



# Chemical Development & Manufacturing

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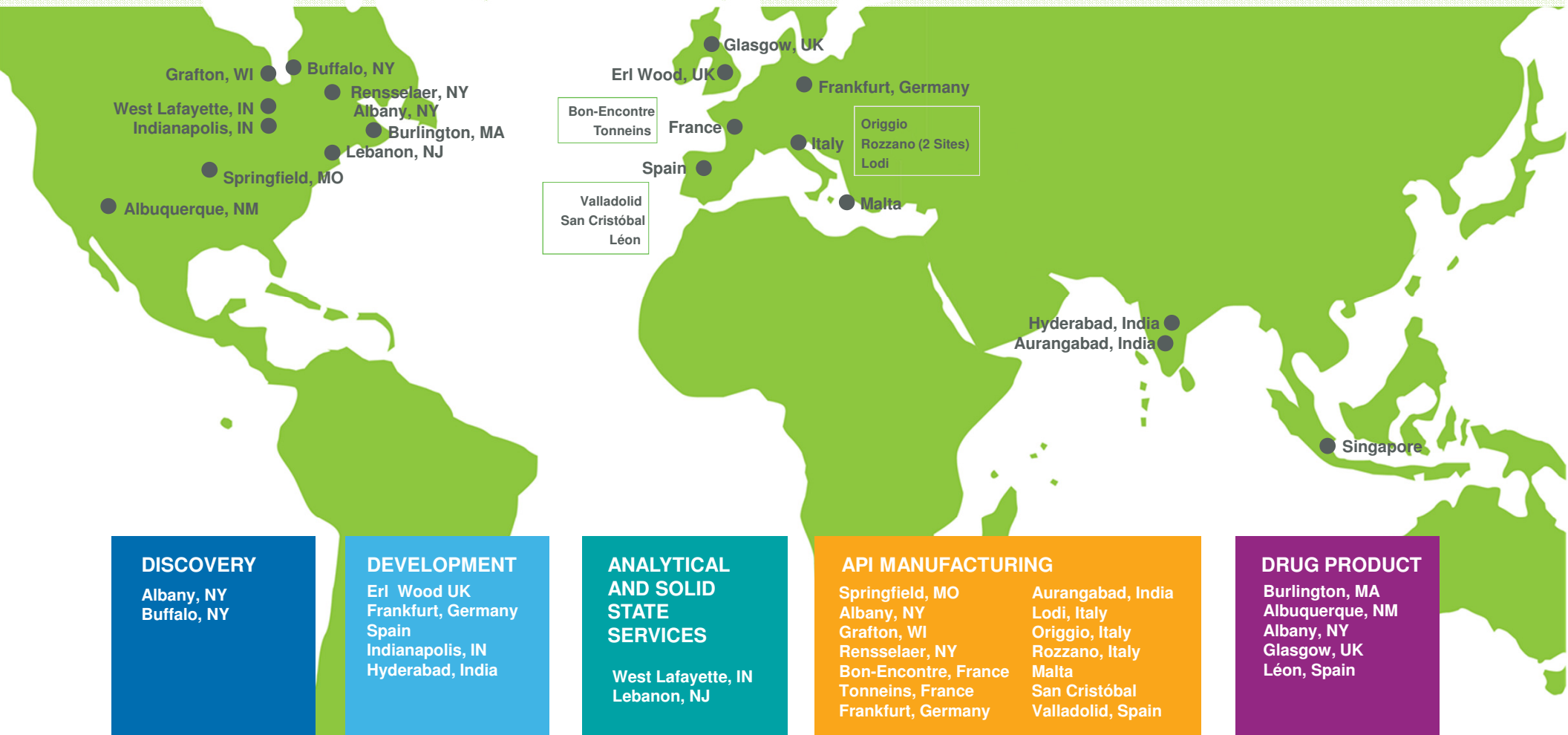
## A Premier Global CRO/CDMO

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

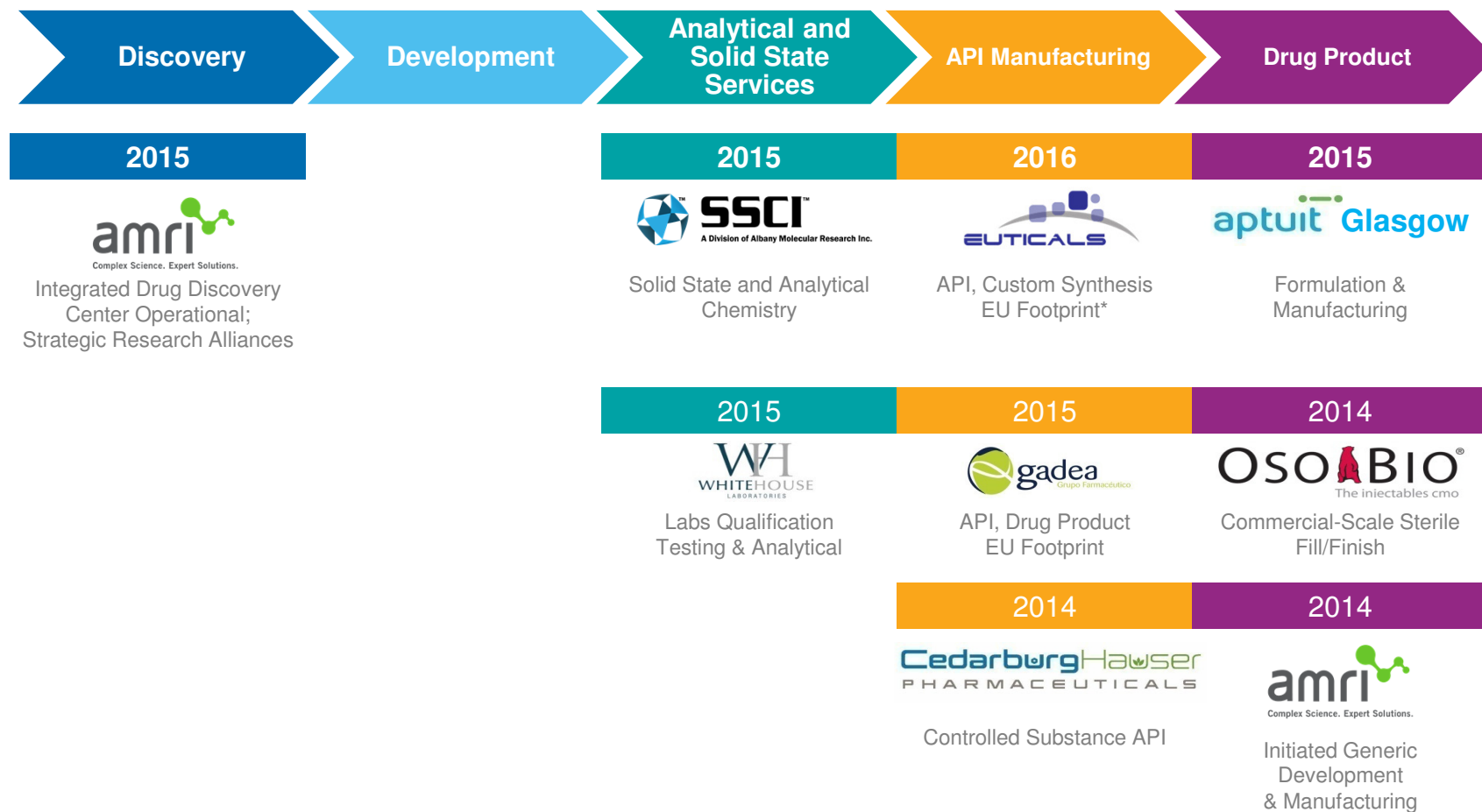
### Specializing in:

- 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

# A Powerful Network > 3,000 Employees Globally



## Investing in Innovation



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## 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

Target  
Discovery

Lead  
Finding

Lead  
Optimization

Candidate  
Selection

Pre-Clinical

Phase I

Phase 2

Phase 3

Product  
Approval

Generic  
R&D

ANDA  
Development &  
Approval

## 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
- Fine Chemicals
- T3P® Technology
- Boronic Acids

## 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





## 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

# Strategic Chemical Development Internal Network



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## 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/m<sup>3</sup> 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

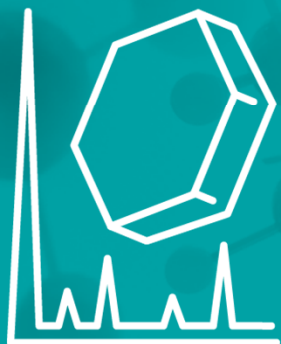
Frankfurt/Aurangabad/Wisconsin/Rensselaer  
/Bon Encontre/Origgio/Rozzano

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





## 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

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## 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

Monobactams	Steroids	Hormones	Other Niche Products	Controlled Substances
<ul style="list-style-type: none"><li>• Manufacturer of Aztreonam, both Oral APIs and Sterile</li><li>• Dedicated plant</li></ul>	<ul style="list-style-type: none"><li>• Dedicated Plant</li><li>• Hydrogenation</li><li>• Phosphates</li><li>• Lyophilization</li><li>• Mill Unit</li><li>• Micronization Unit</li></ul>	<ul style="list-style-type: none"><li>• Dedicated Plant</li><li>• Containment Technology</li><li>• Mill Unit</li><li>• Micronization Unit</li></ul>	<ul style="list-style-type: none"><li>• Ergot Derivatives</li><li>• Immunosuppressant</li><li>• High Potent compounds</li><li>• Curares</li><li>• Tetracyclines</li><li>• Prostaglandins</li></ul>	<ul style="list-style-type: none"><li>• 4 DEA manufacturing areas</li><li>• Research and export registration for schedules I, II &amp; V</li></ul>

# Fermentation, Bioprocessing, Biotransformation and Biocatalysis

## Novel Molecules, Reduced COG, Clean Chemistry



### Albany

Process Innovation/Development



### Spain

Scale-up to cGMP; Intermediate scale API



### Italy

Large scale Manufacturing

Miniaturized to 500-L

Process Innovation/Development  
Discovery & Development / POC Focus  
Non-GMP  
Semisynthetic Chemistry and DSP Process Development  
Strain collection , Isolation & Cultivation

15 tanks from 20-L to 12,000-L

Intermediate scale  
Pilot/Clinical and Intermediate Scale API supply  
Non-GMP and cGMP  
Semisynthetic Chemistry and DSP Scale-up  
Back-up & Working Strain collection

7 tanks from 13,000-L to 48,000-L (+support tanks)

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  
Vallembrosia  
(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



### Main Products

Bromocriptine, Ciclosporin,  
Ergot Alkaloids, Argatroban and  
NMBA



### Capacity

180 m<sup>3</sup> Fermentation  
60 m<sup>3</sup> Synthesis  
Reactors from 50 L to 6.000 L, SS&GL



### Quality

cGMP

Latest FDA inspection: Feb 2015

Latest AIFA inspection: Jul 2014

Latest PMDA inspection: Apr 2015

Latest ANVISA inspection: Jun 2011



### Main Technologies

Hydrogenation, Microbiology,  
Fermentation and Synthesis



### Total Area

20.700 m<sup>2</sup>

7 PRODUCTS with CEP	CEP No.
Dihydroergocristine Mesylate	R0-CEP 2000-073
Dihydroergotamine Mesylate	R1-CEP 2000-183
Ergotamine Tartrate	R0-CEP 2008-291
Pancuronium Bromide	R1-CEP 2005-120
Ticlopidine Hydrochloride	R1-CEP 2001-414
Bromocriptine Mesylate	R1-CEP 2000-151
Ciclosporin	R1-CEP 1999-034



## Rozzano – Valle Ambrosia



### Plant

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



### Main Products

Aztreonam, DHZ Mesyate and  
Monobactams



### Capacity

15 m<sup>3</sup> Synthesis  
Reactors from 500 L to 3.000 L, SS&GL



### Quality

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



### Main Technologies

Hydrogenation, Wittig chemistry,  
Friedel-Craft high temp.



### Total Area

3.300 m<sup>2</sup>



# Origgio



## Plant

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



## Main Products

Minocycline, Propofol, Chlortalidone,  
Ribavirin, Terazosin and Flutamide



## Capacity

550 m<sup>3</sup> Synthesis  
High pr. Hydrogenation from 5 to 15 m<sup>3</sup>  
Reactors from 100 L to 16.000 L, SS&GL



## Quality

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



## Main Technologies

Hydrogenation, Organometallics and  
Cryogenic chemistry and Boronic  
acids. Tetracyclines



## Total Area

163.000 m<sup>2</sup>

5 PRODUCTS with CEP	CEP No.
Chlortalidone Unmilled, Milled, Micronized	R1-CEP 2001-020
Flutamide Unmilled, Milled	R1-CEP 2000-049
Minocycline Hydrochloride Dihydrate	R1-CEP 2007-107
Propofol	R1-CEP 2001-267
Ribavirin	R0-CEP 2007-182



## 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 m<sup>3</sup>

Reactors from 500 L to 8.000 L, SS&GL



### Total Area

22.800 m<sup>2</sup>

1 PRODUCTS with CEP	CEP No.
Hydroxyurea	R1-CEP 2003-120



## Bon Encontre



### Plant

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



### Main Products

Niflumic Acid, Morniflumate, Hexetidine  
and Propacetamol



### Capacity

140 m<sup>3</sup>  
Reactors from 1.600 L to 6.000 L, SS&GL



### Quality

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



### Main Technologies

Bulk Sterile manufacturing,  
Organometallic and Cryogenic  
chemistry, Bromination and  
Hydrogenation



### Total Area

37.400 m<sup>2</sup>

2 PRODUCTS with CEP	CEP No.
Hexetidine	R1-CEP 2005-238
Niflumic Acid	R0-CEP 2012-237



# Tonneins



## Plant

Chemical Plant and sterile line.  
Limited number of products



## Main Products

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



## Capacity

80 m<sup>3</sup>  
Reactors from 1.000 L to 8.000 L, SS&GL



## Quality

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



## Main Technologies

Sterile manufacturing, Oxidation and  
Chlorination



## Total Area

160.000 m<sup>2</sup>



# 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

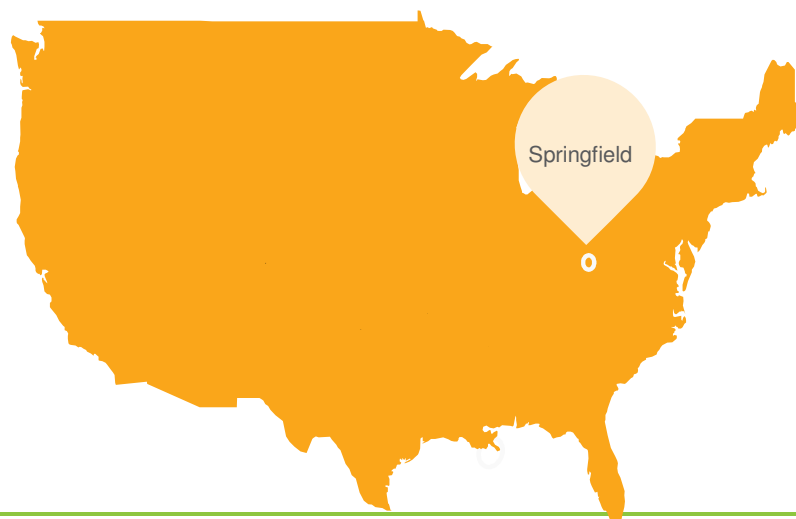
574 m<sup>3</sup>

Reactors from 120 L to 6.000 L, SS&GL



## Total Area

267.000 m<sup>2</sup>



# 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 m<sup>3</sup>  
Reactors from 30 L to 8.000 L





## Cedarburg



### Plant

Chemical Plant. Specialized in  
Complex small molecules production



### Main Products

Fentanyl, Exemestane



### Capacity

6.2 m<sup>3</sup>  
Reactors from 110 L to 1900 L



### Quality

cGMP  
EDQM

Latest FDA inspection: July 2016

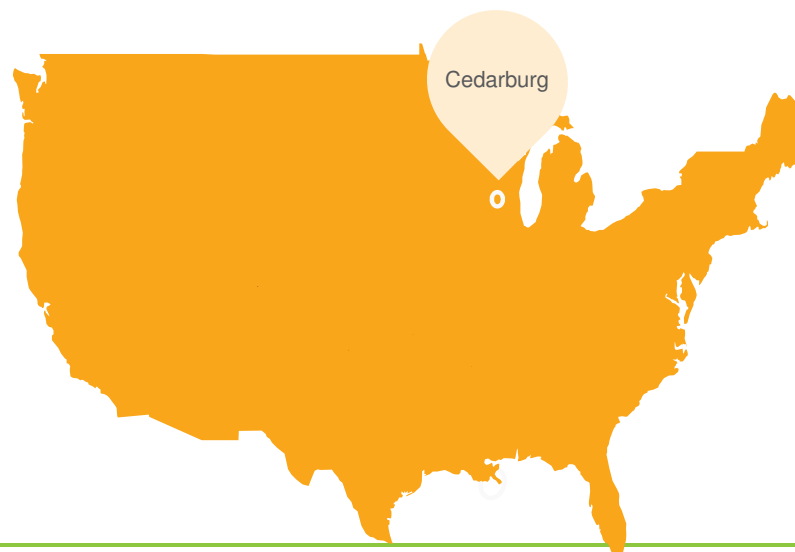
DEA controlled sub. license: since 2013



### Main Technologies

Prostaglandins, Potent Compounds &  
Controlled Substances

3 PRODUCTS with CEP	CEP No.
Brimonidine Tartrate	2015-265
Fentanyl	2005-044
Fentanyl Citrate	2005-081



## Aurangabad



### Plant

Chemical Plant.  
Big size plant



### Main Products

Atenolol, Furosemide and Isosorbide  
Mononitrate (ISMN)



### Capacity

Reactors from 500 L to 6.500 L



### Quality

cGMP  
TGA (2015)



### Main Technologies

Intellectual Property



2 PRODUCTS with CEP	CEP No.
Atenolol	R1-CEP 1999-122-Rev 06
Furosamide	R1-CEP 1999-069-Rev 06

## 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, phosphates,  
Lyophilization, Chiral chemistry and  
Micronization



### Capacity

Chemical :115 m<sup>3</sup>  
Reactors from 26 L to 12.000 L, SS&GL  
Asepsis: 9 m<sup>3</sup>  
Reactors from 250 L to 2.500 L, SS&GL



### Total Area

37.500 m<sup>2</sup>





**Thank You**