- Long term safety information – common side effects, drug interactions, age/rate/gender differences
- Dosing (for labeling)
- Assessment of safety and efficacy

Percentage of drugs that move to the next phase is 25–30%.

After completing the phase III trail the application is filed with the concerned regulatory bodies seeking permission for marketing and after the regulatory bodies grant the required approval, the product is launched into the market.

Phase 4 (Post-marketing Therapeutic Use) – This investigation takes place on the new marketed drug which is approved by the FDA. This phase involves thousands of participants and can last for many years.

Trial Design

Patients: Several hundred to thousand patients with the disease/condition.

Type of study: Randomized, Placebo or active control, Multicenter

Purpose

- Perform Quality of Life Trails (QOL) trails
- Perform pharmacoeconomic trails – Is the drug more effective that other available treatments
- Collection of long term safety information – Epidemiological studies for safety and additional surveillance for unexpected or rare adverse effects
- Add line extensions – New dosage forms and formulations

The Investigational New Drug Process

Drug developers, or sponsors, must submit an Investigational New Drug (IND) application to FDA before beginning clinical research.

In the IND application, developers must include:

- Animal study data and toxicity (side effects that cause great harm) data
- Manufacturing information
- Clinical protocols (study plans) for studies to be conducted
- Data from any prior human research
- Information about the investigator

Asking for FDA Assistance

Drug developers are free to ask for help from FDA at any point in the drug development process, including:

- Pre-IND application, to review FDA guidance documents and get answers to questions that may help enhance their research
- After Phase 2, to obtain guidance on the design of large Phase 3 studies
- Any time during the process, to obtain an assessment of the IND application

Even though FDA offers extensive technical assistance, drug developers are not required to take FDA's suggestions. As long as clinical trials are thoughtfully designed, reflect what developers know about a product, safeguard participants, and otherwise meet Federal standards, FDA allows wide latitude in clinical trial design.

Table 1.1: New drug application forms and rules

Form No. and Rules	*Purpopse*
44	Application for permission to import or manufacture a new drug or to begin a new clinical trial
122-A	Application for permission to import a new drug
122-B	Application for approval to import a new drug
122-D	Permission to import or manufacture fixed dose combination
122-DA	Application for permission to conduct a clinical trial for new drug or investigational new drug
122-DAA	Definition of clinical trial
122-DB	Suspension or cancellation of permission or approval

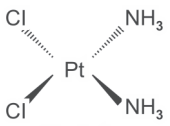
Drug Controller General of India

Clinical Research is regulated in India by Drug Controller General of India (DCGI). The office of DCGI runs under CDSCO. It has main responsibility of regulating clinical trials in India. Permission is necessary from DCGI through Form no 44. Matters related to product approval and standards, clinical trials, introduction of new drug, and import licenses of new drugs are handled by DCGI.

Drugs Technical Advisory Board (DTAB): It has technical experts and this advice the central and state governments on all technical matters arising out of the enforcement of drug control. No rules can be made by the central government without consulting DTAB board.

Drugs Consultative Committee: It has central and state drug control officials as members. Its main function is to ensure the drug control measures and enforce them uniformly over all the states.

Genetic Engineering approval Committee (GEAC): It is authority to approve r-DNA (recombinant DNA) pharmaceuticals products. GEAC's role is to assess the bio-safety/environmental safety aspect of the biotechnological product.

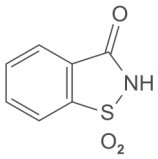


Cisplatin

With the discovery of cisplatin and the breakthrough observation by Lieutenant Colonel Stewart F Alexander, regarding the depletion of WBC by the chemical warfare agent, nitrogen mustard led to the development of alkylation agents.

Saccharin

In the 1870s, Russian chemist **Constantin Fahlberg** worked in the lab of Ira Remsen at Johns Hopkins University. Remsen's team experimented with coal-tar derivates, seeing how they react to phosphorus, chloride, ammonia, and other chemicals. One night, Fahlberg returned home and started to eat dinner rolls. The rolls tasted curiously sweet. The recipe hadn't changed, so what was going on here? He soon realized that it wasn't the rolls. It was him. His hands were covered with a mystery chemical that made everything sweet.



Saccharin

"Fahlberg had literally brought his work home with him, having spilled an experimental compound over his hands earlier that day," writes the Chemical Heritage Foundation in its history of saccharin. "He ran back to Remsen's laboratory, where he tasted everything on his worktable—all the vials, beakers, and dishes he used for his experiments. Finally he found the source: an overboiled beaker."

Fahlberg had actually created saccharin before, but since he never bothered to taste-test his concoctions, the chemist had no idea.

Lithium

In the mid-1800s, lithium was used to treat gout and bladder stones. After World War II, psychiatrist John Cade injected urine from healthy and mentally ill patients into the abdomens of guinea pigs. He found that the guinea pigs injected with urine from healthy patients died faster, which raised the idea that more uric acid was in the urine of the mentally ill patients.

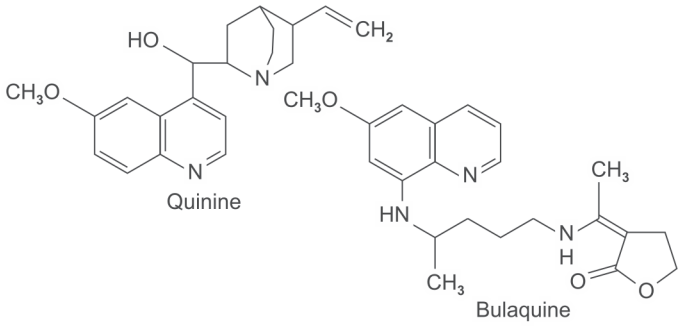
In an attempt to increase the solubility of the uric acid, cade, added a lithium solution. Following injection, he noticed that the guinea pigs were sedated and calm rather than excited.

Interestingly, Cade ingested the lithium himself to ensure that it was safe for humans, and he later began administering it to patients with psychiatric disorders.

Methods of Lead Discovery

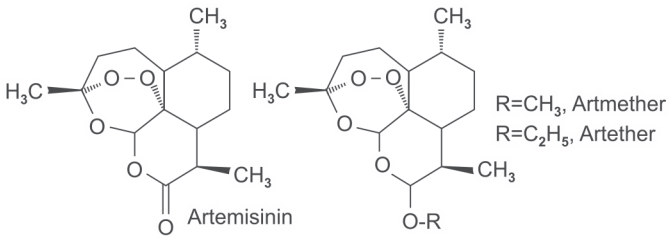
There are several approaches which can be adopted for identifying the lead structure. In order to identify a lead nucleus, in a given series, all compounds in a series should

where it became widely used and was often referred to as "Peruvian bark." With quinine as the model, chemists subsequently synthesized the antimalarial drugs chloroquine and mefloquine, and they have continued to modify the basic structure of quinine to produce even more effective agents, such as the new antimalarial drug, bulaquine (developed by CDRI).



Artemisinin

The Sweet Wormwood plant (*Artemesia annua*) was also used as a treatment for fevers in China for more than 2,000 years (it is called *qing hao* in Chinese), but it was not until 1972 that the active compound artemisinin (*qing hao su*, which means the active principle of qing hao) was extracted and later identified as a potent anti malarial drug by Chinese scientists. This effort was part of a systematic examination at that time of indigenous plants in China as sources of new medicines. More soluble derivatives, artemether, artether, *etc*. have been developed in recent years to overcome its drawback.



These medicines, in combination with other antimalarials such as mefloquine, have proved highly effective in treating malaria, particularly the most deadly form caused by *Plasmodium falciparu*m, which has become increasingly resistant to the first-line treatments chloroquine and sulphadoxine-pyrimethamine—in Asia, South and Central America, and Africa.

Some examples of drugs from plants that served as models for the next generation of drugs are exemplified as follows: Khellin [from *Ammi visnaga* (L.) was used as a bronchodilator in the United States until it was shown to produce nausea and vomiting after prolonged use. In 1955, a group of chemists in England set about to synthesize Khellin analogs as potential bronchodilators with fewer side effects. This eventually led to the discovery of chromolyn (used as sodium cromoglycate), which stabilized cell membranes in the lungs to prevent the allergen induced release of the substance ultimately causing bronchoconstriction in allergic asthma patients. Further studies elsewhere led to the synthesis of amiodarone, a useful antiarrythmic agent.