

# Cryogenics in Newburyport?

## It's not what they think

By Ed Price, President, [PCI Synthesis](#)

Whenever we bring up the topic of cryogenics, we get a few quizzical looks from those who are not familiar with its role in the drug development business. This may be especially true due to the close proximity of our API manufacturing plant to Salem, MA – known as Witch City. We are in the same county as this Halloween capital, and that undoubtedly brings to mind some ghoulish thoughts. But I assure you, nothing eerie is going on in our Newburyport plant, where we develop and manufacture the Active Pharmaceutical Ingredients (APIs) that are at the core of new therapeutic drugs.

No, we are not freezing people to preserve them for some future life, the most common association non-scientists have with the use of extreme cold. That is actually cryonics, not cryogenics.

According to the U.S. [National Institute of Standards and Technology](#) the term cryogenics generally refers to temperatures below approximately  $-150^{\circ}\text{C}$  ( $-238^{\circ}\text{F}$ ). However, In API manufacturing, temperatures of approximately  $-80^{\circ}\text{C}$  are sufficiently cold for most cGMP manufacturing requirements. At PCI Synthesis, we use cryogenic conditions to facilitate specific chemical transformations that require very cold conditions.

This article will expand on mentions in our articles of the broad [range of temperature conditions](#) required for drug development, from high temperatures used in [API purification methods](#) to the coldest discussed below. As well, in our series on how to choose a CMO suggest seeking out those synthesizers who can reliably deliver the wide range of controlled temperatures that may be required to manufacture New Chemical Entities (NCEs).

## Well beyond refrigeration – cryogenic cold

The ability to keep things cold is one of the transformational factors that has enabled us to live life as we know it in the modern era.

We routinely transport food from one part of the country to another in refrigerated trucks to keep it fresh. We keep ice cream in our home freezers. In medicine, we chill some critically ill people in hospitals, lowering their body temperatures and maintaining it a few degrees colder than normal in a process called therapeutic hypothermia. It helps preserve neurologic function.

But there's also a need for extreme cold, or cryogenic conditions. Cryogenics is used for preservation of some biological materials such as livestock semen, human tissue and blood. It is also used in cryosurgery, the freezing of portions of the body to destroy unwanted or malfunctioning tissue. Cryosurgery is used to treat cancers and abnormalities of the skin, cervix, uterus, prostate gland, and liver.

And cryogenics is also used in API manufacturing. Running certain processes under extremely cold temperatures—much colder than standard freezing—can be useful in for certain molecular transformations.

Cryogenic conditions can:

- Limit impurities
- Process highly reactive compounds such as organolithium reagents
- Improve reaction selectivity
- Eliminate or reduce unwanted side reactions
- Limit volatility of compounds for greater safety until conversion is completed
- Prevent ice crystals from forming

Once the desired molecule is formed using one of our jacketed cryogenic reactors, such cold conditions may no longer be required and development and/or manufacturing proceeds under normal conditions for that particular drug substance.

## Cryogenics is a specialized service

Contract Manufacturing Organizations (CMOs) have cryogenic capabilities or know-how.

Running processes under such cold conditions is as much an art as a science. These reactions are very touchy, very sensitive. They have to be run very specifically, which involves controlling an entire system of pumps and heat exchangers to reach, maintain and control the temperature as the reaction progresses.

Specialized measurement tools are required as well. **Measuring cryogenic temperatures** cannot be done with normal mercury or alcohol thermometers. They freeze and become useless at such low temperatures. Cold temperatures to approximately  $-252^{\circ}\text{C}$  ( $-423^{\circ}\text{F}$ ) are measured with a platinum resistance thermometer, which has a well-defined behavior of electrical resistance versus temperature and is considered to measure temperatures accurately.

## Cryogenic capabilities at PCI Synthesis

PCI Synthesis is equipped to run low temperature chemical reaction at research, development, pilot, and commercial scale (4,000 Liter). All of our equipment is ready to carry out reactions to as low as  $-80^{\circ}\text{C}$ . This expertise, along with the proper equipment, enables us to easily perform and scale-up the following reactions that are most often done under low temperature conditions:

- Halogen-metal exchange (e.g. Li)
- Li, Na metal reductions
- Selective deprotonation and subsequent stereoselective, regioselective and chemoselective reactions
- Stereoselective, regioselective and chemoselective reductions of ketones, Imines and Esters
- Asymmetric reactions such as Michael additions
- Selective Friedel-Crafts Acylation (e.g. with Oxalyl Chloride)
- Low temperature Swern Oxidations



We will write more about cryogenics in the near future. If you have questions in the meantime, please call us at (978) 462-5555.