



# High Energy Capabilities

## WORLD-CLASS EXPERTISE IN ENERGETIC CHEMISTRY COMBINED WITH HIGH QUALITY cGMP CAPABILITIES

Cambrex's expertise in high-energy compounds and hazardous materials dates back to the work of Alfred Nobel founding the site in Karlskoga, Sweden in 1896. Our continuous application of highly energetic processes and dedication to quality has laid a solid foundation for our cGMP compliant energetic capabilities.



## INNOVATION

### Remote Controlled cGMP Manufacturing Facility

We utilize a specialized bunkered high energy manufacturing facility built for handling substances with explosive properties.

The facility is cGMP compliant for the production of Active Pharmaceutical Ingredients (APIs) and well-suited for the development and manufacturing of thermally unstable products. To ensure the protection of our personnel, the processes are monitored and safely controlled from a control room situated 50 meters from the plant.



## EXPERIENCE

### Providing Confidence Through Process Safety Management

Our cross-functional process hazard analysis and safety management plan encompasses a methodical and comprehensive review during each step in a synthetic route. Cambrex integrates safety solutions into the cGMP development and manufacture of all drug substances and advanced intermediates made via high energy reactions.

We have extensive experience developing and managing high energy processes that supply key products to many world-leading pharmaceutical companies.

## PERFORMANCE

### Ensuring Safety Through Rigorous Testing

Using state-of-the art process safety analysis techniques, our process safety testing laboratory employs a powerful range of instrumentation. We gather real-time data on hazard potentials for chemical substances and reaction mixtures.

This allows us to perform every step from concept studies through to cGMP manufacturing in a safe and reliable manner.



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## HIGH ENERGY EXPERTISE

### High Energy Compounds

Chemical compounds with energy of decomposition of more than 1500 J/g are considered high energy compounds.

- High-energy APIs
- High-energy intermediates
- Low thermal stability intermediates

### High Energy Reactions

Chemical reactions giving an adiabatic temperature rise of more than 200°C.

- Nitration with nitric acid
- Catalytic hydrogenations
- Oxidation with nitric acid
- Oxidation with hydrogen peroxide
- Diazotization with sodium nitrite
- Grignard - formation and reaction
- Organic azide formation with  $\text{NaN}_3$
- Reduction with  $\text{LiAlH}_4$
- Lithiation with  $\text{BuLi}/\text{HexLi}$
- Sodium hydride as reagent
- Hydroxylamine-HCl as reagent
- Isoxazoles/Oxazoles – manufacture

## HIGH ENERGY EXPERTISE

We offer an integrated safety solution for the cGMP development and manufacture of drug substances and organic intermediates made through high energy reactions. Cambrex can provide thermal or process safety studies to support manufacturing at our facilities or on a consultant basis.

## PROCESS SAFETY TESTING TECHNIQUES

### Differential Scanning Calorimetry (DSC)

DSC is employed as a screening tool to determine the thermal properties of raw materials, reaction mixtures, distillation residues, intermediates and products.

### C80 Calorimetry

As a complement to DSC data, the C80 calorimeter measures pressure release and provides more accurate thermal safety data. This data ensures proper equipment selection through calculation of vent and vessel sizes, as well as cooling capacity requirements.

### Reaction Calorimetry (Chemical Process Analyzer/CPA)

When developing safe process parameters, high energy reactions are studied in the CPA. Collected data are used to calculate reaction enthalpy, accumulation, adiabatic temperature rise and cooling requirements. These essential data elements are implemented in thermal hazard safety review for high energy process scale-up.

### Micro Calorimetry

Micro calorimetry is used to assess the long-term thermal stability of compounds. We use this data to assess safe storage conditions, which in turn provides effective management of intermediates and products that must be stored for long periods of time.

### Additional techniques available on site

To ensure safe handling and transportation of high-energy substances, explosive properties are further investigated using techniques that include the Koenen test, BAM Fall-hammer and BAM Friction Apparatus. These techniques provide data that determine the sensitivity and explosive properties of compounds.

## MANUFACTURING CAPABILITIES

## CAMBREX KARLSKOGA

## CAMBREX CHARLES CITY

Nitration with Nitric Acid	1000 - 3000 L	8000 L
Catalytic Hydrogenation	1000 - 3000 L	1000 - 4000 L
Oxidation with Nitric Acid	Continuous Process Full Scale	
Oxidation with Hydrogen Peroxide	2000 L	4000 L
Diazotization with Sodium Nitrite	4000 L	4000 L
Grignard - Formation and Reaction	500 - 4000 L	400 - 1000 L
Organic Azide Formation with Sodium Azide	1000 L	
Reduction with $\text{LiAlH}_4$	500 - 6000 L	
Lithiation with $\text{BuLi}/\text{HexLi}$	500 - 1000 L	
Sodium Hydroxide as Reagent	500 - 2000 L	400 - 1000 L
Hydroxylamine - HCl as Reagent	500 - 1000 L	
High Energy Compounds	500 - 6000 L	
High Energy Intermediates	500 - 6000 L	
Low Thermal Stability Intermediates	500 - 4000 L	400 - 1000 L
Hazardous/Toxic Chemicals	500 - 2000 L	400 - 8000 L