

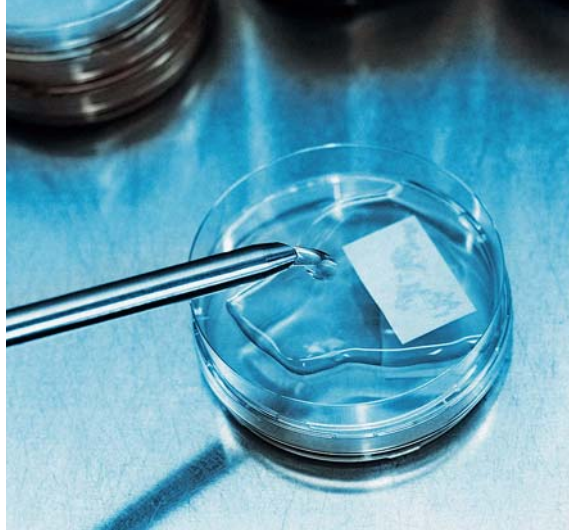
# Antibodies in Clinical Development



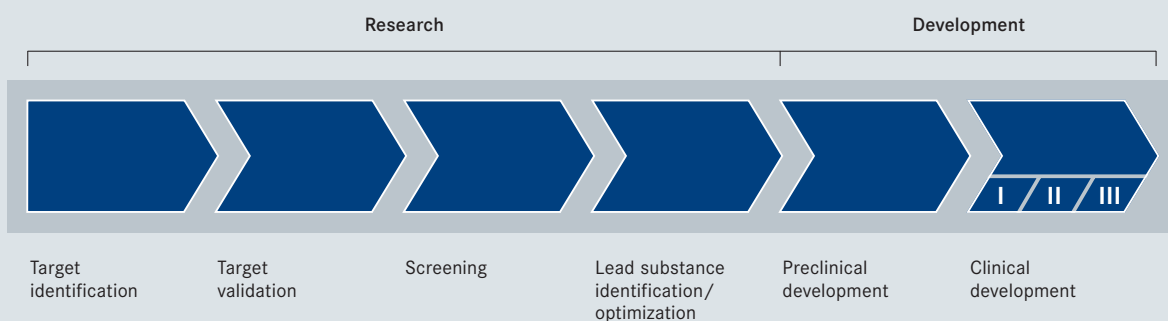
Left Page: Selection of antibodies in the laboratory

Right Page: Steps in preclinical and clinical product development

Annual sales of antibody drugs presently amount to over US\$ 5 billion. Currently, 16 therapeutic antibodies have already been approved and are used in various indications such as cancer, transplant rejection, rheumatoid arthritis, psoriasis, Crohn's disease and antiviral prophylaxis. Of these 16, two have achieved blockbuster status, namely Remicade and Rituxan, both of which generated sales of more than US\$1 billion in 2003. Looking ahead, more than 200 antibodies are presently in various phases of clinical development. Putting this number in perspective, 20% of all biopharmaceutical products in clinical development today are monoclonal antibodies—a clear indication of the increasing importance of antibodies as drugs.



## Steps in Drug Development



### Steps in Drug Development

The idea of specifically using antibodies as therapeutics against various diseases was conceived more than 25 years ago. Antibodies are natural weapons which can be used to remove foreign substances from the human body. It is this ability which researchers seek to exploit when developing antibody drugs.

In the above continuum drug development can be divided into the phases “research” and “development.” One of the first stages of the research phase is the identification of target molecules (target identification). The relevance of the target molecule as a point of therapeutic intervention with regard to particular diseases is subsequently tested (target validation). The next step is the

screening phase and identification of drug lead substances, whose properties are subsequently modified and optimized (so-called lead substance optimization).

After the lead substance has been identified and optimized, preclinical and ultimately clinical development takes place. Many of the steps in preclinical and clinical development are subject to strict regulatory authority, and also include the establishment of procedures for drug manufacture.

**Preclinical studies** are performed in test tubes (*in vitro*) and using animal models (*in vivo*), in order to obtain preliminary information about effectiveness, dosing, and safety of a drug candidate. This phase of drug



development also includes the specification of appropriate manufacturing procedures which guarantee sufficient amounts of the drug, while observing strictly controlled quality criteria. The results of preclinical studies are then submitted for review to regulatory authorities prior to clinical trials in humans.

**Phase I** clinical studies are performed on a small number of healthy subjects and provide the first information concerning appropriate dosage, safety and tolerability. **Phase II** clinical studies include controlled studies with a limited number of patients in order to assess the effectiveness of a product for specific indications, to determine the appropriate dosage and to identify the side effects and risks connected with a drug. **Phase III** clinical studies are controlled studies with a larger number of patients. Long-term administration of the drug is investigated in order to assess the fundamental benefit-risk ratio. In most cases, two or more phase III studies are required before the authorities' approval can be obtained to market a drug.

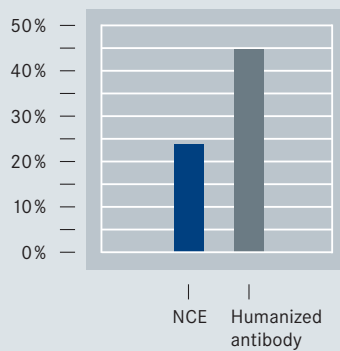


Besides determination of efficacy, three different factors are of importance during clinical product development: cost, failure risk and duration. The cost for individual phases of clinical development depends on a number of factors, but it is determined mainly by the number of patients in the clinical studies, as well as the indication. Generally, the number of patients included in clinical trials is dependent on the indication and the clinical end point. The costs per patient can also vary enormously, depending on the type and duration of treatment. In antibody development, high production costs due to expensive manufacturing procedures add to the cost of clinical development.

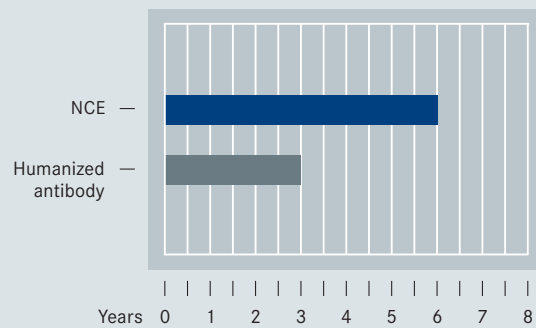
## Why Antibodies?

### 1. Higher success rates than NCEs

Probability that a molecule in phase I will reach market



### 2. Speed to clinic



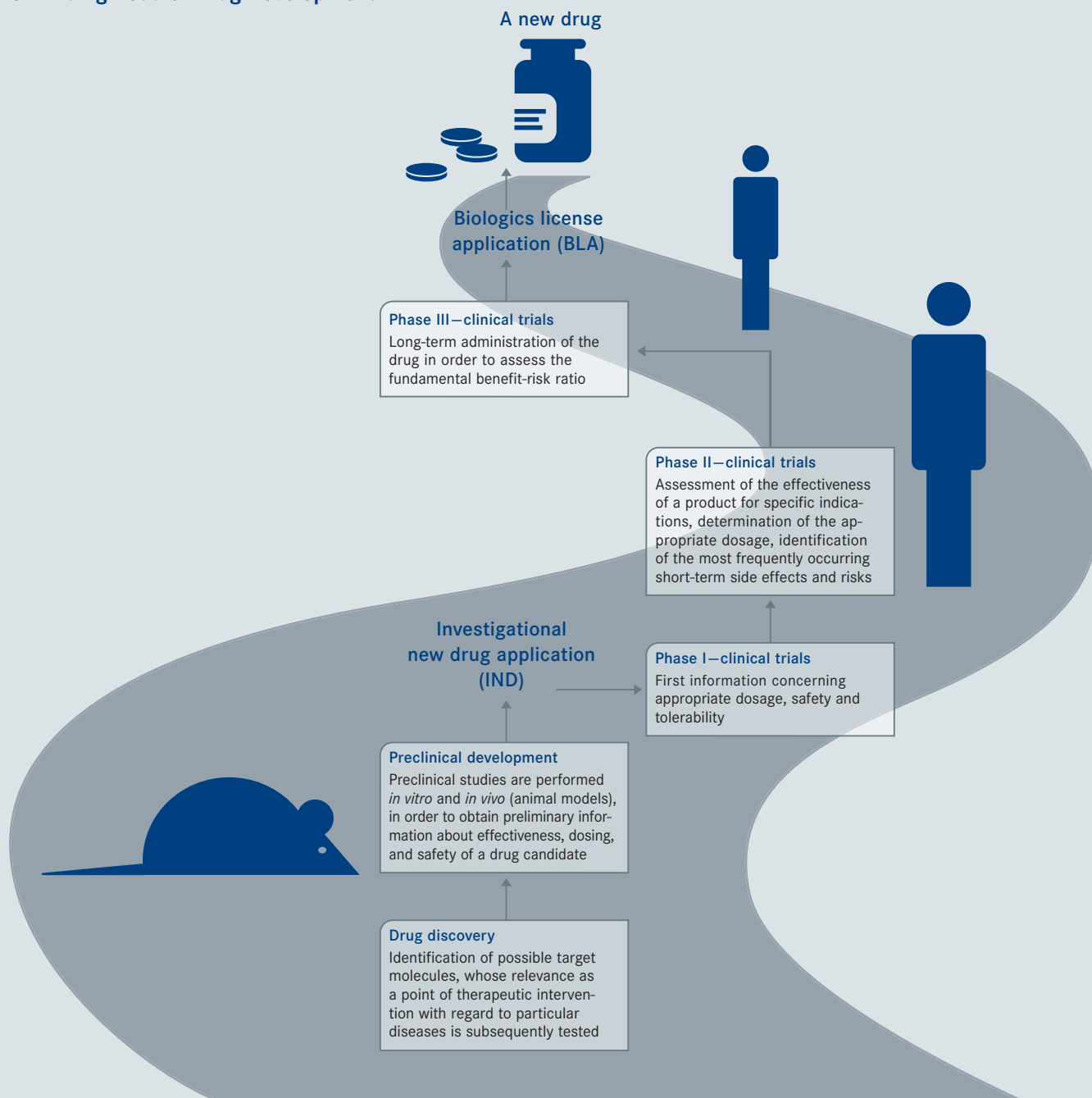
Source: Adapted from Nature Biotechnology

The failure risk for product candidates in clinical development depends on the target molecule, the product class and the indication. The target molecule at which the drug is aimed plays a significant role. The risk of failure is lower when choosing a target of which the biology and disease relevance have been well researched compared to “new,” less well-characterized target molecules.

The duration of development also depends on the required length of therapy and the clinical end point. For this reason, clinical studies for cancer treatment last longer on average, since the effectiveness often only becomes clear in a higher survival rate several months or years after treatment. The duration of development is therefore determined primarily by the indication.



## The Winding Road of Drug Development



### **Advantages of Antibodies in Clinical Development**

Monoclonal antibodies are ideally suited as therapeutic substances as they can bind to very specifically defined target structures. Furthermore, the unique properties of antibodies cannot be mimicked by so-called small molecules (chemical substances which are used as drugs). Today, a clear trend towards antibodies can be seen, as evidenced by the large number of human and humanized antibodies being developed. One major factor underlying this trend is that there are fewer side effects with antibody-based therapies, and they are therefore more likely to be successful in clinical development. There are, however, additional benefits that accrue for drug developers through the use of antibody-based therapeutics:

#### **Shorter Development Periods for Human Therapeutic Antibodies**

An average of six years is estimated from target identification to preclinical development for small molecules.

This time period can be considerably faster for antibody development, and is expected to last two to three years. The time required for subsequent clinical development is then determined by the indication.

#### **Higher Chances of Success for Human Therapeutic Antibodies**

In addition to the shorter time period required for the development of human antibodies, higher success rates are also attributed to antibodies. Due to their mode of action and their very specific binding to a relevant target structure, antibodies are less toxic and have a better side-effect profile. These advantages are further highlighted by the fact that antibodies generated with the HuCAL® technology can be optimized. This ability, combined with a better understanding of disease pathways arising from the sequencing of the genome, should allow for the generation of antibodies with even higher success rates.

