PHARMACEUTICAL TESTING SERVICES

PBL

Pacific BioLabs

The Service Leader in Bioscience Testing

ANAB ACCREDITED ISO/IEC 17025 TESTING LABORATORY

Biocompatibility	
Intramuscular Implant Test	ISO 10993-6 USP <88>
Acute Systemic Toxicity Test	ISO 10993-11 USP <88>
Intracutaneous (Intradermal) Reactivity Test	ISO 10993-10 USP <88>
Rabbit Pyrogen Test	ISO 10993-11; USP <151> , European Pharmacopoeia
Safety Test for Biological Products	USP <88>
Closed Patch Test for Delayed-Type Hypersensitivity Maximization Test for Delayed-Type Hypersensitivity Skin Sensitization-Buehler Method	ISO 10993-10 OECD 406
Mucosa, Ocular, Dermal Irritation	ISO 10993-10, EPA/OPPTS 870.2500, EPA/OPPTS 870.2400, FHSA/16 CFR 1500.41, FSHA/16 CFR 1500.42, OECD 404, OECD 405
Acute, Dermal, Oral Toxicity	ISO 10993-11, Iron Dextran Injection USP Monograph, EPA/OPPTS 870.1200, EPA/OPPTS 870.1100, FHSA, OECD 402, OECD 420, European Pharmacopoeia
Bioassays	
Glucagon Assay	USP <123>
Insulin Assay for Human Insulin – Bioidentity	USP <121>
Cleaning and Disinfection Studies	
Medical Device Cleaning Validations	AAMI TIR12:2010; AAMI TIR30:2011
Steam Sterilization Validation, Biological Indicators	ANSI/AAMI/ISO 17665-1 ANSI/AAMI/ISO 14161
Cytotoxicity	
Agar Diffusion	USP <87> ; ANSI/AAMI/ISO 10993-5
Elution	USP <87> ; ANSI/AAMI/ISO 10993-5
Direct Contact	USP <87> ; ANSI/AAMI/ISO 10993-5
LAL Bacterial Endotoxins	USP and ; ANSI/AAMI ST72:2011; EP 2.6.14, Bacterial Endotoxins
Microbiological	
Antimicrobial Effectiveness	USP <51>
Bacteriostasis / Fungistasis Sterility	USP <71>
Bioburden	USP <61>; ANSI/AAMI/ISO 11737- 1:2006
Sterility Assurance	Sterility AAMI TIR 33, Sterility ANSI/AAMI/ISO 11137-2 Method 1, Sterility ANSI/AAMI/ISO 11137-2, Sterility AAMI/ISO TIR 15844
Microbial Enumeration Testing for Specified Microorganisms	USP <61>; USP <62> ; USP <1111>; EP/BP
Chemical	
Conductivity	USP <645>
Total Organic Carbon	USP <643>
Extractable Leachable Testing	ISO 101993-18

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To view this booklet online, please go to PacificBioLabs.com.

May 2019

PBL is FDA registered and ISO 17025:2017 accredited by ANAB. Our animal science operations are accredited by AAALAC.

THE SERVICE LEADER AMONG PHARMACEUTICAL CROs

Since 1982, **Pacific BioLabs**, a non-clinical GMP/GLP CRO, has provided biological and analytical testing designed to support both growing and established pharmaceutical and biotech companies. As *The Service Leader in Bioscience Testing*, our goal is to provide our clients with a combination of expertise, rigor in our quality systems, and personalized attention that is unique among CROs.

Facility and Location

Pacific BioLabs is housed in a 32,000 square foot facility in Hercules, CA. This state-of-the-art laboratory/vivarium allows us to offer top quality testing services to our clients throughout the world.

Completed in 2000, all major building systems and equipment have been validated to cGMP and GLP standards. A generator supplies back-up electrical service for all critical utilities and equipment. A monitoring system provides 24-hour alerts of any deviations or outages, allowing for rapid resolution, and ensuring optimal facility operation.

Quality Systems

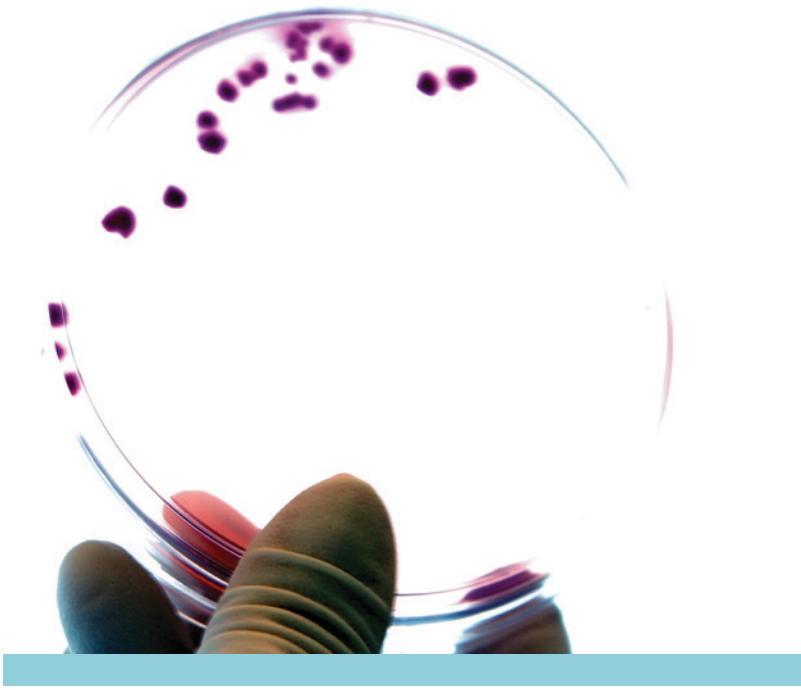
Pacific BioLabs is a cGMP and GLP laboratory that has a world class quality system based on ISO 17025:2017, requirements similar to those for pharmaceutical manufacturing (21 CFR 210, 211 and 610), and incorporates by reference ISO 9001:2015. PBL has an excellent track record of positive outcomes from FDA inspections, hosts over 50 client audits per year and has a culture committed to quality.

- GLP and cGMP compliant
- FDA Registered
- ISO 17025 Accredited
- Electronic SOPs

PHARMACEUTICAL TESTING SERVICES

In Vivo Pharmaceutical Development Support

- Pharmacokinetic *In Vivo* Studies
- Pharmacodynamic *In Vivo* Studies
- Toxicokinetic *In Vivo* Studies
- Regulatory Toxicology Studies (GLP/non-GLP)
- Dose Range Finding
- Custom *In Vivo* Studies
- Biological Reactivity of Materials



Analytical Chemistry and Bioanalysis Development Support

- PK/PD/TK Bioanalysis
- Method Development and Validation
- Biomarker Discovery and Analysis
- Biosimilar Development Support
- Immunogenicity
- Characterization of New Chemical Entities
- Formulation Assays
- Extractable Leachable Testing
- Stability Testing

Microbiology Development Support

- Sterilization Validations
- Time Kill Analysis
- Antimicrobial Preservative Efficacy Testing
- Container Closure Integrity Testing
- Cytotoxicity

Pharmaceutical Manufacturing Support

- *In Vivo* Bioassays
- *In Vitro* Bioassays
- Safety Tests
- Microbial Limits
- Sterility Testing
- LAL / Endotoxin / Pyrogen
- Environmental Monitoring
- Raw Material Testing
- Physicochemical Properties
- Identity and Purity

The management team of the Analytical Services group ensures that testing is performed right the first time and that testing meets the expected timelines.

METHOD DEVELOPMENT AND VALIDATION

Method Development

Pacific BioLabs has vast experience in analytical and bioanalytical method development for a variety of platforms including HPLC, LC/MS/MS, GC/MS or GC/FID, ICP/MS, and ligand binding assays (MSD, ELISA or other cell-based assays). Method development is an important first step to determine that analytes of interest can be reliably detected and quantified for routine sample analysis. Our team includes several PhD lead scientists that each have over 20 years of analytical or bioanalytical experience. They will work with you to understand your needs to ensure that the work we do is done right the first time. Based on our extensive experience with similar products and by drawing upon published literature resources, PBL can swiftly develop the most appropriate method for your product.

Method Validation

After method development, PBL can validate the method according to FDA, USP, EP and ICH guidelines to ensure its suitability for its intended use. PBL is flexible in supporting complete or partial validations, re-validations and method transfers. PBL provides full documentation including a fully QC/QA reviewed protocol, method procedure, and report for the analyses. In addition, many non-confidential methods for marketed drug products have been validated by PBL and are available to our clients.

Instrumentation

PBL maintains a wide variety of analytical equipment to provide analysis of large molecules, small molecules and medical devices to support both lot release, development and CMC work.

- ICP-MS
- HPLC
- LC-MS/MS
- GC, GC-MS
- Laser Light Scattering
- FTIR
- Karl Fisher
- UV/Vis Spectrophotometer
- Polarimeter
- Viscometer
- Osmometer
- Fluorescence Plate Reader
- Meso Scale Discovery Platform - ECLA

PBL routinely performs both small and large molecule PK bioanalysis.

PK / PD / TK

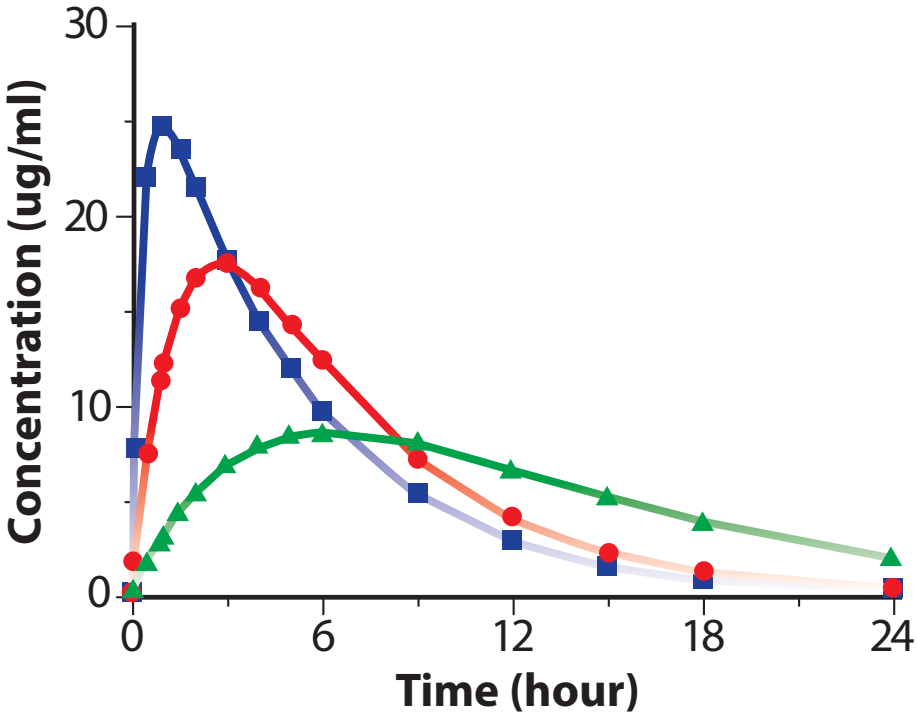
Pharmacokinetic (PK) studies are used to gather information on how a drug compound moves through and is processed by the body whereas pharmacodynamic (PD) studies examine the drug's effect on the body. Toxicokinetics (TK) also examines a drug's effect on the body, but uses exaggerated doses in order to illicit a toxicological response. Pacific BioLabs supports exploratory R&D studies as well as GLP studies required for regulatory submission.

PK / PD / TK Bioanalysis

Pacific BioLabs can seamlessly perform *in vivo* sample generation as well as bioanalysis. PBL performs PK /PD/TK studies in rodents, and has the instrumentation and expertise to provide rapid and sensitive drug concentration determinations from a variety of matrices. LC-MS/MS units are often used for small molecule bioanalysis while the MSD platform is often used for large molecule studies. An ICP-MS is a great analytical tool to use in PK studies if the pharmaceutical contains a heavy metal component.

PK / PD / TK Studies at PBL

At Pacific BioLabs, study designs are flexible and are developed to meet the specific needs of individual development programs. Conducting the bioanalysis and *in vivo* portions of the test at the same site removes complexity and simplifies the management of the study.



TEST CATEGORIES

- Pharmacokinetics (PK)
- Bioanalysis
- Tissue Distribution
- Bioequivalence
- Bioavailability

AVAILABLE SPECIES

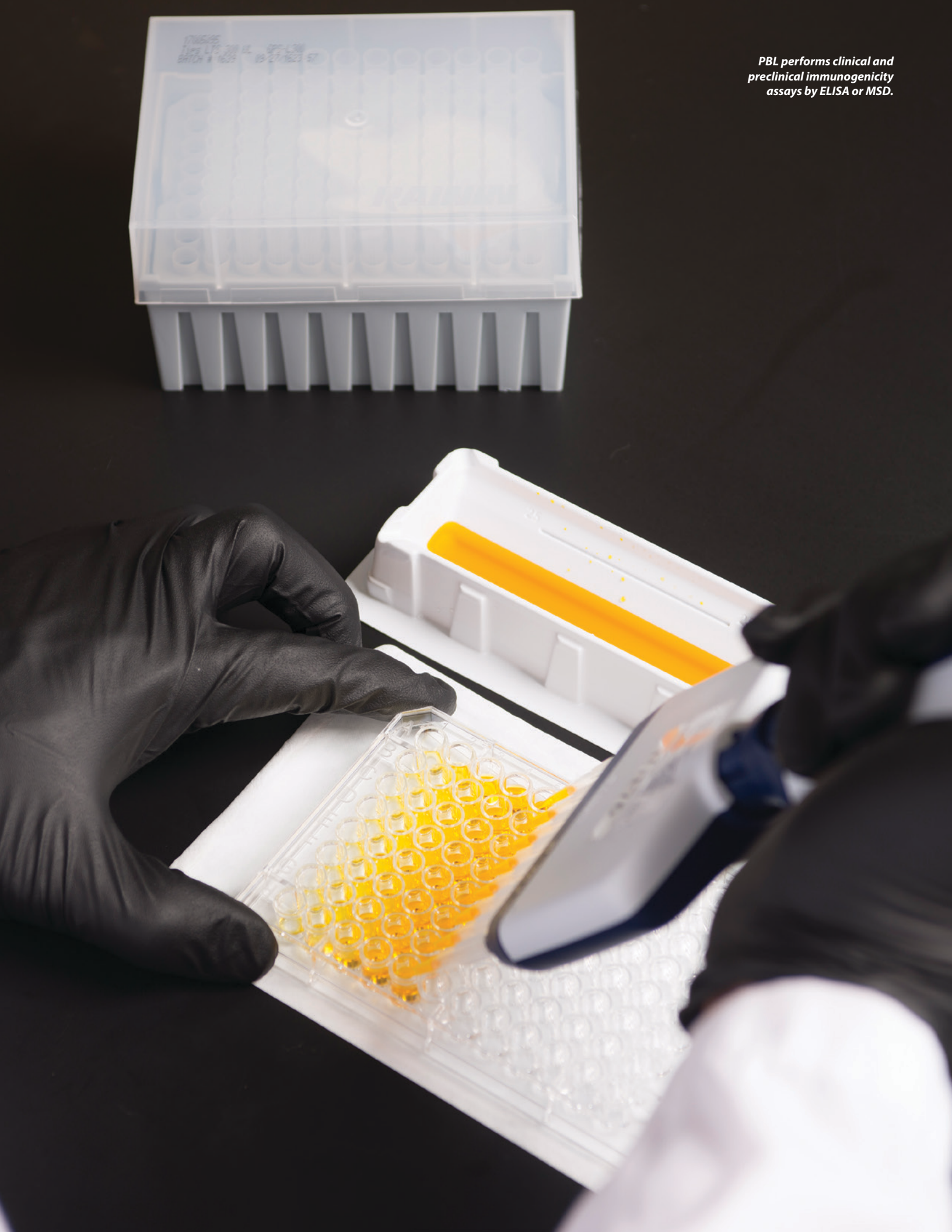
- Mouse
- Rat
- Rabbit
- Guinea Pig

ROUTES OF ADMINISTRATION

- Oral
- Subcutaneous
- Intravenous
- Intraperitoneal
- Intramuscular
- Implantation
- Topical

INSTRUMENTATION FOR BIOANALYSIS

- Meso Scale Discovery
- LC-MS/MS
- TOF MS
- ICP-MS
- GC-MS
- HPLC



PBL performs clinical and preclinical immunogenicity assays by ELISA or MSD.

IMMUNOGENICITY TESTING

Immunogenicity Profiling Services

Pacific BioLabs can develop and validate assays designed to build an immunogenicity profile of your protein therapeutic, and will work with study sponsors to develop a panel of immunogenicity assays based on a risk assessment of each drug and its intended clinical use. Typically a total antibody assay that includes screening, confirmatory, and titer components will provide sufficient data. In other cases, a neutralizing antibody assay or cell based bioassay may be necessary and informative. ELISA and the MSD (Meso Scale Discovery) platforms are availble. Assays to support both non-clinical and clinical studies can be developed. Pacific BioLabs also has *in vivo* capabilities to evaluate drugs in a variety of species in both acute and long-term studies.

Protein Modification Analysis

Immunogenicity of biotherapeutics can be increased due to denaturation, aggregation, and particle formation. Pacific BioLabs can measure aggregates by size exclusion chromatography. In addition, PBL can also characterize protein therapeutic or antibody reagents for stability, post-translational modifications, and degradants.

Pacific BioLabs specializes in customized solutions to bioanalytical problems, and has over 20 years of analytical experience supporting biotech, pharmaceutical, and device companies. PBL operates GLP and GMP compliant systems and validated instrumentation.

NAb Assays

NAb assays, or neutralizing antibody assays, are often required if immunogenicity is observed in patients. If the patient produces anti-drug antibodies, those antibodies have the potential to neutralize the effects of the drug. In a clinical trial it is important to determine not only if the patient is producing antibodies against the drug, but if those antibodies are neutralizing the drug.

Assays and Services

- Ligand Binding Assays
- MSD and ELISA
- Cell-Based Assays
- Total Antibody Assays
- *In Vivo* Analysis
- Screen/Confirm/Titer
- Neutralizing Antibody Assays
- Particle Size Characterization
- Critical Reagent Characterization
- Protein Aggregation Analysis

A PBL microbiologist is preparing to perform an antimicrobial effectiveness test.

MICROBIOLOGY DEVELOPMENT SUPPORT

Antimicrobial Effectiveness Test – USP <51>

The USP <51> Antimicrobial Effectiveness Test is performed on non-sterile products to determine if the chosen preservative is appropriate. Microbes can be inadvertently introduced during manufacturing or during continual product use. To test if the antimicrobial agent is effective the product is inoculated with a prescribed quantity of specified organisms and tested at various time intervals over a period of 28 days.

Time Kill Analysis

Time kill analysis measures the change in a population of microorganisms within a specified sampling time after exposure to an antimicrobial test material *in vitro*. The test article is brought into contact with a known population of microorganisms for a specified period of time at a specified temperature. The test article is then neutralized at the target sampling time and the surviving organisms are enumerated. The percent and/or log10 reduction from an initial microbial population is calculated. Several options for organism selection and growth, inoculum preparation, sampling times, and temperatures can be requested.

Minimum Inhibitory Concentration – MIC

Minimum inhibitory concentration (MIC) is a test which determines the minimum concentration of the preservative needed to completely inhibit the growth of the challenge organism. A suspension of the challenge organism is prepared at a concentration of one million colony forming units (CFU) per mL. The product is then tested neat or diluted and incubated with the challenge organism. The dilution of the product depends on the specifications of the product. Turbidity within the sample would indicate growth of the challenge organism. The lack of turbidity would indicate that the challenge organism has been inhibited.

PBL stability program coordinators ensure that our stability program is operating smoothly and that the pull dates are never missed.

STABILITY STUDIES

Gathering pharmaceutical stability testing data on drug products or drug substances to determine an overall stability profile is a necessary step in the drug approval process. Drug substance, drug product, combination devices, and raw materials need to be assessed for stability.

The PBL stability chambers are monitored 24 hours a day and connected to a backup generator in case of emergency power loss.

ICH Stability Study Storage Conditions

ICH stability guidelines give storage conditions and times for long-term, intermediate, and accelerated stability studies. Below are the general ICH storage conditions.

- 25°C and 60% RH
- 30°C and 65% RH
- 40°C and 75% RH

In addition to the ICH stability conditions, PBL can provide custom storage conditions (including 4°C, -20°C and -80°C) as appropriate for your sample.

ICH Stability Studies: Analysis

PBL is a full service analytical and bioanalytical Bay Area GMP/GLP CRO, and can assess the stability profile of products using numerous analytical techniques: HPLC, LC/MS, and GC among others. In addition, the PBL Microbiology Department can measure sterility, container closure integrity testing, package integrity testing, endotoxin levels, and bioburden on products.

ICH stability data is required as part of an IND or CTA (EU) submission. Since long-term stability studies take 24 months or longer, it is prudent for companies to begin gathering stability data once a suitable drug candidate has been selected.

Stability Study Services Offered

- Storage:
  - 25°C / 60% RH
  - 30°C / 65% RH
  - 40°C / 75% RH
  - Other non-standard temperatures and relative humidity settings
- Analysis (HPLC, LC/MS, GC)
- Forced Degradation Studies
- Photo Stability
- Oxidation
- Thermostability
- Sterility / Microbiological Assessment
- Container Closure Integrity Testing
- Endotoxin Levels (LAL)
- Microbial Limits Test (MLT)

Insulin and glucagon in vivo bioassays are analyzed on PBL's Siemens Dimension Xpand Plus Integrated Chemistry System.

BIOASSAYS

Botulinum Toxin

Botulinum toxin testing is performed through *in vivo* assays, and is conducted in full compliance with CDC regulations and guidelines.

- Potency
- Identity/Safety Testing

Insulin (USP)

For insulin products, PBL can perform GMP bioassays following USP <121> to release your product to the market.

- Biopotency (quantitative)
- Bioidentity (qualitative)

Somatotropin

Somatotropin is also known as synthetic human growth hormone. The somatotropin bioassay is an *in vivo* assay performed according to USP <126>.

Glucagon

Glucagon is a critical drug for the treatment of diabetes. The glucagon potency assay is an *ex vivo* procedure using a primary culture of rat hepatocyte cells. The procedure is prescribed by USP <123>.

Custom In Vitro Potency Assays

Novel biological products often do not have compendial potency methods available requiring a custom assay be developed. *In vitro* assays are most commonly used to determine the potency of novel biologics. PBL performs method development and method validation for custom *in vitro* potency assays. In addition to the development and validation, routine testing can be performed for stability studies and lot release testing.

- Cell Based Assays
- Cell Proliferation Assays
- Reporter Gene Assays
- Cell Signaling Assays
- Binding Assays
- Enzyme Activity Assays

The PBL environmental monitoring team can travel to your facility and sample the air, surface and compressed gas systems for viable organisms.

QC MICROBIOLOGY

Microbial Limits Test – USP <61> and USP <62>

Microbial limits tests are performed on non-sterile products to determine if a product complies with the compendial specifications for microbial loads. Microbial Enumeration, or USP <61>, determines the total amount of organisms on a product. The Test for Specified Microorganisms, or USP <62>, is a test to determine the presence of specific objectionable organisms on the product.

Sterility Testing – USP <71>

USP <71> sterility testing is performed in two different types of media, one specific for aerobic organisms and one that is capable of sustaining growth for both aerobic and anaerobic organisms. The sample is introduced to media by either direct inoculation or by membrane filtration. The amount of sample needed for the test depends on the type of product being tested and the size of the batch produced. Sterility testing requires an incubation period of fourteen days. After the fourteen day incubation, if the media is clear and there are no sign of microbial growth, the samples are considered sterile.

Additional Pharmaceutical Microbiology Testing

- Endotoxin/LAL
- Cytotoxicity
- USP Water Testing
- Environmental Monitoring

An analytical chemist at PBL loads a quartz cuvette to take an absorbance reading.

ANALYTICAL CHEMISTRY LOT RELEASE TESTING

Identity and Purity

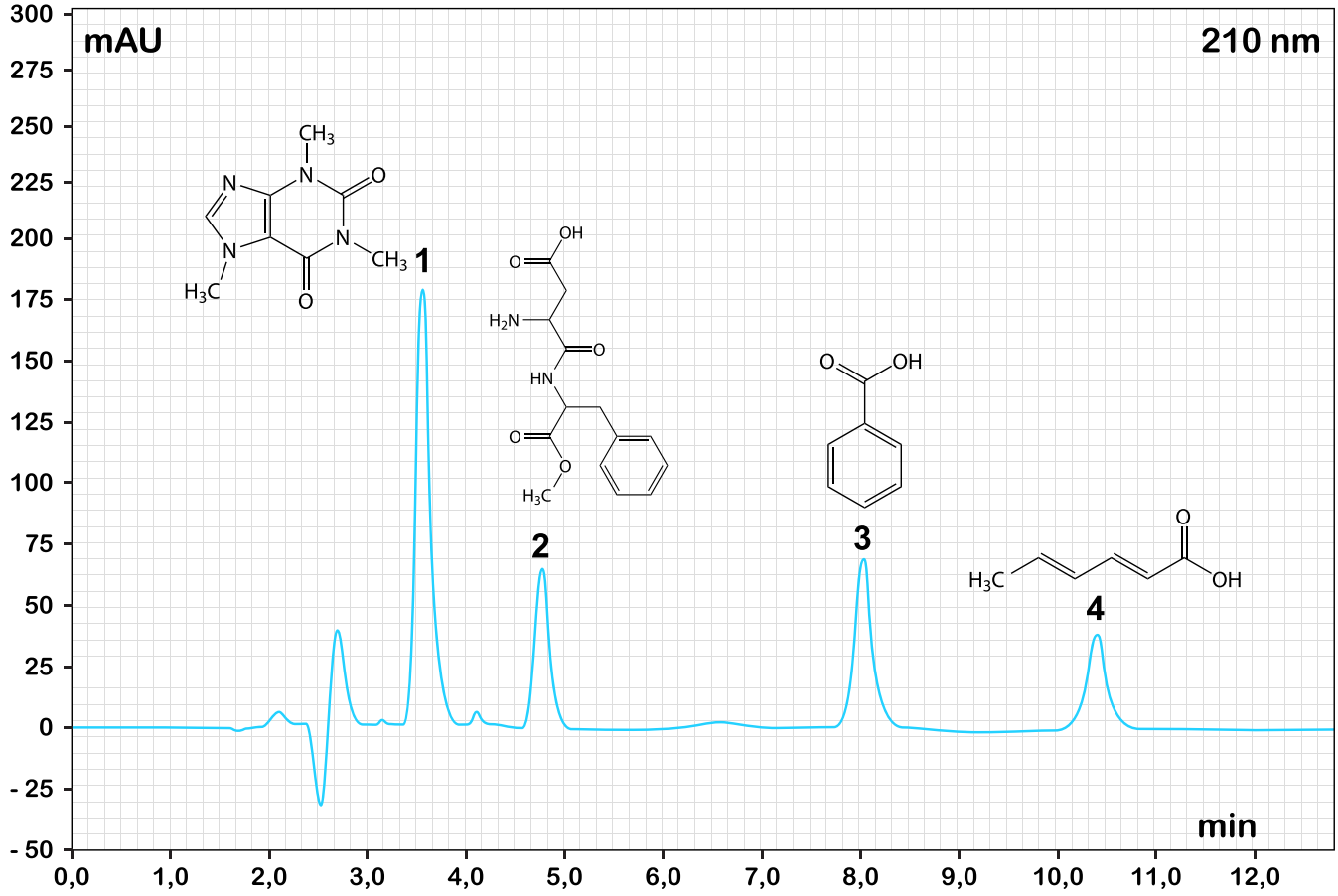
Lot release testing for identity and purity requires that the product conform to predetermined specification. PBL understands that speed and accuracy are important and PBL performs identity and purity testing on both small and large molecules. A variety of different methods can be used to measure identity and purity, but our experienced scientists are experts in each of these techniques employed at PBL:

- HPLC
- Mass Spectrometry
- UV-VIS
- FTIR
- TLC
- SDS-PAGE
- Western Blot
- ELISA
- MSD

Physicochemical Properties

Physicochemical property tests are integral to the verification, manufacturing support, and lot release programs for pharmaceuticals and biologics. It is essential that certain physical and chemical properties do not vary between or within lots, as they can determine critical compound features like drug delivery and absorption of the product *in vivo*. Pacific BioLabs has established a history of reliable testing of key physicochemical features since 1982. We offer a comprehensive suite of testing services that we will tailor to your lot release program, based on manufacturing and quality control needs. PBL tests for:

- Appearance
- pH
- Moisture Content
- Osmolality
- Viscosity
- Optical Activity
- Spectral Analysis



A PBL microbiologist counts the number of colony forming units for a microbial limits test.

RAW MATERIAL TESTING

Before manufacturing begins, all raw materials must be tested for purity, identity and quality. The extent of raw material testing is determined by the manufacturer. A conservative approach would be to perform complete analysis of each lot of raw materials received. USP provides monographs for the most commonly used raw materials in the pharmaceutical industry. Often these monographs detail several different analytical techniques. Karl Fischer moisture analysis, pH, viscosity and titrations are common but more complex techniques such as HPLC, GC-MS and ICP-MS are sometimes required. Microbiological testing, such as a microbial limits test, is also commonly performed for raw materials.

The Importance Of Raw Material Quality

Testing of raw materials is a critical component to maintaining high quality and patient safety. Poor quality raw materials can impact biologic or pharmaceutical drug production in many ways, such as poor production, minor or major changes to a drug's quality attributes, microbial contamination, and costly delay if lots need to be scrapped. Products derived from cells have further complications with growth media, serum source, growth factors and cytokines, all of which should be tested for lot-to-lot consistency. Testing raw materials should be a routine requirement in any drug production operation.

Raw Material Testing offered:

- Physicochemical Properties
- Identity and Purity – Small Molecules
- Identity and Purity – Large Molecules
- Cytokine Testing – USP <92>
- Microbial Limits Test – USP <61> and USP <62>

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