CRAMSN
Research Park

CRAMSN
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Delivering Excellence, Driven by Science

Research | Development |
Manufacturing |
Commercial Supplies

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www.cramsn.com

About CRAMSN

CRAMSN is a One-Stop-Shop CRO, CMO and CDMO service partner for the pharmaceutical industry. We differentiate ourselves with the world class R&D and manufacturing capabilities enabling partners to transform their Ideas from Concept to Commercial. CRAMSN's ability to offer end-to-end solutions or s upport standalone programs with efficiency, quality, and consistency enables faster go-to-market strategies and improved access for patients while placing sustainability and social responsibility at the core of our ambitions.

Vision:

- To be the '**Trusted Strategic Service Partner'** for the Global Pharmaceutical ecosystem by providing Innovative and Novel solutions from Drug Discovery to Commercial phase.

Mission:

To be the **Partner of Choice** in CRO, CDMO & CMO domains by providing

- Best in class infrastructure & Quality systems
- Experienced & competent scientific workforce
- Dedicated world class project management service for seamless delivery
- Regulatory services & support
- Commercial manufacturing capabilities - milligrams to Tonnes

We add accelerated value to customers by playing a pivotal role in the value chain of improving human health with a strong focus on Sustainability.

State-of-the-art & fully-integrated facilities

2 R&D Centers

17 API Units

8 FDF Units

Advantage CRAMSN

- CRAMSN is a comprehensive service provider, offering end-to-end support from early development through commercial phase programs.
- Extensive expertise in Conventional, Complex, and Niche Chemistries, including Oncology, Prostaglandins, Steroids, Peptides, and Oligonucleotides.
- Innovative, safe and cost-effective solutions for both Drug Substance (DS) and Drug Product (DP) needs.
- Advanced, digitally driven tools and technologies, including eLNB, LIMS, DoE, QbD, SAP, ISMS, QMS, PM tools, and Pharma 4.0.
- Specialized in crystallization studies for polymorph, salt, and co-crystal screening.
- Highly experienced in providing regulatory support for IND, NDA, and CTD filings.
- Utmost respect for IP and data security, ensuring confidentiality and protection.
- All 25 manufacturing facilities (API and Formulations) are accredited multiple times by stringent regulatory bodies worldwide.
- Fast decision-making backed by strong financial stability.

Drug Substance Solutions

Service offerings in:

- Small molecules
- Peptides & Oligos
- Steroids & Hormones
- HPAPIs
- Labeled compounds
- Prostaglandins
- Iron-Carbohydrate nano particulate complexes
- Flow chemistry
- Polymeric molecules

CRO

- Med-Chem
- Route scouting
- Library generation
- Process Development
- Lead optimization
- Synthesis & Supply of preclinical / clinical quantities (Tox & cGMP Supplies)
- IND enabling

CDMO

- Route assessments
- Process Optimization (DoE & QbD Studies)
- Process engineering & Safety studies
- Analytical Method development and validations
- Polymorph, Salt & Co-Crystal screening studies
- Scale up studies, Technology Transfer & Manufacturing
- Registration & validation batches
- NDA enabling

CMO

- Technology Transfers
- Familiarization studies
- Scale-up studies
- Validation batches
- Commercial manufacturing up to multi MT scale

Drug Substance Capabilities

- Handling of molecules with multi-step synthesis, involving 30+ stages.
- Expertise in managing chiral molecules with multiple chiral centers through resolution/asymmetric synthesis.
- Capable of performing cryogenic (-80°C to -100°C), high-temperature (up to 180°C), and high-pressure (upto 10 kg) reactions.
- Specialized in synthesizing Oligonucleotides in batch sizes of 10-20 µmol.
- Capable of synthesizing Peptides with more than 30 Amino Acid sequence, from mg to kg scale under cGMP conditions.
- Expertise in handling HPAPI molecules upto OEB5 band (<0.1 µg/m³).
- Two dedicated manufacturing facilities for handling HPAPIs from grams to multi-tons.
- Support from preclinical to commercial phase (mg to MT scales) with cGMP.
- Regulatory compliance and support for IND/NDA/CTD filings.
- Project lifecycle management to ensure quality and on-time deliverables.
- Development of innovative, novel, cost-effective, and eco-friendly processes.
- Strict adherence to EHS recommendations.

Drug Substance Infrastructure

Research and development

- Facility spread over 184,000 sq. ft.
- 40 synthetic labs with ~350 fume hoods
- Dedicated laboratories for HPAPIs, Prostaglandins, Labeled Compounds, Iron-complexes, Flow Chemistry, Peptides, Oligos, particle size engineering, and more
- Specialized engineering laboratories for process safety studies and process intensification
- Dedicated scale-up facility with reactor capacities ranging from 10L to 100L under cGMP, including a clean room facility for supplying material for phase I, II, and III trials

Analytical

- Facility spread over 45,000 sq. ft.
- Equipped with ultra-modern instruments
- Supports lab development, method transfers, validations, scale-up, and commercial manufacturing
- Facilities for solid-state and structural characterization, method development and validations, and purification support

Manufacturing

- 17 facilities with 2,400 reactors, totaling 10,000 KL reaction volume (reactor range: 20 L to 20 KL)
- 2 dedicated HPAPI facilities to handle all band widths (up to 0.01 µg/m³)

API ACCREDITATIONS

FDA | Health Canada | edqm | Hamburg BGV - HAMBURG | EUROPEAN MEDICINES AGENCY | WHO - GENEVA | OGYÉI National Institute of Pharmacy and Nutrition NIP - HUNGARY

JAZMP SLOVENIA | ANVISA - BRAZIL | Cofepris | Australian Government Department of Health | KFDA | MOH - RUSSIA | pmda

Drug Product Solutions

Service offerings in:

- Oncology, Non-Oncology, Immunosuppressant & High Potent product development
- Solid Orals
- Parenterals (Liquids & Lyo)
- Liquid Orals
- Extended/ Modified Release Injectables
- Expertise in handling the various dosage forms
- Ophthalmics
- Prefilled Syringes (PFS) & Pens

CRO

- Feasibility Studies
- Prototype formulation design
- Process identification and development studies
- Selection of a lead formulation candidate
- Preparation of test articles for IND enabling toxicology studies

CDMO

- Formulation optimization and scale-up
- Process Performance Qualification (PPQ)
- Technology transfer and scale-up
- cGMP production and filing support in eCTD format

CMO

- Commercial manufacturing
- On-time deliverables
- Lifecycle management strategies

Capabilities:

- **Solid Orals**
  - Intermittent Release
  - Extended Release
  - Sustained Release
  - Modified Release (Osmotic)
  - Multi-layered formulation
  - Sublingual
  - Pellets
  - Granules
- **Liquid Orals**
  - Oral Suspensions
  - Oral Solutions
  - Unit Dose cups
- **Ophthalmics**
- **Parenteral** (Liquids & Lyo)
  - Vials
  - Ampoules
  - Depo Injections
- **Prefilled Syringes (PFS) & Pens**

Maximized process automation; impeccable quality

Drug Product Infrastructure

FDF Capacity per annum:

~ 15 Billion Tablets	**~ 4.0 Billion** Capsules	**~ 120 Million** Sachets
~ 40 Million (Lyo & Liquids) Parenterals	**~ 8.0 Million** Oral Suspension	**~ 3000 Tons.** Granules

FDF ACCREDITATIONS

US FDA | BGV- GERMANY | SIDC- CZECH REPUBLIC | WHO- GENEVA | SIDC- SLOVAKIA | MHRA - UK | SAUMP- UKRAINE

MOH - ROMANIA | ANVISA - BRAZIL | INVIMA - COLOMBIA | MOH - PERU | FDA - TAIWAN | DSIR- INDIA | DEA

KSFDA - SAUDI | MOH - UAE | MOH - QATAR | MOH - JORDAN | MOH - YEMEN | PPB - KENYA | MCAZ-ZIMBABWE

TFDA | FMHACA - ETHIOPIA | NAFDAC- NIGERIA | MOH- NAMIBIA | PMB - MALAWI | NDA- UGANDA | ISO 9001 :2008

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CRAMSN: Advancements in Crystallization Techniques for API Development

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At CRAMSN, we recognize that understanding the solid-state properties of an active pharmaceutical ingredient (API) is essential for optimizing its stability, solubility, bioavailability, and processability. Our cutting-edge crystallization services enable pharmaceutical companies to identify the most suitable solid form of their API, accelerating the development process while minimizing risks in any downstream activities.

Comprehensive Crystallization Services at CRAMSN:

As a leader in the field, CRAMSN offers extensive crystallization expertise, delivering advanced polymorph, salt, co-crystal, and early crystallization screening programs. These services are designed to ensure the identification of the most developable solid form of your API, crucial for improving API stability and overall drug performance.

Tailored Work Programs to Meet Your API's Needs:

CRAMSN provides bespoke work packages, customized to align with your API's material availability or specific phase in the development process. Our services include:

Polymorph Screening: Comprehensive studies to identify different crystalline forms of an API, essential for optimizing drug efficacy and bioavailability.

Salt Screening: With careful consideration of the API's pKa, dose, and toxicity, our salt screening identifies pharmaceutically acceptable and developable salts of ionizable APIs, improving properties like crystallinity, stability, solubility, and bioavailability.

Co-crystal Screening: We conduct co-crystallization screening using co-formers to create new solid forms that enhance API solubility and formulation stability. This unique route improves patent protection, modeling of molecular synthons, and process scalability(References 1-3).

Crystallization of Difficult-to-Crystallize APIs: Special screens designed to address challenges in achieving crystallization for certain APIs.

Hydrate Mapping & Amorphous Solid Dispersions: In-depth studies of hydrates and non-crystalline forms to enhance drug formulation options.

Advanced Solid-State Characterization & Chemical Identification:

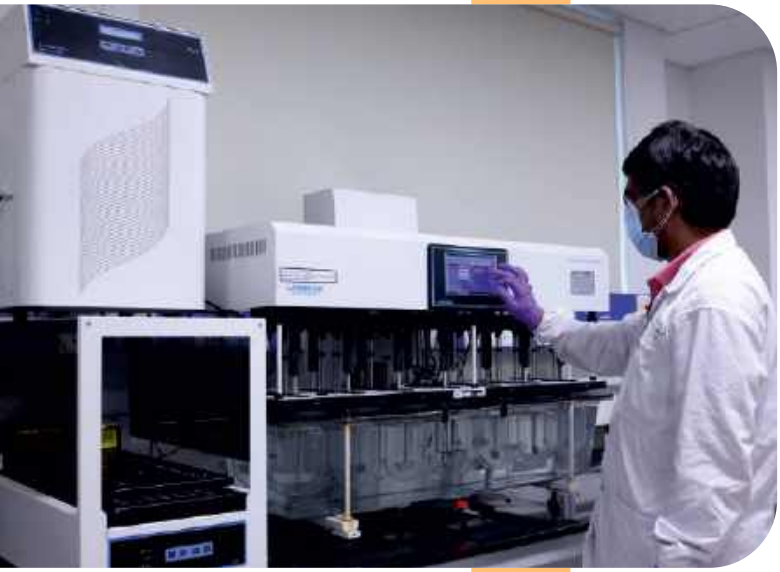
CRAMSN offers comprehensive characterization and identification tools, ensuring accurate analysis of your API's solid-state properties. Our suite of advanced technologies includes:

- Powder X-Ray Diffraction (PXRD) for structural elucidation and indexing
- Polarised Light Microscopy (PLM) to investigate the structure
- Thermal Analysis (TG-DSC, hyper DSC) for thermal profiling
- Scanning Electron Microscopy (SEM)
- Fourier Transform Infrared Spectroscopy (FT-IR)
- Raman Spectroscopy and Terahertz Raman Spectroscopy
- NMR Spectroscopy for solid and liquid-state analysis
- Water Content Analysis using Karl Fischer Titration
- Comprehensive Chromatographic Services (HPLC, UPLC, GC)

Polymorph & Crystallization Screening:

CRAMSN's polymorph and crystallization screening solutions can be applied at any stage of drug development, utilizing experiments such as:

- **Solution-based Techniques:** Evaporation, cooling, anti-solvent precipitation, and pH gradient crystallizations.
- **Solid-state Experiments:** Grinding, freeze-drying, melt quenching, and thermal vapor treatments.
- **Crystallization Experiments:** Temperature cycling, ultrasonic nucleation, and polymer-templated crystallizations, designed to optimize the crystallization process for your API.



Developability Assessments:

CRAMSN evaluates your API's readiness for development with key assessments, including:

- Gram-scale repreparation and small-scale optimization
- Hygroscopicity testing using dynamic vapor sorption
- Stability testing in line with ICH Conditions
- Thermodynamic solubility profiling for biorelevant media dissolution testing
- Intrinsic dissolution testing to predict API performance in vivo

Why Choose CRAMSN?

By partnering with CRAMSN, pharmaceutical companies gain access to a broad array of crystallization and solid-state development services. Our expert teams collaborate with you to understand your API's unique challenges and offer the most robust, scalable, and efficient crystallization solutions to drive your drug development forward.

Reference:

1. Kammari, B. R.; Saladi, V. N.; Garai, A.; Sagyam, R. R.; Srinivasan, R. T.; Mathad, V. T. Novel Pharmaceutical Cocrystal of Voxelotor, a Hemoglobin Oxygen Affinity Modulator: Synthesis, Crystal Structure, and Physicochemical Properties. Cryst Growth Des 2023, 23 (11), 8065–8075.

2. Saladi, V. N.; Kammari, B. R.; Mandad, P. R.; Krishna, G. R.; Sajja, E.; Thirumali, R. S.; Marutapilli, A.; Mathad, V. T. Novel Pharmaceutical Cocrystal of Apalutamide, a Nonsteroidal Antiandrogen Drug: Synthesis, Crystal Structure, Dissolution, Stress, and Excipient Compatibility. Cryst Growth Des 2022, 22 (2), 1130–1142.

3. Saladi, V. N.; Kammari, B. R.; Maruthapillai, A.; Mahapatra, S.; Chennuru, R.; Sajja, E.; Rajan, S. T.; Mathad, V. T. Stable Fatty Acid Solvates of Dasatinib, a Tyrosine Kinase Inhibitor: Prediction, Process, and Physicochemical Properties. ACS Omega 2022, 7 (8), 7032–7044.

Speak with CRAMSN today to learn how we can enhance your API's potential, ensuring a more successful and accelerated path to the clinic.

Meet our expert: **Dr. Vijayavitthal T.Mathad** COO, CRAMSN

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High Potent APIs at

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Unlock the Future of Pharmaceutical Innovation!

Partner with Us!

Ready to drive innovation in HPAPIs?

Join CRAMSN Research Park today and be at the forefront of pharmaceutical advancements!

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Future of Medicine!

Comprehensive Capabilities:

At CRAMSN Research Park, we offer integrated solutions that encompass the entire lifecycle of High Potent Active Pharmaceutical Ingredients (HPAPIs), from discovery to commercialization.

- **Discovery & Process R&D:** Collaborate with our experts to expedite the route evaluation, pre-clinical supplies, process optimization and scale-up of innovations effectively
- **Clinical Supplies to Commercial Manufacturing:** Transition seamlessly from clinical to commercial production, ensuring the processes are safe, robust and compliance w.r.t. quality and regulatory aspects

cGMP Manufacturing Excellence:

Our facilities are specifically designed to handle cytotoxic, cytostatic, and high potent compounds, with Occupational Exposure Limits (OEL) ranging from >100 µg/m³ to 0.01 µg/m³(OEB 5).

- Advanced Isolators: Equipped for a full spectrum of unit operations, including:
  - Sampling
  - Dispensing & Weighing
  - Reactor Charging
  - Filtration & Drying
  - Milling & Sieving
  - Packing
- **Diverse Reactor Options:** Choose from stainless steel, glass-lined, and Hastelloy reactors tailored to your process needs.
- **Dedicated HPAPI Facility:** Specialize in Prep-HPLC and lyophilization processes for HPAPI molecules.

Specialized Development:

- **Antibody-Drug Conjugates (ADCs):** Expertise in linker development, optimization, and characterization to ensure cutting-edge solutions.

Our Highlights:

- **Experienced Team:** Work alongside highly skilled process chemists, analytical chemists, process engineers, and a dedicated manufacturing and quality control team.
- **Regulatory Compliance:** Our cGMP facility supports lab-scale to commercial-scale manufacturing, including registration and validation batches for regulated markets.
- **Integrated Facilities:** Our separate cGMP facility ensures the manufacturing of non- potent compounds, enhancing your project flexibility.
- **Scalable Solutions:** Provisions for additional reactors and downstream equipment to boost capacity and capabilities as needed.
- **API Registration:** Comprehensive support for PAI (Pre-Approval Inspection) inspection and API registration and validation batches.

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Unlock Your
Oligonucleotide
Potential

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Comprehensive Oligonucleotide Solutions

Process Development:

- **Expertise in Oligonucleotides:**
  - Natural & Modified Oligonucleotides
  - siRNA, ASOs, Anti-microRNA
  - Aptamers, CpG Oligos
- **Specialized Formats:**
  - Conjugated Oligos
  - Molecular Beacons
  - Fluorescent Oligos
  - Probes & Primers
- **Modifications for Enhanced Performance:**
  - Backbone Modifications
  - Base Modifications
  - Sugar Modifications
- **Synthesis Capabilities:**
  - Small single stranded deoxyriponucleotides
  - Scale: 250 µmol - 6 mmol
  - Yield: 100 mg - 5 g per batch (non-GMP)

Analytical Support:

- **Comprehensive Analytical Solutions:**
  - Method Development & Validation
  - -Combination of Orthogonal Techniques
- **Key Analytical Services:**
  - Impurity Analysis
  - Identification
  - Sequencing
  - Characterization
- **Release Specifications:**
  - General, Compendial, Oligo-Specific Methods
- **Stability Studies:**
  - Forced Degradation
  - Informal Stability
  - ICH Stability

Synthesis

Synthesis and Laboratory Development:

- **Oligonucleotide Synthesizer:** ÄKTA Oligosynt
  - Scale: 10 µmol to 12 mmol
  - Yield: ~0.2 to 30 g post purification
  - Flow Rate: 150 mL/min (2 pumps)
  - Amidite Inlets: 16
- **Sensor Monitoring:**
  - Conductivity, UV, Pressure, Air, Temperature

Purification

process development and scale-up

- **Purification System:** ÄKTA Pure 150
  - Flow Rate: 150 mL/min

Tangential Flow Filtration:

ÄKTA Flux 6 TFF

Lyophilization

- VirTis AdVantage Pro Freeze Dryer
- Maximum Condenser Capacity: 6L

Your Partner in Oligonucleotide Innovation and Excellence!

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Your Trusted Partner in
cGMP Synthetic Peptides &
Lyophilized Drug Products

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Introduction:

At CRAMSN, we are committed to excellence in the development and manufacture of synthetic peptides and lyophilized drug products. Our state-of-the-art facilities in India are designed to meet the highest standards of quality and compliance, ensuring that our products are safe, effective, and ready for clinical use. With a dedicated team of experts and advanced manufacturing techniques, we strive to be a leader in the biopharmaceutical industry.

Drug Substances

Manufacturing Methods

Our facility employs cutting-edge manufacturing methods, including:

- **Solid Phase Peptide Synthesis (SPPS):** Utilizing linear and fragmented approaches for efficient peptide synthesis.
- **Liquid Phase Peptide Synthesis (LPPS):** Facilitating the production of complex peptide structures.
- **Convergent Approach:** Enhancing efficiency and yield in peptide synthesis.

Proven Expertise

We have extensive expertise in various peptide chemistries, including:

- **Fmoc & Boc Chemistry:** Handling all peptide types.
- **Disulfide Bond Formation:** Specialized in peptides like Linaclotide and Plecanatide.
- **Semi-synthetic Approaches:** For compounds such as Caspofungin acetate.
- **Large Peptide Production:** Capable of producing peptides with over 30 amino acids, including Teriparatide and Exenatide.
- **Unnatural Amino Acids:** Production of innovative peptides like Icatibant.

Manufacturing Capabilites:

Our capabilities allow us to produce significant batch sizes, including:

Current Scale-Up Capacity for SPPS:

INPUT	OUTPUT
10-25 Kg/batch	30-75 Kg/batch of Resin Bound Peptide (RBP)

Global De-protection:

INPUT	OUTPUT
20 Kg/batch	10 Kg/batch

Current API Batch Sizes:

<20 Amino Acids	20-39 Amino Acids
0.2 Kg/batch	1.2 Kg/batch

Range of cGMP Peptides

To date, we have successfully supplied cGMP peptides ranging from 5 to 39 amino acids for clinical use.

Quality Assurance

The manufacturing and testing of our APIs adhere strictly to cGMP standards, ensuring safety and efficacy.

Drug Products

Manufacturing Lines for Injectable Solutions

Vial Formats: Our facilities are equipped to manufacture a variety of vial sizes including 2 mL, 5 mL, 10 mL, 20 mL, 50 mL, and 100 mL.

- **Mixing Tanks:**

Nominal Capacity:	Mixing Speed:
10 L / 30 L / 90 L / 300 L	600 RPM to 2700 RPM

Heating and Cooling Capabilities:
All tanks are equipped with heating and cooling systems.

- **Filling Machine:**

Capacity:
10-140 Vials/Minute

Sterilization and Quality Testing

Sterilization Filtration Process: Integrity testing is conducted using advanced equipment from PALL.

Testing Facilities: In-process, release, and stability tests are conducted at the same facility.

Quality Inspections

We maintain rigorous standards and have undergone multiple quality inspections by the USFDA, EMEA and other regulatory bodies.

Our Commitment:
To deliver high-quality peptide APIs and drug products while ensuring compliance with international standards.

For inquiries, collaborations, or further information, please contact us today!