Safe Outsourcing of Energetic Chemistry

a report by

Roland Ohlsson *and* **Ann Gidner**

Specialist in safety handling at the Cambrex Karlskoga site, and Director of Commercial Development at Cambrex Pharma & Biopharmaceuticals

Roland Ohlsson

Ann Gidner

Roland Ohlsson joined Cambrex in 1984. He has several years of pharmaceutical manufacturing experience and has been responsible for thermal and chemical reactions hazards since 1998 .

Ann Gidner is Director of Commercial Development at Cambrex Pharma & Biopharmaceuticals, and part of her work is leading a High Energy initiative for the company. Ms Gidner joined Cambrex corporation in 1994 and has served in operations roles as well as in commercial roles, going from plant management to new products management, marketing and commercial development.

How important is it to avoid energetic materials or highly exothermic reactions in pharmaceutical development? Is it necessary to replace the convenient azide or nitration steps utilised at the laboratory scale? While the answer to these questions may seem obvious, one would be alarmed to know how many companies routinely ignore development and manufacturing steps that ensure the safety of their employees and the environment. This is why it is vital to secure a dedicated outsourcing partner with experience in high energy chemistry and the proper equipment and safety procedures in place. For example, in many cases, direct routes utilising energetic chemistry are replaced with longer synthetic routes, when a more efficient and safer energetic chemistry could have been applied. Staying with an energetic route requires an appreciation for the risks and consequences involved and the average pharmaceutical company might be well advised to avoid such transformations.

The area of energetic chemistry, or high energy chemistry, can be separated into two segments. One is the handling of energetic chemical compounds – starting materials, intermediates and/or final products. At Cambrex, this segment is defined as all compounds with an energy of decomposition of more than 1,500J/g. The second segment is the performance of highly exothermic reactions. At Cambrex this is considered to be any chemical reaction giving rise to an adiabatic temperature rise of more than 200ºC.

A number of well-known compounds and reactions are contained in the energetic chemistry area such as:

- nitrations;
- most catalytic hydrogenations;
- oxidation with nitric acid or hydrogen peroxide;
- diazotisations;
- grignard reactions;
- azide reactions;
- metal complex reductions;
- hydride reactions;
- hydroxylamine reactions; and
- a number of other intermediates of low thermal stability.

Any handling of these reactions or compounds requires a serious approach using integrated safety processes, whatever the phase of product development or manufacturing.

Integrated Safety in Every Step

More than a century ago, Alfred Nobel worked at what is now the Cambrex site in Karlskoga. His legacy and revolutionary accomplishments in the area of making nitroglycerine safer to handle have had a profound impact on how we view process safety at Cambrex.

The driving forces towards safer chemistry were the properties of nitroglycerine and its high sensitivity to mechanical impact as well as its rapid transition from a liquid to huge volumes of gaseous components when decomposing. The volume of expansion, while useful for demotion or weaponry, proves devastating while manufacturing the material for drug development. Over the years, several manufacturers of nitroglycerine experienced tragic accidents with complete destruction of plants and loss of life. Once an accident of this magnitude occurs, it becomes a sobering lesson in ensuring every precaution is taken to avoid another catastrophe. Today, passive or physical safety measures like bunkering the plant and remote control are taken for granted in the manufacturing of explosives.

Cambrex Karlskoga is a spin-off company from the civil applications of explosive technologies and has been producing active pharmaceutical ingredients since the 1940s. Originally the manufacturing was based on the use of nitric acid for nitration reactions and later oxidations were added to its capabilities. These were hazardous and energetic reactions that were done concurrently with other difficult processes such as diazotisations, azide chemistry and organic peroxides.

Today, Cambrex has a comprehensive safety programme that is implemented in every step from the evaluation of a customer request to manufacturing at commercial scale. Over the years, considerable efforts have been undertaken to foresee and hopefully minimise the consequences of a chemical runaway reaction or a thermal decomposition. This is a vital and daily task for chemists, process engineers and operators at the Karlskoga site.

Energetic processes can be dealt with providing reaction heat and the mechanism of decomposition are well explored. In fact, the hazard caused by a given heat release rate will depend more on its environment than on its magnitude. A very slow heat release rate may cause trouble if it occurs under heat accumulation. On the other hand, a highly exothermal reaction – even some decompositions – can be handled safely with the appropriate cooling capacity. Among other safety principles, Cambrex believes the semi-batch mode principle is the most important. For example, one reactant is added over time with a rate and at a temperature level that minimises the heat accumulation. The outputs from practical safety testing are crucial input data for dealing with thermal and chemical reactivity hazards. For almost 15 years Cambrex has conducted extensive in-house testing fortifying its experience in the behaviour of chemical reactions and providing it with a useful source of thermal data.

Safety Testing

For several years now differential scanning calorimetry (DSC) has been used as a screening instrument to identify thermal hazards of substances, such as exothermic decompositions. Every new raw material, reaction mixture, distillation residue, intermediate and product is tested. A reaction calorimeter is mainly used for studies of the desired reaction, but can also be useful for thermal stability tests for in-house testing. When applicable, adiabatic calorimetry and micro calorimetry for substances and mixtures are added to the testing programme when scaling up to full scale. For substances with functional groups in the molecule that confer high energy and instability (nitro, azide, diazo, peroxide, etc), and require extra attention and complementary testing for their explosive properties (friction, mechanical impact and thermal shock) is always conducted.

The data are evaluated and safety limits are identified in safety review meetings and measures are employed prior to pilot and full-scale operation.

For the most energetic processes, Cambrex uses a special facility, which is a bunkered plant with remote control, where pharmaceutical ingredients can be produced safely and under current good manufacturing practice (cGMP) conditions.

Case Study – Safe Containment

There are several cases in custom development work where Cambrex has identified hazardous exothermic decompositions, and thereafter found and defined appropriate safety limits for temperature levels throughout the process.

One example is a reaction mixture after formation of a diazonium salt (treatment with sodium nitrite), where the onset for decomposition was detected with DSC at 70°C, which is when decomposing nitrogen is formed at a rate that would blast a reactor with conventional sizing of pressure release system (rupture disc). By further extensive isothermal and adiabatic testing with a reaction calorimeter, an autocatalytic behaviour was defined and the maximum allowable reaction temperature set to 20°C for maximum 24 hours.

Another example is the storage of an azide-intermediate. The intermediate was tested by DSC and showed a highly exothermic decomposition with an autocatalytic profile at 125°C. No risks were detected while processing. However, there was still a major concern about storing the intermediate due to the autocatalytic profile. A complementary study with a micro calorimeter was carried out in order to provide safer conditions for its storage. With the high sensitivity calorimeter the detection of heat flow rates can be used to simulate storage up two years at specific temperatures. It was found that only wet (water) material in maximum 50l packings and for a maximum of four months would be appropriate.

Case Study – Route Modification

Sometimes minor changes within the synthetic route may dramatically enhance safety. In several cases, sodium azide is used as a strategic reagent in the development of new pharmaceutical ingredients, but its use involves the risk of formation of the toxic and explosive hydrazoic acid. In an acidic environment excess of sodium azide will form hydrazoic acid and, because the component boils at a low temperature (37°C), it will easily boil off and condensate at high concentrations in the overhead equipment of a batch reactor. The hydrazoic acid decomposes violently at low temperature and even at mechanical impact, which are properties that constitute a substantial risk. Ideally, one would avoid the formation of hydrazoic acid to begin with. This can be done by precipitating the product as a sodium salt under basic conditions with sodium hydroxide, which keeps the excess of sodium azide dissolved in the mother liquid. After separation of the mother liquid the excess can later be taken care of by treatment with a mixture of sodium nitrite and nitric acid and thereby transformed into harmless nitrogen.

Another example of route modification is a nitration reaction with fuming nitric acid. Originally the method was outlined with an addition of the substrate as a solid to 20 equivalents of nitric acid. The following reaction mixture was tested with DSC and showed a high heat evolution (2,8MJ/kg) at 110°C, which would follow with a huge release of toxic gaseous nitrogen oxides. After modification of the method including several runs with reaction calorimeter into an addition of 1.1 equivalents of nitric acid to the substrate dissolved in acetic acid and sulfuric acid, the resulting reaction mixture only showed a heat evolution of 0.2 MJ/kg at 115°C. This modification improved safety substantially.

Energetic chemistries can be safely performed on a large scale with the correct approach and an experienced team of experts utilising the appropriate equipment and safety procedures. In many cases an energetic route is more economical with a high product purity and a shorter reaction path, and the high energy expertise is of great value. However, a serious outsourcing partner should also explore and demonstrate whether an alternative, more conservative chemistry can be applied without increasing costs or losses in yield and or quality, in order to always offer client services in the safest and most economic way possible. ■