

US Manufacturing Facility



US Development Facility



European Development Facility



CHEMISTRY THAT WORKS

CAMBRIDGE MAJOR LABORATORIES AT A GLANCE:

- More than 190+ employees
- 50+ Ph.D. Scientists
- Three facilities in the United States and Europe
- More than 120 satisfied customers worldwide per year
- >20% growth rate past 10 years
- Stellar Reputation for 10 years and counting
- Grams to multi-ton production in US/European based assets
- FDA-inspected facilities

Cambridge Major Laboratories is a global organization that develops and manufactures Active Pharmaceutical Ingredients (API) at sites in the United States and Europe. We were founded on the simple notions that high science, project execution and delivery are the most fundamental tenets of the long-term relationship.

At Cambridge Major we provide advanced chemistry services to the world's leading pharmaceutical and biotechnology companies. And because we deliver time

and time again, our customers always come back. Fast, flexible and fair, Cambridge Major doesn't get bogged down in endless meetings and bloated bureaucracy. Simply said, we make decisions quickly, and are totally focused on getting the product into your hands as fast as possible.

Company stability is a term you don't hear too often these days. Cambridge Major is strong, stable and constantly growing. Through a strong vision, hard work, determination and dedication to our customers, Cambridge Major's growth has been truly exceptional. The company has been in business for years and we intend on being in this business for the long haul. You can count on it!

Our state-of-the-art, fully qualified facilities contain ultra-modern R&D

laboratories, GMP kilo lab suites, and multiple reactor suites; all comprising highly engineered systems to support development and production of your API up to ton scale, from preclinical development through post-NDA commercial manufacture. And our quality systems are unparalleled as we are proud of our long and successful FDA inspection history, as well as multiple DMFs filed the past several years.

So when you are looking for a trusted global partner to help take your compound from concept to clinic and beyond, look to Cambridge Major.

WE DELIVER!

CAMBRIDGE MAJOR
LABORATORIES
CHEMISTRY THAT WORKS®



- 4 Process R&D Labs (8 Walk-In Hoods; 8 Bench-Top Hoods)
- 5 GMP Kilo Lab Suites (10 Walk-In Hoods; 5 Bench-Top Hoods)
- 1 Hydrogenation Suite (parr and 20-Liter Medium Pressure Vessels)
- 3 Isolated HEPA-Filtered Drying Suites
- 1 Isolated HEPA-Filtered Packaging Suite
- 1 Spectroscopy Suite (300 MHz NMR; In-Process GC's, HPLC's)
- 2 Walk-in Cold Rooms
- 3 Chemical Storage Rooms
- Hazard Lab (RC-1, DSC, TGA)

Kilo Labs have independent air handling systems with once-through air. Each has temperature, humidity, and room pressure control. GMP suites are isolated under positive pressure with ASHRAE 95 filtration. Labs have central vacuum as well as Glycol loops for reaction cooling or chilling of condensers. Each lab can accommodate a wide variety of glassware up to 50-liter scale.

BUCHI-ROTOVAP BENCHES

Each lab is equipped with Buchi-Rotovap benches and can accommodate multiple rotovap systems. Therminol loops (-20°C) are available at each Buchi bench for more efficient use of condensers.

KEYCARD SECURITY SYSTEM

The kilo lab areas are accessed via a keycard security system.

HYDROGENATION SUITE

The hydrogenation suite contains once-through air with an appropriate level of safety to house several parr

shakers and a 20-liter medium-pressure hydrogenator (300psi).

HAZARD LAB

CML's Hazard Lab contains RC-1, DSC, and TGA for performing calorimetry studies on intermediates and final products. CML will perform hazards analysis on projects going from laboratory to plant, as well as any materials where a potential hazard exists.

DRYING AND PACKAGING SUITES

The drying suites are each HEPA-filtered once-through air, with an air lock corridor. Each accommodates a vacuum tray drying oven. The packaging suite is also once-through HEPA-filtered air, and accommodates a walk-in hood where the packaging occurs. All rooms are accessed via keycard security system.

DESIGN OF EXPERIMENTS

CML can perform process research with automated parallel experimentation, analogous to combinatorial chemistry in drug discovery. CML has the resources to incorporate design of experiments (DOE) to set up modeling. Through DOE experiments, multiple variables are changed simultaneously to find the optimum process, as opposed to the more classical approach of changing one variable at a time (OVAT) and finding the best value of one parameter before moving on to the next.



4 PROCESS R&D LABS:

- 4 walk-in hoods; 20 bench top hoods
- 250 ml to 25 Liters
(50 total reactors totaling > 500 L)

4 SCALE-UP GMP KILO LABS (CLASS 100.000):

- 30 L glass lined reactor
- 50 L glass lined reactor
- 50 L Hastelloy-C reactor
- 60 L vacuum filter (stirred)
- 20 L, 30 L, 2 x 50 L separating funnels
- 2 Hastelloy closed filters

DRYING AND STORAGE CAPABILITIES

- Drying capabilities up to kg level
in vacuum tray dryer
- GMP storage

NEW LABS COMPLETE

- 10 bench top hoods for Process
R&D in 2 separate labs
- 2 fully isolated GMP suites
 - Class 100.000 equipped with
1 bench top hood and 2 walk-in
hoods
 - 250 ml to 35 Liter scale
- Solid State Lab (see separate list)

The facility houses a complete capability for process research, development, and scale-up with a variety of benchtop and walk-in hoods to accommodate projects from gram scale up to multi-kilo production in a GMP environment. Labs are outfitted with glassware up to 80 liters, rotary evaporators, and drying capabilities up to kilogram scale.

The laboratories contain equipment capable of -100C up to 250C, as well as high pressure equipment and capabilities for high vacuum distillations. The design and layout of the laboratories ensures that projects will flow smoothly in a controlled environment from lab scale up to pilot plant. Several jacketed reactor systems mimic the plant environment, thus making process scale-up into the plant as predictable as possible.



SUITE 1 CONTAINS:

- 1 x 50 Gallon GLR (DeDeitrich)
- 1 x 100 Gallon GLR (DeDeitrich)
- 1 x 100 Gallon Stainless Steel (Apache)
- 1 x 50 Gallon Stainless Steel Receiver
- Various Stainless Steel Nutsche Filtration Units

SUITE 2 CONTAINS:

- 1 x 50 Gallon GLR (DeDeitrich)
- 1 x 100 Gallon GLR (DeDeitrich)
- 1 x 25 Gallon Stainless Steel (Apache)
- 1 x 50 Gallon Stainless Steel Receiver
- Various Stainless Steel Nutsche Filtration Units

Our facilities house 2 mini plant suites with reactors up to 100 gallons. Each suite uses ASHRAE filtered air, and is fully isolated to ensure no cross contamination during API production runs.

FILTRATION /DRYING:

Supporting each suite are a variety of enclosed stainless steel Nutsche filters, centrifuges and tray dryers which are located in HEPA-filtered drying suites.

CONTROL SYSTEMS:

Heating and chilling is accomplished via a computer-controlled series of hot, ambient, and cold loops allowing for a temperature range of -20°C to 165°C. Vacuum is controlled via the computer system using water-ring or high-vacuum Bush oil pumps. A full scrubber system is also employed. Each suite has a control room with an Allen Bradley control system with graphical user interface.



REACTOR BAY 1:

- 1 x 50 Gallon GLR (DeDeitrich)
- 1 x 100 Gallon GLR (DeDeitrich)
- 1 x 300 Gallon GLR (DeDeitrich)
- 1 x 500 Gallon GLR (DeDeitrich)
- 1 x 200 Gallon GL Receiver
- 1 x 40" Centrifuge
- Various enclosed Stainless Steel Nutsche Filtration Units

REACTOR BAY 2:

- 1 x 75 Gallon, 250 psi Hydrogenator (Apache Stainless) in Separate Building
- 1 x 500 Gallon GLR (DeDeitrich)
- 2 x 300 Gallon GLR (DeDeitrich)
- 1 x 75 Gallon Cryogenic (-90°C) Reactor (Apache Stainless)
- 2 x 100 Gallon GLR (DeDeitrich)
- 1 x 50 Gallon GLR (DeDeitrich)
- 1 x 200 Gallon GL Receiver
- Various Stainless Steel Nutsche Filtration Units
- 1 x 26" Centrifuge
- 1 x 40" Centrifuge
- 1 x 80L Agitated Cone Dryer

The Washington Drive facility houses 2 main plant bays with reactors up to 500 gallons. Each bay contains several reactors and utilizes ASHRAE 95 filtered air.

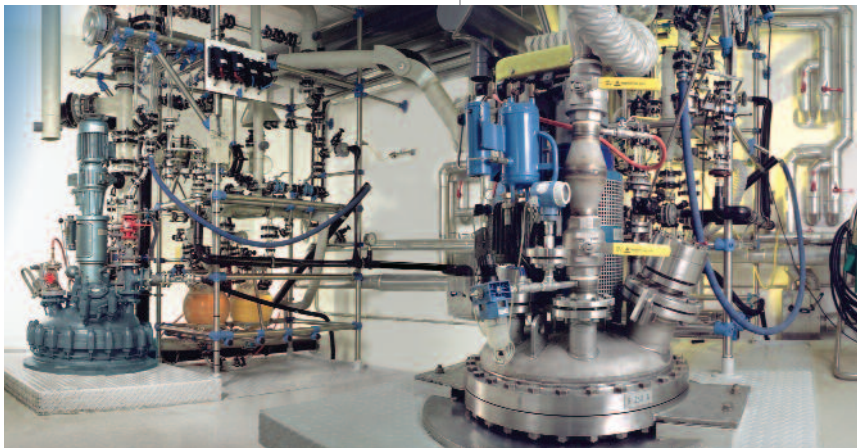
FILTRATION/DRYING:

HEPA-filtered drying rooms and accommodating tray dryers are also available to both plant bays. Filtration is accomplished using portable, enclosed Nutsche filters, centrifuges, or agitated cone dryer with continuous liner to insure containment.

CONTROL SYSTEMS:

Heating and chilling is accomplished via a computer-controlled series of hot, ambient and cold loops allowing for a temperature range of -20°C to 165°C. Vacuum is controlled via the computer system using water-ring or high-vacuum Bush oil pumps. A full scrubber system is also employed. A cryogenic reactor system is computer controlled using a liquid nitrogen loop system with control down to -80°C.

Each bay has a control room with an Allen Bradley control system with graphical user interface.

**HEATING:**

- Steam; up to 9 bar (170°C)
- Oil heating up to 300 °C

CHILLERS:

- Chillers 5°C and -25°C
- Cryogenic cooling on Hastelloy C22 350 L Reactor (-100°C)

PRESSURE:

- -1 up to 6 bar at pilot plant scale
- Pressure reactors:
2 and 4 L; 40 bar, 20 L; 10 bar,
350 L; 6 bar

Our facility houses reactors in separate suites to accommodate the most challenging projects at the multi-kilogram scale. The facility is designed with isolation and containment in mind, and we routinely provide rapid scale up from early development batches in the lab, to plant scale under GMP conditions. Our plant has been designed to maximize flexibility, not only in reactor parameters (temperature, pressure, materials of construction), but flexibility to rapidly move from project to project, thus speeding overall development time.

GMP:

- 1 x 250 L GL
- 2 X 450 L GL
- 1 x 300 L Hastelloy C22
- 1 x 1,000 L GL
- All multi-purpose reactors
- Minimum stirring volume: 10 L
- Receiver vessels: 4 x 200 L glass, 250 L GL, 100 and 200 L stainless steel

ISOLATION EQUIPMENT:

- Pressure filters; 2 x 30 L Seitz (stainless steel), 60 L (stainless steel) Seitz 100L (stainless steel) and 2 x 200 L (stainless steel and GL)
- Vacuum filters; 4 x 200 L
- Centrifuge; 5 kg and 90 kg
- Hast-C Filter/dryer; 380 liter
- Separating funnels; 4 x 200 L glass
- Rotavapors; 1 x 10 L, 3 x 20 L
1 x 50 L
- Freeze dryer; 12 L
- Wiped film evaporator (WFE)

DRYING EQUIPMENT:

- Vacuum drying chambers (kilogram quantities)
- Filter dryer (50 kg)

**SOLVENT TANK FARM:**

- 5 X 8000 Gallon Bulk Solvent Tanks
- 2 x 6000 Gallon Organic Waste Storage Tanks
- 2 x 6000 Gallon Aqueous Waste Storage Tanks

REACTOR BAY 1 – CRYOGENIC REACTIONS:

- 1 x 500 Gallon 316L SS Reaction Vessel
- 1 x 1000 Gallon 316L SS Work-up Vessel

REACTOR BAY 2 – HYDROGENATION:

- 1 x 300 Gallon 316L Hydrogenation Vessel
- Enclosed Catalyst Removal Filter
- 1 x 500 Gallon Hastelloy C-276 Multi-phase Reactor (Cryo/Hydro)

REACTOR BAY 3:

- 2 x 2000 Gallon GLS Reactor (DeDietrich Optimix)
- 1 x 1000 Gallon GLS Reactor (DeDietrich Optimix)
- 800 mm Horizontal Peeler Centrifuge (Kraus-Maffei)
- 800 liter Helix Conical Dryers (Kraus-Maffei)

REACTOR BAY 4:

- 2 x 2000 Gallon GLS Reactor (DeDietrich Optimix)
- 1 x 1000 Gallon GLS Reactor (DeDietrich Optimix)
- 800 mm Horizontal Peeler Centrifuge (Kraus-Maffei)
- 800 liter Helix Conical Dryers (Kraus-Maffei)

REACTOR BAY 5:

- 1 x 1000 Gallon GLS Reactor (DeDietrich Optimix)
- 1 x 1000 Gallon 316L SS Reactor
- 1 x 500 Gallon 316L SS Reactor
- Plate Filters
- Tray Dryer
- 0.4 M² Filter/Dryer with Glove Box

REACTOR BAY 6:

- 1 x 1000 Gallon GLS Reactor (DeDietrich Optimix)
- 1 x 1000 Gallon 316L SS Reactor
- 1 x 500 Gallon GLS Reactor (DeDietrich Optimix)
- Plate Filters

CML's Grant Drive facility is located adjacent to the existing Washington Drive development facility which provides a seamless technical transfer during scale-up of large scale manufacturing processes. The facility incorporates the latest in cGMP manufacturing design, adhering to the Q7A guidelines.

The facility is a multi-story structure which features multiple reactor bays with

separate HVAC and product isolation suites to minimize the possibility of cross-contamination. Each bay provides a different mix of vessel sizes and/or metallurgies in order to address the variety of process requirements for multi-purpose facility. The facility also houses separate bays for hydrogenation and cryogenics.

Process control is accomplished through the combination of a single fluid system (Therminol) and a PLC-based automated control system. The system not only provides control of both process and safety limits, but is also the primary means for process data acquisition. The reactors are capable of being controlled between -20°C to 160°C. The cryogenic system is capable of controlling to temperatures as low as -100°C. The vessels have high vacuum capability via Busch dry seal pumps or utility vacuum via liquid ring pumps. Process gases are vented through local scrubbers before going to the on site Thermal Oxidizer to ensure complete destruction of any hazardous or flammable vapors.

Product isolation and drying is a critical design consideration in CML's large scale API manufacturing facility. Separation trains feature identical horizontal peeler centrifuges with a direct connection to agitated Helix conical dryers, capable of extremely low vacuum and precise temperature control. CML also employs filter/dryer technology, as well as a range of pressure filters in the facility. All incoming air into the areas where final product is exposed and packaged are provided by HEPA filtered air from separate air handling systems. Product containers are then transferred to the appropriate storage rooms located nearby.



CML'S SOLID STATE CHEMISTRY SERVICES

- **Crystallization Study** – Crystallize to obtain stable solids, for purification or isolation
- **Material Characterization** – Polymorph identification
- **Solubility Determination** – In production solvents and buffer solutions
- **Salt Selection** – Suitable form selection
- **Polymorph Study** – Behavior in production solvents
- **Crystallization Process Development** – Combine optimal synthesis conditions with optimal crystallization conditions
- **Crystal Habit Optimization** – Control of particle size and shape

Cambridge Major Laboratories (CML) has established a new Center of Excellence for Crystallization and Solid State Chemistry in our Active Pharmaceutical Ingredient (API) development facilities in the Netherlands. Significant investments have been made in equipment and personnel as part of CML's expansion into solid state services.

FormSelect™

Are you approaching candidate nomination? This is a key milestone in all drug development programs, and often directly linked to your next round of funding. Many times the HCl salt, or the free form of the molecule is taken as a default into toxicology studies. After all, this was what was generated in the medicinal chemistry phase. Unfortunately, many compounds have been rejected due to suboptimal properties, whereas the choice of a different (salt) form might have improved solubility and stability considerably. Don't let your next compound get rejected in early development due to sub-optimized form.

FormSelect is the CML approach to risk-mitigation in the early development phase. Polymorphic behavior and stability of a range of free form(s) and salts are studied in parallel, maximizing your chances of success.

By using only pharmaceutically-acceptable counter ions and solvents, and applying only scalable crystallization methods, a directed experimental program will rapidly generate information to aid in the selection of a "developable" form of your API.

CML employs state-of-the-art crystallization tools and highly experienced experts in drug substance solid state chemistry to drive your program. Make the right choice with FormSelect!

ProCryst™

ProCryst is the combination of CML's leading position in PROcess chemistry with CRYSTallization science to provide our clients the most optimal solutions ranging from polymorph studies to optimizing crystallization conditions along a synthetic pathway.

How many times have you lost yields, or extended cycle times because an intermediate is difficult to filter, or product is lost to the mother liquors? In a world where development timelines are continually squeezed, there is an opportunity to optimize the drug substance development path by having the solid state chemist work in close collaboration with the process chemist at every step of the synthesis pathway. This is the essence of CML's ProCryst approach. Careful project management allows the developmental chemistry results to feed into the program, helping to direct the best choice of solvents and conditions.

EQUIPMENT:

- **Symyx Crystallization Platform** – Well-plates
- **Crystal16™ Parallel Crystallizer** – 1 ml Scale
- **Radleys Parallel Crystallizer** – 10-250 ml Scale
- **Mettler-Toledo LabMax** – 1L Scale

ANALYTICS

- **Bruker D2 XRD**
- **TGA**
- **HPLC**
- **Ion Chromatography**
- **Optical Microscopy**
- **SEM**
- **DSC**
- **FT-IR**
- **¹H-NMR**
- **KF**
- **HSGC**



MAJOR EQUIPMENT:

- GC-FID (Agilent 6890 and 7890) with Headspace/Liquid Injection Capabilities
- GC-MS
- HPLC (UV, Diode, CAD, RI)
- LC-MS
- FT-IR
- NMR (300 MHz)
- UV/Vis
- KF (volumetric and coulometric)
- Melting Point
- DSC-TGA
- ICP-OES
- Particle Sizer (Malvern Mastersizer)

The facilities house state-of-the-art analytical laboratory and controlled environmental chambers to support ICH stability studies. Cambridge Major provides analytical support for in-process controls, quality control release testing, reference standard qualification, and method development/validation in compliance with FDA cGMP requirements and ICH guidelines.

CML performs most compendial testing according to USP/NF, EP, BP, JP, and ACS monographs. This can be for raw materials, intermediates, or API release testing.

Our method development and validation services includes:

- Stability Indicating Methods
- Organic Volatiles Impurities
- Cleaning Validation/Verification method (specific and non-specific)
- In-Process Controls
- Forced Degradation and Impurity Identification

CML also offers comprehensive stability storage & testing by ICH guidelines. This includes ambient, intermediate, and accelerated conditions.





The Weert facility houses fully equipped analytical laboratories to support in-process controls, QC release testing, reference standard qualifications, and method development/validation in compliance with GMP requirements and ICH guidelines.

METHOD DEVELOPMENT AND VALIDATION SERVICES INCLUDE:

- **Stability indicating methods**
- **Residual solvents**
- **Cleaning validation**
- **In-process controls**
- **Forced degradation and impurity identification**

Comprehensive stability storage and testing services are also offered under ICH guidelines. This includes the following stability conditions $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \text{ RH} \pm 5\% \text{ RH}$, $30^{\circ}\text{C} \pm 2^{\circ}\text{C}/65\% \text{ RH} \pm 5\% \text{ RH}$ and $40^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\% \text{ RH} \pm 5\% \text{ RH}$.

Also, custom stability conditions are available.



ANALYTICAL EQUIPMENT:

- **HPLC systems equipped with UV, DAD, RID, ELSD & MS detection**
- **1 x U-HPLC**
- **LC-MSD**
- **Gas chromatographs with FID detectors**
- **GC-headspace**
- **GC-MS (EI/CI)**
- **UV/VIS spectrometer**
- **Titration equipment**
- **Halogen moisture analyser**
- **Differential Scanning Calorimeter**
- **Ash oven + incubator oven**
- **FT-IR**
- **Polarimeter**
- **Particle size counter**
- **Air monitoring equipment (microbial)**
- **4 x Climatic testing chambers**
- **Ion chromatography**
- **Karl Fischer equipment**
- **Stability storage: $-20^{\circ}\text{C} \pm 5^{\circ}\text{C}$, 5°C , $\pm 3^{\circ}\text{C}$,**
- **TGA**
- **XRPD**