Website address:
https://www.gesundheitsindustrie-bw.de/en/article/dossier/no-new-drugs-to-be-placed-on-the-market-without-clinical-trials

No new drugs to be placed on the market without clinical trials

New pharmaceuticals are subject to approval by drug authorities. The approval is preceded by a lengthy and expensive clinical drug development process. These comprehensive clinical trials are performed to ensure the drug's efficacy and safety in human beings.

Prior to approval of a new pharmaceutical, several hurdles such as preclinical and clinical studies need to be cleared. Clinical trials are performed to ensure the quality, efficacy and safety of a medicinal product. Clinical development is a time-consuming and costly process and takes on average ten to fifteen years before a pharmaceutical company can apply for the approval of the drug. The costs, including failures, can amount to approximately one billion US dollars per drug.

A strongly regulated market

Various legal requirements must be met before a manufacturer can commence a clinical trial. The first step in an application is to obtain a EudraCT (European Union Drug Regulation Authorities Clinical Trials) number from the European Medicines Agency (EMA). This number is required in order to get a written permit for the intended trial from the relevant national medicine regulatory authorities, which in Germany are the Federal Institute for Drugs and Medicinal Devices (BfArM) and the Paul Ehrlich Institute (PEI). At the same time, the pharmaceutical company needs to submit an application to the relevant ethics commission. If a study and study design conform with the quality and safety criteria of the competent federal medicines regulatory authority and the relevant ethics committee has issued a favourable opinion, the application needs to be registered with the competent state regulatory authority and the clinical trial can begin.

The different phases of a clinical trial

Attrition rate in the biopharmaceutical product pipelines

Once a compound has been identified in the laboratory, it must be thoroughly evaluated in preclinical and clinical phase 1, 2 and 3 studies before it can be sold to patients. The preclinical phase is characterised by lead optimisation, in vitro efficacy and toxicity tests and in vivo animal experiments. After around five years of preclinical testing, the original number of 5,000 to 10,000 active substances has usually decreased to around eight that can be further tested in phase 1 clinical trials. Phase 1 clinical trials are done to evaluate a new drug's safety, the safe dosage range and identification of side effects. Phase 1 trials usually involve 20 to 80 healthy volunteers. If a drug/treatment appears safe at the end of a phase 1 clinical trial, it may then enter a phase 2 trial to test its efficacy in patients with the particular disease targeted by the medication. Phase 2 trials are aimed at obtaining initial proof of concept (POC). These studies help determine the correct dosage, efficacy and tolerability and involve between 50 and 200 patients. If a drug is deemed effective in a phase 2 trial, it will enter a phase 3 clinical trial. Phase 3 clinical trials are conducted with several thousand patients with the disease of interest and are done to confirm efficacy and monitor side effects with a high statistical significance. These trials compare the drug candidate to commonly used treatments and also collect information on potential interactions with other drugs. In general, phase 3 trials are randomised double-blind studies, which are the so-called gold standard of clinical trial design. The grouping of patients into specific treatment groups, i.e. groups that receive either the study treatment or commonly used treatment, is done according to the principle of random sampling; neither patients nor researchers know which treatment is being given to any given subject in order to prevent bias or placebo effect.

Looking for suitable patients

The approval of new drugs is based on a complex set of rules, which were among other things put in place following drug disasters such as the thalidomide tragedy in 1961/1962. (Eds. note: Thalidomide is a sedative drug introduced in the late 1950s to help pregnant women with the effects of morning sickness, but was withdrawn from the market due to the fact that

it caused birth defects.) The negative effects of the compound led to the exclusion of women of childbearing age from early clinical studies (phase 1 and 2). In the early 1990s, the American Food and Drug Administration (FDA) revised the exclusion of women from clinical trials as gender-specific differences in the effect of dosage of drugs moved more and more into the foreground. In Germany, the 12th Amendment of the Medicines Act (2004) requires pharmaceutical manufacturers to demonstrate in the application for the approval of clinical trials that the chosen gender distribution is appropriate. Following the introduction of AMNOG (Pharmaceuticals Market Reorganisation Act) on 22 December 2010, the Joint Federal Committee (G-BA) requires pharmaceutical companies to submit a gender-specific analysis of clinical trial data. Clinical trials may not be approved when such an analysis is lacking. In addition, any drug that is approved for sale in the EU must also be tested on minors; phase 1 studies involving minors are however forbidden. Therefore, minors are only usually part of clinical trials from phase 3 onwards. If the disease under examination only affects minors, this age group can be part of phase 2 studies.

EU-wide harmonisation of clinical trials

The application for drug marketing approvals in the various member states of the European Union is currently not only time-consuming, but also very expensive. This is one of the reasons why many clinical trials are conducted outside the EU, for example in Africa and India. Experts estimate that a pharmaceutical manufacturer can reduce trial costs by 30 to 50 percent when testing a new compound in India rather than in the EU.

In July 2012, the European Commission adopted a proposal for a "Clinical Trials Regulation" to ensure that the rules for conducting clinical trials are identical throughout the EU and make it easier to conduct multinational clinical trials. The new authorisation procedure for clinical trials will allow for more transparency, simplified reporting procedures and a faster assessment of the application (see link "EuroConsults" on the right-hand side).

The proposal was heavily criticised in Germany by the German Medical Council and the Working Group of Medical Ethics Committees in Germany, amongst other organisations. They saw in the regulation an infringement of the Declaration of Helsinki which, in 1964, laid down the ethical guidelines of clinical research involving human subjects and human experimentation based on the findings of the Nuremberg trials in order to ensure that human subjects were never again misused in the service of science. The critics believed that the rights of minors and patients who are unable to give their consent were no longer sufficiently guaranteed. In addition, they were also of the opinion that the responsibilities of ethics committees were limited. 2013 will show how the proposal will be implemented. The new regulation will come into force in 2016.

AMNOG – Pharmaceuticals Market Reorganisation Act

AMNOG came into force on 1st January 2011 with the objective of curbing the growing expenditure on medicinal products by the statutory health insurance funds. AMNOG is not aimed at preventing innovative pharmaceutical research, but at paving the way towards greater affordability. AMNOG obliges pharmaceutical companies to subject their new products to an early evaluation of their additional benefit by the Joint Federal Committee (G-BA) after being launched on the market. The G-BA is in charge of coordinating the evaluation of drugs and may commission the Institute for Quality and Efficiency in Healthcare (IQWIG) or other organisations to evaluate a new compound and prove any additional benefit in comparison to a comparative therapy.

Symbolic image: Prior to approval of a new pharmaceutical, several hurdles such as preclinical and clinical studies need to be cleared.

If any additional benefit is proven, the pharmaceutical company can negotiate with the National Association of Statutory Health Insurance Funds (GKV-Spitzenverband, GKV-SV) on a supplement over and above the price of the expedient comparative therapy. If it is not possible to prove any additional benefit, the pharmaceutical is allocated to a fixed group with comparable active ingredients. Since the introduction of AMNOG, 24 of a total of 37 drugs were rated positive and evaluated as follows (as of May 2013): The G-BA attested seven drugs a considerable additional benefit, fourteen a reduced benefit and was unable to quantify the benefit of three drugs. However, the G-BA decided in many of the evaluations to limit the additional benefit to small patient groups. Another major criticism of the AMNOG procedure is the selection of a comparative therapy by the G-BA, as this therapy sets the basis for the evaluation of the additional benefit and subsequent price negotiations.

In Germany, the introduction of AMNOG has led to a paradigm change. The benefit evaluation is generally considered positive, but there is criticism with regard to procedural matters. At present, two years after AMNOG came into force, it is still too early for a comprehensive review.

Publication of trial results

Clinical trials are conducted in order to provide the basis for assessing whether a drug can receive marketing authorisation or not. This requires the complete documentation of all study results, whether positive or negative for the manufacturer. However, many examples from the recent past demonstrate that clinical studies are often glossed over in order to manipulate the public. In 2009, Pfizer only made clinical trial data on the antidepressant Edronax (active ingredient: reboxetine) available to the IQWIG following massive public pressure. The IQWIG could not attest any additional benefit to reboxetine.

Another example is Tamiflu (Roche), which is the best-selling drug for the treatment of flu worldwide. Scientists have long had doubts about the efficacy of the drug. In 2002, the WHO was still recommending that governments around the world stockpiled Tamiflu and other antivirals. Tamiflu was again prescribed in huge quantities during the 2009 swine flu pandemic. Since the introduction of Tamiflu in 2002, Roche has achieved revenues of more than ten billion Swiss Francs (as of 2013). However, research carried out by the independent Cochrane Collaboration showed that the selective publication of the Tamiflu study results has led to an incorrect public perception of the drug. Although the Cochrane review concluded that Tamiflu alleviated the symptoms of flu, the reviewers also found that the duration of flu symptoms was only reduced by about one and a half days from the typical six or seven days. The reviewers could not confirm that it reduced hospitalisations. Roche has in the meantime thrown in the towel and stated that it intends to disclose the results of all Tamiflu studies.

In Germany, the publication of clinical trial results is stipulated in § 42 b of the German Medicines Act, according to which all study data must be made available to the competent federal authority. Although the obligation to disclose all clinical trial results is regulated by law, pharmaceutical companies are rather reluctant to do so.

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