PRECLINICAL TOXICOLOGY

Points to Consider in Program Design



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PACIFIC BIOLABS – YOUR PARTNER FOR PRECLINICAL SAFETY TESTING

As ***The Service Leader in Bioscience Testing***, Pacific BioLabs (PBL) strives to help our clients deliver safe and effective pharmaceuticals to the patients who need them. Well designed and executed preclinical studies are critical to the success of any drug development program. They must reliably assess the safety of a new drug entity, laying the groundwork for clinical trials and ultimately, regulatory approval.

Pacific BioLabs interacts closely with our clients, providing quality nonclinical testing results to meet regulatory requirements and guide your drug development decisions. As part of our commitment to clients, we have prepared a pair of publications that will assist you in planning your preclinical testing program. This publication, ***Preclinical Toxicology – Points to Consider in Program Design***, gives an overview of the drug development process, describes the contents of a typical Common Technical Document, shows the relative timing of various studies required for a successful IND and NDA, and presents advice on selecting and working with contract toxicology labs and other CROs.

PBL's companion publication, ***Preclinical Toxicology – Guidance for Industry – ICH Guidances***, is available on our website at PacificBioLabs.com. It presents two major ICH guidance documents that directly address safety testing of new pharmaceuticals: *Guidance M3 – Nonclincal Safety Studies for the Conduct of Human Clinical Trials for Pharmaceutical* and *Guidance S6 – Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals*.

The FDA website http://www.fda.gov/cder/guidance contains these two documents along with a variety of other references on regulatory expectations for the nonclinical development of NCEs. Topics include various aspects of safety (e.g. reproductive, carcinogenicity and genotoxicity), ADME (e.g. bioanalytical, pharmacokinetics and toxicokinetics), and safety pharmacology.

We hope you find these resources useful, and we wish you the best in your continuing quest to develop safe and effective new medicines.

Tom Spalding
President
Pacific BioLabs

PRECLINICAL TOXICOLOGY

POINTS TO CONSIDER IN PROGRAM DESIGN

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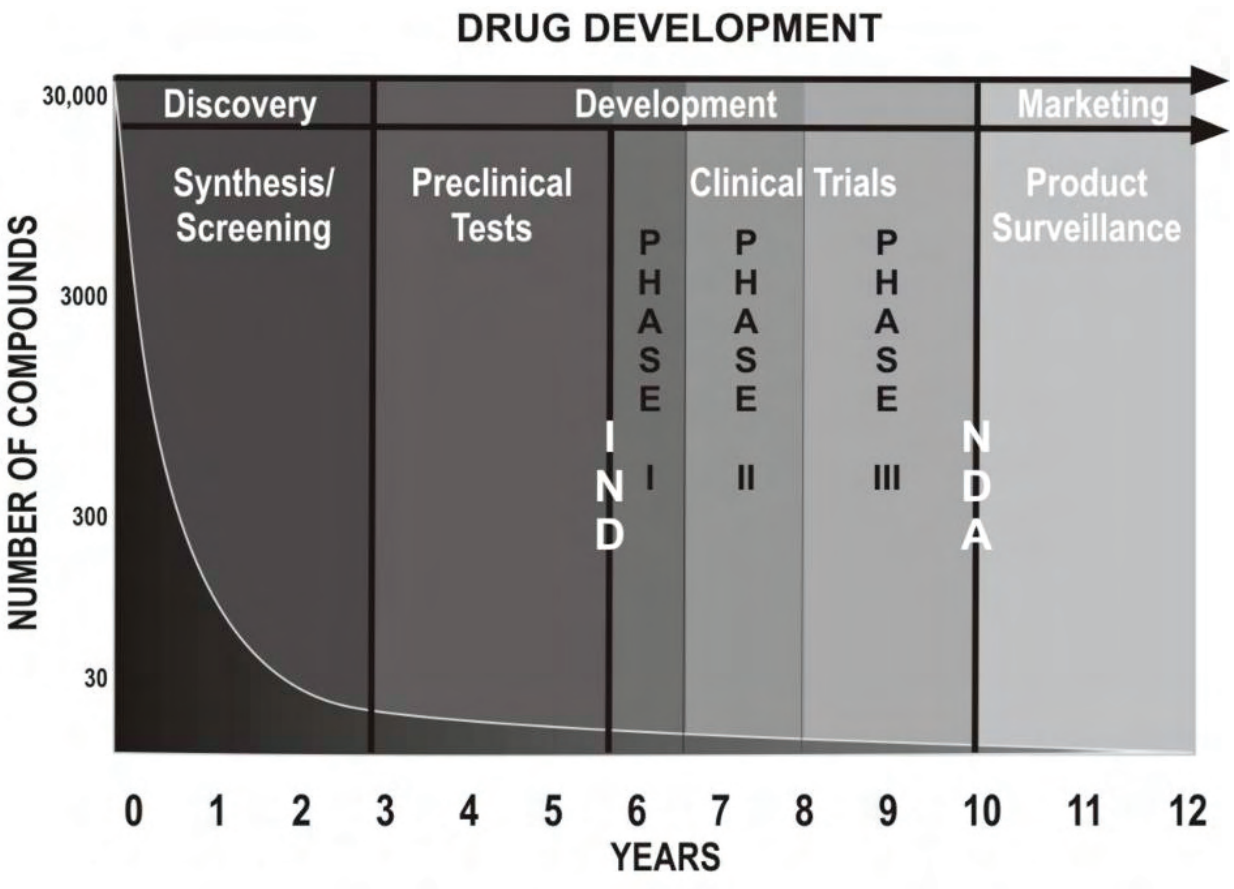
INTRODUCTION

Drug development is a high-risk enterprise. The typical new drug takes 10-12 years to get to market and costs up to $500 million. Pharmaceutical companies face continually increasing challenges in drug development—shorter product life cycles, global competition, as well as daunting technical and regulatory hurdles. Meanwhile, as a result of the Human Genome Project and high throughput drug development methods, there are many more drug candidates to test. Thus, there is growing pressure on pharmaceutical and biopharmaceutical companies to be efficient in their drug discovery and development programs.

Roughly 80% of candidate drugs will fail during the preclinical phase of their development. A well thought out nonclinical pharmacology/ toxicology program is critical for the long-term effectiveness of a drug development effort. Because they help drug developers avoid clinical trials that are destined to fail, nonclinical studies can be a major tool for reducing drug development costs.



PHASES OF A DRUG DEVELOPMENT PROGRAM

Drug development is often divided into the following phases: Discovery, Preclinical Development, Clinical Development, and Marketed Drug/Post-Marketing studies. These are somewhat arbitrary delineations of a complex process that must include a significant amount of flexibility if it is to succeed. A brief description of these phases and some of the nonclinical activities associated with them follows.

The process of drug development has several well-defined benchmarks, including selection of a lead candidate, preparation of an IND (or similar document) that supports first-in-human dosing, and preparation of an NDA (or similar document) that supports marketing of a new drug. At the end of this discussion is included an overall summary of the timing for the nonclinical ADME, Safety Pharmacology and Toxicology studies typically associated with each of these benchmarks.

DISCOVERY

Discovery often begins with target identification – choosing a biochemical mechanism involved in a disease condition. Drug candidates are then tested for their interaction with the drug target. Screening for target interactions, which can include functional genomics and/or proteomics, can result in a significant number of molecules under test. Modern high-throughput screening methods can evaluate tens to hundred of thousands of compounds for interaction with a single disease target. Once an interaction with a target is identified, the target is typically validated by checking for *in vivo* activity versus the disease condition for which the drug is being developed.

Candidate lead selection from amongst these thousands of molecules is often based on strength of interaction with the molecular target, e.g. IC_{50} or K_i. However, compound characteristics that affect subsequent ease of development can also be used to select lead compounds. These include factors such as solubility, chemical stability, ease and cost of manufacture, ease of formulation, etc. Preclinical development characteristics that can be used in the lead selection process include permeability (e.g. Caco-2), metabolic stability (e.g. microsomal or hepatocyte), exposure (e.g. bioavailability), potential drug-drug interactions (e.g. cytochrome P450 screens), and initial toxicology screens (e.g. cytotoxicity, genetic toxicity, *in vivo* toxicity, etc.). All screening procedures should be evaluated in light of the intended use of a compound in the clinic. For example, is a short or long half-life drug desired, is a wide distribution or restricted distribution (throughout the body) required, etc.

PRECLINICAL DEVELOPMENT

The focus of Preclinical Development activities in the drug development process is two-fold. Lead compounds (typically a handful) are evaluated for their "drugability" characteristics, i.e. the likelihood that they will be successful drugs. The list of "drug-like" factors that can be applied to selection of one or several potential drug candidates is quite long. It can include factors that determine exposure (solubility, metabolic stability, absorption, bioavailability, half-life), toxicity (formation of reactive metabolites, effects on target organs, potential drug-drug interactions) and ease of manufacture and formulation (chemical stability, solubility, polymorph form).

Once a single compound or a limited number of compounds has been designated as the lead development candidate, Preclinical Development activities are necessarily focused on obtaining sufficient information to allow the conduct of the "first in human" study that will start the next phase of drug development. For new chemical entities (NCEs) this Preclinical Development process will culminate in a regulatory document such as the IND (Investigative New Drug exemption) that will in turn support a Phase 1 human clinical trial. The nonclinical studies required prior to the first in human trials are described in regulatory guidances published by the US Food and Drug Administration (www.fda.gov/cder/ guidance) and the European Medicines Association (www.emea.europa.eu/ htms/ human/ich/background.htm). These studies include both GLP and non-GLP Toxicology, Safety Pharmacology and ADME studies. The intent of these studies is to identify the toxic effects (target organs) of an NCE that should be monitored in human clinical trials, and to establish safe starting doses and dose escalation paradigms that ensure safety for the healthy human volunteers that are typically enrolled in a Phase 1 clinical trial. Much of the nonclinical work conducted at this stage of

drug development focuses on extrapolation of results from animal (or human *in vitro*) studies to humans. These include a comparison of pharmacology (e.g. based on target interactions), ADME (e.g. based on exposure or metabolic routes), and Safety Pharmacology and Toxicology (e.g. based on target organ) characteristics.

Drug manufacturing and formulation work also continues through the Preclinical Development stage of drug development, with the intent of providing formulations that result in proper drug delivery characteristics for subsequent clinical trials. Chemical stability (under various conditions of heat, light, and time), dissolution characteristics (for an oral dose form), and manufacturing process development are part of the activities started during Preclinical Development. Often, the drug formulation used in Phase I clinical trials is very different from the final marketed form and may be as simple as an oral solution or suspension dose.

CLINICAL DEVELOPMENT

Clinical studies are grouped according to their objective into three types or phases:

Phase I Clinical Development (Safety and Exposure) – Thirty days after a biopharmaceutical company has filed its IND, it may begin a small-scale Phase I clinical trial. Phase I studies are used to evaluate exposure and tolerance, typically in healthy volunteers. These studies may include initial single-dose studies, single dose escalation studies, and short-term repeated-dose studies.

Phase II Clinical Development (Safety and Efficacy) – Phase II clinical studies are small-scale trials to evaluate a drug's efficacy and side-effect profile. These studies are usually conducted in patients – typically selected because they could benefit from the new drug. They may vary in size, but are often from 100 to 250 patients. Additional safety and clinical pharmacology studies are also included in this category.

Phase III Clinical Development (Safety and confirmation of Efficacy) – Phase III studies are larger scale clinical trials for safety and efficacy in a significant number of patients. While Phase III studies are in progress, preparations are made for submitting the Biologics License Application (BLA) or a New Drug Application (NDA) for registration. BLAs are currently reviewed by the FDA's Center for Biologics Evaluation and Research (CBER); NDAs are reviewed by the Center for Drug Evaluation and Research (CDER).

Nonclinical activities to define safety continue throughout the Clinical Development phase of drug development. These nonclinical activities may include ongoing ADME studies to define metabolic pathways, potential drug-drug interactions and distribution, and long-term safety studies designed to define the reproductive and carcinogenic risk to human subjects. These studies are timed to coincide with the various phases of Clinical Development and to provide safety information to support those trials – for example, as the subject population changes from normal healthy volunteers to patients, as the size of the trials increases and more subjects are treated, and as the length of exposure increases.

Nonclinical activities during the Clinical Development phase may also include *in vivo* exposure studies in animal models to evaluate the pharmacokinetic behavior or determine the relative bioavailability of various drug formulations. Drug formulations are often refined continuously throughout the Clinical Development phase, culminating in a final dosage form that can be used in definitive clinical trials and allow registration of the NCE as new drug.

MARKETED DRUG/POSTMARKETING STUDIES

Nonclinical activities continue throughout the lifetime of a drug. These may include continued characterization of drug behavior in new pharmacology models, and nonclinical models of metabolism, distribution and safety. These studies are often conducted in response to observed effects of the new drug in the general patient population. As more individuals are treated with a new drug, more information becomes available about potential and unexpected pharmacological, ADME or safety effects. In addition, nonclinical support of ongoing drug formulation efforts may continue as new dosing needs become evident (e.g. alternative dose levels, extended release, etc.).

CONTENT OF THE NEW DRUG APPLICATION (NDA)

The preferred format for presenting nonclinical data to the FDA via the Common Technical Document (CTD) is in: M4S: The CTD – Safety (http://www.fda.gov/cder/guidance/4539S.htm). Agency expectations for the Nonclinical Overview are adapted from this M4S guidance. This section provides a sense of the breadth and quality of the nonclinical studies required to register a new drug and covers issues that must be addressed in the Discovery through Clinical Development processes described above.

2.4.1. Overview of the Nonclinical Testing Strategy. The Nonclinical Overview should present an integrated and critical assessment of the pharmacologic, pharmacokinetic, and toxicologic evaluation of the pharmaceutical. Where relevant guidances on the conduct of studies exist, these should be taken into consideration. Any deviation from these guidances should be discussed and justified. The nonclinical testing strategy should be discussed and justified. There should be comments on the Good Laboratory Practice (GLP) status of the studies submitted. Any association between nonclinical findings and the quality characteristics of the human pharmaceutical, the results of clinical trials, or effects seen with related products should be indicated, as appropriate.

Except for biotechnology-derived products, an assessment of the impurities and degradants present in the drug substance and product should be included, along with what is known of their potential pharmacologic and toxicologic effects. This assessment should form part of the justification for proposed impurity limits in the drug substance and product and be appropriately cross-referenced to the quality documentation. In addition, the availability of information on the quality of batches of drug substance used in these referenced studies should be discussed.

The implications of any differences in the chirality, chemical form, and impurity profile between the compound used in the nonclinical studies and the product to be marketed should be discussed. For biotechnology-derived products, comparability of material used in nonclinical and clinical studies and proposed for marketing should be assessed. If a drug product includes a novel excipient, an assessment of the excipient's safety should be provided.

Relevant, scientific literature and the properties of related products should be taken into account. If detailed references to published, scientific literature are to be used in place of studies conducted by the applicant, this should be supported by an appropriate justification that reviews the design of the studies and any deviations from available guidances.

2.4.2. Pharmacology. Studies conducted to establish the pharmacodynamic effects, the mode of action, and potential side effects should be evaluated, and consideration should be given to the significance of any issues that arise.

2.4.3. Pharmacokinetics. The assessment of the pharmacokinetic, toxicokinetic, and metabolism data should address the relevance of the analytical methods used, the pharmacokinetic models, and the derived parameters. It might be appropriate to cross-refer to more detailed considerations of certain issues within the pharmacology or toxicology studies (e.g. impact of the disease states, changes in physiology, antiproduct antibodies, cross-species consideration of toxicokinetic data). Inconsistencies in the data should be discussed. Interspecies comparisons of metabolism and systemic exposure comparisons in animals and humans (AUC, Cmax, and other appropriate parameters) should be discussed and the limitations and utility of the nonclinical studies for prediction of potential adverse effects in humans highlighted.

2.4.4 Toxicology. The onset, severity, and duration of the toxic effects, their dose dependency and degree of reversibility (or irreversibility), and species- or gender-related differences should be evaluated and important features discussed. Particular notice should be made of pharmacodynamics, toxic signs, causes of death, and pathologic findings.

Evaluation of genotoxic potential should include consideration of chemical structure, mode of

action, and relationship to known genotoxic compounds. Carcinogenic potential should be evaluated in the context of the chemical structure, relationship to known carcinogens, known genotoxic potential, and exposure data. If epidemiologic data are available, they should be taken into account in estimating the carcinogenic risk to humans.

Reproductive risk should be evaluated for effects on fertility, embryofetal development, pre- and postnatal toxicity. Studies in juvenile animals should be evaluated for effects on the developing organism. The consequences of use before and during pregnancy, during lactation, and during pediatric development should be discussed.

Additional studies that were conducted to clarify particular problems or potential uses should be discussed. These could include local tolerance or other toxicity studies.

The evaluation of toxicology studies should be arranged in a logical order so that all relevant data elucidating a certain effect or phenomenon are brought together. Extrapolation of the data from animals to humans should be considered in relation to the animal species used, the numbers of animals used, the routes of administration employed, the dosages used, and the duration of treatment or of the study.

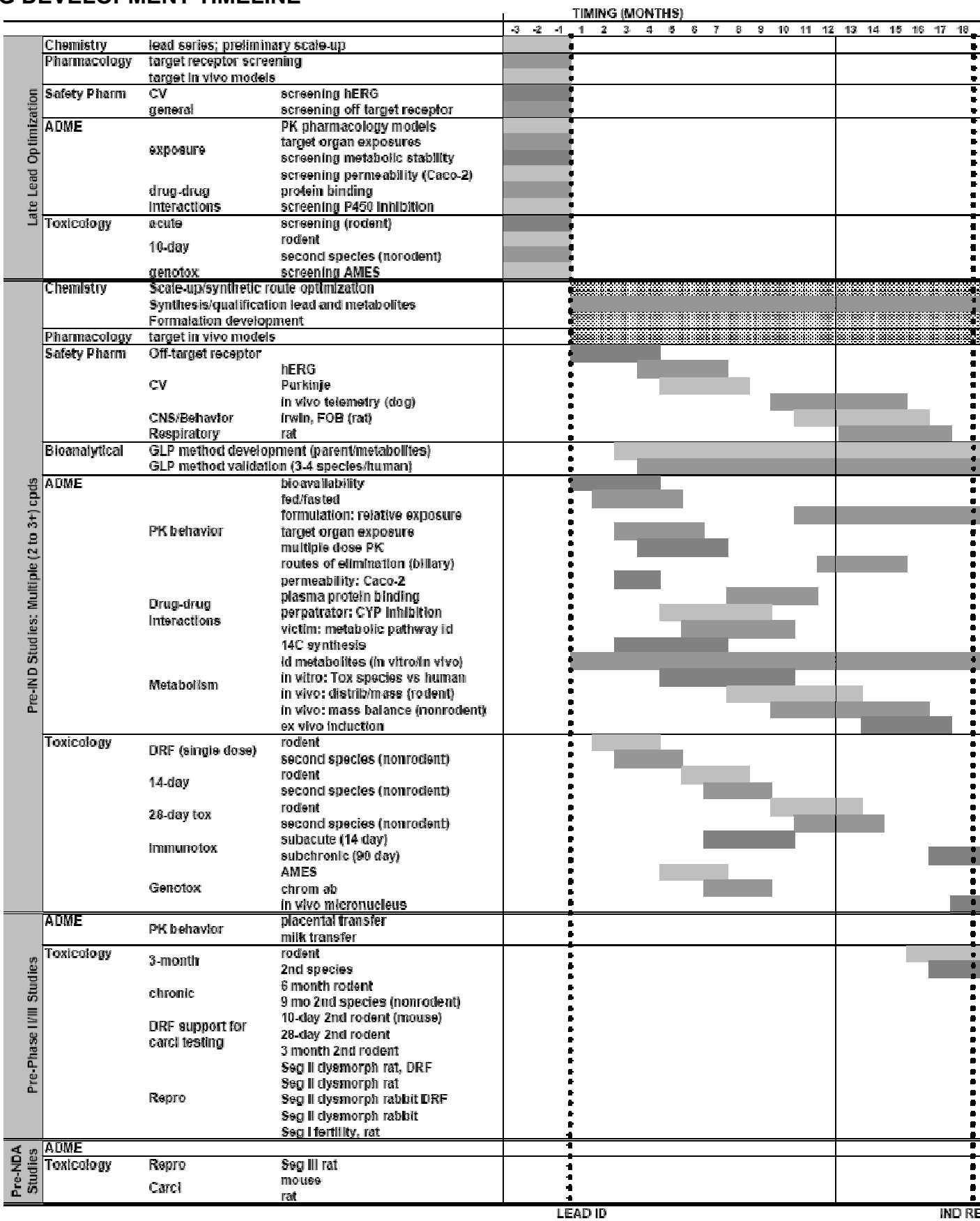
Systemic exposures in the toxicology species at no observed adverse effect levels and at toxic doses should be related to the exposures in humans at the maximum recommended human dose. The effect of the drug substance observed in nonclinical studies should be related to that expected or observed in humans. If alternatives to whole animal experiments are employed, their scientific validity should be discussed.

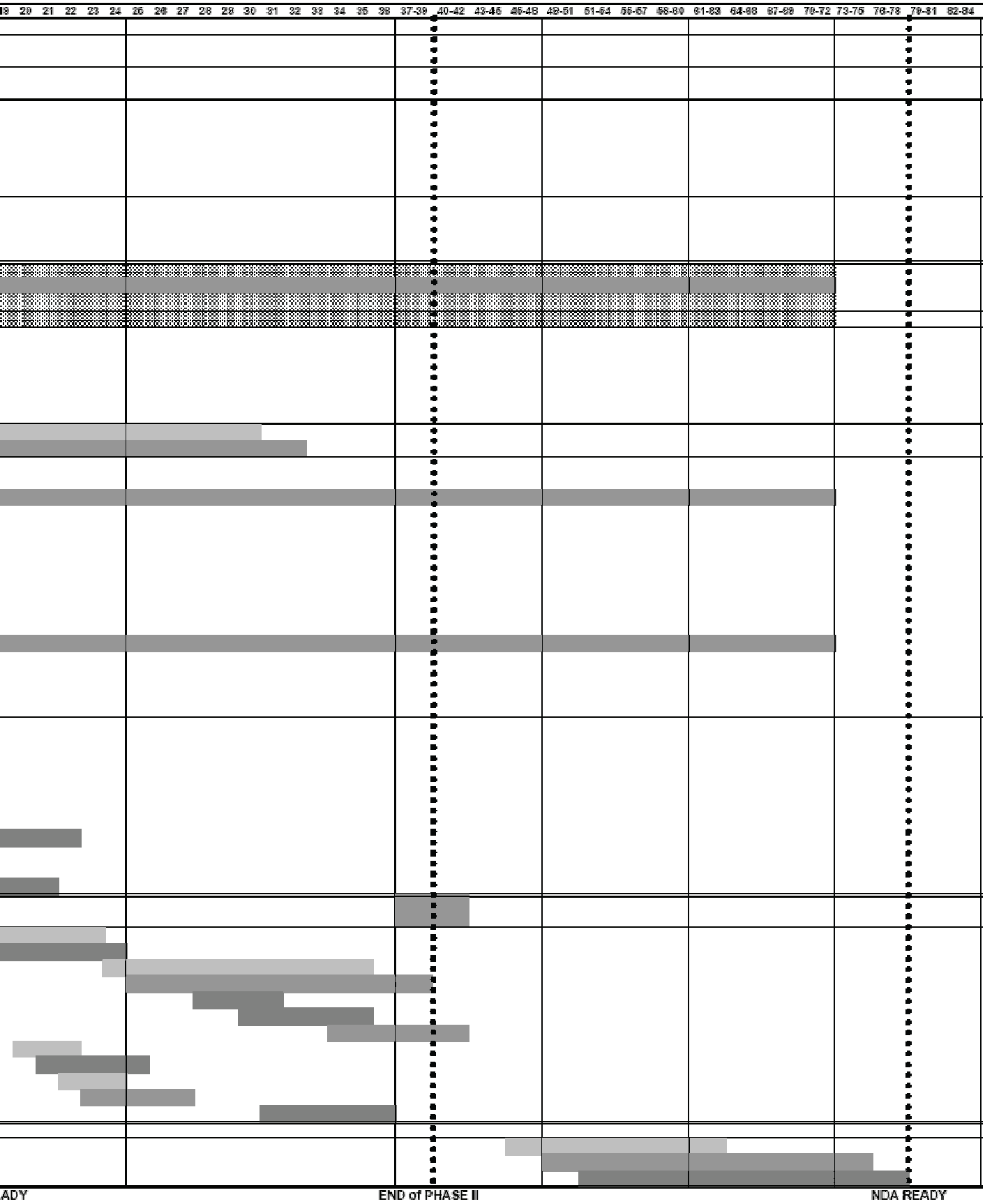
2.4.5 Integrated Overview and Conclusions.
The integrated overview and conclusions should clearly define the characteristics of the human pharmaceutical, as demonstrated by the nonclinical studies, and arrive at logical, well-argued conclusions supporting the safety of the product for the intended clinical use. Taking the pharmacology, pharmacokinetics, and toxicology results into account, the implications of the nonclinical findings for the safe human use of the pharmaceutical should be discussed, especially as it applies to labeling.

SAMPLE TIMELINE FOR PRECLINICAL STUDIES

An example of the timing and duration for some of the nonclinical activities that contribute to the registration of a new chemical entity via an IND and NDA is presented in the timeline on the following pages. This is a very brief outline that concentrates on the Safety Pharmacology, ADME and Toxicology aspects of the nonclinical development process discussed above. Many of the myriad formulation, medicinal chemistry, and pharmacology activities associated with the process of new drug development are not captured in this timeline. Also, the actual studies and timing of the studies required for each stage of drug development will vary on an individual case basis.

DRUG DEVELOPMENT TIMELINE




18 19 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37-39 40-42 43-45 46-48 49-51 51-54 55-57 58-60 61-63 64-66 67-69 70-72 73-75 76-78 79-81 82-84
ADY
END of PHASE II
NDA READY

REGULATORY COMPLIANCE

Development of new drugs is a governmentally-regulated process that has developed over the past decades to ensure the safety of the public. New drugs must undergo intense scrutiny by regulatory authorities (FDA in the U.S., EMEA in the European Union, and the Ministry of Health and Welfare in Japan) before they may be shipped and sold on the market. By understanding and taking into account the regulatory considerations in getting a new drug approved, problems in nonclinical and clinical testing can be minimized.

CODE OF FEDERAL REGULATIONS (CFR) TITLE 21

Good Laboratory Practice (GLP)

Preclinical safety studies must be performed in compliance with Good Laboratory Practices (GLP) regulations as detailed in 21 CFR part 58. The GLP regulations clearly define the roles and responsibilities of the study Sponsor as well as of the Study Director, Quality Assurance Unit, and Management at the testing laboratory. They require thorough documentation of all phases of a preclinical study. A key feature of GLP treatment is the role of the QAU in monitoring the conduct of the study and auditing study data and the final report.

Good Manufacturing Practice (GMP), Current Good Manufacturing Practice (cGMP)

U.S. pharmaceuticals must be manufactured under current Good Manufacturing Practice (cGMP) conditions as specified in CFR Title 21, Parts 210, 211, and 600. Process validation, equipment qualification, quality assurance, quality control, and documentation are vital in satisfying these requirements. Documented standard operating procedures (SOPs) must be used to assure consistency in the manufacturing process. With some minor exceptions, cGMPs must also be followed in manufacturing samples for clinical trials.

Investigational New Drug (IND) Application

21 CFR Part 312 details the requirements for an Investigational New Drug application. The IND application is a request to the FDA to allow for experimental testing of the drug with human volunteers and patients who have the disease under study.

GUIDANCES

Regulatory guidances published by the US Food and Drug Administration (www.fda.gov/cder/guidance) and the European Medicines Association (www.emea.europa.eu/htms/human/ich/background.htm) describe the content and conduct of preclinical studies used to support drug registration. To harmonize worldwide requirements for preclinical safety studies during the drug development process, FDA and the EMEA have released a series of ICH (International Conference on Harmonisation) guidelines covering the nature and timing of preclinical safety and efficacy studies for new drug entities. Because animal safety studies and human clinical trials should be approached from the most scientifically and ethically appropriate standpoint for the particular pharmaceutical agent under development, the guidelines are not to be construed as rigid requirements. Rather, they were designed to provide general guidance for conducting these studies. Certain drugs deserve a case-by-case approach designed to expedite or optimize development. Such drugs include biotechnology-derived therapeutics and drugs for life-threatening diseases for which no treatments currently exist.

NIH AND AAALAC

Animal studies are critical to the success of any drug development process. Regulations and standards issued by the National Institute of Health (NIH) and the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) set requirements for the care and handling of the laboratory animals and help ensure their welfare.

SELECT SOURCES AND REFERENCES

1. Food and Drug Administration (FDA), "Guidance Documents" www.fda.gov/cder/guidance/index.htm
2. European Medicines Association (EMEA), "International Conference on Harmonization (ICH)" www.emea.europa.eu/htms/human/ich/background.htm
3. "Preclinical Regulatory Requirements for Drug Development," Faraneh Attarchi, Ph.D., RAC, Regulatory Affairs Focus, April 2003, pp. 5-10.
4. "Drug Discovery: Filtering out Failures Early in the Game," Mairin B. Brennan, Chemical Engineering News, June 5, 2000, pp. 63-73.
5. "Preclinical Outsourcing: How to Design a System for Executing Preclinical Partnerships," Julie Pedeline, Contract Pharma, November/December 2000, pp. 44-49.
6. PPD Annual Report, 2000 pp. 4-6.
7. "Getting the Most from Contract Service Providers: Moving Past the Clichés to Establish a Strong Out-sourcing Relationship," Richard S. Woodward, Contract Pharma, November/December 2000, pp. 40-43
8. "Integrated Product Development: A New Paradigm from Discovery to Peak Sales," Christian Gabel et al, Contract Pharma, November/December 2000, pp. 20-27.
9. www.regsource.com (source for U.S. and international regulatory documents)

MANAGEMENT OF PRECLINICAL OUTSOURCING

BENEFITS OF OUTSOURCING

Outsourcing of nonclinical development studies has continued to increase as pharmaceutical companies maximize their resources. Many aspects of nonclinical studies require a great deal of time and capital expenditure. Vivarium costs and GLP compliance are two areas in which resource allocation can be minimized by outsourcing nonclinical studies. Additional benefits to use of outsourcing nonclinical studies to a Contract Research Organization (CRO) include:

- A wider range of available expertise in specific areas of pharmacology, ADME, or toxicology
- Increased flexibility to change research or testing paradigms as business priorities shift.

To take full advantage of outsourcing nonclinical studies, the project must be well thought-out and carefully planned. Consider the following general points when designing the study:

- What are the goals and objectives of the study?
- What are the timelines for the study?
- What is the budget for the study?

Study-specific issues will vary according the design and purpose of the individual study under consideration. The following should be considered when conducting any *in vivo* study:

- Species and numbers of animals required to meet scientific and regulatory requirements.
- Number and strength of doses required to meet scientific, regulatory and business requirements.
- Route of administration appropriate to final clinical use.
- Formulation required to achieve exposure requirements.
- Known toxicity or side-effects.

In addition, GLP studies generally require a well-characterized test article and usually a measure of exposure in the test system. The following are typically included in a GLP safety study:

- A measure of the purity and composition of the test article.
- A measure of the stability of the test article.
- Measurement of exposure via a validated bioanalytical method.
- Measurement of dose solution analysis (strength, homogeneity, stability)

SELECTING A CONTRACT RESEARCH ORGANIZATION (CRO)

When the decision has been made to outsource a study with a contract research organization (CRO), a variety of issues should be considered in selecting the appropriate CRO. Begin with an evaluation of the scientific expertise of the staff:

- Are they experienced with the route of administration?
- Are they experienced with the type of molecule?
- Are they experienced with the species used in the study?
- What is their reputation in the scientific community (reputation for quality)

Structural or procedural components to consider include:

- Is an in-house QA staff available for review of GLP studies?
- Is the facility AAALAC accredited?
- What is their Regulatory compliance record (FDA history)?
- How responsive is their customer service (communication, timeliness, transparency)?

GENERAL TIMELINE FOR CONDUCT OF A NONCLINICAL SAFETY STUDY

Activity	Pre-study activities					In-Life Phase	Post-study activities				
a) Initial planning	●										
b) Master Services and Confidentiality agreements	●										
c) Request and approval of quote	●	●									
d) Initial study plan – consider:			●								
1) Animal husbandry			●								
2) Health/safety			●								
3) Test and control article handling and storage			●								
4) Supplies			●								
5) Dosing: route of administration, regimen, duration			●								
6) Dose preparation			●								
7) Analysis of dose solutions (method and schedule)			●								
8) Clinical operations			●								
9) Clinical chemistry parameters			●								
10) Necropsy/gross pathology			●								
11) Histopathology parameters			●								
12) Analysis of data (statistics)			●								
e) Draft study protocol				●							
1) Sponsor review				●							
2) IACUC review				●							
3) QA review				●							
f) Pre-study Sponsor- CRO meeting					●						
1) Review and clarify protocol, study background,					●						
2) Finalize Protocol					●						
g) Protocol approval					●						
h)Sponsor transfers test article to CRO					●						
i) Conduct study						●					
i) Sponsor and QA review draft report							●	●	●		
j) Sponsor receives final report										●	
k) Team review/evaluation with CRO											●

NOTES

THE PACIFIC BIOLABS ADVANTAGE

THE SERVICE LEADER IN BIOSCIENCE TESTING

Pacific BioLabs (PBL) is an independent laboratory offering GLP/GMP testing services to the pharm/biopharm and medical device industries. PBL specializes in regulatory toxicology supporting FDA and international submissions, and in drug development support projects such as disease model development, drug delivery studies, and PK/ADME.

SERVING THE BIOSCIENCE INDUSTRY SINCE 1982

Pacific BioLabs clients range from small start-ups to Fortune 500 giants. Our staff is widely recognized for their experience, technical competence and commitment to client service. Over the years, PBL has gained a national reputation for quality in service and excellence in science.

STATE OF THE ART VIVARIUM AND LABS

Pacific BioLabs conducts its operations in a stunning 32,000 square foot facility in Hercules, CA overlooking the San Francisco Bay. The building houses a 12,000 square foot vivarium with a surgery suite, necropsy lab, radiation lab, procedure rooms, and ample support areas. The semi-barrier SPF rodent suite has a HEPA filtered air supply and dedicated procedure space. Animal facilities and critical equipment are monitored 24/7. Emergency power is supplied by an on-site generator. The site can accommodate a planned 20,000 square foot facility expansion.

RIGOROUS REGULATORY COMPLIANCE

In the regulatory science arena, quality means compliance. PBL has an outstanding track record in audits by FDA, EPA, MHRA, and other agencies, not to mention hundreds of client auditors.

At Pacific BioLabs we conduct all testing in accordance with applicable Good Manufacturing Practice (cGMP) and Good Laboratory Practice (GLP) regulations. To insure data integrity, our Quality Assurance Unit staff routinely audit all aspects of lab operations and administer our world class CAPA system. PBL's extensive body of Standard Operating Procedures is at the core of a thorough, documented training system which ensures that all technical staff can capably perform their assigned procedures.

Pacific BioLabs is FDA registered and certified by Intertek to ISO 9001:2000. Our animal science program is AAALAC accredited.

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