

## Introduction

Chemical and pharmaceutical companies routinely work with controlled substances, and must have adequate controls in place to meet the rapidly changing legislative requirements of the countries in which they operate.

This legislation is becoming increasingly complex and changes frequently as legislators try to keep up with emerging “legal highs”. Meanwhile, externalization of R&D means that compounds are synthesised, stored and transported across a multiplicity of geographies with differing laws.

In 2013 Scitegrity, in conjunction with the Pistoia Alliance and a number of pharmaceutical companies, developed Controlled Substances Squared™ (CS<sup>2</sup>) to address this challenge.

The system is able to scan large chemical libraries (millions of compounds) and determine whether a compound is considered as controlled in a country and what controls are needed.

## Not all countries are the same

Often companies work under the misconception that if they follow the controlled substance laws of one country then they will be compliant with another. Fig 1 shows the controlled status for 400 compounds across 3 countries with major Pharmaceutical R&D activities. As can be seen, if a company simply followed the controlled substance laws of the USA for example, they would likely be in breach the laws of the UK and Switzerland.



Figure 1 – Whether a substance is classed as controlled or not varies from country to country. Analysis and image courtesy of the Pistoia Alliance

## Working with small amounts does not exclude you

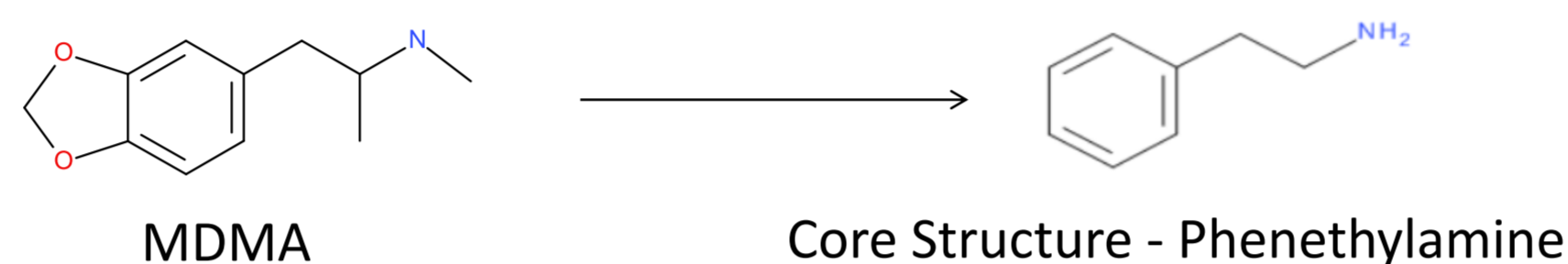
Most countries do not have an exception based on amount. So, if a company has 100,000 compounds, each with only a few ug or mg then they must still know which ones are controlled and typically record and handle these separately. Controlled substance licences allow scientists to use them, but you must still clearly know which compounds are controlled in your collection. You also have to apply for special permits to ship controlled substances.

It is also worth noting that you usually must comply with the controlled substance laws of both the sending and receiving country. So the onus is on the sender to ensure that what you are sending to a country is not controlled in the receiving country or that the receiver has appropriate licenses if it is controlled.

## It's not just lists of compounds

All countries use lists of named controlled substances. However, the legislations often additionally controls variations of these named substances - typically ethers, esters, salts and stereoisomers. Therefore, a list of several hundred named substances will immediately translate into tens of thousands of controlled substances.

Added to this many countries use ‘Markush like’ rules. These control entire areas of chemical space rather than a single named substance. A good example is MDMA, aka ecstasy, in UK legislation. This is not actually specifically named as a substance – rather it is generically controlled under a Markush rule for compounds structurally derived from Phenethylamine.



## UK legislation wording...

Any compound (not being methoxyphenamine or a compound for the time being specified in sub-paragraph (a)) structurally derived from phenethylamine, an N-alkylphenethylamine,  $\alpha$ -methylphenethylamine, an N-alkyl- $\alpha$ -methylphenethylamine,  $\alpha$ -ethylphenethylamine, or an N-alkyl- $\alpha$ -ethylphenethylamine by substitution in the ring to any extent with alkyl, alkoxy, alkylenedioxy or halide substituents, whether or not further substituted in the ring by one or more other univalent substituents

Some of these Markush rules are so complex that they cover millions, or even technically an infinite number, of possible structures. Markush rules have to be encoded into the system in addition to the lists of specifically named controlled substances – a considerable challenge. Markush rules are especially prevalent in European countries e.g. UK, Ireland, France, Denmark, Italy and Switzerland.

## Imprecise legislation

Some countries, notably the US and Canada are deliberately vague on what is actually controlled. They use terms such as “substances similar to x” or “analogues of y”. Unfortunately no further guidance or clarification is given – instead compounds are assessed individually as required. This is obviously impractical when dealing with millions of compounds.

To address this CS<sup>2</sup> utilises (where appropriate for the legislation) similarity searching algorithms and will return a “possibly controlled” status with a degree of similarity to any legislation substance under control.

## Controlled Substances Squared Enterprise and Hosted editions

CS<sup>2</sup> Enterprise is installed on your own servers and is designed to enable the enterprise-wide detection and control of controlled substances. It is able to rapidly scan millions of compounds and determine the controlled status in many countries based on the compounds structure. CS<sup>2</sup> Enterprise has 2 main modes of operation:

- A web based interface for users to query lists of compounds via name, corporate ID or structure. This is designed to be simple to use with no prior knowledge of controlled substances or laws.

- A daily automatic overnight scan of your corporate compound collection to ensure everything that should be controlled is flagged. This controlled status information is stored within CS<sup>2</sup> allowing on demand search speeds of > 100,000s compounds per minute for these existing corporate compounds. An advanced set of APIs is available to allow CS<sup>2</sup> to be called from other applications to return controlled status for both existing corporate compounds and yet to be synthesised / purchased compounds

Scitegrity also offer a ‘Cloud’ based Hosted version of CS<sup>2</sup>. This provides a web based user interface for a small per user, per year fee - no software installation is required. This is ideal for controlled substance compliance officers or smaller companies who require instant access to the system to check smaller numbers of compounds. Structures can be uploaded via a number of methods including webservice.

## Key Features (CS<sup>2</sup> Enterprise Edition)

- Automatic overnight scans check your newly made substances and any legislation amendments. Legislation changes are automatically picked up by the system
- Easy integration with internal systems via webservices, SDKs and Pipeline Pilot components. Check compounds before you even make them or automatically check every compound shipped or purchased.
- Fast and scalable – scan millions of compounds even on small servers with query rates of 100Ks per minute via Fastlookup of corporate IDs.
- Flexible - search by structure, name, synonyms, CAS / DEA numbers, corporate IDs and more. Setup ‘favourites’ to speed searches. Schedule automatic routine searches.
- Comprehensive - 15 core countries (UK, USA, France, Ireland, Belgium, Denmark, Germany, Italy, Netherlands, Spain, Sweden, Switzerland, Canada, UN (INCB), EU Precursors) covered with more that can be added rapidly.
- Copies of the legislation, translations, legislation overview, contacts and company internal SOPs / guidance can all be accessed with a single click from a ‘hit’.
- Robust - searches extend to markushes, isomers, salts, esters, ethers, etc. (where applicable) to ensure total compliance.
- Customisable – add your own additional substances, restrictions, guidance, documents and Markush rules. Generate summary pdf reports from searches.
- Built on Pipeline Pilot - industry leading technology from Accelrys/BioVia™ (note- you do not require Pipeline Pilot to run CS<sup>2</sup>)