

Why can you trust the drugs you take? (and how statisticians contribute)

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Suppose you go to your doctor because you sometimes have difficulty breathing. Your doctor tells you that you have asthma, and that there is a new drug that can help you breathe better. How do you know the new drug will work and will be safe for you to take? You might also wonder where this new drug comes from. You can trust the drugs you take because current drug approval regulations require extensive, extremely accurate testing to demonstrate the safety and efficacy (i.e., effectiveness) of drugs before marketing. Statisticians enable scientists and reviewers to establish the accuracy and validity of these tests. This article provides an overview of the various phases of the drug development process, and describes the how statisticians participate in that process.

In the United States, the 1962 amendments of the Food, Drug, and Cosmetics Act require substantial evidence of the safety and efficacy of drugs before they can be sold. They charge the Food and Drug Administration (FDA) with (1) evaluating the adequacy of the evidence, and (2) approving drugs with adequate evidence for marketing. Most countries around the world have an agency similar to the FDA which evaluates drug research and approves drugs for marketing. Consequently, the FDA and regulatory agencies of other countries have drafted numerous guidelines, including statistical guidelines, for studying and documenting the safety and efficacy of drugs. These guidelines are modeled after the four basic steps of the scientific method: hypothesis, experimentation (observation), interpretation, and conclusion (or refined hypothesis for the next experiment). In order to ensure adherence to these guidelines, there is extensive critical review within sponsor companies which make the drug, by the FDA (and/or other regulatory agencies), and by independent academic experts (FDA Advisory Committees), of all aspects of drug's safety and efficacy from experimental studies prior to approval.

Statisticians play a key role in the drug experimentation process leading to drug approval, particularly in determining the extent and complexity of the experiments, and interpreting the results of those experiments. However, before a drug can be studied for its safety and efficacy in humans, it must be discovered! Statisticians are actually involved in the development of new drugs from the discovery of new

drug chemicals through marketing approval, and in post-marketing surveillance for any safety problems (see attached Drug Development Time Line).

Drug discovery begins in the laboratories of basic research scientists. Samples of natural substances are collected from the far reaches of the globe and run through screening experiments to identify drug chemical candidates with desired effects; these are referred to as active drug candidates. Each screening experiment is designed to reveal active chemicals for a specific targeted disease. Statisticians work with basic research scientists to design these experiments (1) so that they make the most efficient use of time and materials, and (2) to ensure that the analyses of resultant data lead to appropriate identification of active drug chemicals (also called compounds) and do not lead to incorrect identification of inactive compounds as active. Once a natural substance is found to possess activity towards a disease target, chemists work to isolate the particular molecule which is responsible for the activity.

Another way drugs are discovered is by combinatorial synthesis. In combinatorial synthesis, molecules of several different types, each known to have a certain desirable chemical property, are chemically combined to form all possible combinations of resultant combination molecules. In this way, thousands of potential drug chemical candidates are produced and tested in screening experiments like those mentioned above for natural product screening. Statisticians work with chemists and use probability theory to ensure that sufficient quantities of all combinations of molecules are produced for the screening experiments so that no potential active drug candidate is missed.

Once an active drug candidate is identified, its safety is tested, under strict ethical guidelines, in laboratory animals. This laboratory safety assessment ensures that harmful properties of the drug candidate are identified before it is tested in humans. Statisticians work with scientists who study the drug's safety in lab animals to design these experiments and their analyses to identify unsafe compounds using minimal numbers of research animals. In addition, statisticians work with other scientists to design and analyze experiments which yield the best production processes for making the raw drug chemical. Other experiments are designed and analyzed to formulate the drug chemical into tablets, capsules, solutions, etc., with appropriate properties for use, including dissolution (i.e., dissolving in solution), potency over long term storage, etc. This research must occur before a single human takes the drug.

Once a drug candidate is demonstrated safe in animals and can be reliably produced, it goes through three phases of testing in humans before marketing. Phase I clinical trials verify the drug's acute safety in

humans and document its basic pharmacologic properties, i.e., effects on targeted enzymes, hormones, tissues, etc., in the body. Next, in Phase II, the candidate drug is tested in patients with the target disease to identify proper dose(s) for further testing. Once the proper dose range is found, large scale Phase III clinical trials are designed to definitively document the drug's safety and efficacy in the target population. Statisticians play an integral part in this clinical study process. They assist the clinical research scientists, usually physicians, to design the clinical trials, including selection and validation of study measurements, and definition of subsequent statistical analyses. This design work must be carefully done in order to yield valid scientific conclusions in support of particular properties of the drug's safety and efficacy. Statisticians are key drug development project team members; they help plan the overall experimental strategy (sequence of clinical trials) and execute it. They co-author the reports of the trials' results which are assembled into volumes which are submitted to drug regulatory agencies worldwide for approval to sell the drug. Statisticians also make presentations at national and international scientific meetings and co-author research journal articles; these presentations and articles summarize original statistical methodology and/or unique medical results for the worldwide research community.

Statisticians in regulatory agencies review the new drug applications (NDA's). Sponsor (drug company) statisticians meet with their counterparts in the regulatory agencies and other reviewers to address questions during the review. The drug's labeling for prescribing physicians and patients contains information about the drug's proper use. Statisticians contribute to the design and content of the product's labeling. The labeling information is reviewed by statisticians for correctness. The entire drug development effort from discovery to approval can take at least 6 years and cost on average \$400,000,000. The attached schematic summarizes the drug development time line.

After drug approval, the statistician's job is not over. Further testing may be necessary to address specific questions from regulatory agencies (Phase IV of the clinical development process) or for new and different

uses of the drug (Phase V). Statisticians work with economists to document the drug's impact on costs in comparison to the costs of necessary treatment of the disease for various alternatives which do not involve the drug. Market research involves statisticians who help assess the drug's potential financial impact on the company. Statisticians help design strategies and interpret results for studies of drug safety during marketed use.

In summary, statisticians are key collaborators in all aspects of drug discovery, development, approval, and marketing. Consulting statisticians must learn as much as possible about the specific scientific areas in which they work to most effectively contribute their expertise to the research team. In the pharmaceutical industry, statisticians work with research scientists in many fields including biology, chemistry, pharmacology (i.e., the study of drugs' actions in humans), pharmacokinetics (i.e., the study of the drug chemical's passage through the body), and clinical medicine (i.e., its effect on the target disease). Opportunities for statisticians exist in all phases of pharmaceutical research including pre-clinical (i.e., laboratory) research, clinical trials (i.e., studies in humans), epidemiology (i.e., studies of the spread of disease), health economics, market research, and publications in scientific journals at all stages of research.

Returning to the title question, you can trust the safety and efficacy of the drugs you take because they are extensively tested according to strict guidelines. The results of this testing are carefully reviewed by the world's leading medical and statistical experts prior to approval for marketing. Without extensive statistical analysis, the implications of scientific data would be less clear, and important information might be lost. Statisticians are essential in the drug development process because they ensure the validity and accuracy of findings at all stages of drug discovery, development, approval, and marketing.

Drug Development Time Line

Creation: laboratory testing →	IND Submission →	Human Testing →	NDA Preparation →	FDA Approval →	Post- Marketing Testing →
2-4 Years	2-3 months	3-7 years	6-12 months	6-12 months	Ongoing

notes:

IND (Investigational New Drug) application is filed with FDA (Food & Drug Administration, an agency of the federal Department of Health & Human Services); it summarizes all laboratory and animal testing, and requests approval to **study** the new drug candidate in humans.

NDA (New Drug Application) is filed with the FDA; it summarizes all of the previous animal and human testing results in evidence of the drug's safety and efficacy, and requests approval for marketing.