Screening Protocol to Identify Potentially Explosive Compounds in Early Stage Development

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Introduction

Route development to a new active pharmaceutical molecule goes through various stages in its life cycle from small scale laboratory work through to full scale plant manufacture. During this process the chemical route may change significantly and proceed through differing intermediate stages, each stage and scale having its own unique inherent hazards and potential risks. The ideal approach to process safety is to remove hazards completely if practical to do so. If this cannot be done then mitigation is required by other means to achieve safety. For this approach to be most effective, it is important that the hazard assessment of the process commences at an early stage of development.

There is no standard procedure that can be followed for all reactions and the scenario of assessing each new process with the same thoroughness independent of the scale or point in the lifecycle is not practicable in a research environment. Increased pressures to compress timelines without using additional resources and the speed of development are always going to be a major factor in commercial success. However, safety must not be compromised and the old adage still holds that if a process cannot be carried out safely then it should not be carried out at all. The aim therefore is to obtain sufficient data, in an efficient manner, so that the risk can be assessed adequately and this then has the benefit of giving time to adopt inherent safety approaches to potential issues. The depth of a chemical hazard assessment should reflect the complexity of the reaction, the size of the risks involved and the scale of operation.

On the laboratory scale containment can be used as the basis of safety, i.e. operations are on sufficiently small scale that any uncontrolled exotherms or gas evolution will be contained in the fume cupboard. The caveat for this is that there are no explosives, used generated or isolated during the process. Even a small amount of explosive material poses a significant hazard, and these have been summarised in literature as follows.[1]

- 1g Serious injury to a person holding the material
- 10g Very serious injury to a person close to the explosive
- 100g Almost certain death of persons in very close proximity (e.g. holding the material)

Potential initiation of an explosion from such a material in the laboratory environment can include mechanical forces, (friction, impact), heating (e.g. during isolation), EMR (e.g. light, microwave), etc. For materials that contain ‘explosible’ functional groups, it is not readily possible to predict with certainty whether a material will ultimately be classifiable as an explosive (Class 1[2]) without experimental testing. A specific assessing potential explosive material is presented within the UN Model Regulations.[3] Such testing can require significant quantity of material and it is therefore necessary to be able to identify and safely process potential explosives at the laboratory scale and if necessary to allow sufficient quantities to be produced for UN explosivity testing purposes if manufacturing at scale is proposed. This paper outlines the philosophy and procedures that AstraZeneca use internally to address the issue of screening for explosive material and outlines guidance for reducing risk during usage and handling explosive and potentially explosive compounds.

Identification of Potential Explosives

Prior to carrying out laboratory experiments all reagents should undergo appropriate safety assessment, including physicochemical and toxicological hazards, and part of this initial screening should include identification of ‘explosible’ functional groups which could impart explosive properties.[2,4] If any explosophoric group is flagged by this initial screen then under normal good laboratory practices the scientist will initiate a dialogue with the process safety department to seek advice and guidance on the safe usage and handling best practice and initiate a testing regime if appropriate. Table 1 gives a list of these potentially explosive functionalities:

Compounds Containing Carbon (not N, O)
Acetylenes, Acetylides , Halo-arylmetals, Haloarenemetal π complexes
Compounds Containing Carbon and Nitrogen (not O)
Azides, Diazo substances, Diazonium, N-Haloamines, N-Metal derivatives (heavy metals), N-Halo containing/ Difluoroamino containing molecules, N-Sulphur compounds, Poly(dimercuryimmonium salts), Triazenes alphaticaliphatic/cyclic, Tetrazoles aliphatic /cyclic.
Compounds Containing Carbon and Oxygen (not N)
Chlorates, 1,2 Epoxides, Hydroperoxides, Hypohalites, Iodosyl compounds, Ozonides, Peracids, Perchlorates, Peroxides, peroxyesters, metal peroxides, Xenon-oxide containing molecules.
Compounds Containing Carbon, Nitrogen and Oxygen
Fulminates, Metal fulminates, Hydroxylamine salt, Nitrates, Nitrites, N-oxides, Nitro substances, Nitroso substances, Oximes, Perchlorylamide salts, N-Sulphur-O compounds.

Table 1 – Examples of Explosible Functional Groups (Explosophores).

In addition, there are energetic functional groups which do not in themselves impart explosive properties but in combination with an 'explosible' group can increase the probability of the material being an explosive. A list of such groups is given in Table 2.

Strained rings	Epoxides, Aziridines, Azetidines and certain highly unsaturated penta-rings…
Isocyanates, isothiocyanates	(-N=C=O), (-N=C=S)
Sulfoxides	(>S=O)
Sulfonyl Chlorides	($-SO_2Cl$)
Acid chlorides and chloroformates	(-COCl), (-O-COCl)
Hydrazides (and sulfonyl hydrazides)	(-NH-NH-)
a-b Unsaturated aldehydes & nitriles	(-C=C-CHO, -C=C-CN)
Xanthates	($-O-CS_2K$)
Phosphites	(-P-O)
Vinyl ethers	(-C=C-O-)
Acetylenes/ butadienes/ allenes	(-C≡C), (-C=C-C=C-), (-C=C=C-)

Table 2 - Examples of energetic functional groups which in combination with an "explosible" functional group can increase the probability of a material being an explosive

Screening Method for Potential Explosive Properties

UN Screening Method

For materials containing 'explosible' functionality, there are three tests specified by the UN to determine whether a material is potentially classifiable as a Class 1 explosive.[5] Materials identified as potential Class 1 explosive should be subject to UN Series 2 testing - time/ pressure test (T/P), Gap test and Koenen tube test.[3] Recently, the UN Committee of Experts on the

Transport of Dangerous Goods has approved the use of the Trauzl test as a screening test for the Gap test. This test has the advantage of requiring substantially less material (~30 g *cf.* 1 kg)[6] and inherently more safe to carry out?

However as these tests require a substantial quantity of sample it is clearly impractical and potentially unsafe to consider carrying out these straightaway in the early stage of a project lifecycle due to the limited material available. Therefore to assess the chemical properties of new materials that contain 'explosible' functional groups the use of screening methods that require less material have to be employed. Whilst a specific screening method for assessing potential explosive materials is documented in the UN Model Regulations[9] the regulations do allow for the use of alternative screening procedures *"provided that adequate correlation has been obtained with the classification tests on a representative range of substances and there is a suitable safety margin*." However no examples are given in the guidance.

Within the UN Screening Procedure, two exemptions from UN Series 2 testing are of particular applicability to the materials typically manufactured and processed:[7]

1) Where there are no chemical groups associated with explosive properties present in the molecule.
2) When the organic substance contains groups associated with explosive properties but the exothermic decomposition energy is less than 500 J/g.

By applying these exemptions, it is possible to state that the majority of materials manufactured and processed within AstraZeneca do not need to be considered for classification as an explosive. A minority of materials, and some early R&D materials, do however "fail" this exemption and would need to be considered as potential explosives requiring UN 'explosive' testing. However in practice, the UN criteria (Series 2 testing) for identifying potentially explosive compounds are generally considered in industry to be significantly over-conservative with respect to general chemical processing operations.[8]

To address this, and mitigate the need for a disproportionate number of chemical entities unnecessarily undergoing the UN series 2 tests, an alternative small scale screening procedure was considered in order to achieve an improved discrimination between explosive and non explosive substances whilst still meeting the requirements of "adequate correlation" and "suitable margin of safety".

AstraZeneca Screening Method

It has been demonstrated that the rate of pressure rise is a better indicator of explosive properties in a material than simply the decomposition energy alone. Correlations have been established between UN Series 2 Koenen, time/ pressure test (TPT), the series 1 GAP/ BAM 50/60/ Trauzl tests and the Miniautoclave test.[9-11] The Carius Tube (ICI 10 g test)[12] and the miniautoclave test[(9-11)] are similar in the sense that they are both closed cell tests in which decomposition is thermally induced by ramping the oven temperature at a pre-set rate. Results for both tests are interpreted by quantification of the pressure-rise rates It was envisaged that the AstraZeneca 'in-house' equipment, Carius tube apparatus with a high rate data capture system (figure 1), could be used to investigate the relationship between the rate of pressure rise and Series 2 UN Koenen, Time Pressure Tests. With a view to using this as a robust conservative screening tool with the ability to assess the explosive properties of a molecule, but requiring significantly less material than currently required by the UN Series 2 specified tests and safer and reduce the number of unnecessary UN Series 2 tests being carried out.

High Rate Carius Tube Test (HRCT)

The ability of the high rate Carius tube (HRCT) equipment to distinguish between different rates of pressurisation was initially investigated. Once this was determined the effect of sample weight, tube volume and effective pressure transmission through the pressure link were also examined. With consideration given to the optimum sample and tube size were determined mindful to balance the sensitivity and capture ability of the pressure transducer and the need to handle an appropriate amount of potentially explosive material. The ability of the Carius tube oven to withstand a detonation was also considered. Pentaerythritol tetranitrate, PETN (3 g) was detonated 5 cm above the standard Carius tube oven bottom. The bottom of the oven was dished out but otherwise survived the test intact.

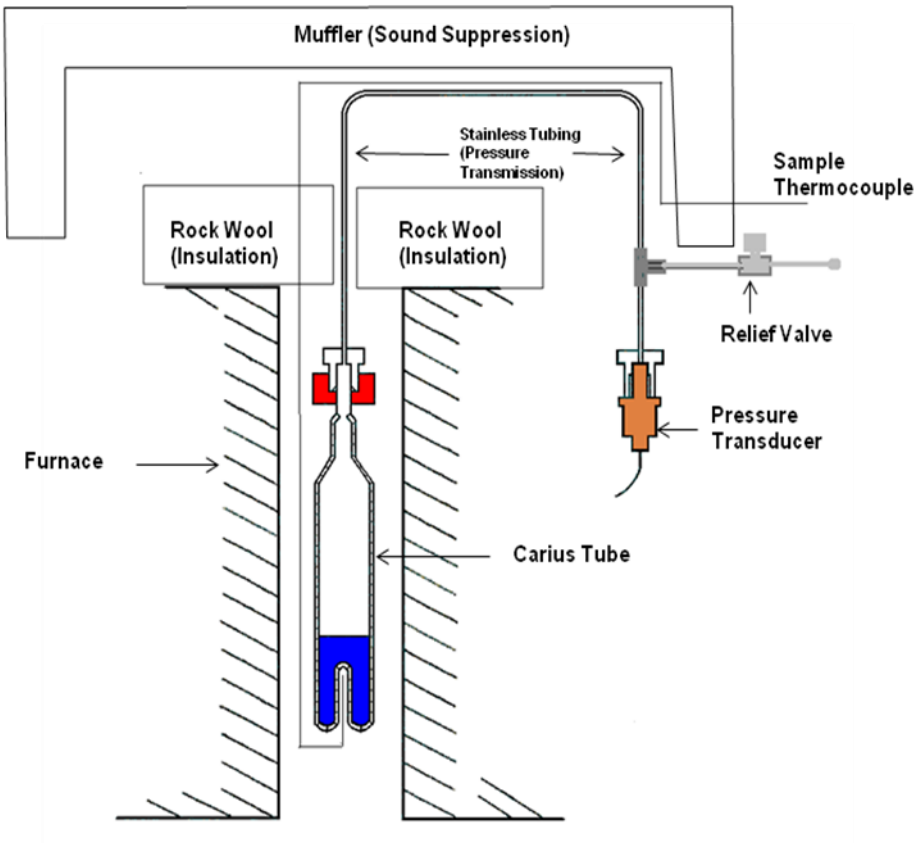

Figure 1: Schematic of the High Rate Carius Tube equipment (HRCT) - Pressure link setup: An approximately 0.5m length of $^{1}/_{4}$ ″ OD stainless steel HPLC tubing with an internal diameter of $^{1}/_{32}$ ″. To reinforce this tube it is placed inside another suitable stainless steel tube. This is Swaged onto the pressure transducer at one end and the Carius Tube via a glass to metal kovar seal at the other end of the $^{1}/_{4}$ ″ stainless steel line. This is then filled with suitable oil, ensuring there are no air bubbles using the vent line.

Correlation data of HRCT with Koenen/ TPT

The HRCT test differs markedly to the UN Series 2 tests in both its means of initiation of the decomposition reaction and in how a 'positive' or 'negative' result is derived. As such, if the HRCT test is to be effectively used as a screening test to identify all materials that may have potential to give a positive result in any of the UN Series 2 tests then correlations over a suitable range of materials must be established. Accordingly the HRCT assessment criteria will necessarily be over-conservative in most cases in order to successfully identify all potential explosive substances. Table 3 gives selected examples of correlation test data.

Entry No.	**Material**	**HRCT** 200-400 psig (ms)*		**Koenen** (mm) #		**T/P** (ms)◊	
1	Benzoyl peroxide 70-75%	< 2	+	≥ 2.0	+	< 30	+
2	Azo-isobutyronitrile	13	+	2.0	+	68	-
3	Azodicarbonamide	55	+	1.5	-	63	-
4	4-Carboxybenzenesulfonazide	6	+	≥ 2.0	+	> 30	-
5	2,4-Dinitrotoluene (dry)	7	+	1.5/ 1.0	-	> 30	-

6	2,4-Dinitrotoluene (water-wet)	1940000 (10% wet)	-	1.5 (30% wet)	-	No	-
7	2,4-Dinitrophenylhydrazine (dry)	4	+	≥ 2.0	+	≥ 30	-
8	2,4-Dinitrophenylhydrazine (30% wet)	53000	-	≥ 2.0	+	No	-
9	4-Methyl-3-nitrobenzonitrile	26	+	No	-	No	-
10	4-Fluoro-3-nitrotoluene	4555	-	< 2.0	-	No	-
11	2-methyl-4-nitroindole	68	+	2.0	+	No	-
12	2-Methyl-4-nitroindole (4% wet)	1436	-				
13	*t*-Butyl peroxybenzoate	24	+	3.5 / 4.0	+		
14	Glycidyl nosylate	32	+	2.0	+		
15	2-Methyl-4-nitroindole	68	+	≥ 2.0	+		
16	75% t-Butylperoxy-isopropyl carbonate (~ 25% mineral oil)	91	+	2.0	+		
17	TBTU	88	+	2.0 / 1.5	+		
18	4-Nitrobenzenesulfonyl chloride	85	+	1.5	-		
19	3-Nitrobenzenesulfonyl Chloride	44	+	2.0	+		
20	2-Chloro-5-nitrobenzoic acid	5400, 5400	-	1.5	-		
21	5-Nitro-3-pyrazolecarboxylic acid**	140000	-	2.0	+		
22	Hydroxybenzotriazole hydrate	< 4	+	3.0	+		
23	Deoxo-Fluoe™ ((Bis(2-methoxyethyl)aminosulfur triflouride))	58	+	≥ 2.0	+		
24	(S)-4-Methylisoxazolidin-4-ol HCl Salt	40	+			>30	-
25	*t*-Butyl peroxide	5000	-			100	-
26	2-Methylglycidyl nosylate	17	+			89	-

* A positive result is obtained if the pressure rise from 200-400 psig is <100 ms
# A positive result is obtained if an explosion occurs with a vent size ≥ 2.0 mm
◊ A positive result is obtained if the pressure rise from 100-300 psi is < 30 ms
** Decomposition via an initial low-energy gas-evolving event precedes a high-energy event

Table 3: Selection of data obtained from the HRCT, Koenen and time pressure test for various compounds. Data from the BAM Trauzel and GAP test omitted.

Overview of High Rate Carius Tube Test (HRCT)

Based on the test data obtained to date, fulfilling the UN criteria for the use of alternative screening procedures, it is considered reasonable to conclude that it is unlikely that a material will be an explosive if the time for the pressure to rise from 200-400 psig is > 100 ms, provided that the following apply:

- The material does not contain a significant quantity of solvent.
- The material is not likely to decompose in a two-step chemical mechanism in which a low-energy gas-evolving event precedes a high-energy event (such as occurs in the case of 5-nitro-3-pyrazolecarboxylic acid).
- It is accepted that materials for which a 'negative' Carius result is obtained may still be detonable under very high confinement if subjected to detonative shock (i.e. the Carius test may not in certain cases correctly predict the result of Gap test) and for use in AZ manufacturing plant no source of detonative shock is present.

Whilst the recommendation is that the primary criterion used is based upon the time from 200-400 psig being less than or greater than 100 ms, it is considered that the full data set acquired in the test should ideally be evaluated. It is not intended that the HRCT equipment be used as a replacement for UN testing. As such it is intended that the test results should be used on a case-by case basis to classify a material in terms similar to the following:

- > 100 ms - "Highly (or extremely) unlikely to be an explosive"
- ≤ 100 ms - "Potentially explosive, UN Series 2 testing required"

Materials that are potentially solvent wet or can desolvate on heating, or can potentially generate some gas early in the decomposition mechanism, e.g. decarboxylation of a material, can result in the rate of pressure potentially falsely being over the criterion. Therefore careful consideration of the whole data set, along with some information/ insight on the possible sample composition and decomposition mechanism, may be necessary.

Using the criteria above the correlation between the HRCT test and limited results from the BAM Trauzel or GAP Test results which we had access to gave a poor correlation, with the HRCT test correctly predicting approximately 70% of the positive results therefore not reasonably correlated. As a result without carrying out a UN Gap test, it is considered that it is not possible to definitively state that a material will not be detonable by that specific initiation mechanism. However, provided it has been shown that a material will not directly undergo a detonating explosion when subjected to heat, local ignition or impact, it is considered reasonable to assume, prior to bulk-scale use at least, that a material is not an explosive for the purpose of manufacture and storage (on the basis that no credible initiation mechanism will exist that could trigger possible detonation). The need for carrying out a definitive UN Gap test may still need to be considered if the material were to be considered for transport from the site of manufacture.

Explosive Screening Procedure Overview.

The procedure for the screening of explosive properties of compounds in early stage development carried out within AstraZeneca is outlined in figure 2 -

1) For materials with functional groups which could impart explosive properties, the energy criterion is increased from 500 J/g to 800 J/g. The UN appendix 6 Screening Procedure allows for the exemption from carrying out the GAP test if the energy of decomposition is 800J/g (as opposed to the threshold of > 500 J/g applied for the Koenen and Time Pressure test. Neither a series 1 type (a) propagation of detonation test nor a Series 2 type (a) test of sensitivity to detonative shock is required if the exothermic decomposition energy of organic materials is less than 800 J/g). [7,13]
2) The substance contains chemical groups associated with explosive properties which include oxygen and the calculated oxygen balance is less than -200.[2] This test however has limitations.[9]
3) A small scale test, the High Rate Carius Tube Test (HRCT) or Miniautoclave is conducted which assesses the pressurization rate attained during thermal decomposition. Results from this have been correlated with data for two out of the three UN Series 2 tests (Koenen and Time Pressure Test)
4) If the compound contains an azide group then limited quantities would be recommended until further testing is carried out.
5) The test results are only valid for material with a comparable level of purity/ strength and impurity profile

We are currently evaluating our historical screening data in a Yoshida calculations/ plot in order to develop a reliable, conservative screening tool to predict shock sensitive and explosion propagating properties of materials from DSC data and integrate that into the AstraZeneca screening protocol.[10]

Explosive Screening Flow Chart

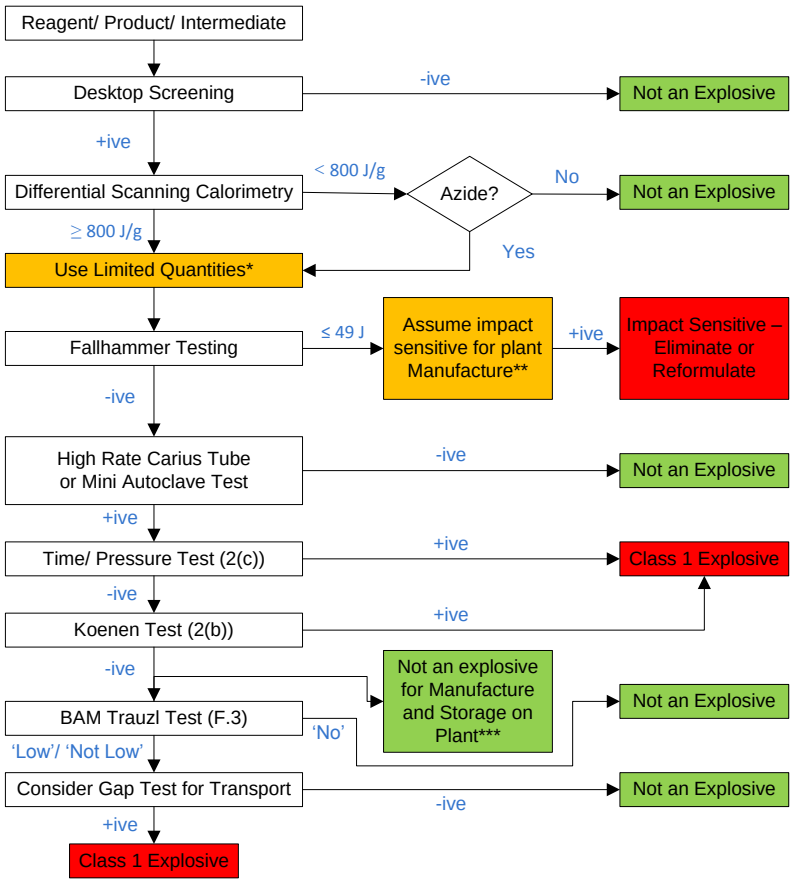

Figure 2 - Explosive Screening Flow Chart - Following the explosive flow chart for a given chemical entity will ascertain if that entity is considered for inclusion as a Class 1 explosive or not a explosive and can be used for manufacture.

*See section on general precautions (lab scale) and risk ranking
** See section on Fallhammer
*** See section on general precautions (large scale lab/ pilot plant scale)

Test Procedure

Although some of the procedures and criteria of the test methods used are fully described in literature , some details of the test methods will be given below for a better understanding of the results.

Differential Scanning Calorimetry (DSC)

In this test 1-3 mg of sample is sealed in a high pressure gold plated crucible. The sample crucible together with a reference crucible is then heated at 5K /minute up to a sample temperature of 500 °C. Any heat generation (exotherm) or heat absorption (endotherm) is observed as a deviation from the baseline. Exotherms with heat generation rates of at least 20 W/kg can be detected. Onset temperatures of thermal events together with their associated heat generation are obtained. DSC measurements include uncertainties regarding surface effects, representation of the sample, etc. and do not include gas evolution data. Thus, conclusions drawn solely from DSC measurements are valid for small scale manufactures only. As with other small scale tests, the onset of exothermicity can be significantly lower (100 K) on the large scale and therefore care must be taken in its application.

Fallhammer (FH)[2]

The Fallhammer is used to measure the sensitivity of solids and liquids to impact. A small sample (100 mg for solids, 40 ml for liquids - enclosed in aluminum) is placed in an impact device consisting of two co-axial steel cylinders, one above the other in a hollow cylindrical steel guide ring. The filled impact device is placed on the main anvil and the drop weight is

released from a defined height. The impact energy is calculated from the mass of the drop weight (1, 5 or 10 kg) and the fall height (e.g. 10 kg × 0.49 m ≈ 49 J). A maximum impact energy of 49 J is used in this case as it is considered that the force applied in the test is greater than that which can be achieved in a normal plant environment, under normal operating conditions.

A positive result, ("explosion") is reported if cracking; sparking or inflammation is observed in any test out of a series of 8 trials. Negative results include "decomposition", "Smoke" and "No Reaction". A substance is considered too dangerous for transport if the lowest impact energy at which an explosion occurs is 2 J or less in the form in which it was tested.

Mini Autoclave (MA)[11-13]

In this test approximately 1 g of material is placed in a glass vial, which itself is placed in a high-pressure Stainless Steel vessel fitted a re-entrant thermocouple and a pressure transducer. The pressure transducer itself is connected to a high rate recorder enabling pressure monitoring at a frequency of more than 1000 Hz. The vessel is then placed into an oven and heated from 30 to 400 °C using a heating rate of 2.4 K/min.

The exothermic activity is indicated by the deviation from the baseline. The "event temperature" refers to the temperature of the temperature peak maximum. The logarithmic average of at least two runs which fulfill a certain quality control check is taken for evaluation. Based on the maximum pressure rate and event temperature, the tested substance can be assessed as being "potential explosive" or "no explosive properties with respect to transport classification". Details of the assessment principle and criteria can be found in literature. Table 4 summarise the evaluation criteria. It is known that this test can be over conservative e.g. mono nitro compounds give Class 1 Rank A due to the large volume of gas generated during decomposition and high level of containment in test/access to high pressures.

Miniautoclave Criteria	Explosive Class
$(dP/dt)_{max} \geq 1240$ bar s^{-1}	Class 1, Rank A
1240 bar $s^{-1} > (dP/dt)_{max} \geq 150$ bar s^{-1} and $T_p < 167°C$	Class 1, Rank B
1240 bar $s^{-1} > (dP/dt)_{max} \geq 150$ bar s^{-1} and $T_p > 167°C$	Not Class 1, Rank C
$(dP/dt)_{max} < 150$ bar s^{-1}	Not Class 1, Rank D

Table 4. Classification Criteria for the Mini Autoclave.

High Rate Carius Tube Test (HRCT)

In this test, approximately 3 g of materials are sealed into a thick walled glass tube fitted with a re-entrant thermocouple and a pressure transducer, which is connected to a high rate recorder. The tube is then placed in an oven which is heated up at 2 K/minute. The time taken for the pressure to increase from 200 to 400 psig is measured, a potential explosive being indicated if the rise time is less than or equal to 100 ms (a positive result).

Time Pressure Test (TPT)[2]

The Time/Pressure test is used to determine the effects of igniting the substance under confinement in order to determine if ignition leads to a deflagration with explosive violence at pressures which can be attained with substances in normal commercial packages. The test apparatus consists of an instrumented pressure vessel with a rupture disk. An ignition system (typically an electric fuse head) and a 5-gram test sample are placed in the pressure vessel. The pressure vessel is secured and the match is initiated. The pressure is recorded during the reaction. A time/pressure profile is obtained. A substance is considered an explosive if the time interval for the pressure to rise from 100 to 300 psi is less than 30 ms in any one of three trials. The rupture disk provides relief to the pressure vessel above 300 psi.

Koenen Test[2]

The Koenen test is used to determine the sensitivity of a substance to the effect of intense heat under defined confinement. The apparatus consists of a non-reusable steel tube (25 mm outer diameter, 24mm inner diameter, 75mm length, mass about 25–28 g), which is closed by a plate made from heat-resisting chrome steel. Gases from the decomposition of the sample escape through a hole in the closing plate. The diameter of this hole may vary from 1.0 to 20.0mm in well-defined increments. The tube is heated by a set of four propane gas burners at a strictly defined heating rate. The tube is filled with 27 cm3 of the substance, closed with the plate and the closing device and then suspended in a protective box. The burners are lit simultaneously and the time to reaction and its duration are measured. When the tube is split into three or more fragments in at least one out of three experiments with the same diameter hole, the result is evaluated as "explosion". Substances causing an "explosion" at ≥ 2.0 mm diameter of the hole are considered to present a danger of explosion.[2/6]

BAM Trauzel Test[6]

This test is used to measure the explosive power of a substance. The sample is confined in a hole in a massive cylindrical lead block (200mm height and 200mm diameter) and initiated with a commercial detonator. The explosive power is expressed in the form of the increase in volume of the cavity in the lead block per 10 g substance. At a given strength of initiation, the explosive power increases with the volume of expansion. The test criteria for self-reactive substances are as follows:

• "no" - The expansion is less than 10 cm^3.

• "low" - The expansion is less than 25 cm^3 but more than or equal to 10 cm^3;

• "not low" - The expansion of the lead block is 25 cm^3 or more;

GAP Test[2]

This test is used to measure the ability of a substance, under confinement in a steel tube, to propagate a detonation by subjection it to the detonation from a booster charge. The sample loaded in to a carbon steel tube 48 mm in diameter 400 mm long the bottom end is sealed with thick polyethene sheet separating the detonator charge from the material in question and it is confined at the other end with a steel sheet (witness plate). After detonation of the booster charge tests are assessed on the basis on the on the type of fragmentation of the tube and on whether a hole is punched through the witness plate. The test is considered +ive if the tube is fragmented completely or a hole is punched through the witness plate, any other result is considered –ive and the substance not propagate a detonation.

Risk Ranking of Potentially Explosive Material

For a specific molecular entity, based on searches of the literature[1,16,17,] it is possible to categorise new compounds into higher or lower risk on the basis of the likelihood of encountering explosive decomposition initiated by impact or friction when working on a laboratory scale, (This assumes normal good laboratory practices are observed within the laboratory environment as a standard)

Within our R&D facilities AstraZeneca have used the following demarcation:

Lower Risk:

Materials with the presence of only a single "explosible" functional group and no other high-energy functional group as stated below:

- N-Oxides and mononitro aromatics / aliphatics, all with at least 8 carbon atoms;
    - These materials may still give a positive result when heated strongly under confinement in the absence of solvent (e.g. 2-methyl-4-nitroindole) but are unlikely to be shock sensitive or present a hazard in controlled small-scale lab use.
- Azides and tetrazoles with < 5 % by weight azide nitrogen and no other high-energy functional groups within the molecule.
    - The lowest known nitrogen-containing *potentially* explosive azide is 2,4,6-tribromophenylazide (~ 11% w/w N).
- Monohaloamines and oximes with at least 8 carbon atoms
- Non-metal acetylenes and other highly unsaturated compounds

Higher Risk:

Materials <u>not</u> falling within the "lower risk" category; typically of lower molecular weight or with multiple "explosible" functional groups; examples of higher risk materials include:

- Materials with multiple "explosible" functional groups or with a high energy functional group in addition to the "explosible" group:
    - e.g. Glycidyl 3-nitrobenzenesulfonate
- Dinitroaromatics
    - e.g. dinitrophenol, dinitrophenylhydrazine
- Perchlorates
- Trihaloamines
- Ozonides
- Hyper-valent (V) iodine reagents

- Diazonium salts
- Azides and tetrazoles with ≥ 5 % by weight azide nitrogen
- Low molecular weight tetrazoles
    - e.g. 1-H-tetrazole

Organic Peroxides / Peracids:

There is authoritative published information for nearly all commercially available organic peroxides.[18] All formulations listed can be regarded as non-explosive unless "Subsidiary Risk 3" is identified (e.g. as for high-purity benzoyl peroxide). It is recommended that only non-explosive formulations be used in all laboratory work.[19]

General Precautions and Handling Recommendations for Potentially Explosive Materials on a Laboratory Scale.

The following recommendations are made to Chemists working with such materials within R&D facilities at AstraZeneca.

- Use appropriate personal protection equipment, e.g. work behind shields in the fume cupboard.
- Maximize distance between yourself and the material. Do not carry flasks or vials by the base, hold them on the top. Ideally place vials and flasks in a second container.
- Avoid enclosing the material as gas evolution may rupture the container or vessel.
- Do not subject the material to excessive heat; it could trigger the potential explosion.
- If the material is an intermediate consider other routes.

General precautions for "lower risk" materials

< 1 g Scale:

- Avoid heating in the absence of solvent, (e.g. for drying)
- Do not subject to impact of friction (eg mortar & pestle)
    - Use plastic spatulas and take care with handling
- Do not use in microwave equipment unless diluted with at least 10 weight equivalents of solvent

1-10 g Scale:

- Avoid heating in the absence of solvent, (e.g. for drying)
- Do not subject to impact of friction (eg mortar & pestle)
    - Use plastic spatulas and take care with handling
- Do not use in microwave equipment unless diluted with at least 10 weight equivalents of solvent and experimental process safety testing has been completed
- Store material in plastic container to minimise containment and projectile hazard >10 g scale:
- Consult Process Safety Group
- Avoid isolating material; keep diluted with at least two equal weights of solvent
    - Unless other advice received from Process Safety Group
- When heating solutions of potential explosives, ensure that the solvent cannot be inadvertently lost (e.g. by condenser failure). Use of oil baths is preferable to heating blocks or heating mantles to avoid localised high surface temperatures.

General precautions for "higher risk" materials

< 100 mg scale:

- Avoid heating in the absence of solvent (e.g. for drying)
- Do not subject to impact of friction (eg mortar & pestle)
    - Use plastic spatulas and take care with handling
- Do not use in microwave equipment unless diluted with at least 10 weight equivalents of solvent and appropriate experimental safety testing has been completed (see later protocol)

- Store material in plastic container to reduce confinement and projectile hazard

> 100 mg scale:

- Avoid isolating material; keep diluted with at least five equal weights of solvent
    - Unless experimental testing and advice received from process safety group
- Do not use in microwave equipment
- When heating solutions of potential explosives, ensure that the solvent cannot be inadvertently lost (e.g. by condenser failure). Use of oil baths is preferable to heating blocks or heating mantles to avoid localised high surface temperatures.

General Precautions and Handling Recommendations for Potentially Explosive Materials on a Large Scale Lab / Pilot Plant Scale in Early Development.

For on-site use within AstraZeneca, if it can be shown that detonation of material cannot be initiated by:

- Self-heating arising from thermal degradation under normal storage conditions (SADT significantly higher than maximum credible storage temperatures) or,
- Intense heating under defined confinement (negative Koenen result) or,
- Local ignition (negative Time/Pressure result) or,
- Shock (negative Fall-hammer result) then,

it can be argued that the only means of initiating a detonation might be:

- Subjecting the material to detonative shock (the means of initiation in the Gap test or as might occur if the material was in the proximity to another detonating explosive substance on site) or,
- Through a deflagration to detonation transition (this is considered unlikely for non-bulk-scale quantities and for materials that do not deflagrate rapidly in a deflagration test).

Accordingly it can be argued that in the early phase of development that thermally stable materials which could only be capable of detonation under very high confinement or when initiated by detonative shock from another material in its proximity, will be extremely unlikely to present a hazard or significant risk when stored and handled appropriately on a Chemical Manufacturing Site. For bulk-scale use and for transportation it may be somewhat more difficult to argue this case and as such it is likely to consider the need to carry out the definitive UN Gap test.

Where this in not the case and the material is classified for inclusion into Class 1 the recommendation is to eliminate/ replace so the material is removed from the synthesis or to ensure that the chemical entity is not isolated (remains in solution/ suspension) which may mean the telescoping of synthetic steps.

Conclusion

The screening protocol and general precautions / handling recommendations used by AstraZeneca allow material in development to be synthesized and screened for their explosive properties in a safe manner. The use of the HRCT within AstraZeneca has proven to be a useful and conservative screening tool when assessing the explosive properties of compounds in early development, and is deemed to have met the UN requirements for an alternative screening tool as out lined in the UN guidance.[7]

References

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2. United Nations “Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria – 4th revised edition
3. UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria, 5th revised addition, **2009**, Appendix 6, 439
4. Bretherick’s Handbook of Reactive Chemical Hazards, 5th edition
5. For both transportation and manufacturing purposes, the definition of an explosive that is used by the regulatory authorities is based on the results that would be obtained by carrying out the tests as per the schedule defined in the UN Recommendations on the Transport of Dangerous Goods; in these regulations, explosives are either classified as falling within “Class 1” or as being “too sensitive” to be included within Class 1.

6. The Trauzl test is also specified within the EU Directive 92/69/EEC "Classification, Labeling and Packaging of Dangerous Substances".
7. UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria, 5th revised addition, **2009**, Appendix 6, 439
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15. Committee of Experts on the Transport of Dangerous Goods and on the Globally Hrmonized System of Classification and Labelling of Chemicals – UN documents ST/SG/AC.10/C.3/2008/40, 11 April 2008
16. Bretherick's Handbook of Reactive Chemical Hazards, 5th edition
17. AstraZeneca's internal compound/ report database HazDoc is also searched.
18. United Nations "Recommendations on the Transport of Dangerous Goods, Model Regulations Volume 1, 14th revised edition. ISBN 92-1-139106-7, pg 97.
19. Subsidiary Risk 3, indicates that the material requires an "EXPLOSIVE" subsidiary risk label for transport