



## Quality control and quality assurance

- Test and Release all raw materials, starting materials, product contact materials, intermediates and finished products in support of full cGMP operations
- Review and Approval of all quality documents in support of full cGMP operations (including but not limited to Specifications, Change Control Requests, Master Production Instructions, Standard Operating Procedures etc)
- Maintain internal instrument calibration program
- Qualified ICP-OES instrument that allows for ICP in-house testing for R & D process support and cGMP batch in-process check and product release testing
- Perform annual product quality reviews

## Regulatory support

- Provide support for IND, NDA, MAA submissions
- Preparation of DMF
- Preparation of annual product reviews for commercial products

## Regulatory history

Year	Regulatory agency	Audited for	Out come	No. of 483
1996	US-FDA	NDA	Drug approved	11
1998	US-FDA	NDA	Drug approved	1
2001	US-FDA	NDA	Drug approved	2
2004	Korean-FDA	NDA	Drug approved	None
2005	US-FDA	NDA	Drug approved	None

# Clinical phase API development and manufacturing – Canada

## Chemistry capabilities

- Suzuki and Buchwald/Hartwig coupling reactions, Sonogahira reaction and other coupling reactions catalyzed by metals – have in-house ICP to monitor metal removal
- Low temperature reactions (~ -65°C) and high temperature reactions (200°C)
- Hydrogenation/hydrogenolysis of Nitro group, double bond and CBZ group
- Horner-Wittig reaction
- Solid supported metal sequestering agents
- Reduction with reactive reagents (LAH, Alane, Dip-Cl, metal borohydride, borohydride exchange resin, borane, Zinc)
- Mitsunobu reaction
- CATHy reaction
- High temperature decarboxylation
- Enzymatic reaction (e.g. hydrolysis)
- Sulfur ylide chemistry
- Grignard reaction
- Bromination/ radical bromination

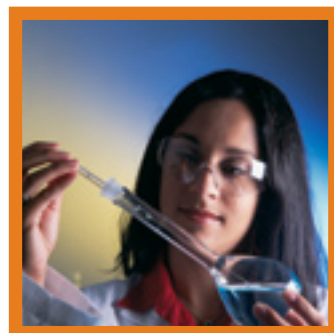
## Analytical services

### Method development, validation and transfer

- Analytical support for drug development, pre-clinical, clinical and commercial manufacturing
- Develop analytical methods for testing raw materials, IPCs, intermediates, active pharmaceutical ingredients (API) and drug products
- Develop stability indicating methods
- Validate analytical methods in accordance with FDA and ICH guidelines
- Provide validation protocols and comprehensive reports
- Transfer methods formally to external laboratories at client's request
- Analytical support for cleaning verification and validation

### Stability studies

- Conduct stability studies on advanced intermediates, APIs and, in certain instances, formulated drug products
- Protocol design in adherence with ICH guidelines: long term, intermediate and accelerated conditions
- Store samples in fully mapped, qualified and monitored stability chambers: 25°C/60% R.H., 30°C/65% R.H., 40°C/75% R.H.; refrigerator: 4°C, freezers: -20°C & -80°C
- Data evaluation and summary reporting at each time point
- Recommended storage/packaging conditions re-test and expiry periods



## Analytical services (continued)

### Photostability studies

- Conduct photostability studies on APIs and drug products
- Performed in adherence with ICH Q2B, option 2
- Issue photostability protocols and final reports summarizing observed light degradation

### Impurity identification and structure elucidation

- Identify unknown impurities/ degradants in intermediates and APIs
- Use of various techniques, such as LC/MS, GC/MS, NMR

## Analytical capabilities

### High Performance Liquid Chromatography (HPLC) Analysis

- Reverse phase chromatography
  - Related substances
  - Assay
- Normal phase chromatography
  - Chiral chromatographic separations
- Various Detection Capabilities
  - PDA
  - Fluorescence
  - Evaporative light scattering

### Spectroscopy

- LC/MS (TOF)
- GC/MS
- 400 MHz NMR
- React – IR

### Gas chromatography (GC) analysis

- Direct Inject GC
- Headspace GC
  - Organic volatile impurities determination

### Trace metals

- Inductively Coupled Plasma (ICP/AES)

### Analytical testing, API characterization and standard qualification

- Fully characterize APIs
- Qualify APIs, intermediates and impurity reference standards
- Carry out wet chemistry and compendial testing
- Offer full range of analytical testing techniques and instrumentation
- cGMP compliant analytical laboratories

### Capillary electrophoresis

- Anion and cation determination
- Amino acids analysis
- Chiral chromatographic separation

### Ion chromatography

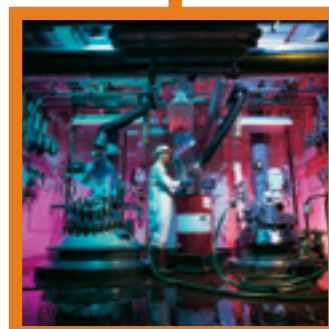
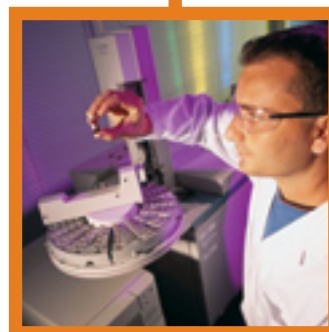
- Anion and cation determination

### Wet chemistry and compendial testing (USP/NF and EP monographs)

- Titrations
  - Aqueous acidimetric and alkalimetric
  - Non-aqueous acidimetric and alkalimetric
  - Halide determinations (i.e. chloride and bromide)
  - Water content (volumetric and coulometric)
- Heavy metals, Loss on Drying, Residue on Ignition, pH, FTIR, UV/Vis, Differential Scanning Calorimetry, Optical Rotation

### Auxillary instruments

- FBRM Lasentec probe
- Laboratory Automation Station MMART 1200 (Mettler Toledo)



## Production equipment

### R & D scale-up laboratory

#### Reactors

- 50 L H S Martin; 1 x 15 L HS Martin; 1 x 25 L
- Glass-lined steel – 1 X 50 L Buchi
- HS Martin 25 liter agitated glass receiver system (jacketed for cold temperatures)
- Ednecotts Fluid Bed Dryer (1 Kg Capacity)
- Buchi Rotary Evaporatory System (10 to 20 Litres; ca. 5 Kg capacity)
- R&D Scale-Up Vacuum Oven, 0.75 cubic ft
- Aurora filters: Stainless steel/Halar Coated – 2 X 14 inch (round filters), 1 X 26 inch (stainless steel)
- Nitrogen heater assembly (for accelerated drying on Pilot Robot Filter)

### Pilot plant

#### Reactors

- Stainless steel (5) – 200, 800, 1200, 2 X 2000 L
- Glass-lined steel (9) – 2 X 200, 235, 2 X 450, 2 X 1500, 2 X 2000 L

### Kilo laboratory

- cGMP Preparative HPLC – 20.0 cm ID X 50.0 cm length
- Rotovap – Glass 20 L Buchi (Continuous Operation)

### Reactors

- Glass – 1 X 50 L H S Martin – 3 X 80 L Buchi
- Glass-lined steel – 3 X 50 L Buchi
- Hastelloy – 1 X 50 L Buchi

### Small scale manufacturing capabilities

- Full cGMP lab with vacuum dryer and rotovaps
- Capability up to 5 L flasks

### Hydrogenation unit

#### Reactors

- Glass-lined steel (2) – 200 L (150 psi), 800 L (100 psi)

### Temperature capability

#### Pilot Plant

- Hot and refrigerated Dowtherm loops: 30°C to 180°C
- Cryogenic cooling (two reactors): down to 75°C
- Supra heating (two reactors): up to 230°C

#### Kilo lab

- Independent cooling and heating units: - 50°C to 150°C

### Filters

- Aurora filters: Stainless steel/Halar Coated – 3 X 48 inch, 3 X 26 inch, 3 X 14 inch, Stainless steel – 1 X 48 inch
- Geudu ML500 Hastelloy filter/dryer

### Dryers/solid handling

- Hastelloy Agitated Pan Dryer, 300 to 1300 L and temperature range of 15°C to 90°C
- Kilo-laboratory Vacuum Oven, 0.75 cubic ft
- Vacuum Tray Dryer (2) composed of stainless steel with 150 L capacity and temperature range of 15°C to 90°C
- Quadro CoMill 197S grinding machine with capacity of 45 to 450 kg/hr
- Orbital Micron-Master Jet Pulverizer with 25/kg/hr capacity
- Mixomat product blender with 50 to 200 kg capacity

