

# Explosivity: An unusual challenge in drug development

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## INTRODUCTION

There remains an urgent global need for new drugs to combat diseases such as malaria, tuberculosis and cancer, as well as overcoming increasing antibiotic resistance. Chemists are moving into 'new chemical space' for drug design (1,2) and with this comes the possibility of traditional (and stable) 'carbon-carbon' bond structures being replaced by more 'exotic' bonding arrangements. While the implication of this on pharmaceutical stability can often be mitigated by suitable formulation and storage strategies, we came across an unusual case of chemical stability: the possibility that the drug was an explosive! By pushing drug designing into uncharted chemical space it could be argued that the possibility of finding explosive molecules of pharmaceutical interest will increase.

In this short paper we discuss the implications of a molecule found to require formal explosivity testing and the impact on the development of a clinical product.

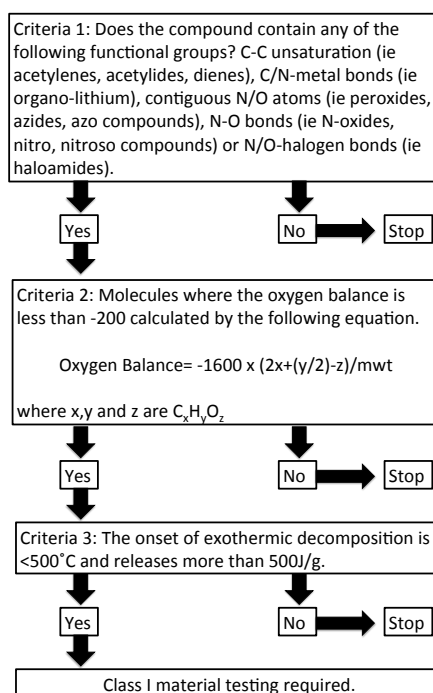
## EXPLOSIVITY TESTING

Formal explosivity testing can take a variety of forms. The UN guidance document (3) contains a wide array of tests and equipment that can be used to determine explosive testing. Additionally, negative and positive outcomes to the various tests move the testing onto other procedures. There is an initial series of tests (Test Series 1 to 4) which would apply to materials meeting Criteria 1 to 3 above which may determine material as Class I. This may be followed by a further series of tests which may classify the material into subgroups (division Group 1.1 to 1.6). These tests determine the ability of the material to be handled and transported. The tests generally use quantities of powder in the range of tens to hundreds of grams, and so are considerable undertakings for an early phase clinical development program.

## CASE STUDY

The authors routinely develop novel drug candidates for early phases clinical trial, and as part of that role received a novel di-N-oxide drug compound for scale up synthesis (Onyx Scientific) and drug product production.

### Flowchart to determine if formal explosivity testing might be required.



## MITIGATING RISK IN DRUG DESIGN

The identification of relevant groups using the flow chart above can easily be performed at the drug design stage, before any material is synthesised. Materials that match the criteria could be synthesised and then assessed by differential scanning calorimetry (which would only require a few milligrams).

Rather than the formal explosivity testing it would be highly desirable, in light of the new chemical bonding arrangements that may appear in the future, to determine a set of small scale tests (milligram to gram) which could establish the risk presented by a potentially 'explosive' new chemical entity. This could be used during early clinical development, leaving formal and costly UN Test Series experiments until the larger scale production required for later clinical stages.

## References

- [1] Reymond, J., Awale, M., Exploring Chemical Space for Drug Discovery Using the Chemical Universe Database, ACS Chem. Neurosci., 3, 649-657 (2012).
- [2] Reymond, J., The Chemical Space Project, ACS Chem. Res., 48, 722-730 (2015)
- [3] UN Secretariat. Recommendations on the Transport of Dangerous Goods Manual of Tests and Criteria, 5th revised edition.

## CASE STUDY (cont'd)

Routine physico-chemical characterisation showed no usual features. However, upon review it was discovered that the 'sharp melting point' - which would normally indicate high purity material - was incorrectly assigned to an endothermic event, and that the material demonstrated a strongly exothermic event! Occurring at 190°C, the energy values indicated that the compound released up to 1000 J/g (which compared to gunpowder and TNT at 3000 and 4000 J/g, respectively). Further study showed that the compound matched the three criteria specified above and was considered for explosivity testing through the Test Series specified in reference 3.

Several challenges immediately presented themselves: understanding the Test Series and finding a commercial provider who could both conduct the tests and was able to handle a pharmaceutically active anti-cancer compound; scaling up the API production so that enough material was available to conduct the Test Series; handling the tens of grams onsite at the formulation production facility uncertain about the explosive potential of the material; and finally the implication of project timelines.

It took several weeks to find a facility that could both handle the material and conduct the testing. Initial tests on the 'tens grams' indicated that the material should be processed through a formal Test Series 1 requiring 200-250 grams of material costing in excess of £72,000, before showing that the novel drug was not explosive and could be handled as a normal drug substance. The time between observing the strong exothermic decomposition and obtaining the final result was over a year. While this did not stall the project, all further development, scale up and production work needed additional considerations to allow for the uncertainties over the explosivity issue.

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