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A OVERVIEW ON DIFFICULTIES AND DRAWBACKS ASSOCIATED WITH ANIMALS IN DRUG DEVELOPMENT

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ABSTRACT

Drug development is the process of bringing a new pharmaceutical drug to the market once a lead compound has been identified through the process of drug discovery. It includes pre-clinical research (microorganisms/animals) and clinical trials (on humans) and may include the styles of preclinical research. During preclinical drug development, a sponsor evaluates the drug's toxic and pharmacologic effects through in vitro and in vivo laboratory animal testing. Genotoxicity screening is performed, as well as investigations on drug absorption and metabolism, the toxicity of the drug's metabolites, and the speed with which the drug and its metabolites are excreted from the body.

INTRODUCTION

Development of new agents with potential for beneficial impact on human health is an area of significant interest in the department. These include construction and study of agents with potent anti-viral, anti-biotic or anti-cancer properties, development of artificial blood, study of structure-activity relations and enzyme mechanism and inhibition, as well as understanding general mechanisms of drug action and the molecular basis of cancer chemoprevention [1].

Chemical modification of a known drug

- Random screening of natural and synthetic chemicals to detect useful activity.
- Rational drug designing based on the chemical structure.

After identification the structure of the new compound and its purity are determined by the analytical chemist. The compound is screened for the presence any useful biologic activity by a series of test like bioassays, molecular and cellular studies followed by test in whole animals. If the compound is found to be promising then it is subjected preclinical evaluation in animals and clinical tails in humans [2].

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DRUG DEVELOPMENT

The last few decades have seen the development of several new drugs which have revolutionized the practice of medicine. The discovery and development of a new a drug is a time consuming and expensive procedure. A new drug may be identified by the following processes

CLINICAL STUDIES

Phase 1 Clinical Studies

Phase 1 includes the initial introduction of an investigational new drug into humans. These studies are closely monitored and may be conducted in patients, but are usually conducted in healthy volunteer subjects. These studies are designed to determine the metabolic and pharmacologic actions of the drug in humans, the side effects associated with increasing doses. During Phase 1, sufficient information about the drug's pharmacokinetics and pharmacological effects should be obtained to permit

the design of well-controlled, scientifically valid [3].

Phase 1 studies also evaluate drug metabolism, structure-activity relationships, and the mechanism of action in humans. These studies also determine which investigational drugs are used as research tools to explore biological phenomena or disease processes. The total number of subjects included in Phase 1 studies varies with the drug, but is generally in the range of twenty to eighty.

Phase 2 Clinical Studies

Phase 2 includes the early controlled clinical studies conducted to obtain some preliminary data on the effectiveness of the drug for a particular indication or indications in patients with the disease or condition. This phase of testing also helps determine the common short-term side effects and risks associated with the drug. Phase 2 studies are typically well-controlled, closely monitored, and conducted in a relatively small number of patients, usually involving several hundred people.

Phase 3 Clinical Studies

Phase 3 studies are expanded controlled and uncontrolled trials. They are performed after preliminary evidence suggesting effectiveness of the drug has been obtained in Phase 2, and are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug. Phase 3 studies also provide an adequate basis for extrapolating the results to the general population and transmitting that information in the physician labeling. Phase 3 studies usually include several hundred to several thousand people.

Pre-Clinical Research

Under FDA requirements, a sponsor must first submit data showing that the drug is reasonably safe for use in initial, small-scale clinical studies. Depending on whether the compound has been studied or marketed previously, the sponsor may have several options for fulfilling this requirement

- Compiling existing nonclinical data from past in vitro laboratory or animal studies on the compound
- Compiling data from previous clinical testing or marketing of the drug in the United States or another country whose population is relevant to the U.S. population
- Undertaking new preclinical studies designed to provide the evidence necessary to support the safety of administering the compound to humans [4].

At the preclinical stage, the FDA will generally ask, at a minimum, that sponsors:

- Develop a pharmacological profile of the drug
- Determine the acute toxicity of the drug in at least two species of animals
- Conduct short-term toxicity studies ranging from 2 weeks to 3 months, depending on the proposed duration of use of the substance in the proposed clinical studies [5].The new drug application (NDA) is the vehicle through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale in the United States. To obtain this authorization, a drug manufacturer submits in an NDA nonclinical (animal) and clinical (human) test data and analyses, drug information, and descriptions of manufacturing procedures [6].

An NDA must provide sufficient information, data, and analyses to permit FDA reviewers to reach several key decisions, including:

Whether the drug is safe and effective for its proposed uses, and whether the benefits of the drug outweigh its risks.

Whether the drug proposed labeling is appropriate, and, if not, what the drug's labeling should contain.

Whether the methods used in manufacturing the drug and the controls used to maintain the drug's quality are adequate to preserve the drug's identity, strength, quality, and purity.

The purpose of preclinical work--animal pharmacology/toxicology testing--is to develop adequate data to undergird a decision that it is reasonably safe to proceed with human trials of the drug. Clinical trials represent the ultimate premarket testing ground for unapproved drugs. During these trials, an investigational compound is administered to humans and is evaluated for its safety and effectiveness in treating, preventing, or diagnosing a specific disease or condition. The results of this testing will comprise the single most important factor in the approval or disapproval of a new drug [7].

Although the goal of clinical trials is to obtain safety and effectiveness data, the overriding consideration in these studies is the safety of those in the trials. CDER monitors the study design and conduct of clinical trials to ensure that people in the trials are not exposed to unnecessary risks [8].

New Drug Application Actions

Once an approval, approvable, or non-approvable recommendation is reached by the reviewers and their supervisors, the decision must be evaluated and agreed to by the director of the applicable drug review division or office. For the director's review, the consumer safety officer assembles an "action package" that contains the action letter and any data, CDER reviews and memos, and other information supporting the reviewers' recommendation.

Following his/her review of the action package, the division director may begin a dialogue with the reviewers and their supervisors. The division director generally serves as the final FDA ruling. In this sense, the division director is said to have "sign-off" authority for such drugs. The level of "sign-off" authority needed is determined by the classification of the drug under

consideration. Class 1 drugs, for example, cannot be "signed off" by division directors; they require office level "sign-off" on action letters.

Once the division director (or office director, as appropriate) signs an approval action letter, the product can be legally marketed starting that day in the United States [9].

ANIMALS IN CLINICAL TESTING

In animal testing, drug companies make every effort to use as few animals as possible and to ensure their humane and proper care. Generally, two or more species are tested because a drug may affect one species differently from another. Animal testing is used to measure how much of a drug is absorbed into the blood, how it is broken down chemically in the body, the toxicity of the drug and its breakdown products and how quickly the drug and its metabolites are excreted from the body [6, 10].

Animal drug applications

Animal drug is defined, in part, as any drug intended for use in animals other than man, including any drug intended for use in animal feed but not including the animal feed, the composition of which is such that the drug is not generally recognized as safe and effective for the use under the conditions prescribed, recommended, or suggest in the labeling of the drug There are three different types of new animal drug applications [10].

NADAs and supplements - An NADA is used to seek approval of a new animal drug and includes any subsequent supplemental applications made to an approval.

ANADAs and supplements - An ANADA is used to seek approval for a generic new animal drug and includes any subsequent supplements to an approved ANADA. A generic new animal drug is a copy of an approved new animal drug for which patents or other periods of exclusivity are near expiration [11].

Fig 1. Different Phases of Clinical Studies

Fig 2. For dose testing

Fig 3. For Eye Irritancy

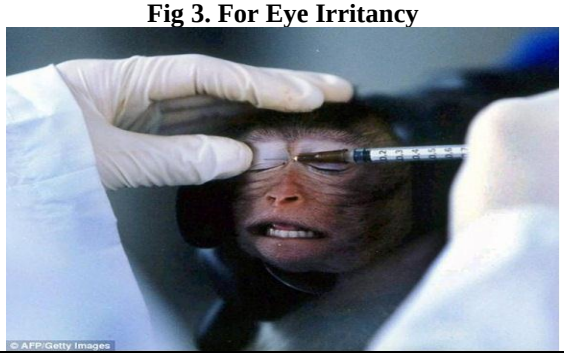

Fig 4. For Acute Toxicity

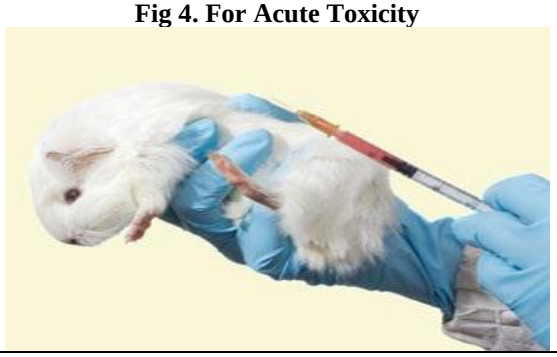

Fig 5. Repeated Dose Toxicity

Fig 6. Skin Corrosivity/Irritation

Fig 7. Skin Sensitization

Fig 8. Pharmacokinetics/Toxic and Metabolism

Fig 9. Dermal Penetration

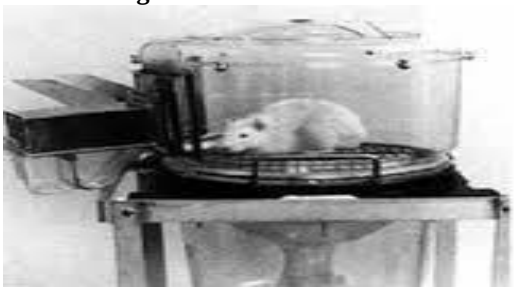

Fig 10. Mutagenicity

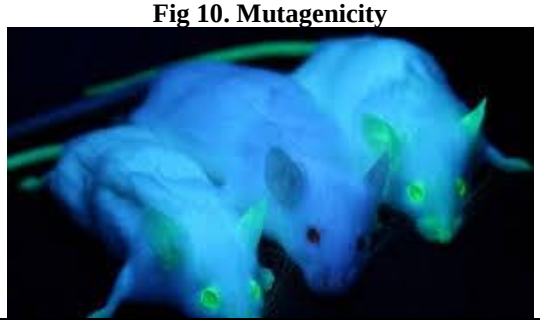

Fig 11. Carcinogenicity

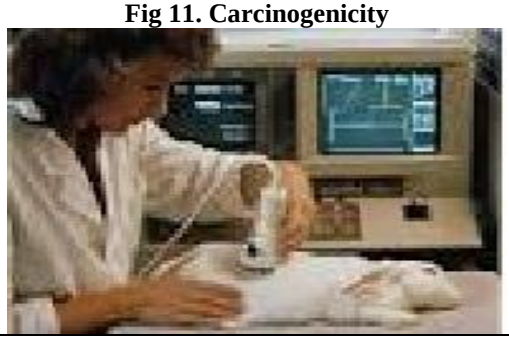

Fig 12. Reproductive and developmental toxicity

CONCLUSION

Animals have proven to be poor models for human disease research. Because they are genetically different from humans, studying diseases in animals can give us inadequate or erroneous information. The difficulties associated with using animal models for human disease result from the metabolic, anatomic, and cellular differences between humans and other creatures.

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CONFLICT OF INTEREST:

The authors declare that they have no conflict of interest.

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