Contract Drug Product R&D | Complex Injectable Formulations | Clinical Trial Materials

www.ddelabs.com
Specialists in injectable drug formulations and combination drug product development

Injectable solution to complex formulation
  - Immediate to extended-release
  - Small molecule to antibody

GMP clinical trial material manufacture for early phase clinical development

Extensive experience in biologics, drug development, device, and delivery systems

Highly-qualified Ph.D. scientists working in state-of-the-art R&D lab in heart of San Diego
CONTRACTED DRUG PRODUCT R&D

- Leveraging a deep understanding of molecular properties, formulation, device
- Integrating delivery system R&D projects into your development program
  - Optimizing target product profile to enhance value proposition

Discovery Support
- Lead molecule profiling
- Clinical candidate evaluation
- Biologic half-life extension

Drug Product Development
- Formulation design
- Drug product development
- Analytical methods

Integration with device
- Device identification
- Formulation compatibility
- Device product development
Pharmaceutical R&D Laboratory
- Formulation, analytical, process, chemistry, device development
- Specialists in complex drug product development
- Peptide and small molecule chemistry, conjugation (e.g., PEGylation)
- Lead candidate selection for peptide and small molecules
- Crystal and salt form selection for small molecules

GMP Fill Finish for Injectable Formulations
- Test article for GLP toxicity studies
- Certified parenteral facility and quality system
- Clinical trial materials in vials and syringes
- QC and stability testing
LEADERS WITH DEEP DOMAIN EXPERIENCE

Chris Rhodes, Ph.D.
President & CEO
Founded Drug Delivery Experts in 2014 after 20 years in biotech and drug delivery companies in both technical and executive leadership roles.

Sharon Lee Rhodes, Ph.D.
Executive Chairman
Sharon is a proven strategic leader with a potent combination of skills in the technical, corporate, academic and non-profit arenas.

Lawrence D’Souza, Ph.D.
Scientific Director
Discovery, Chemical and Process Development, Formulation
Organic chemist with discovery and early development experience in small molecule, peptide, and protein synthesis.

Laxma Reddy, Ph.D.
Scientific Director
Formulation and Process Development, Small Molecules and Biologics
Protein biophysical chemist with experience in extended-release drug delivery product development

Franco Ferrari, Ph.D.
Scientific Director
GMP Operations and Manufacturing
Over 30 years of experience in quality system regulations, GMP facility management, and product development
Our Leaders Have Worked at These Companies

- PersImmune
- MannKind Corporation
- SurModics
- 3M
- DIOMICS
- Protein Polymer
- MitoKor
- Amylin
- Bristol-Myers Squibb
- AstraZeneca
- OHR Pharmaceutical Inc.
- Guilford Pharmaceuticals
- Biologics Technologies

Our Leaders Developed These Products

- Byetta (exenatide) injection
- LUSEDRA (laspagliatide) injection
- SymlinPen (pramlintide acetate) pen-injector
- myalept (metreleptin) for injection
- Afrezza (insulin human inhalation powder)
- BYDUREON exenatide extended-release for injectable suspension
- GLIADEL Wafer (carmustine implant)
- Aldara (imiquimod 5% cream)

LEADERS WITH >100 YEARS EXPERIENCE
SUPPORT ACROSS DRUG DEVELOPMENT

LEAD MOLECULE SELECTION
• Peptides
• Small Molecules

INJECTABLE FORMULATIONS
• 5C solution in a Vial / Bag
• Lyophilized powder for reconstitution

PRECLINICAL

PHASE I

PHASE II

PHASE III

COMMERCIAL

GMP Fill Finish
• Toxicity Test Articles
• Clinical Trial Materials

DEVICE INTEGRATION
• Pre-filled Syringe
• Cartridge
• Pen
• Auto-Injector

LIFE-CYCLE MANAGEMENT
• Reformulation
• Long-Acting System
• Non-Injectable Delivery (Oral, Nasal, Pulmonary)
**MOLECULE AND DELIVERY EXPERIENCE**

**Small Molecules**
- IV, SC, IM
- Nasal
- Oral

**Peptides**
- SC
- Inhalation
- Nasal
- Ocular
- Oral

**Proteins**
- SC
- Nasal
- Ocular
- Inhalation

**Oligos**
- SC

**Antibody**
- SC

~ 1K Da

~ 10K Da

~ 100K Da

08/22
Lead Molecule Selection

- Analytical Research
- Development Assessment
- Lead Molecule Design

Molecule Design
- Peptide/Protein Conjugates for Half-Life
- Small Molecule

Delivery System Selection

- Analytical Development
- Preformulation
- Delivery System Feasibility
- Formulation PK Screening

Delivery System Design
- Aqueous or Non-Aqueous Vehicle
- Sustained Release Formulation
- Triggered or Targeted Systems

Drug Product Development

- Formulation Development
- Process Development Scale-Up
- Analytical Methods Qualification
- Technology Transfer GMP Mfg.

- Device Selection & Development
- Development Stability
- Stability

Drug Product Design
- Pen/Auto-Injector
- Pre-Filled Syringe
- Nasal/Ocular Drops/Spray

Clinical Trial Materials

- GMP Fill Finish
- QC Release and Stability Testing
- GMP Manufacture
- Clinical Trial Materials
- QC Release Testing
- Stability Studies
Developability Assessment
Pharmaceutical Development
Solutions and Suspensions
Aqueous and Non-aqueous systems
Scale from 1 ml to 10 liter batch size
Stability and Preclinical Supplies

Analytical Development
HPLC Stability Indicating Methods
Content assay and impurity profiles
Various drug product specific QC tests

Delivery Systems
PLGA Microspheres and Implants
Nanoparticles and Liposomes
Extended-release Suspensions
Nasal and Pulmonary

SubQ Biologics™
Modulate solubility & dissolution
Alter subcutaneous absorption
Improve PK profile and ISR

Long-Acting Technology
Proteins
Peptides
Oligonucleotides
Antibodies

IP License Agreement

Contracted Fee for Service
Proprietary Delivery Technology
EXTENDED-RELEASE INJECTABLE APPROACH

Liposome for Drug Delivery

- Protective layer against immune destruction
- DNA
- Homing peptide
- Drug crystallized in aqueous fluid
- Lipid bilayer
- Lipid-soluble drug in bilayer

Drug Delivery System Comparison:

- **Suspension**
  - Daily
  - Weekly
  - Monthly
  - Quarterly
- **Liposome**
  - Daily
  - Weekly
  - Monthly
  - Quarterly
- **In Situ Gel-Forming System**
  - Daily
  - Weekly
  - Monthly
- **Microsphere**
  - Daily
  - Weekly
  - Monthly
- **Non-Aqueous Solution/Suspension**
  - Daily
  - Weekly
  - Monthly
- **Implant**
  - Quarterly
## EXTENDED-RELEASE INJECTABLE PROGRAMS

**Compound Type** | **MW (kDa)** | **Injection Frequency** | **Liposome** | **Salt** | **Gel** | **Microsphere** | **Suspension**
--- | --- | --- | --- | --- | --- | --- | ---
Small Molecule | <1, several | Monthly and longer | | | | | |
Peptide | 1 | Weekly to Monthly | | | | | |
Peptide | 2 | 3 to 4 Months | | | | | |
Peptide | 3, 4 | Daily | | | | | |
Peptide | 4 | Weekly to Monthly | | | | | |
Peptide | 4, 5 | Weekly to Monthly | | | | | |
Insulin | 6 | Daily to Weekly | | | | | |
Oligonucleotide | 8 | Daily to Weekly | | | | | |
Oligonucleotide triple combination | 10 | Daily to Weekly | | | | | |
Protein | 15 | Weekly | | | | | |
Protein | 50 | Weekly | | | | | |
Antibody | 150 | Weekly to Monthly | | | | | |

*Note: Biologics salt forms are based on proprietary SubQ Biologics™ technology*
FORM SELECTION & PARTICLE SUSPENSION

Drug Substance: Free base or acid

Salt or Co-crystal Form Selection

Insoluble Crystal Form <0.01 mg/ml at 37°C PBS Low rate of saturation solubility

Dry Ball mill

Or Wet Bead mill

Micro-particle Suspension

Horizontal oscillatory ball mill for small scale grinding
Tube Roller for low energy grinding
Vertical planetary ball mill for high energy grinding

Nano-particle Suspension
STATE-OF-THE-ART DRUG PRODUCT LAB

- HPLC Supplies
- Balances
- 5°C Refrigerator
- 5°C Freezer
- -30°C Freezer
- -80°C Freezer
- R&D Labs
- Wastewater
- Shipping Receiving
- GMP Manufacturing
- Kitchen
- Open Office
- Conf Room
- Restrooms and Shower
- Main Entry
- Open Office
- Conf Room
- Restrooms and Shower
- Main Entry
DDE LABS EQUIPMENT & CAPABILITIES

Analytical Development
- 15 HPLC (diode array UV Vis, fluorescence, ELSD, RID)
- UV/Vis & fluorescence plate readers and nanodrop
- Particle size analyzer (laser diffraction, 1µM – 500 µM)
- Dynamic light scattering / zeta potential (1 nm – 10 µM)
- Stability Chambers certified and monitored
  (ICH 25°C/60RH, 40°C/75RH, 2-8°C, -20°C, -80°C)
- Osmometer and Viscometer for characterization
- Scanning electron micrograph, visual microscopy

Formulation and Process Development
- Microfluidizer, homogenizer, emulsifiers
- 37°C incubators for In vitro release testing for extended-release injectables (water bath and shake-flask)
- Intron Injection force measurement
- Nano assembler for nanoparticle & liposome
- Shelf–stoppering lyophilizer for cycle development
- Ball mill, tube roller, planetary ball mill for grinding
- Capsule hand-fill for powder and liquid formulations
- 2 laminar flow hoods for development work

GMP Manufacturing Suite
- 2 Laminar flow hoods (ISO 5)
- Process Suite (ISO 7) with pass through
- Gowning Vestibule (ISO 8)
- Material handling, QC, Stability
- Depyrogenation oven, autoclave, chemical fume hood
- HPLC (2), osmometer, endotoxin, particle size, pH testing

Bioanalytical Development
- MSD ELISA for bioanalysis
- Gel electrophoresis imager for imaging protein gels

Chemistry and Chemical Development
- Organic synthesis reactors
- Rotary evaporator
- Jacketed reaction vessels
- Manifold lyophilizer
- FPLCs for protein purification
- Preparatory HPLC
- Salt, co-crystal, and prodrug selection
GMP Vial and Syringe Fill for Clinical Materials

GLP Toxicity Test Article Supply

Fill / Finish Suite (ISO 7) with Hoods (ISO 5)

Gowning Vestibule (ISO 8)

QC Lab for Incoming / Outgoing Materials

GMP Stability Chambers Monitored 24/7
Manufactured over 250 stability and preclinical batches in the past 6 years

Batch sizes from up to 2 liters (Capability to go to 20 liter batches)

Batch records signed off ahead of fill

Batch release with analytical test results
  • Concentration, purity, pH, osmolarity, endotoxin, and others

Formulation composition and process methods
  • Aqueous and non-aqueous solutions and suspensions
  • Liposomes, microspheres, gels, salts, and others

Formulation and development stability manufacturing
  • 24 month shelf life now supporting phase 2 program
  • Stability studies to support ANDA filing
  • Several development studies for toxicology and clinical formulation selection
6 YEARS & OVER 60 CLIENTS & GROWING

- Over 6 years, 39 lab projects / 38 consulting projects
- 90% of clients in US / remainder EU and JP
- 6 multinational corporations
- Over the last 3 years
  - Average of 22 clients each year (17 lab / 5 consulting)
  - Yearly average of 11 new clients and 11 repeat clients
  - 2/3 business yearly from repeat clients
  - 80% business from clinical and commercial companies
PARTNERSHIP OPTIONS

Project Specific Work
- Shorter well-defined projects
- Typically 3 to 9 months
- Time and materials fee-for-service
- Payment milestones

Dedicated R&D Team
- Longer term and broader R&D programs
- Typically 1 to 3 years
- Dedicated resources for program
- Regular quarterly or monthly payments
Veru Healthcare
• Compositions and Methods for Long Term Release of Gonadotropin-Releasing Hormone (GnRH) Antagonists, US 15/885,464
• ASCO presentation on preclinical results

Aileron Therapeutics
• Peptidomimetic macrocycles and formulations thereof, US 20160101145 A1

Abvance Therapeutics

Iogen LLC
• Emolient topical disinfectants, WO 2018/017645 A1
OUR EXPERTISE

Combination Drug Product Development and GMP Manufacturing

- Peptide and protein development
- Lead molecule profiling and half-life extension
- SC, IM, IV, topical ocular and intraocular formulation design and development
- Extended-release injectable and implantable formulations
- Translation from research through clinical trials and commercialization
WE THRIVE ON
SOLVING YOUR MOST
CHALLENGING PROBLEMS
ORAL AND TOPICAL FORMULATIONS

Capsule Capabilities at DDE Labs

Hand-filled Capsule batches
• Powder blends
• Microparticle-filled
• Microsphere-filled
• Nanoparticle formulations
• Oil-based suspensions
• Permeation enhancing for peptides

Controlled Release Oral Formulations Through KYDES Partnership

Tablet Processes
• Direct compression
• Dry granulation
• Wet granulation
• Enteric coating
• Bi-layer and mini tablets

Oral Controlled Release
• Instant release
• Sustained release
• Enteric or delayed release

Capsules
• Powder blends
• Microparticle-filled
• Microsphere-filled

Topical
• Transdermal cream
• Topical Spray

XX/22
Non-invasive delivery for small molecule, peptide, protein
• Painless, no needles or injections
• Easy administration by patient or caregiver

Formulation and analytical development
• Dosage forms: solution, suspension, and dry powder
• Chemical and physical stability

Drug product device assessment
• Dose delivery/content uniformity
• Particle/droplet size distribution
• Spray pattern
• Plume geometry
• Leachable and extractable
<table>
<thead>
<tr>
<th>Client</th>
<th>Type of Project</th>
<th>Scope of Lab Work</th>
</tr>
</thead>
</table>
| SENSULIN | DDE is responsible for full R&D Program | • Develop liposomal glucose-responsive insulin drug delivery system  
• Formulation, Process, Analytical, PK / BA  
• Drug Development Team Leadership (Mfg., Reg, Tox, Clin, BD) |
| DIAVACS | DDE runs Product Development Program | • Develop oligonucleotide nano-particle drug delivery system  
• Formulation, Process, Analytical, In vitro cell culture model, in vivo POC |
| ABVANCE | DDE runs Product Development Program | • Develop Insulin Pump Co-Formulation, Process, Analytical, PK/BA |
| VERU | DDE developed the product formulation in partnership with Veru | • Small Volume Subcutaneous 3-month PLGA-gel Depot Injection |
39 LAB PROJECT CLIENTS IN 6 YEARS
38 CONSULTING CLIENTS IN 6 YEARS

Area of Consulting
- Due Diligence
- Life-Cycle Planning
- Delivery Technology Assessment
- CMC Support

Client Size
- Size of Client Based on Valuation & Market Cap

Project Type
- Consulting Only
- Consulting & Lab Work
<table>
<thead>
<tr>
<th>Phase</th>
<th>Formulation Type</th>
<th>Services</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRECLINICAL</td>
<td>Small Organic</td>
<td>- Topical Ocular Formulation for a Diagnostic, Analytical, PK</td>
</tr>
<tr>
<td></td>
<td>Formulation</td>
<td></td>
</tr>
<tr>
<td>LEAD SELECTION</td>
<td>Protein PEGylation</td>
<td>- Process, Formulation, Analytical, Tech Transfer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- CMC and Drug Development Team Consulting (Mfg., Reg, Tox)</td>
</tr>
<tr>
<td>PHASE 1</td>
<td>Small Organic</td>
<td>- IV Injection Formulation, Analytical, CMC</td>
</tr>
<tr>
<td></td>
<td>Formulation</td>
<td></td>
</tr>
<tr>
<td>PHASE 2</td>
<td>Peptide Formulation</td>
<td>- Optimize IV Aqueous Formulation Stability</td>
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<tr>
<td></td>
<td></td>
<td>- CMC Consulting</td>
</tr>
<tr>
<td>PHASE 3</td>
<td>Peptide Re-formulation</td>
<td>- Life Cycle Support, Immediate Release to Extended-Release Injection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- CMC Consulting</td>
</tr>
</tbody>
</table>
## LAB CASE STUDIES — POST-MARKET

| ANDA | Peptide Formulation | • Process, Analytical, and Tech Transfer  
• CMC and Drug Development Team Consulting (Mfg., Reg, Tox, BD) |
|------|---------------------|-----------------------------------------------------------------------------------|
| COMMERCIAL | Protein Re-formulation | • Analytical, PK/BA, Solution, Particulate Suspension, ISR Improvement  
• Defined Product Life Cycle Plan as Consulting Team |
<p>| COMMERCIAL | Oligonucleotide Re-formulation | • Nanoparticle Development, Process Development, Analytical, Scale-Up for Delivery Improvement |
| COMMERCIAL | Small Molecule Re-formulation | • Long-Acting Injectable, Small Molecule, Particle Suspension Formulation |</p>
<table>
<thead>
<tr>
<th>Project Type</th>
<th>Program</th>
<th>Scope</th>
</tr>
</thead>
<tbody>
<tr>
<td>DUE DILIGENCE</td>
<td>Peptide Phase 1 Asset</td>
<td>CMC Due diligence for VC investment</td>
</tr>
<tr>
<td></td>
<td>Peptide/Microneedle Phase 3</td>
<td>CMC Due diligence for company acquisition</td>
</tr>
<tr>
<td></td>
<td>Biologics Oral Delivery</td>
<td>Due diligence for VC investment</td>
</tr>
<tr>
<td>LIFE CYCLE PLANNING</td>
<td>Protein in Commercial Product</td>
<td>Recommend life cycle options for product improvement</td>
</tr>
<tr>
<td>DELIVERY TECH ASSESS</td>
<td>Biologics Polymer Delivery</td>
<td>Evaluate drug delivery polymer applications to biologics</td>
</tr>
<tr>
<td></td>
<td>Cell Penetrating Peptide</td>
<td>Evaluate therapeutics applications for CPP delivery</td>
</tr>
<tr>
<td></td>
<td>Small Molecule Oral Delivery</td>
<td>Recommend therapeutics for oral delivery system</td>
</tr>
<tr>
<td></td>
<td>Biologics Oral Delivery</td>
<td>Evaluate oral delivery as leader of advisory board</td>
</tr>
<tr>
<td></td>
<td>Biologics Ocular Delivery</td>
<td>Evaluate ocular drug delivery technologies for biologics</td>
</tr>
<tr>
<td>CMC SUPPORT</td>
<td>Biologics Ocular Delivery</td>
<td>Advise R&amp;D program for biologics ocular drug delivery</td>
</tr>
<tr>
<td></td>
<td>Peptide R&amp;D Project</td>
<td>Evaluate formulations and guide R&amp;D program</td>
</tr>
<tr>
<td></td>
<td>Peptide Drug Delivery</td>
<td>Advise CMC team for delivery system development</td>
</tr>
<tr>
<td></td>
<td>Long-Acting Injectable</td>
<td>Advise CMC team for delivery system development</td>
</tr>
</tbody>
</table>
ADVISORS AND EXPERTS

William Vincek, Ph.D.
President Pharma CMC, formerly SVP Development, Alpharma, Guilford Pharmaceuticals, GSK, Merck

Phil Duffy
Operations consultant in life sciences, previously SVP Pacira, VP at Ligand and Schein Bayer

Solomon Steiner, Ph.D.
Serial entrepreneur, previously CEO and Founder of Perosphere, Biodel, Mannkind, and Emisphere Technologies

Will Clodfelter, M.B.A.
Market & Device Development

Mark Longer, Ph.D.
Regulatory Strategy

Nelson Lugo, M.B.A.
Manufacturing

Bill Van Antwerp
Device and Diagnostics R&D
Dan Bradbury
*Pharma Advisor*
CEO Equilium, Chairman BioBrit, Former Amylin CEO

Donald Rindell
*Business Advisor*
Principal, Camino International, corporate strategy and business development

Eddie Rodriguez
*Legal Advisor*
Attorney at Troutman Sanders, corporate and legal advisor

Magda Marquet
*Contract Services Advisor*
Founder of Althea and Althea DX, successful sterile manufacturing