
FDA

Food & Drug Administration (FDA)

1862, started with a single chemist in the USDA

1927, Bureau of Chemistry changed to the Food, Drug, & Insecticide Administration

1930, name was shortened to the present version

2001, staff ~9,100 employees & a budget of $1.3 billion

Adulteration and misbranding of foods & drugs have always been a problem in the U.S.

The problem increased by the late 19th C.

Drugs such as Quinine were cut with fillers to increase profit

Sufferers of serious illnesses were sold worthless drugs or therapies

Preservatives added to foods & drugs were useless or worse toxic

http://www.fda.gov/cder/about/history/Graphics/OilKingLrg.jpg

Dr. Mixer's Condition
After Cured by
his Cancer and Scrofula Syrup.

DRS. MIXER,

SOLE MANUFACTURERS
AND PROPRIETORS OF

SPECIAL TREATMENT GIVEN

MIXER'S CANCER AND SCROFULA SYRUP

Cancer, Tumors,
Erysipelas,
Abscesses, Ulcers,
Fever Sores, Goiter,
Catarrh, Salt Rheum,
Scald Head, Piles,
Rheumatism
and ALL BLOOD DISEASES.

The World Renowned
BLOOD PURIFIER.

ESTABLISHED 1862

DR. CHAS. W. MIXER,
GEN'L MANAGER.

Not a Physician.

http://www.fda.gov/cder/about/history/Gallery/gallery21.htm

Harvey Washington Wiley, chief chemist concerned about chemical preservatives, initiated "poison squad" experiments

Healthy volunteers consumed varying amounts of questionable food additives to determine their impact on health

Officially designated the “Hygienic Table.”

Chemicals fed to the young men included borax, salicylic, sulfurous, and benzoic acids, & formaldehyde

Wiley became convinced that chemical preservatives should be used in food only when necessary

That the burden of proving safety should fall on the producer

That none should be used without informing the consumer on the label

Wiley unified a variety of groups behind a federal law to prohibit the adulteration and misbranding of food and drugs

Food and Drugs Act of 1906

First nationwide consumer protection law made it illegal to distribute misbranded or adulterated foods, drinks and drugs across state lines

Offending products could be seized & condemned; persons could be fined & jailed

Drugs had either to abide by standards of purity and quality set forth in the UNITED STATES PHARMACOPEIA & the NATIONAL FORMULARY

Presence & quantity of alcohol or certain narcotic drugs had to be stated on proprietary labels

There were however, shortcomings in the 1906 law

Law prevented blatant fraud, but it did not prevent deception

Numerous examples of foods deceptively packaged or labeled began to show up

The law also did not insist that products be tested for safety

Flavoring Extract Bottle

thick glass obscures how much expensive flavoring extract is really in the bottle

http://www.fda.gov/oc/history/slideshow/Slide_182_139.html

Lash-Lure, an eyelash dye that blinded many women

http://www.fda.gov/oc/history/

A disaster in 1937 prompted Congress to act

A Tennessee drug company marketed a form of the new sulfa wonder drug that would appeal to pediatric patients, Elixir Sulfanilamide

The solvent in this untested product was diethylene glycol

Over 100 people died, many of whom were children

Elixir Sulfanilamide

http://www.fda.gov/cder/about/history/Page18.htm

1938 Federal Food, Drug, and Cosmetic Act

For the first time, required companies to prove the safety of new drugs before putting them on the market

Over the years new responsibilities were added including the requirement that drugs and medical devices be proven effective as well as safe before they can be sold

Currently the FDA is charged with:

Safeguarding the nations food supply, by ensuring that all ingredients used in foods are safe, & that food is free of contaminants

Approves all new food additives before they can be used

Monitors the safety of dietary supplements & the content of infant formulas & medical foods

Protects the public from unnecessary exposure to radiation from electronic products. (microwave ovens, cell phones, x-ray equipment, lasers, medical ultrasound & MRI machines)

Monitors cosmetic products to be sure that they are safe & properly labeled

Medical products need to be proven safe and effective before they can be used by patients

The product categories covered by this requirement include:

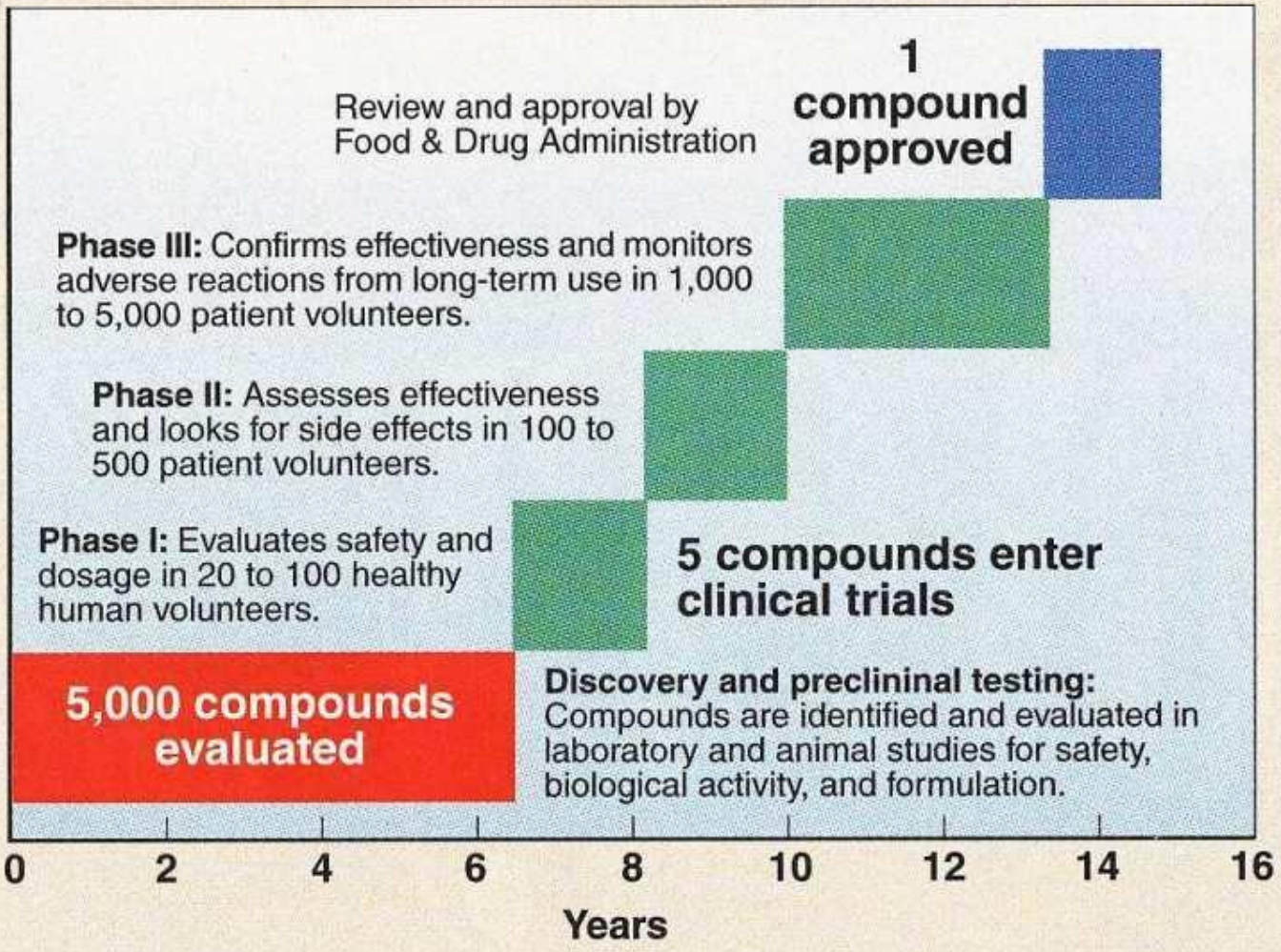
Medicines used for the treatment and prevention of disease

Biologics, vaccines, blood products, biotechnology products and gene therapy

Medical Devices, FDA regulates all medical devices, from very simple items like tongue depressors or thermometers to very complex technologies such as heart pacemakers and dialysis machines.

Drug Review & Approval

Bringing a new drug to market can take 15 years



Source: Tufts Center for the Study of Drug Development

The majority of prospective new drugs fail testing, many never make it passed the pre-clinical stage

The pre-clinical stage involves testing in either animals or cells and looks at the potential drugs efficacy in a model of the the disease

This stage also involves looking for possible toxicity or side-effects that may be significant if the compound moves ahead to human studies

If a compound shows promise during the pre-clinical phase the drug maker may decide to move forward with human testing

Human testing of a drug is known as a clinical trial

For a drug to be tested in humans the Sponsor must submit an application to The Center for Drug Evaluation and Research (CDER), part of the FDA

This application is known as an

Investigational New Drug Application (IND)

Investigational New Drug Application (IND)

The IND is reviewed by both the FDA and a local IRB

An Institutional Review Board (IRB) is a panel of physicians, scientists, & lay persons who oversee research done using humans

Each hospital or research institution must have an IRB if it allows human research

The IRB approves the clinical trial protocols, these describe who may participate in the trial, the schedule of tests and procedures, the medications and doses, the study's length, and finally its objectives

After approval by the IRB and the FDA, clinical trials can begin

There are up to four different phases of trials, each with a specific objective.

If any problems arise during any of these phases the FDA is notified and the IND application is canceled

Phase I Studies

Conducted in healthy volunteers, between 20 to 80

Goal is to determine safety and look for possible side effects

The studies are usually open-label meaning the volunteers & the physicians know who is getting the drug

The Pharmacokinetics of the drug is often investigated

If no unacceptable toxicity is revealed, phase II studies can be initiated

Phase II Studies

Shift in emphasis from safety to effectiveness

Collection of preliminary data on whether the drug works in people who have a certain disease or condition

Usually two groups of patients are compared, one group receiving the drug is compared to a second group who receives either a placebo or a different drug

Studies are often done in the double blind method, this means the neither the patient, physician, nor the drug company know which patients are getting the drug & which are getting the placebo

The number of subjects rages from a few dozen to 300

Phase III Studies

If effectiveness is shown during phase II the study is expanded to a phase III

The goal during this phase is the continued collection of safety and effectiveness data

These data are collected on a larger population that is more varied than that studied during phase II

Phase III also often studies the drug at different doses and in combination with other drugs

The number of subjects ranges from a few hundred to a few thousand

Phase IV Studies

Occur after a drug is approved

Explore other aspects of the drug such as usage in new populations, such as children

Long term effects are also explored

Often after approval, some drugs are found to have unintended usages

These are referred to as off-label uses

It is legal for a physician to prescribe a drug for off-label use, but the drug company cannot advertise these uses until further studies are performed

New Drug Application (NDA)

Once clinical trials are finished the sponsor places a formal request with the FDA to consider approving the drug

This request is known as a New Drug Application (NDA)

Once a NDA is filed the FDA has 60 days to review the application for filing

If the FDA decides to file the application a review team of physicians, chemists, statisticians, microbiologist, and pharmacologists is assembled

Only 1 in 5 drugs that enter clinical trials is ultimately approved by the FDA

Review Process

The review team analyzes all aspects of the study results looking for possible problems, such a weaknesses in the study design or analyses

Reviewers determine if they agree with the sponsor's results and conclusions or if additional information is needed

Each reviewer then prepares a written evaluation with their recommendation about the application

If the FDA decides that the benefits of the drug outweigh any risks the drug can then be marketed in the US

If there are problems with the NDA, the FDA may decide that the drug is approvable or not approvable

Approvable means that the drug may eventually be approved, but that some issues need to be resolved first

Not approvable means there are significant problems that cannot be overcome without substantial additional data

These could be safety problems or failure to demonstrate the drug's effectiveness

Accelerated Approval

Given to drugs for serious and life-threatening illnesses that lack satisfactory treatments

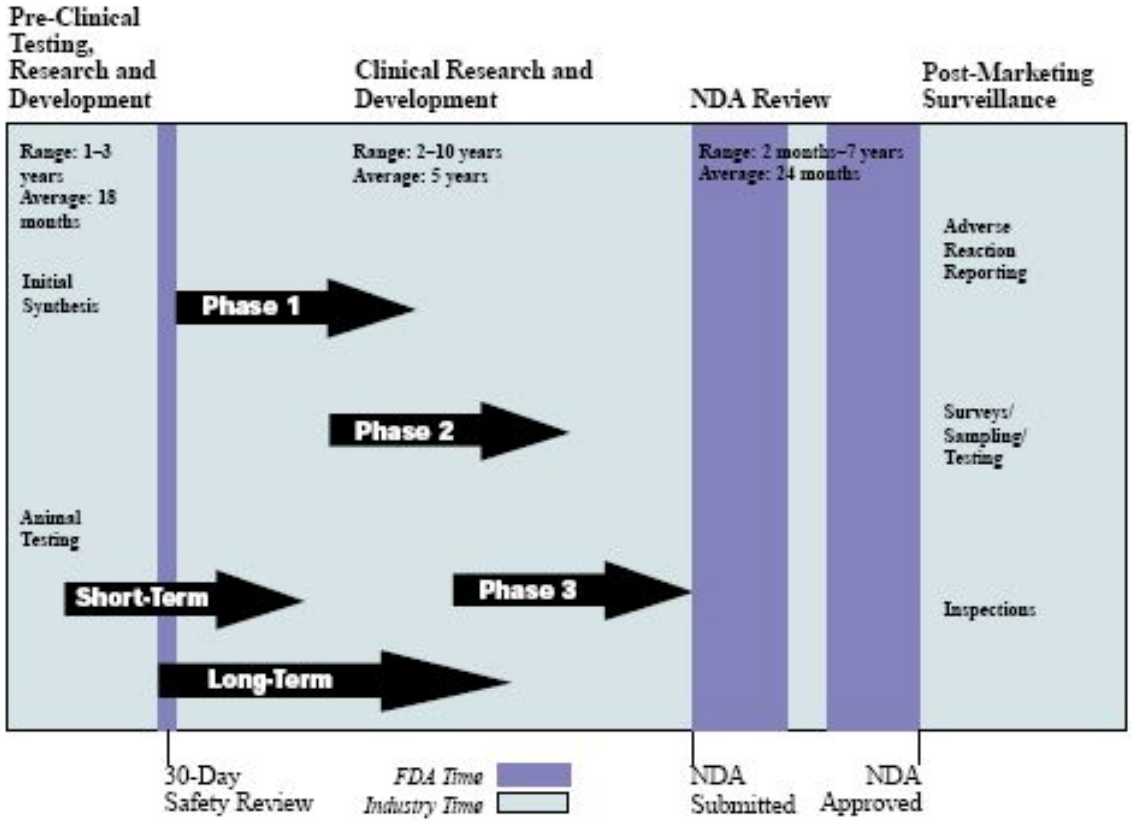
Uses surrogate endpoints instead of traditional measures

These can be laboratory findings that are not directly related to patient survival or function

Most HIV drugs have been approved through this process with the provision that the companies continue to perform studies to confirm the drug's ultimate benefit

If future studies do not confirm initial results the FDA may withdraw approval

New Drug Development Timeline



http://www.fda.gov/cder/handbook/develop.htm

Abbreviated New Drug Application (ANDA)

Provides for the review and ultimate approval of a generic drug

A generic drug is one that is comparable to an innovator drug in dosage form, strength, route of administration, quality, performance characteristics and intended use

Termed abbreviated because they are generally not required to include preclinical and clinical data to establish safety and effectiveness

Applicants must scientifically demonstrate that their product is bioequivalent

Bioequivalence

In order to demonstrate bioequivalence scientists measure the time it takes the generic drug to reach the bloodstream in 24 to 36 healthy, volunteers

This gives them the rate of absorption, or bioavailability, of the generic drug, which they can then compare to that of the innovator drug

The generic version must deliver the same amount of active ingredients into a patient's bloodstream in the same amount of time as the innovator drug

Orphan Drugs

In 1982 Congress passed the Orphan Drug Act

The goal was to promote the development of products that demonstrate promise for the diagnosis and/or treatment of rare diseases or conditions

More than 200 drugs & biological products for rare diseases have been brought to market since 1983

Prior to 1983 fewer than ten such products came to market

Adverse Events Reporting System (AERS)

The FDA requires manufacturers to report adverse drug reactions

Health care professionals & consumers can also send reports voluntarily through the MedWatch program

If there are significant adverse effects the FDA may take regulatory actions to improve product safety and protect the public health

Such as updating a product's labeling information, sending out a "Dear Health Care Professional" letter, or re-evaluating an approval decision

If a drug has severe side effects, but is kept on the market a black box warning is placed on the label

Recent black box warnings have been issued for:

Advair/Serevent: small, but significant increase in asthma deaths particularily in African-Americans

Depo-Provera: significant decrease in bone density

Serzone: life-threatening liver failure

All antidepressants for increased adolescent suicide

Acetaminophen: life-threatening liver failure increased when taken with alcohol

Recent Drug Controversies

Vioxx, voluntarily withdrawn due to increases in heart attacks & strokes

Prempro, Premarin; hormone replacement therapy, a long term study showed increases in breast cancer & coronary heart disease

Baycol (cerivastatin), removed from the market because of ~31 reports of fatal rhabdomyolysis, destruction of muscle tissue that can lead to kidney failure

Crestor (Rosuvastatin) approved in August, 2003 has the same problem

If you have questions about medications your or your family are taking:

http://www.fda.gov/medwatch/index.html

Rex Babin is on vacation

Anderson / Courier Journa