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Drug Discovery: A Modern Decathlon

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Introduction

Over the last 15 years, the number of newly approved drugs has decreased, while the development costs have increased. Recent data from 2012 indicate a reversal of the trend, although it is too early to be certain.[1] Although the development chain for new drugs has for a long time been regarded as the domain of the pharmaceutical industry, many participants work on drug development—from small start-up companies that focus on a single product or product segment to highly specialized companies that provide a defined service (independent of the product), such as clinical trials. The possible contribution of German academia, inspired by successful examples in the USA,[2] is thus being discussed more and more. The journal *Angewandte Chemie* provides a platform for this discussion and four related articles were published in 2012.[3] We aim to highlight, from the point of view of German academic pharmaceutical sciences, the contexts in which contributions from academia are particularly reasonable.

The Costs

The development of a drug can be subdivided into three phases. The first phase is generally referred to as drug discovery and covers the search for a hit, its further development as a lead structure, and its optimization as a development candidate.

The second phase covers preclinical development—the operations necessary to create the technical and regulatory requirements for the first application in humans.

The clinical development phases that follow are comprised of more than 100 studies. An overall schedule, a so-called "Development Master Plan" listing all operational procedures with time, costs, and goals, consists of over 1000 single procedures. Thus, the overall risk is enormous, even with a 99% likelihood of success for each individual procedure. These risks differentiate drug development from a complex project, such as the construction of a cruise liner or a railway station. The development of a drug has scientific and regulatory risks in addition to the technical and financial risks. Consequently, the costs of failed projects are an important factor in the overall scheme. As regards the development costs of new drugs, each value tends to surpass the last, and 2 to 4 billion US dollars are already being discussed. The last well-grounded scientific analyses are available from 2003, and form the basis for Figure 1, which summarizes the time, cost, and probability of success.[4]

The study by DiMasi et al.[4] is based on 68 new developments, and calculated development costs of up to 802 million

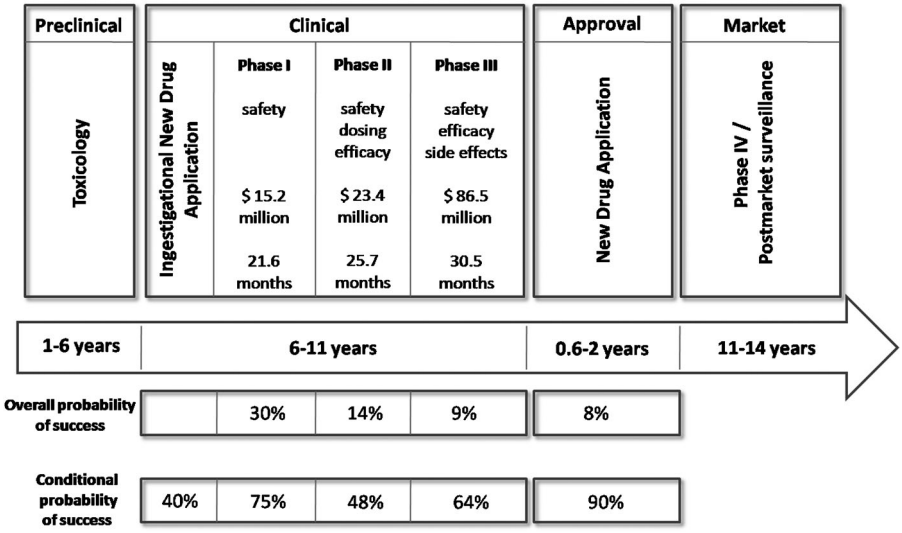

Figure 1. Chronological sequence and success rate of the individual phases of drug development.

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US dollars (MUSD). Closer examination shows that the "actual" costs are only 403 MUSD (out-of-pocket expenses), with the remaining costs being costs of capital (CoC).

In contrast to the common opinion that only late clinical costs make significant contributions to high overall costs, early phases such as lead optimization are considerable cost drivers. This effect becomes clear when the costs of failed compounds are considered. Milne[5] provided interesting insights into this subject (Figure 2); although the data are from 2003, the study is still a suitable reference point.

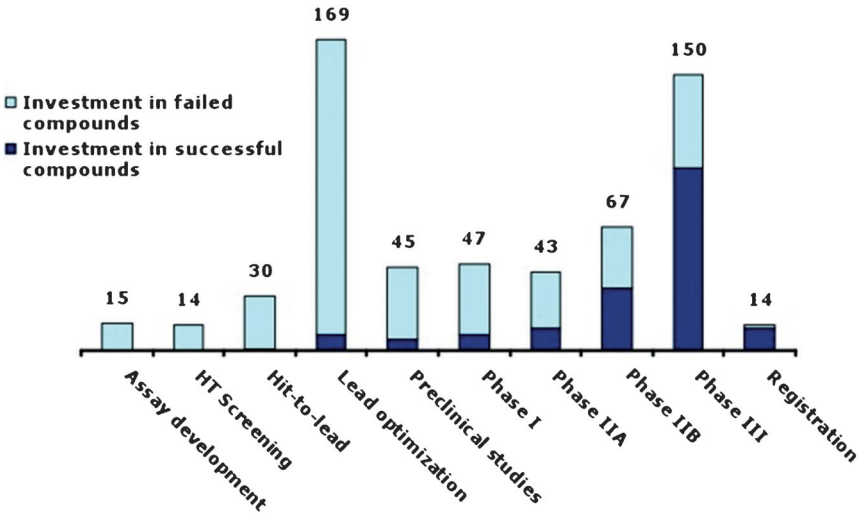


Figure 2. Costs (in MUSD) per phase of drug development and the development of a successful candidate.[5]

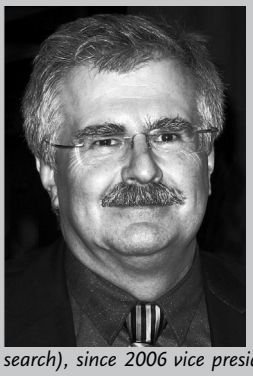
Another interesting aspect is the heterogeneity of development projects. Costs and risks vary greatly depending on the indication of each individual drug and, interestingly, from company to company. The innovation potency of small companies seems to be much higher: 60% of all new drugs are not derived from the Big Pharma pipeline in the US.[6] Certainly, the pronounced entrepreneurial culture and corresponding financial options play a role, and the large research budget of the National Institutes of Health (NIH) in the US likely has an impact.

University cooperation creates interesting aspects for academia and small and medium enterprises (SMEs). If risky drug discovery phases are carried out with early scheduled and specific cooperation, the CoC can be reduced dramatically.

Big Pharma already licenses such projects, but this is driven, to a large extent, by opportunity. Superior quality can be achieved by systematic embedment in the academic world. Sanofi and Bayer have already created new resources for "scouting" and have closed deals with universities, respectively.[3d]

Drug Discovery—Search for a Chemical Lead and Optimization

The discovery of a suitable chemical lead and its optimization as a drug suited for preclinical studies means much more than maximizing enzyme inhibition or increasing the affinity for a receptor that should be activated or inhibited by antagonists or inverse agonists. This process resembles



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a decathlon in many aspects, as many disciplines have to be controlled to turn an initial hit into the desired drug for clinical applications.

1. Modern drug discovery commonly starts with the validation of the target by, for example, knocking out an enzyme to prove that the inhibition of the enzyme in an organism leads to the desired effect. Genomics, proteomics, transcriptomics, and other "omics" can thus provide important information. However, the contribution of these techniques tends to be overrated. Thus, Elliot suggested to, "*Go after compounds, not targets*".[7] A basic approach in this direction is "multiparameter phenotypic screening", which investigates not only the effects of the substances on the target, but also provides more or less complex profiles of action depending on the technology used. Inverse correlations generally exist between the number of parameters investigated and the number of drugs screened per unit of time. This approach considers that reducing a therapeutic approach to a single target fails to take into account the complex interactions of signaling processes within a single organism. Furthermore, active and adverse reaction profiles can be obtained for a substance at an early stage.
2. Drug discovery requires more than high-throughput screening of large substance libraries produced combinatorially. Screening has to be performed with reasonable care to discover false positives arising from, for example, insoluble substances. An open mind has to be maintained to observe unexpected results; for example, Alexander Fleming observed the inhibition of bacterial growth by *Penicillium chrysogenum* settling on an agar plate.
3. Drug discovery requires simple and variable methods of synthesis to vary the lead structure extensively,[8] which is essential for the derivation of structure–activity relationships (SARs, ligand-based design) and rapid optimization to obtain the active ingredient.[9] The efficient optimization of drugs and the provision of sufficient amounts for further biological characterization is the central task of medicinal chemistry.
4. Drug discovery does not only imply the search for natural products and the design of their (frequently complex) synthesis. Natural products are compounds selected from nature, but mostly for another purpose. A marginal number of natural products can be used therapeutically without further chemical modification (e.g. cyclosporine or morphine). Natural products are, for the most part, structurally very complex and frequently contain stereogenic centers. These characteristics should be avoided in drugs because they complicate the synthesis and require an increased effort in biological investigations. All isomers have to be characterized in terms of their pharmacology and toxicology. However, natural products are frequently excellent hits, fragments, or leads,[10] especially for antibiotics and cytostatic drugs. However, as natural products are not suitable for direct application as drugs, because of their complex structures, much "fine-tuning" is needed to turn them into active substances. Therefore, except in the area of antibiotics, natural products are not good clinical candidates.
5. In the case where the target structure can be analyzed by a structural biologist through the X-ray analysis of proteins, including inhibitors, agonists, or antagonists, structure-based design determines the drug discovery process. Virtual screening, pharmacophore design, fragment-based design, docking studies, and many other techniques may help identify and optimize a lead compound. Even though progress has been made regarding the structural determination of enzymes, and even G-protein-coupled receptors over the last few years (e.g. the Nobel prize was awarded to Kobilka and Lefkowitz),[11] the conformational flexibility of proteins should not be forgotten in structure-based design. Flexibility cannot be predicted easily and, therefore, foils rational drug design. The determination of K_i and IC_{50} values is superior to ED_{50} values in structure-based processes because they include the targeting of the target structure. Further biological experiments and syntheses of substances beyond the structure suggested by a computational chemist are irreplaceable.[12]
6. Drug discovery also includes the new discipline of chemical biology, which aids in understanding the interactions between an active ingredient and the biological system, such as proteins, DNA, and RNA. This field is closely related to structural biology, which has been a constant part of the drug discovery process for a long time.
7. Drug discovery requires the knowledge of "druggable" basic structures; this demands a broad knowledge of active ingredients far beyond the actual project, even more than that commanded by pharmacists through their education in medicinal chemistry. Not only is knowledge of the substance structure important, but also its behavior in the human body: how does the drug affect the organism and what does the organism turn the substance into (keyword metabolic stability)? This approach helps avoid adverse reactions by targeting "off-targets" or high first pass effects.
8. Drug discovery requires detailed knowledge of pharmacology and polypharmacology,[13] which can frequently end in toxicology (toxicology could also be described as a special form of polypharmacology). Systems biology can also help avoid undesired off-target effects because it investigates the effect of a chemical on the organism.
9. Drug discovery requires intelligent determination of the absorption, distribution, metabolism, elimination, and toxicology (ADMET) of a drug,[14] which implies more than just keeping to "Lipinski's Rule of Five".[15] Lipinski's rule tries to predict oral bioavailability in a simplified manner. However, small lipophilic compounds with a log*P* value between 2 and 3 can be insoluble and possess poor bioavailability; antibiotics and cytostatic drugs frequently possess a considerably higher molecular weight than the limit of 500 Da, and many other new drugs suffer from "molecular obesity",[16] but are bioavailable and effective.
10. Drug discovery requires knowledge about pharmaceutical technology to render the active substance into a bioavailable compound. Close cooperation between

a pharmaceutical technologist and medicinal chemist is preferable at an early point of time to eliminate compounds with unsuitable physicochemical properties or to, for example, convert a poorly water soluble substance (many highly active substances are poorly water soluble, if at all; e.g. diazepam) into a form that can be injected, infused, or applied and absorbed orally, buccally, or as a suppository. However, drug discovery also includes knowledge about using chemical modification to render active compounds bioavailable without losing their pharmacological effect.

Many of these steps, as well as additional aspects, were summarized previously by Hann and Keserü,[17] and are not discussed in detail here. The skill consists in selecting appropriate development candidates against the background of adequate affinity, selectivity, bioavailability, and metabolic stability, as well as marginal toxicity, good tissue distribution, and the simultaneous lack of predictive models and biomarkers.

How To Use Universities To Develop Innovative Drugs

The question that generally arises, is: how do we get new and innovative drugs efficiently? Of the 252 new drugs approved by the FDA between 1998 and 2007, approximately half were derived from the US. Of these active substances derived from the US, more than 60% were discovered at universities or small biotech companies associated with universities. In contrast, 80% of the new drugs in Germany, UK, and Japan were derived from big pharmaceutical companies.[6] Thus, the contribution of public institutions or small biotech companies associated with universities is relatively small. This difference is certainly related to the traditionally less pronounced cooperation between enterprises and universities.[18] Furthermore, this cooperation originates from academia, where stereotypical thinking and a strong focus on one's research area or subject tends to predominate. Drug research requires integrative thinking and interdisciplinary cooperation to transform therapeutic approaches into the precise development of drugs. Fundamental researchers tend to classify the further development of a chemical lead that arises from their findings as a trivial task, but this is where the decathlon starts. Many background-oriented approaches fail because of characteristics that are assumed to be trivial (e.g. a peptide or aptamer is effective against a recombinant target protein but does not enter the cell, or a drug has only a short half-life in vivo or accumulates in the wrong organ and does not reach its required place of action).

A challenge in the future will be the creation of networks that unite fundamental researchers and drug specialists to enable the efficient development of chemical leads. Paul A. Janssen, who participated in the development of more than 80 drugs, once stated "*A good scientist is someone who succeeds in getting the different disciplines to work in harmony with one another*."[19] Particularly in Germany, different disciplines need to be integrated to close the gap between fundamental researchers and drug specialists, and thereby increase the efficiency of drug discovery. Fundamental sciences and drug developers have to be consolidated. Collaborative innovation, as described by H. Wild, is certainly a move in the right direction.[3d]

Drug discovery can be represented by the multidisciplinary nature of a university. Guided by pharmacists or scientists who have mastered all disciplines of drug discovery, biologists, chemists, toxicologists, pharmacologists, microbiologists, technologists, clinicians, information scientists, theoretical chemists, physicochemists, physicists, and engineers can form an ideal team for developing new drugs. Study courses in "Drug Discovery Research" are offered at many Institutes of Pharmacy in Germany. The university lecturers often possess experience in the pharmaceutical industry. In the US, "Drug Discovery Centers" have been established at 10 universities, which may serve as a reference point.[3a,19,20] Examples in Germany are the establishment of new centers such as the Helmholtz-Institut für Pharmazeutische Forschung Saarland (HIPS) in Saarbrücken, the Center of Drug Absorption and Transport (C_DAT) in Greifswald, the Helmholtz-Zentrum für Infektionsforschung (HZI) in Brunswick, the Fraunhofer Projektgruppe Translationale Medizin und Pharmakologie (Fh-TMP) in Frankfurt, the Interfakultäre Zentrum für Pharmakogenomik und Arzneimittelforschung (ICEPHA) in Tübingen-Stuttgart, the Chemical Genomics Center at MPI Dortmund, and the Lead Discovery Center founded by the Max Planck Gesellschaft in Dortmund, or the promotion of the DFG in the context of Sonderforschungsbereiche (SFBs), groups of researchers or Graduiertenkollegs (SFB 630 (Recognition, Preparation and Functional Analysis of Agents against Infectious Diseases) in Würzburg, FOR 1406 (Exploiting the potential of natural compounds: Myxobacteria as source for therapeutic leads and chemical tools in cancer research) in Munich, KFO 216 (Characterization of the Oncogenic Signaling Network in Multiple Myeloma: Development of Targeted Therapies) in Würzburg, GRK 1172 (Erforschung, Entwicklung und Sicherheit von biotechnologisch hergestellten Arzneimitteln—Biologicals) in Frankfurt), or several EU projects that systematically promote cooperation between universities and SMEs. Examples with considerable participation of pharmaceutical sciences are the Macrocept and Kinacept projects (FP6 Craft-Programm, FP7 "Research for the benefit of small and medium sized enterprises", Tübingen). Additional examples are provided by the BioProfile program of the BMBF, and applications with relevant pharmaceutical participation have been successful. This is, however, not a complete list.

Summary and Outlook

Big Pharma is currently undergoing a structural change; only a portion of new drugs arise from their pipeline. Small spin-offs and companies are responsible for the further development from hits to lead structures and active ingredients, and from active substances to drugs. German univer-

sities can contribute to the drug discovery process, especially the pharmaceutical sciences. The DPhG, as a representative of the pharmaceutical sciences, has recognized the signs of the times.

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