Supplement: Drug Development and Clinical Testing

Overview of Drug Regulation

1906—Pure Food and Drug Act regulates "purity" and labeling.
1914—Food, Drug, and Cosmetic Act charged the FDA with ensuring that foods and drugs were safe.
1938—Food, Drug and Cosmetic Act required safety testing of drugs and vehicles prior to marketing.
1962—Kefauver-Harris Admendment. Teratogenicity testing required. Proof of efficacy required. Old drugs (pre-1938) were grandfathered in.
1984—Patent Restoration Act gave back some years of patent protection to manufacturers to compensate for time in approval process.
1992—Expedited Drug Approval Act provided for "fast-tracking" of drugs deemed to be therapeutically important (e.g. most new HIV drugs). Required post-marketing surveillance.

Drug Discovery

Sources of New Chemical Entities

1. Random screening of natural products. This is still an important source of toxins and complex plant alkaloids which find their way into therapy. Examples include the cancer drug, *paclitaxel*, which comes from the yew, and the investigational analgesic, *epibatidine*, which is derived from a frog.
2. Chemical modification of existing compounds. This sometimes is based on first principles of structure-activity, but serendipity has often played a large role in creating entire classes of therapeutic agents. For example, the early antibacterial agent, *sulfanilamide*, and its derivatives were found to produce several side effects:
    - Sulfanilamide produced metabolic acidosis by inhibiting carbonic anhydrase. Chemical modification of this sulfonamide led to the development of the clinically useful carbonic anhydrase inhibitor *acetazolamide* and later, *chlorothiazide* and the other thiazide diuretics.
    - Another derivative caused hypoglycemia, and modification of its structure led to the development of *chlorpropamide* and the other sulfonylurea oral hypoglycemic agents.
    - Sulfadiazine and sulfaguanine caused goiters in rats, and further chemical screening led to the development of the antithyroid drugs, *propylthiouracil* and *methimazole*.
3. Rational drug design based on three dimensional structural data of candidate receptors and enzymes or knowledge of the relevant genetic sequence. An early example of the former was the development of pralidoxime (2-PAM) to reactivate cholinesterase. More recent examples are the development of angiotensin converting enzyme inhibitors for hypertension and GABA agonists for the prevention of seizures.

Preclinical Screening

1. A **lead compound** is identified by screening of hundreds of candidate molecules. The screens run an enormous gamut from receptor binding assays, metabolic profiles, and second messenger systems, to cells and tissues, all the way to the structure and function of intact animals.
2. In most cases the screening process includes a model system thought to predict clinical response in a particular area of interest. For example, an approach-avoidance behavioral test in rats might be used as a screen for a potential anti-anxiety drug.
3. The medicinal chemists usually apply for patents on the pivotal compounds as well as their close congeners and major metabolites (the 20 year clock starts ticking when the patent is issued).
4. The most promising molecular entity is then sent on for further characterization and toxicology testing. The drug must be tested in several species for acute, subacute, and chronic toxicity, and screened for teratogenicity and other reproductive effects. This is an important decision point because animal toxicology experiments are extremely expensive and time-consuming. Of course, they are mandatory if the compound is to be taken on to human testing.
5. The patent holder files a Notice of Claimed Investigational Exemption for a New Drug (IND) with the FDA. After review of the material, FDA will meet with the applicant to draw up an initial plan for human trials.

Clinical Trials

1. **Phase One** is the first introduction to human volunteers (or sometimes patients, if volunteers are inappropriate). The aim is usually to establish safety rather than efficacy and to determine initial pharmacokinetics as well as the dose range where effects occur. Starting doses are typically tiny fractions of threshold doses in animals. A typical phase one cohort may have 50-75 volunteers.

2. **Phase Two** consists of somewhat larger trials in patients. These are designed to show efficacy and establish the likely clinical doses. These trials typically include large numbers of screening laboratory tests, ECGs, etc.

3. **Phase Three** trials are large, usually multicenter trials in hundreds or thousands of patients. These usually establish dose-response relationships and give a much better idea of the likely side-effect profile. The material from these trials is submitted to the FDA as a New Drug Application (NDA), and the approval process may take several years.

   The FDA approves a drug only on the basis of the testing that was submitted with the NDA. Thus the approval specifies not only the indication, but also the specific formulation, the route of administration, and the dose range. Approval of a drug by injection does not constitute approval for an oral form—this requires a new submission (referenced to the old one). Interestingly, the approval of a drug does not

mean that its metabolites are approved as drugs (consider the cases of N-acetyl procainamide or morphine 6-glucuronide).

On the basis of the safety testing, the agency may require warning language on the package insert. Of course, there is a tremendous amount of drug prescribing for "unlabeled indications." Drug companies are not allowed to market drugs for these indications, but this rule is often circumvented (see attached article on the use of topical tretinoin).

4. **Phase Four** is designed to monitor the safety of the drug under conditions of actual clinical use. Many drugs are approved after study in only 2-3000 patients, so low-frequency adverse effects (i.e., 1/1000 or less) may not be detected prior to marketing. There have been a number of postmarketing drug withdrawals recently for significant, unexpected toxicity, leading some to suggest that a different form of safety monitoring is needed (see attached articles). In addition to the morbidity and mortality, these drug failures can be financially disastrous for the companies concerned. It may take 500 million dollars to bring a new drug to market, and litigation resulting from injury may cost even more.