

Epidemiology in Drug Development

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It is time well spent in multidisciplinary workgroups to work to understand the basic concepts and principles of disciplines outside of our own area of expertise. This paper provides an introduction to epidemiology and risk management as implemented in a pharmaceutical company setting.

EPIDEMIOLOGY – BASIC DEFINITIONS

The discipline of epidemiology is long-standing and has evolved from the study of epidemics of infectious origins to be more widely applicable and so carry a wider definition: the study of the distribution, occurrence, and patterns of health-related outcomes. Epidemiological studies are often referred to as observational. Rather than modifying factors and recording effects (as in clinical trials), an epidemiologist most frequently designs and conducts studies that rely solely on recording and reporting observations in free-living beings, thus dealing in observational studies. Typically, observational studies have a broad eligibility criteria and large sample size.

Two main segments of epidemiology are descriptive and analytical. Descriptive epidemiology is the reporting of the distribution, occurrence and patterns of health-related outcomes. For example, increasing age is a consistent predictor of higher rates of most cancers and cardiovascular disease. A descriptive epidemiological approach would be to tabulate age categories and corresponding incidence rates for cancer and cardiovascular disease. In contrast, analytical epidemiology frequently relies on statistical approaches to evaluating the impact of factors on disease occurrence. For the example of age and cancer, the analytical approach might be to use statistics to control (using matching designs or statistical techniques) for other important predictors of cancer such as smoking status, while focusing the primary research question on age and cancer occurrence.

Two types of studies that are used on analytical epidemiology are the case-control and cohort studies. In case-control studies, the comparison groups are defined by their disease status and their prior exposure status is compared. In cohort studies, the comparison groups are defined by their exposure status; individuals with or without exposure are followed to determine outcomes.

Epidemiologists who work in the pharmaceutical industry may design and conduct studies to help understand a disease that may be modified by a pharmaceutical or biologic agent. These studies may be referred to as “natural history of disease” studies. The Framingham Heart study that has been running since the 1940s is well-known example of both a cohort study and a natural history of disease study. The Framingham Heart study has provided a wealth of findings including that the best simple test for predicting coronary artery disease is the ratio of total:HDL cholesterol (Castelli 1988).

PHARMACOEPIDEMIOLOGY – A BRANCH OF EPIDEMIOLOGY

Some observational studies have pharmaceuticals or biologic agents as a focus of the investigations. These require some special considerations that are part of the field known as pharmacoepidemiology. It is the study of the uses and effects, both adverse and beneficial, of drug in populations. Examples include the Anti-Epileptic Drug (AEDs) Pregnancy Registry, an observational cohort study or registry of women who become pregnant while on AEDs (Holmes 2004). The registry records birth outcomes and investigates whether adverse birth outcomes vary with use of specific AEDs. Because the information is primarily collected prospectively, this study is a prospective cohort study.

Pharmacoepidemiologists must make appropriate comparisons between treated and untreated patients. Among the challenges include channeling bias (that groups treated by drug x vs. drug y are different in ways that predict outcome); this bias is a constant consideration that has driven the development of approaches such as the development of propensity scores to minimize channeling bias.

STAGES OF DRUG DEVELOPMENT

To begin to consider how epidemiology is used in the pharmaceutical industry, a review of the stages of drug development is useful as provided in Table 1 below.

TABLE 1. STAGES OF DRUG DEVELOPMENT

Stage	Focus
Pre-clinical	Animal Toxicology Studies
Phase 1	Clinical Pharmacology Studies
Phase II	Dose Response Studies
Phase III	Determine Efficacy and Safety

Stage	Focus
Phase IV	Determine Safety of Product as if is used in a population

EPIDEMIOLOGIC STUDY DESIGN IN DRUG DEVELOPMENT PHASES

PHASE I

During Phase I of development of a new product, epidemiologists will review existing observational studies and consider initiation of new studies to describe the natural history of the target disease. Questions to be addressed are how common is the disease (incidence and prevalence) and the characteristics of the affect population (i.e. gender, age, geographical distribution, co-morbid conditions). This information sets the stage for understanding the targeted population prior to introduction of the new agent. Observational studies may also record the current treatment options and the anticipated adverse events related o the condition under study.

PHASES II AND III

Phase II and III of drug development is frequently a long and busy period for drug development teams with a focus on clinical trials that have required randomization of subjects. The randomization of subjects within a trial is a key difference between clinical trials and observational studies. The information collected during trials is designed to primarily assess efficacy and will collect some limited safety information. The safety information is limited because the database is small (less than 10,000 patients) and so will not provide accurate estimates of rare events. Additional limitations are that the clinical trial sample is healthier than the larger group of patients who will eventually get the product, the duration of treatment is shorter and the use of the product is protocol-driven so variation in actual practice cannot be assessed. The epidemiologist can work during Phases II and III to evaluate these considerations and review the scientific literature to assess the importance of the limitations of the clinical development program on what is possible to know about the safety of the product upon completion of the clinical trials. For example, in investigating a product for atrial fibrillation, it would be tempting to treat only early stage patients without congestive heart failure (CHF). However, there is a very high rate of CHF among patients with atrial fibrillation. An epidemiologist would be able to work from the scientific literature to provide estimates of the occurrence of CHF among patients with atrial fibrillation and rates of adverse outcomes among atrial fibrillation patients with and without CHF.

PHASE IV

A product that successfully gains FDA or EMA approval, upon launch by the Sponsor, will often be the subject of safety studies in the marketplace. Epidemiologist may be involved with descriptive studies for the purpose of post-marketing surveillance or to detect signals. Regulatory authorities require that Sponsors compile and periodically provide safety reports based on unsolicited individual safety reports, also called spontaneous adverse events. A company's adverse event database is thus used for post-marketing surveillance. Often they are used to develop a case series or may be used with disproportionality analysis for signal detection purposes.

For case series using the spontaneous adverse events, a first step is to create a case definition to determine which of the adverse events will be included in the analysis. This type of investigation does not include a control group because there is no "non-treated" comparison group within a sponsor's adverse event database. However, this approach is useful to develop a clinical spectrum of adverse events, to describe the aggregated characteristics of the cases, and to compare to similar events in the general population as reported in the scientific literature.

Signal detection approaches are also sometimes used in evaluating spontaneous adverse event databases. Often a disproportionality approach is taken to compare the number of observed events (reported for a specific product) to the number of expected events if all drugs had the same reporting rate. An a priori cut-off is established and those that fall above the pre-stated cutoff are candidate signals for further evaluation. Among the approaches to signal evaluation are to compare the findings to what has been seen in pre-clinical studies, clinical trials, to compare to other products in the same class, to consider the biologic plausibility of the finding and to perform additional investigations such as observational studies or clinical trials.

Additionally, Sponsors may write protocols to conduct studies to actively collect additional information regarding the safety profile of a product. If the goal of the additional studies is to estimate incidence rates of adverse events among users of a product, a cohort or registry approach is necessary because incidence cannot be calculated from case-control designs. Registries with ascertainment of patient (all with the same disease) or product (all taking the same or similar products) can be and most often are designed to collect a breadth of information including demographics, diagnostic information, treatment information (drugs, procedures, etc), medical resource utilization (hospitalization, outpatient visits, home therapy) and mortality. Possible uses of registry data are to calculate outcome estimates, estimate trends over time, evaluate treatment modalities, serve as a source of cases for case-control studies, or to provide an established cohort for future studies.

Phase IV studies can be quite varied depending on the research question. In addition to cohort studies, case-control studies are sometimes undertaken to study rare events. While case-control studies are more susceptible to selection and recall bias, they are sometimes undertaken because they are quick, relatively inexpensive, more easily repeated and can evaluate multiple risk factors for a single disease.

Phase IV also provides an opportunity to conduct large, simplified trials. These are large undertakings that are necessary to evaluate important safety questions. A recently published example is the Zodiac trial to evaluate mortality following ziprasidone and olanzapine use (Strom 2011).

Other important tools in post-marketing pharmacoepidemiology are large computerized administrative databases. Examples of these are those maintained by Kaiser Permanente Health plans. The primary reason for the existence of these databases is for administrative purposes for the health plan. However, those that have been well-created, maintained and used for research purposes can be used for pharmacoepidemiological research. Advantages of these databases include that they are a form of active surveillance, use existing databases, and typically have a useful comparison group that are in the same database. Methodological challenges in using databases include that some of the important data including outcomes may not have been verified, that it is necessary to wait for market penetration of a product to be adequate to meet the required sample size, and that important confounding factors such as smoking status or use of over-the-counter medications are often missing.

CONCLUSIONS

Epidemiology provides a critical line of evidence in the evaluation of products' benefit/risk profiles and can be useful through the stages of a product's development. A variety of epidemiologic approaches are available to evidence generation pre- and post-launch.

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