Chemical Development & Manufacturing
A Premier Global CRO/CDMO

Dedicated to improving patient outcomes through end-to-end global contract research and manufacturing services for more than 25 years

Specializing in:

• Early discovery to candidate selection
• Discovery and development with translational innovations
• Diverse, end-to-end chemistry from milligrams to commercial kilo scale
• Development and manufacturing of APIs, ingredients, custom intermediates and other substances
• Preclinical to commercial-scale parenteral formulations for sterile drug product manufacturing
• Strategic, novel business models
Investing in Innovation

Discovery
- 2015
- Integrated Drug Discovery Center Operational; Strategic Research Alliances

Development
- 2015
- SSCI
- Integrated Drug Discovery Center Operational

Analytical and Solid State Services
- 2015
- Solid State and Analytical Chemistry

API Manufacturing
- 2016
- Euticals
- API, Custom Synthesis EU Footprint*

Drug Product
- 2015
- Aptuit Glasgow
- Formulation & Manufacturing

- 2015
- Whitehouse Labs
- Labs Qualification Testing & Analytical

- 2015
- Gadea
- API, Drug Product EU Footprint

- 2014
- OsoAbio
- Commercial-Scale Sterile Fill/Finish

- 2014
- Cedarburg Hauser Pharmaceuticals
- Controlled Substance API

- 2014
- Amri
- Initiated Generic Development & Manufacturing
AMRI Business Operations

**Drug Discovery**
- Harness the power of broad target class coverage, state-of-the-art technology platforms and expertise in multiple disease areas supporting comprehensive drug discovery and candidate selection

**Development**
- Advance the development of your compound and gain strategic insight into manufacturing through our rapid robust solutions

**Analytical and Solid State Services**
- Speed product development and improve the quality of your compound with solid state chemistry and analytical testing services

**API Manufacturing**
- Power API production with global, cost-effective commercial manufacturing of your niche and high-barrier-to-entry compounds and with our growing catalog of more than 240 APIs

**Drug Product**
- Optimize the critical path of your API through product development and commercialization by accessing our comprehensive sterile dosage form development and manufacturing expertise and capabilities
AMRI Service Platform

Discovery
- Hit to Lead to Candidate Services
- Medicinal Chemistry
- High Throughput Screening
- *In Vitro* Biology and Pharmacology
- Library Design & Custom Synthesis
- Biocatalysis and Biotransformation
- Profiling & Structure ID
- Bioprocess Development

Development
- Early ADME
- Metabolite ID
- Process and Analytical Development
- Kilo Lab Scale-Up
- Phase I GMP
- Salt & Polymorph Investigations
- Formulation Development

API Manufacturing
- Phase II/III API
- Commercial API
- High Value Intermediates
- High Potency
- DEA Regulated API
- Complex API R&D
- Global Regulatory
- Niche Generics

Drug Product
- Sterile Fill and Finish Drug Product
- Formulation Manufacturing

Analytical and Solid State Services
Fully integrated platform spans drug development spectrum from discovery to manufacturing, providing comprehensive service offering to customers.
Introducing Discovery and Development Services (DDS)
Continuous Improvement, Growth, & Investment

Organic
- Compound library consortium established
- Insourcing business expanded
- Enhanced Discovery services under one roof in NY
  Key alliances extend capabilities and speed
  - Structure based drug design
  - Ion channels, transporters and GPCRs – assays and cell lines
- Investment in key technologies including: flow chemistry, high content screening to Signals® translational platform
- Chem Dev growth in small scale cGMP cytotoxic and controlled substances

Inorganic
- Significantly expanded analytical, qualification and testing services
  - SSCI - Solid state chemistry
  - Whitehouse Labs - Product and container qualification and integrity testing
- Gadea – Biocatalysis capabilities from discovery to large scale
- Euticals – Addition of custom synthesis capacity in EU
A Robust Pipeline of Niche APIs

- Phase I & II: 97
- Phase III: 31
- Registration: 44
- Commercial: 245

Development Supporting These Programs
End-to-End Sterile Drug Dosage Form Development and Manufacturing

- Pre-formulation activities in Albany (material sciences, solubility enhancement and formulation screening)
- Solubility enhancement, formulation and lyophilization development and early clinical GMP supply in Glasgow
- Early/mid clinical, process development and small-scale commercial manufacture in Burlington
- Phase III and commercial manufacturing in Leon and Albuquerque
Chemical Development Capabilities
Chemical Development – Process Chemistry Capabilities

- Pragmatic route selection & phase-appropriate process development & “Rapid Response” scale-up intermediates, API, etc.
- Expertise in DoE, reaction modeling/simulation, crystallization, polymorph control, process hazard assessment, critical process parameters (CPP)
- Rare Disease focus – flexible, nimble to dynamic shifts in timelines
- Continuous Flow processing up to Kilo scale
- Enzymatic reactions
- Small & MFG scale hydrogenation, cryogenic capability, heterocyclic chemistry
- Early phase toxicology batches (NCSS)
- Early phase clinical batches (cGMP)
- Potent compound handling up to Safebridge Category 5; containment down to < 0.1 μg/m3 OEL
- Controlled substance handling (I-V)
- Process registration & validation
Program Progression – From Early Phase to Late Phase
...from the med chem route to a robust, scalable chemical process

Lab Scale  Kilo Lab  Pilot Plant

- Process Innovation/Development
- GMP API, GLP Tox batches, Intermediates
- Large Scale Intermediates, Starting Materials, API Manufacturing

Albany/Hyderabad/Wisconsin/Frankfurt  Albany/Hyderabad/Frankfurt  Frankfurt/Aurangabad/Wisconsin/Rensselaer/Bon Encontre/Origgio/Rozzano

All Development Programs begin at AMRI in the Chemical Development Labs for Process Feasibility/Development/Optimization
Chemical Development – Personnel and Experience

• ~ 55 chemists in the Albany, NY, area
  – ~50% Ph.D., experience levels from 3-25+ years
• ~15 chemists in Grafton, Wisconsin
  – ~50% Ph.D.
• 18 chemists in Frankfurt
  – ~ 40 % Ph.D.
• ~ 95 chemists in India
  – ~ 30 % Ph.D.
• Dedicated team of analytical chemists supporting development
• Diverse range of synthetic organic chemistry skills
• cGMP trained team of ~ 14 chemists
• Specialized team in biotransformations and fermentation
• High Potency trained personnel in Albany; access to Non-GMP & GMP HP suites
• DEA licensed for controlled substance (Schedule class I-V) research in Albany
Analytical, Pre-Formulation, Formulation Capabilities
Analytical Support/Method Development
For All Phases of Pharmaceutical Development & Manufacturing

Services
- Release Testing
- Method Development & Validation
- Drug Stability Studies
- Impurity Isolation
- Impurity Identification
- Global Quality Control
- Reference Standard Certification
- Chiral & achiral separations via GC, HPLC & SFC

Capabilities
- Chromatography-HPLC/UPLC
- Chromatography-GC
- LC-MS/MS
- NMR/LC-NMR, solid state
- Stability
- Spectroscopy
- Wet Chemistry

State-of-the-art technologies and instrumentation along with close collaboration with synthetic organic chemists ensures that the right questions are asked and the right tools are used to solve even the most difficult problem.
# Solid State Chemistry – Core Capabilities

| Preformulation          | • Early candidate screening: solid form and physchem characterization  
|                        | • Dissolution, pH solubility profiles  
|                        | • Excipient compatibility  
|                        | • Pre-clinical formulations and bioavailability enhancement  
| Analytical Technology   | • Testing services for small and large molecules (normal, rush and urgent)  
|                        | • Drug product and medical device characterization  
|                        | • Stability program support and commercial product release  
|                        | • Contaminant identification  
| Material Science        | • Polymorph, salt, cocrystal screening and selection  
|                        | • IP protection strategy of APIs  
|                        | • Comprehensive physical properties investigation  
|                        | • Thermodynamic relationship  
| Particle Engineering    | • Crystallization process development  
|                        | • API control & consistency and API filtration & drying  
|                        | • Critical process parameters  
|                        | • Particle characterization  
| Analytical Development  | • API and drug product method development and validation  
|                        | • Advanced analytical technology expertise  
|                        | • Complex chemical structure elucidation  
|                        | • Litigation support  

*Image* (not visible in the text): 
- Preformulation: Various capabilities related to early candidate screening and physchemical characterization. 
- Analytical Technology: Services for small and large molecules, including stability support and commercial product release. 
- Material Science: Focus on polymorphs, salts, cocrystals, and IP protection strategies. 
- Particle Engineering: Development of crystallization processes and particle characterization. 
- Analytical Development: Advanced analytical methods for API and drug product development and validation. 

Niche Analytical Testing Services

Container Qualification and Container Closure Integrity (CCI) Testing
- Can assist with USP, EP, & JP testing for all Container Systems
- Packing Validation and Distribution Testing
- Micro testing
- Full compendial testing

Physical Drug Delivery & Device Testing
- Extractables & Leachables Testing
- ICP-MS USP 232/233 Heavy Metals Testing
- ISO 11608 – Dosing Accuracy for Needle Based Injection Systems
- USP <698> Deliverable Volume
- USP <905> Dosage Uniformity
- Cleaning and Sterilization Validations
Formulation Capabilities – Solid Dosage Drug Product (Albany & RLS)

Non-GMP Formulation Development
- Excipient Compatibility
- Wet granulation
- Roller compaction
- Milling
- Sieving
- Mixing
- Tableting
- Fluid bed processing
- Spray drying

Clinical Supplies Manufacturing-cGMP
- Capsule Filling
  - Capsugel's Xcelodose technology
  - Hand encapsulation
  - Powder-in-a-Bottle
Small to Large Scale Manufacturing
## AMRI Key Technologies

### Sterile APIs
- Dedicated plant
- Sterilization via aseptic filtration and crystallization
- Crystallization and Lyophilization
- Mill and Micronization unit

### Enzymatic Chemistry
- Lipase applications
- Chiral Cyclopentenol acetates
- Alcohol Dehydrogenase (ADH) & other applications

### Fermentation
- Ergots Alkaloids and Immunosuppressant
- Absorption/Silica Gel/Ion Exchange Chromatography

### Organometallics
- Lithiation
- Boronic Acids
- Tri-F Methyl Pyridines
- Grignard
- X-Coupling
- C-O Couplings

### Heterocycles
- Nicotinic Acid derivatives
- Piperazines
- Naphthyridines
- Furans
- Indoles
- Triazoles
- Pyrimidine

### Other Capabilities
- Cryogenic Chemistry
- Hydrogenation
- Preparative HPLC
- T3P® & Amides preparation
- Phosphates chemistry
- Complex molecules chemistry
- Chiral chemistry
### AMRI Key Product Families

<table>
<thead>
<tr>
<th>Monobactams</th>
<th>Steroids</th>
<th>Hormones</th>
<th>Other Niche Products</th>
<th>Controlled Substances</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer of Aztreonam, both Oral APIs and Sterile</td>
<td>Dedicated Plant</td>
<td>Dedicated Plant</td>
<td>Ergot Derivatives</td>
<td>4 DEA manufacturing areas</td>
</tr>
<tr>
<td>Dedicated plant</td>
<td>Hydrogenation</td>
<td>Containment Technology</td>
<td>Immunosuppressant</td>
<td>Research and export registration for schedules I, II &amp; V</td>
</tr>
<tr>
<td></td>
<td>Phosphates</td>
<td>Mill Unit</td>
<td>High Potent compounds</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lyophilization</td>
<td>Micronization Unit</td>
<td>Curares</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tetracyclines</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Prostaglandins</td>
<td></td>
</tr>
</tbody>
</table>
## Fermentation, Bioprocessing, Biotransformation and Biocatalysis

**Novel Molecules, Reduced COG, Clean Chemistry**

<table>
<thead>
<tr>
<th>Location</th>
<th>Processes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Albany</strong></td>
<td>Process Innovation/Development</td>
</tr>
<tr>
<td></td>
<td>Discovery &amp; Development / POC Focus</td>
</tr>
<tr>
<td></td>
<td>Non-GMP</td>
</tr>
<tr>
<td></td>
<td>Semisynthetic Chemistry and DSP Process Development</td>
</tr>
<tr>
<td></td>
<td>Strain collection, Isolation &amp; Cultivation</td>
</tr>
<tr>
<td></td>
<td>Miniaturized to 500-L</td>
</tr>
<tr>
<td><strong>Spain</strong></td>
<td>Scale-up to cGMP; Intermediate scale API</td>
</tr>
<tr>
<td></td>
<td>Pilot/Clinical and Intermediate Scale API supply</td>
</tr>
<tr>
<td></td>
<td>Non-GMP and cGMP</td>
</tr>
<tr>
<td></td>
<td>Semisynthetic Chemistry and DSP Scale-up</td>
</tr>
<tr>
<td></td>
<td>Back-up &amp; Working Strain collection</td>
</tr>
<tr>
<td><strong>Italy</strong></td>
<td>Large scale Manufacturing</td>
</tr>
<tr>
<td></td>
<td>Large scale Manufacturing</td>
</tr>
</tbody>
</table>

- **Albany:** Process Innovation/Development
- **Spain:** Scale-up to cGMP; Intermediate scale API
- **Italy:** Large scale Manufacturing

### Scale Information:
- **Albany:** 15 tanks from 20-L to 12,000-L
- **Spain:** 7 tanks from 13,000-L to 48,000-L (+support tanks)
- **Italy:** Large scale Manufacturing

### Sites and Services:
- **Albany:** Process Innovation/Development, Discovery & Development / POC Focus, Non-GMP, Semisynthetic Chemistry and DSP Process Development, Strain collection, Isolation & Cultivation
- **Spain:** Scale-up to cGMP, Intermediate scale, Pilot/Clinical and Intermediate Scale API supply, Non-GMP and cGMP, Semisynthetic Chemistry and DSP Scale-up, Back-up & Working Strain collection
- **Italy:** Large scale Manufacturing, Commercial API focus, cGMP Manufacturing, Large scale Semisynthetic Chemistry and DSP, Working Strain collection
AMRI Manufacturing Sites

API BU Plants:
- Rensselaer (RLS)
- Springfield (SPN)
- Rozzano Quinto (ROZ)
- Aurangabad (ILS)
- Cedarburg (CDG)
- Lodi (LO)
- Rozzano Valleambrosia (VAM)
- Tonneins (TON)
- Valladolid (CP)
- Origgio (OR)
- Bon Encontre
- Frankfurt

To DDS BU
Rozzano - Quinto de' Stampi

Plant
Chemical and Fermentation Plant, R&D Lab. Medium Size, Niche productions

Quality
CGMP
Latest FDA inspection: Feb 2015
Latest AIFA inspection: Jul 2014
Latest PMDA inspection: Apr 2015
Latest ANVISA inspection: Jun 2011

Main Products
Bromocriptine, Ciclosporin, Ergot Alkaloids, Argatroban and NMBA

Main Technologies
Hydrogenation, Microbiology, Fermentation and Synthesis

Capacity
180 m³ Fermentation
60 m³ Synthesis
Reactors from 50 L to 6,000 L, SS&GL

Total Area
20,700 m²

7 PRODUCTS with CEP

<table>
<thead>
<tr>
<th>Product</th>
<th>CEP No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dihydroergocristine Mesylate</td>
<td>R0-CEP 2000-073</td>
</tr>
<tr>
<td>Dihydroergotamine Mesylate</td>
<td>R1-CEP 2000-183</td>
</tr>
<tr>
<td>Ergotamine Tartrate</td>
<td>R0-CEP 2008-291</td>
</tr>
<tr>
<td>Pancuronium Bromide</td>
<td>R1-CEP 2005-120</td>
</tr>
<tr>
<td>Ticlopidine Hydrochloride</td>
<td>R1-CEP 2001-414</td>
</tr>
<tr>
<td>Bromocriptine Mesylate</td>
<td>R1-CEP 2000-151</td>
</tr>
<tr>
<td>Ciclosporin</td>
<td>R1-CEP 1999-034</td>
</tr>
</tbody>
</table>
Rozzano – Valle Ambrosia

**Plant**
Chemical Plant and R&D Lab
Small plant with limited capacity, dedicated to Monobactam productions

**Quality**
cGMP
Latest FDA inspection: Nov 2012
Latest AIFA inspection: Mar 2015

**Main Products**
Aztreonam, DHZ Mesyate and Monobactams

**Main Technologies**
Hydrogenation, Wittig chemistry, Friedel-Craft high temp.

**Capacity**
15 m³ Synthesis
Reactors from 500 L to 3.000 L, SS&GL

**Total Area**
3.300 m²
**Origgio**

**Plant**  
Chemical and Solvent Recovery Plant. Big Size plant for both generics and high volume CS and CMO projects

**Quality**  
cGMP  
Latest FDA inspection: Mar 2014  
Latest AIFA inspection: Jun 2014  
Latest PMDA inspection: Jan 2014

**Main Products**  
Minocycline, Propofol, Chlortalidone, Ribavirin, Terazosin and Flutamide

**Main Technologies**  
Hydrogenation, Organometallics and Cryogenic chemistry and Boronic acids. Tetracyclines

**Capacity**  
550 m$^3$ Synthesis  
High pr. Hydrogenation from 5 to 15 m$^3$  
Reactors from 100 L to 16,000 L, SS&GL

**Total Area**  
163,000 m$^2$

<table>
<thead>
<tr>
<th>5 PRODUCTS with CEP</th>
<th>CEP No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlortalidone Unmilled, Milled, Micronized</td>
<td>R1-CEP 2001-020</td>
</tr>
<tr>
<td>Flutamide Unmilled, Milled</td>
<td>R1-CEP 2000-049</td>
</tr>
<tr>
<td>Minocycline Hydrochloride Dihydrate</td>
<td>R1-CEP 2007-107</td>
</tr>
<tr>
<td>Propofol</td>
<td>R1-CEP 2001-267</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>R0-CEP 2007-182</td>
</tr>
</tbody>
</table>
Lodi

**Plant**
Chemical Plant. Medium size, multipurpose dedicated to generics. Big volumes APIs.

**Quality**
cGMP
Latest FDA inspection: Sep 2014
Latest AIFA inspection: Dec 2014
Latest PMDA inspection: Oct 2012
Latest KFDA inspection: Oct 2011

**Main Products**
Oxcarbazepine, Hydroxyurea, Mianserin, Sucralfate and Choline Alfoscerate

**Main Technologies**
Large scale use of Pyridine, Fluorinations reactions, Grignard and Oxidation. Dedicated line for Oral Anticancer

**Capacity**
190 m³
Reactors from 500 L to 8.000 L, SS&GL

**Total Area**
22.800 m²

<table>
<thead>
<tr>
<th>1 PRODUCTS with CEP</th>
<th>CEP No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxyurea</td>
<td>R1-CEP 2003-120</td>
</tr>
</tbody>
</table>
Bon Encontre

**Plant**
Chemical Plant. Medium size plant. Strong expertise in CMO and CS

**Quality**
cGMP
ISO 9001:2008
ISO 14001:2004
OHSAS 18001:2007
Latest FDA inspection: Nov 2014
Latest ANSM inspection: Dec 2013

**Main Products**
Niflumic Acid, Morniflumate, Hexetidine and Propacetamol

**Main Technologies**
Bulk Sterile manufacturing, Organometallic and Cryogenic chemistry, Bromination and Hydrogenation

**Capacity**
140 m³
Reactors from 1.600 L to 6.000 L, SS&GL

**Total Area**
37.400 m²

<table>
<thead>
<tr>
<th>2 PRODUCTS with CEP</th>
<th>CEP No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hexetidine</td>
<td>R1-CEP 2005-238</td>
</tr>
<tr>
<td>Niflumic Acid</td>
<td>R0-CEP 2012-237</td>
</tr>
</tbody>
</table>
Tonneins

Plant
Chemical Plant and sterile line.
Limited number of products

Quality
cGMP
ISO 9001:2008
ISO 14001:2004
Latest FDA inspection: Nov 2014
Latest ANSM inspection: Apr 2015

Main Products
Aztreonam Sterile, sterile L-Arginine.
Chloro nicotinic acid (CNA)

Main Technologies
Sterile manufacturing, Oxidation and
Chlorination

Capacity
80 m³
Reactors from 1.000 L to 8.000 L, SS&GL

Total Area
160.000 m²
Springfield

**Plant**
Chemical Plant. Big size plant specialized in Controlled Substances production (schedule I, II and V)

**Quality**
cGMP
Latest FDA inspection: Aug 2014
DEA controlled sub. license: since 2005

**Main Products**
Phenidates, Tapentadol, Choline Fenofibrate and Lacosamide

**Main Technologies**
Organometallic and Cryogenic chemistry, Chiral epoxides and Cyanide handling

**Capacity**
574 m³
Reactors from 120 L to 6.000 L, SS&GL

**Total Area**
267.000 m²
Rensselaer

**Plant**
Large scale API plant. Potent Compounds and Controlled Substances

**Quality**
cGMP, PMDA (2013), KFDA (2012)
Latest FDA inspection: 2Q 2015
DEA controlled sub. license: since 2015

**Main Products**
Amphetamine Salts, Mafenide Acetate and Meperidine HCl, Lisdexamphetamine, ABA.

**Main Technologies**
Spray Drying Aqueous and Organic Solvent (10kg batch size).
Ultrafiltration. Micro Fluidic reactors

**Capacity**
180 m³
Reactors from 30 L to 8,000 L
Cedarburg

**Plant**
Chemical Plant. Specialized in Complex small molecules production

**Main Products**
Fentanyl, Exemestane

**Main Technologies**
Prostaglandins, Potent Compounds & Controlled Substances

**Capacity**
6.2 m³ Reactors from 110 L to 1900 L

**Quality**
cGMP  
EDQM  
Latest FDA inspection: July 2016  
DEA controlled sub. license: since 2013

**3 PRODUCTS with CEP**

<table>
<thead>
<tr>
<th>Product</th>
<th>CEP No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brimonidine Tartrate</td>
<td>2015-265</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>2005-044</td>
</tr>
<tr>
<td>Fentanyl Citrate</td>
<td>2005-081</td>
</tr>
</tbody>
</table>
Aurangabad

Plant
Chemical Plant. Big size plant

Quality
CGMP TGA (2015)

Main Products
Atenolol, Furosemide and Isosorbide Mononitrate (ISMN)

Main Technologies
Intellectual Property

Capacity
Reactors from 500 L to 6,500 L

2 PRODUCTS with CEP

<table>
<thead>
<tr>
<th>2 PRODUCTS with CEP</th>
<th>CEP No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atenolol</td>
<td>R1-CEP 1999-122-Rev 06</td>
</tr>
<tr>
<td>Furosemide</td>
<td>R1-CEP 1999-069-Rev 06</td>
</tr>
</tbody>
</table>
Valladolid

**Plant**
- 2 Pilot Plants
- 5 Chemical APIs Plants
- Plants specialized in Steroids, Hormones and Complex chemistry APIs production
- 2 Aseptic Plants (Sterile APIs)

**Quality**
- cGMP
- Latest FDA inspection: March 2014 KFDA

**Main Products**
- Hydrocortisone sodium succinate sterile
- Triamcinolone acetonide sterile
- Dorzolamide, Betamethasone Dipropionate, Betamethasone Valerate
- Dexamethasone sodium phosphate

**Main Technologies**
- Organometallic and Cryogenic Hydrogenation
- Reactions, phosphates
- Lyophilization, Chiral chemistry and Micronization

**Capacity**
- Chemical: 115 m³
- Reactors from 26 L to 12,000 L, SS&GL
- Asepsis: 9 m³
- Reactors from 250 L to 2,500 L, SS&GL

**Total Area**
- 37,500 m²