentages vary over time and depend on the intended indications for the drug candidate. Lack of efficacy, animal toxicity, adverse effects in humans, pharmacokinetic properties of the drug and portfolio considerations are the main attrition factors (Kubinyi H. 2003).

Reasons for abandonment of drug development were reported by DiMasi in 2007 to be the following:
Economics 33.8%
Efficacy 37.6%
Safety 19.6%
Other 9.0%

Thus, attrition rates (failure rates) are high in drug development, up until the successful completion of phase III clinical trials, and these late clinical trials are also costly. The attrition factors have also been analysed in more detail (Arrowsmith J. Feb 2011). The main attrition factor in phase II trials were reported to be lack of efficacy in patients. Pharmaceuticals having higher attrition rates when tested in phase II trials, include pharmaceuticals for treatment of metabolism diseases, neurological diseases and cancer, see figure below.

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Phase II failures 2008-2010

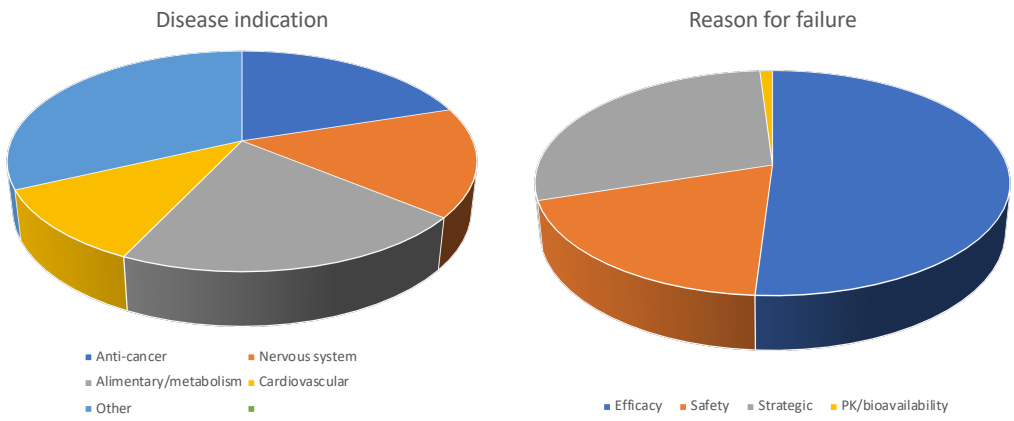

Figure. Phase II clinical trial failure reasons and distribution into different disease indications (Arrowsmith J. Feb 2011).

Lack of efficacy in patients is also the main attrition factor in phase III trials and in the regulatory submission phase (Arrowsmith J. May 2011). Drugs for metabolism indications and cancer, and those involving neuroscience, also appear to have higher attrition rates when tested in phase III trials, as the figure below shows.

Phase III and submission failures 2007-2010

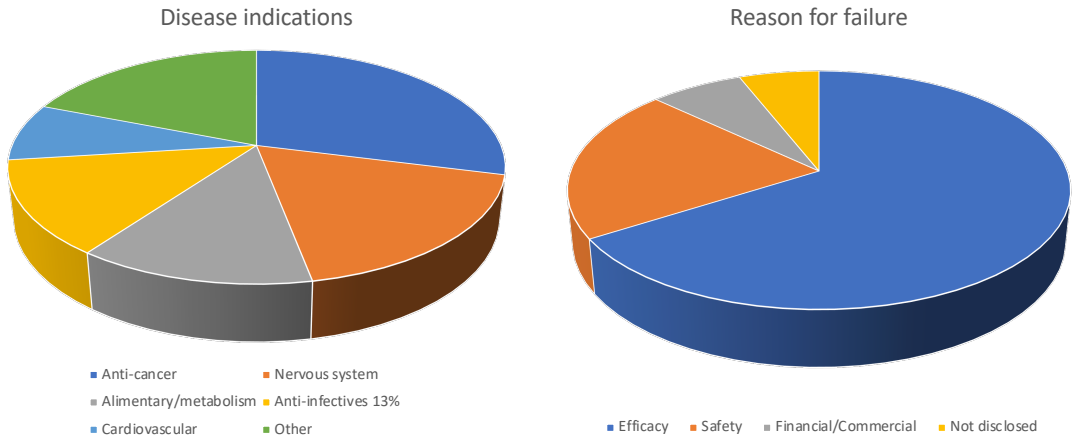

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Figure. Phase III clinical trial failure reasons and distribution into different disease indications (Arrowsmith J. May 2011).

Regulatory approval

The companies will prepare a common technical document for regulatory approval purposes, it includes a complete documentation complying with all requirements defined in the legislation.

The regulatory authorities may issue a marketing authorisation needed for the company to sell a pharmaceutical drug. The marketing authorisation includes a label. The label is the most important part of the marketing authorisation as it provides information to physicians for use of the pharmaceutical product (efficacy and safety information), information to patients (use and side effects) and a framework for appropriate company promotion.

Regulatory focus has shifted over the years from efficacy in 1990´s to drug safety in the 2000´s to the benefit/risk ratio in the 2010´s.

References and information sources

Arrowsmith J. Phase III and submission failures: 2007-2010. Nature Review Drug Discovery vol 10, 1, February 2011.

Arrowsmith J. Phase II failures: 2008-2010. Nature Review Drug Discovery vol 10, 1, May 2011.

Bogdan B. and Villiger R. Valuation in life sciences. Springer publisher. ISBN 978-3-540-7847-6, 2008/2010.

Dickson M. and Gaynon JP. Key factors in the rising cost of drug discovery and development. Nature Review Drug Discovery vol 3, 417-429. May 2004.

DiMasi J.A. and Grabowski H.G. The cost of biopharmaceutical R&D: is biotech different? Managerial and Decision Economics vol 28, 469-479, 2007.

DiMasi J.A., Hansen R.W. and Grabowski H.G. The price of innovation: new estimates of drug development costs. Journal of Health Economics vol 22, 151-185, 2003.

Grabowski H. Follow-on biologics: data exclusivity and the balance between innovation and competition. Nature Review Drug Discovery vol 7, 479-488, June 2008.

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Kubinyi H. Drug research: myth, hype and reality. Nature Review Drug Discovery vol 2, 665-668. Aug 2003.

Munos B. Lessons from 60 years of pharmaceutical innovation. Nature Review Drug Discovery vol 8, 959-968, Dec 2009.

Wehling M. Assessing the translatability of drug project: what needs to be scored to predict success? Nature Review Drug Discovery vol 8, 541-546. July 2009.

Web information available includes:
Scientific publications: Scopus, Pubmed, Web of Science

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