

**SESSION 1: Veterinary Pharmacology in
Human Health Pharmaceuticals**

Chairperson
Dr. Scott A. Brown

Development of a New Pharmaceutical For Use in Man

Hugh E. Black, D.V.M., Ph.D., Dipl., ACVP, Dipl., ACT
President, Hugh Black Associates, Sparta, New Jersey 07871

Introduction

The development of a drug for potential use in man is a complex and protracted process. Because it is such a difficult, costly and high risk endeavor, most pharmaceutical companies select specific therapeutic categories in which to concentrate their efforts. This strategy permits them to develop the expertise and resources required in chemistry, pharmacology and clinical evaluation, etc. to pursue a specific area.

The ideas that lead to the development of a new medicine come from numerous sources. Many begin as a concept that a scientist has developed. Otx and protracted process. Because it is such a difficult, costly and high risk endeavor, most pharmaceutical companies select specific therapeutic categories in which to concentrate their efforts. This strategy permits them to develop the expertise and resources required in chemistry, pharmacology and clinical evaluation, etc. to pursue a specific area.

The ideas that lead to the development of a new medicine come from numerous sources. Many begin as a concept that a scientist has developed. Otany. Many compounds are purchased either from other companies, a university or even an individual.

Discovery

Chemistry

The process of developing a drug begins in the laboratory with the complex process of synthesizing and characterizing a desired molecule or series of molecules.

Once these steps have been completed, scaling up the synthesis must be accomplished to make sufficient quantities of the pure compound for study in pharmacologic screens.

Pharmacology

From this point there follows a very close interaction between Chemistry and Pharmacology with the latter developing and using *in vitro* and *in vivo* assay models to reveal either the presence or the absence of the desired pharmacologic activity. The screens used in pharmacology to evaluate compounds are usually designed to become increasingly more specific for the trait in the molecule that is being sought. Relevant potency (ED_{50}) for a specific activity is developed for different molecular modifications of a given structure as well as for comparative compounds. All of this information is used to further refine the selection of the lead molecule. These early studies also make it possible for the chemist and pharmacologist to develop an understanding of the basic structure(s) within the molecule that are critical for its efficacy in the target assay system. Studying the chemical structure of the molecule also identifies points in its structure where instabilities may occur. If sites of rotation are identified, studies will follow to determine how to stabilize these sites yet maintain the desired pharmacologic activity.

Further molecular modifications of the basic structure of the lead compound(s) are made and the new molecules are again studied to establish relative potencies compared to either the lead compound in the series or to a comparative control

compound shown to have potent activity in the assay. One or more of the lead structures may be selected for more detailed *in vivo* study in appropriate animal model systems.

From the results of these *in vivo* studies selection is made of both a compound and a dose that it is believed would be associated with efficacy in man.

Drug Metabolism Support of Discovery

Support studies in Drug Metabolism are initiated at about the same time the pharmacology *in vivo* screens are being conducted. The metabolism studies provide early information about relationships between dose, route of administration, absorption, T_{max} , C_{max} , $T_{1/2}$ and AUC estimates. This early drug metabolism data also provides early information about the pharmacokinetic/pharmacodynamic characteristics of the molecule.

After the lead compound has been identified for development, the safety pharmacology studies for cardiotoxicity, CNS toxicity and renal toxicity are initiated. These studies assure that the structure doesn't carry acute liabilities in these organ systems.

The last studies that may be completed before a drug is recommended for development are two-week toxicity studies in a rodent and a non-rodent species. The purpose of these studies is to identify any severe toxicity associated with repeated daily administration of the compound at a high dose, toxicity that would clearly say, "*Do not proceed.*"

When all of the studies have been completed that identify and characterize the chemistry and preclinical pharmacology of a chemical structure, the reports documenting all of this information are written and issued. If evaluation of this information package clearly suggests the compound is a viable candidate drug, a recommendation to proceed with development is made to management.

This recommendation is not made lightly because it initiates a costly and division wide series of activities that must go forward together to assure the

timely completion of an Investigational New Drug application in the minimal amount of time.

The Drug Development Process

Preclinical Drug Metabolism

Planning and executing the preclinical Drug Metabolism program must take into account the needs and the expectations of the countries in which the drug applications will be filed.

An early and critical activity is the development and thorough validation of the assays necessary to determine the levels of the candidate compound in the biological fluids of the species in which the drug will be studied.

ADME Studies

The single and multiple dose ADME studies are conducted in rodents using radiolabeled material to provide a more definitive indication of how the animal model is exposed to a drug and its metabolites. In the non-rodent species ADME studies that don't require sacrifice of the animals are conducted.

The single-dose ADME studies provide important information needed to understand the relative absorption of radiolabeled drug when administered by the intended clinical route, how the drug distributes in the tissue, the profile of the metabolites in the plasma, urine, bile and feces and the route(s) by which the drug is excreted.

The data from multiple dose studies, when compared to single-dose study results, provide comparative information about changes that may occur in these parameters at steady state following repeat dosing. The single- and multiple-dose studies may include whole body autoradiography as a component to compliment the understanding of tissue distribution of the drug.

Tissue Distribution Studies

The tissue distribution studies conducted in rodents determine the distribution and retention/depletion of

radiolabeled compound in all organs of the body as a function of time. This information can be important in the interpretation of target organ changes in the toxicology studies and in the interpretation of ADME studies.

Relative Bioavailability

The relative bioavailability of a compound when administered by the clinical route is determined by comparing blood levels achieved by the clinical versus the intravenous route when the same amount of drug is administered by either route. By comparing the total radioactivity in the plasma after equal doses administered by the intravenous and the clinical routes, i.e. oral, it is possible to determine the amount of total drug-derived material that is absorbed by the clinical route. By isolating the amount of radiolabel associated with the parent compound from the total radioactivity in the plasma, it is possible to determine what percent of an administered dose is represented by parent compound.

Toxicology Support

The availability of plasma assays prior to the conduct of the toxicology studies are most important. One must assure, by the presence of plasma concentrations of drug in the test animals, that any minimal toxicity or the apparent lack of toxicity of a compound doesn't in fact reflect a lack of absorption and therefore a lack of exposure to the drug.

Plasma data in multiple-dose studies in addition to validating that the drug was absorbed, indicates if absorption was either dose related or dose proportional or if there was saturation of absorption above a certain dose level. Single time point data collected at selected intervals over the course of a toxicology study can also indicate if a drug has the potential to accumulate with continued dosing or has the potential to induce its own metabolism.

Toxicokinetics

Toxicokinetic studies are conducted in the species and at the doses used in the

toxicology studies to characterize the kinetics of the drug at high doses over relatively long periods of administration.

Changes in the toxicokinetic parameters between the initiation and the termination of a study, along with changes in C_{min} values at selected intervals over the course of the study may suggest that the drug has the potential to either accumulate with repeated dosing or to induce its own metabolism. Toxicokinetic data provides information which makes it possible to determine and compare the relative exposure of animals given high doses of a compound in toxicology studies to patients given the drug at the clinical dose.

Comparative *In Vitro* Metabolism Studies

Comparative *in vitro* studies using tissues of both animal and human origin can be of significant value. Metabolites can be isolated, characterized and compared following exposure of the same tissues (i.e. liver) from different species.

Enzyme Induction Studies

Because the potential for a drug to alter the P-450 drug metabolizing enzymes in the liver has significance for the drug's future development, it is important to have this information early in the development cycle. Inducing potential has at least two points of significance. The first is the potential for a drug to interact with a second drug that a patient may receive. The second is the fact that most potent inducers increase the incidence of liver tumors in rodent bioassays and thereby present significant regulatory problems for the approval of the drug.

Protein Binding Assays

Early in the development of a drug it is important to understand its protein binding potential. Compounds that have high binding constants, (i.e. 99%) need to be identified early. If a drug is able to displace only 1% of a second drug from plasma proteins, it has already effectively doubled the exposure of the patient to the second drug.

The Toxicology Program

The toxicology program required to support the administration of a new drug to man for either a short or a long period of time is governed by both regulation and good science. All studies conducted and used for this purpose must be conducted by Good Laboratory Practices (GLP's) as defined by regulation.

There are four major components to a preclinical toxicology program and the studies are designed accordingly. The studies can be broken down to those that identify either (a) genotoxicity, (b) reproductive/fetal toxicity, (c) target organ toxicity in the whole animal and (d) carcinogenic potential.

General Toxicology

The objectives of the general toxicity studies are to identify (1) how well a compound is tolerated clinically when given at high doses over varying periods of time, (2) the target organs of toxicity, (3) the multiples of the clinical dose at which the changes were observed, (4) the no-effect-dose and (5) if there are any effects observed that would indicate development of the drug should be stopped.

The general toxicology studies vary in length from single high-dose studies where the compound is given by two routes to at least two species to studies that vary in length from 1, 3 or 6 months in a rodent model and 1, 3 or 12 months in the dog/monkey. For compounds to be administered clinically for any protracted period of time, carcinogenicity studies in 2 species also must be conducted.

Additional information can be obtained from the three-month studies related to the potential for enzyme induction with repeated long-term dosing. Increased total liver weights and microscopic evidence of centrilobular cell hypertrophy are strongly suggestive. Demonstration of increased total microsomal protein per gram of liver, increased total cytochrome P-450 per milligram of microsomal protein and increased specific markers such as benzphetamine-n-demethylase, 7-ethoxycoumarin-0-deethylase and aniline

hydroxylase activities will confirm induction potential.

The carcinogenicity studies require a separate set of three month studies in the rat and mouse to determine the route and maximum dose to use in the two-year studies. Toxicokinetic data is an important part of these studies as it will demonstrate the relative exposures (AUC's) achieved by the oral or dietary routes at the same dose. It will also demonstrate the relative C_{max} values to which the animals will be exposed at the same dose given by the two routes.

Genetic Toxicology

The studies conducted for the detection of genotoxic potential include the AMES assay for point mutations, the CHO assay for chromosomal aberrations, the *in vivo* Mouse Micronucleus Assay for chromosomal aberrations and the Human Peripheral Blood Lymphocyte Cytogenetics Assay for chromosomal aberrations in a human cell. Additional studies may be needed and may include an assay for unscheduled DNA synthesis, an assay for DNA adduct formation, etc.

Reproductive Toxicology

The battery of reproduction assays are conducted for the purpose of identifying any potential for the drug to (a) adversely effect reproductive performance of either the male or the female (Segment I Studies), (b) to express teratogenic activity in the fetus (Segment II Studies) and (c) to adversely effect parturition, lactation or fetal development or (d) to have residual effects in the offspring that would express themselves as either defects in reproductive performance or fetal abnormalities (Segment III Studies). In the reproductive battery, the Segment I studies are routinely conducted in the rat, the Segment II studies in the rat and the rabbit and the Segment III studies in the rat.

As part of the Good Laboratory Practice (GLP) requirements for toxicology studies the conduct of *in vitro* and *in vivo* studies for preclinical toxicology requires that for each study there is complete

documentation of the batch, the purity, the stability and the homogeneity of the compound in the vehicle used in that study.

The Clinical Program

The clinical program is divided into broad and overlapping phases termed Phases I, II, III and IV. The program begins with the Phase I studies.

Phase I Studies - Clinical Pharmacology

The first studies in clinical pharmacology are the single-dose safety studies. In this and all following pharmacology studies, blood samples are collected at selected intervals following drug administration to determine the levels of drug in the plasma and the pharmacokinetics associated with its absorption metabolism and excretion. Groups of human volunteers are administered the drug beginning with doses significantly below the proposed clinical dose. This dose group is completed and the data is collected and analyzed. If the results indicate a lack of toxicity at this dose, the next highest dose is administered. This process of dosing a group of volunteers and analyzing the data is continued until there is a suggestion at some dose of some drug-related adverse observation, i.e. headache, that is considered to indicate a maximum tolerated dose has been achieved.

The single-dose study is followed by a rising-multiple-dose study designed to characterize the safety and the pharmacokinetics of the compound with repeated dosing in the human volunteer. Healthy volunteers are given daily low doses of the drug for a defined number of administrations. As in the single-dose studies the data from this group of individuals is collected and evaluated before the next higher dose is administered to another group of volunteers. This process is repeated until a dose is reached where there appears to be an increase in the numbers of adverse experiences

suggesting that a maximum tolerated dose has been reached. The blood, urine and fecal samples collected from this group of patients are analyzed and the pharmacokinetics associated with the repeat administration of the compound are determined.

Additional clinical pharmacology studies follow later in the development process to determine how specific patient populations respond to the drug. These studies are conducted in patients with renal disease, patients with hepatic disease, elderly patients or, if appropriate, patients who are young or very young.

In the clinical studies, pharmacokinetic parameters are developed in specific studies for the purpose of developing pharmacokinetic/pharmacodynamic characteristics of the drug.

Phase II Studies

The objectives of the Phase II studies are to demonstrate efficacy in the target population and to identify the dose and the dose regimen that yields the maximum desired therapeutic effect with the lowest patient exposure to the drug. In a series of studies the drug is administered to target patient populations by repeat administration in a clinical setting. The maximum period of exposure in these studies is dictated by the length of the toxicology studies that have been completed. Once efficacy has been established in the target population, additional studies may be conducted to characterize the dose and a dosing regimen that provides the patient with the maximum efficacy with minimal exposure to the compound.

Another goal of the Phase II programs is to finalize the formulation that will comprise the final marketed product that will be used in the Phase III studies.

Phase III Studies

Upon completion of the Phase II program, two independent clinical studies, each with large patient populations are initiated. The objectives of these studies are to independently confirm the efficacy and the dose and dose routes identified in

the Phase II program. These studies frequently involve many investigators at multiple sites. They require strong statistical support in both their planning and evaluation to assure they have the statistical power to assure that the conclusions of the studies are defensible.

Phase IV Studies

Studies conducted in Phase IV are studies usually conducted after a compound has received approval. A commitment by the company to conduct a Phase IV study may be part of the negotiations that occur during the approval process for a compound. They are usually conducted to clarify some specific issue that of itself was not sufficient to prevent the approval of the drug.

Conclusion

The discovery, development and approval for marketing of a pharmaceutical for use in human medicine is a complex, high-risk, long-term project. It is estimated to take an average from 7 to 11 years to complete and to cost, on average, about \$230,000,000.00. Many things can change both within and outside a company during the development process over this many years. New drugs in the therapeutic class may receive approval, regulations and requirements may change, and complications may arise at any point in the process that have the potential to either significantly complicate the approval process or to even end the project. Thus the discovery and development of "breakthrough" drugs is relatively rare and what might appear to be an unique medicine during the discovery and early development phase can end up being a "me too" drug by the time it receives regulatory approval.