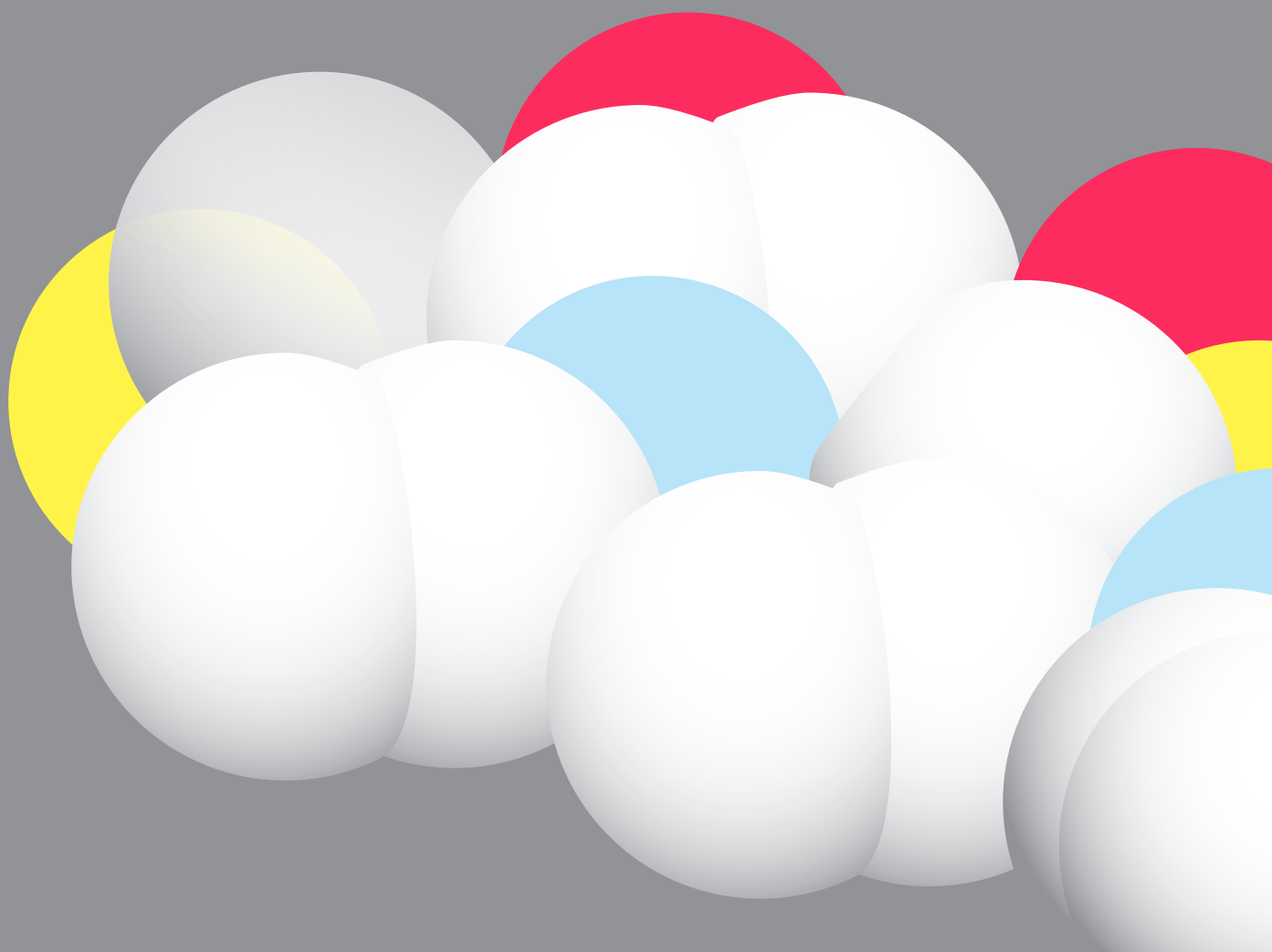


Scitegrity

Controlled and Regulated chemicals

Ensuring compliance in research and
manufacturing



The ‘is this regulated?’ headache

Any industry that handles large amounts of chemicals needs to correctly identify and handle both controlled and regulated substances.

In this white paper, we discuss some of these challenges and simple steps that can be taken to improve compliance, identify regulated chemicals and make compliance more robust.

The modern chemicals and pharmaceuticals industry face demanding regulatory requirements relating to the safe and legal use, storage and supply of chemicals. For most people, the legislation that immediately comes to mind usually relate to the correct use of COSHH, MSDS and possibly REACH when using chemicals on bulk.

However, for chemicals and regulatory managers this is only a small subset of the regulations which need to be considered. Complex regulations exist relating to controlled drugs, chemical weapons and the precursor chemicals that can be used to make them, ozone depleting, military and dual use chemicals and the PIC/Rotterdam convention are amongst others that may need to be taken into account. Many common chemicals and intermediates fall within the scope of these laws. Often the biggest hurdle to achieve compliance is to first identify what regulated or controlled chemicals you

have. For some regulations such as REACH’s substances of very high concern, which deals with well defined, bulk, commercially available chemicals this is relatively easy. It is usually possible to search with a CAS RN™, trade name or similar identifier.

However, for larger chemical libraries, especially those with proprietary or novel chemicals the approach of trying to match via key words or names does not work.

Furthermore, most modern legislation no longer attempts to regulate just a single substance. Instead they use “generic statements” to attempt to control areas of chemical space that are likely to have similar properties.

Using name searching approaches with these generic statements is a non-starter as the vast majority of chemicals they control are not named and may not yet exist.



“Often the biggest hurdle to achieve compliance is to first identify what regulated or controlled chemicals you have.”





What can you do to ensure compliance?

The answer lies in the ability to search legislation by chemical structure. There are hundreds of ways to name a chemical, but it only has one chemical structure.

Searching via structures allows automation and allows areas of chemical space or “generic structures” to be searched, along with common variations such as all stereoisomers, ethers, ester and salts of named controlled substances.

Computational structure based searching for chemicals has been in existence for over 30 years. The fundamental challenge is that regulatory legislation is not written in a machine readable chemical structure aware format. It is also often written in legalistic terms requiring specialist expertise and knowledge to interpret. As the legislation is often amended several times per year, it also requires constant monitoring

In this white paper you will discover how by encoding chemical legislation from around the world, Scitegrity’s Controlled Substances Squared allows automatic compliance checking based on a

chemical’s structure.

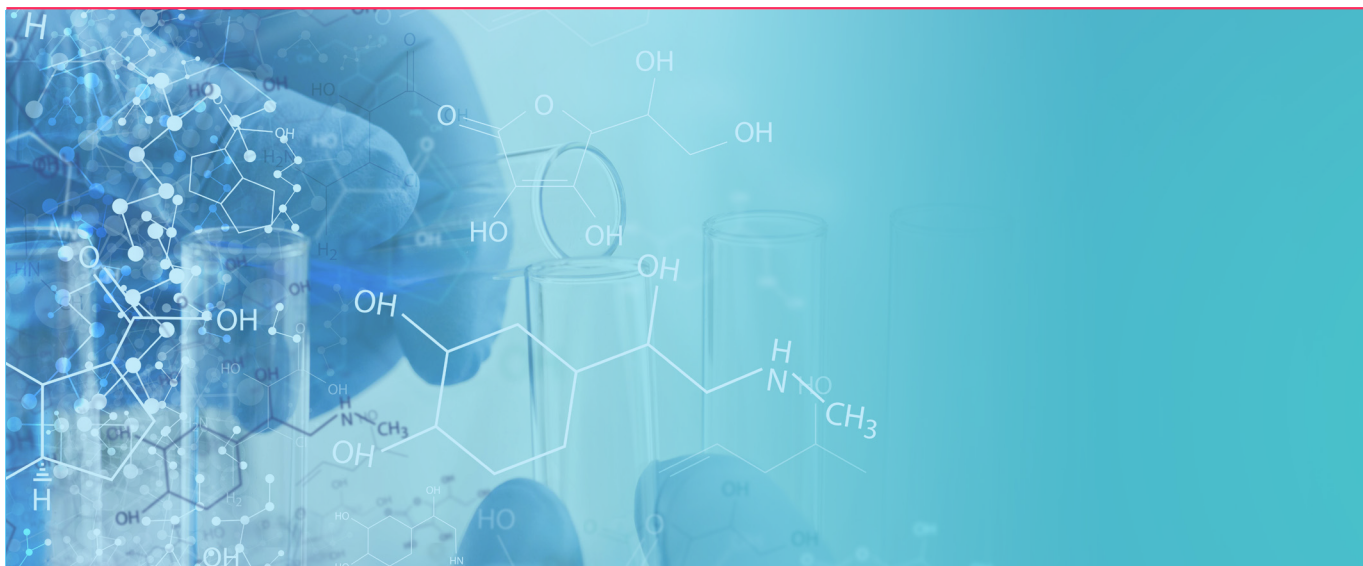
This proven and reliable approach allows you to easily and automatically answer the question “is this chemical regulated or controlled” - even for chemical libraries of proprietary chemicals running into 10s of millions of substances (turn to page 7 for more details).

Over the next few pages of this whitepaper we explain how legislation varies between countries and common legislative approaches taken by the regulators, answer some common questions and address misconceptions around the use of controlled and regulated chemicals within research.

Finally we present some case studies of how we’ve helped both small and large companies address and prevent compliance issues and expand international sales markets.



“Controlled Substances Squared allows automatic compliance checking based on a chemical’s structure... even for collections with 10s of millions of proprietary chemicals”.



Regulated chemical space

Rarely is a single named chemical controlled in legislation, instead all closely related chemicals are also controlled. So just checking the list of “named substances” does not deliver compliance

Markush notation was originally developed in 1924 to describe areas of chemical space covered in patents. In the 1970s the UK was the first legislator to use this Markush notation in its chemical legislation (Misuse of Drugs Act). Termed “generic statements” the aim was to prevent chemically similar substances to a named controlled substance from being sold as a way to bypass the law, e.g “legal highs”.

In response to the increasing sales of “legal highs”, this last decade has seen a significant increase in the use of these generic statements by most legislators around the world, including the USA, Switzerland and China. This is not limited to controlled drug legislation, but also other legislation such as the Chemicals Weapon Convention, Montreal Convention on Ozone depleting chemicals and US ITAR and Commerce Control Lists.

Even prior to the use of “generic

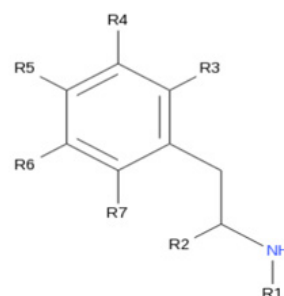
statements” laws rarely just regulated just the core named substance, with terms such as “all ethers, esters, salts and stereoisomers of” very commonly applied.

A typical example of a generic statement for Phenethylamine is given below. Chemicals structurally similar to Phenethylamine are widely controlled around the world, often using generic statements. Although the exact wording and hence chemicals controlled in each generic statement differs between countries. This relatively simple example shows why structural searching is always required to achieve compliance.

Any compound (not being methoxyphenamine or a compound for the time being specified in sub-paragraph (a)) structurally derived from phenethylamine, an N-alkylphenethylamine, α-methylphenethylamine, N-alkyl-α-methylphenethylamine,

α-ethylphenethylamine, or an N-alkyl-α-ethylphenethylamine by substitution in the ring to any extent with alkyl, alkoxy, alkylendioxy or halide substituents, whether or not further substituted in the ring by one or more other univalent substituents

A slightly easier way to read and understand and visualise is to show it graphically in Markush notation.



Where R1 = an alkyl group
 Where R2 = a methyl or ethyl group
 Where R3 to R7 inclusive = alkyl, alkoxy, alkylendioxy or halide substituents, whether or not further substituted in the ring by one of more other univalent substituents.

What is controlled and regulated varies between countries, even within Europe

Contrary to popular belief, within Europe most legislation relating to Psychoactive, Narcotic, and controlled chemicals occur at the national level

While regional and international conventions do exist relating to the regulation of chemicals, these typically only set a minimum international baseline for which most countries build on. Notable examples of these are the International Narcotics Control Board (INCB) Red, Yellow and Green Lists (relating to psychoactive, narcotic chemicals and their precursors), the Chemical Weapons Convention and the Montreal Protocol on Ozone depleting chemicals.

However, almost all countries go far beyond these international minimums, especially for Psychoactive and Narcotic chemicals, controlled drugs and their precursors.

Contrary to popular belief, within Europe most legislation relating to Psychoactive, Narcotic, and controlled chemicals occur at the national level and vary significantly from country to country. Only a very small subset of common drug precursors are regulated at the EU level.

This means that as well as considering EU level law, the individual member countries laws also need to be complied with as 99% of the actual legislation relating to controlled substances occurs at the national level. So each country's laws need to be considered when shipping

within Europe as well as into or out of Europe.

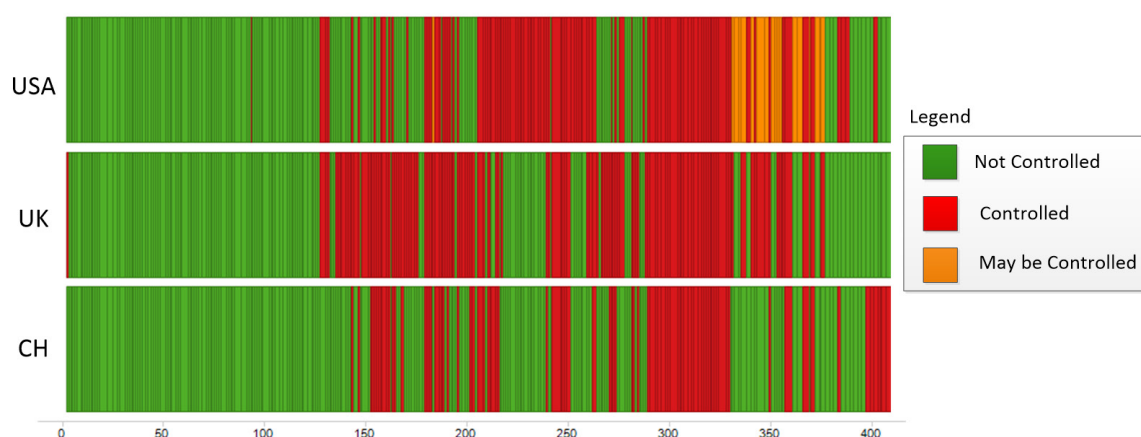
The graphic below shows how the controlled status of 400 chemicals differs between the USA, UK and Switzerland. Note that in the USA the 'analogues law' also regulates substances similar to a controlled substance, but does not define what similar means, hence the "maybe controlled".

Our experience working with many chemical suppliers and pharmaceutical companies indicates that a compound collection of 1 million compounds will likely have several thousand regulated or controlled substances. These include common building block chemicals, solvents and salts that can be converted into, or used to manufacture, controlled substances, chemical weapons, military or dual use chemicals.

Within pharmaceutical R&D, a common source are library compounds from previous drug discovery programs that are now controlled by legislation, examples include programs for CB1, opioid and many pain targets, sleep disorders and anti-depressants programs.



“an R&D collection of 1 million compounds will likely have several thousand regulated or controlled substances.”



The “research exemption” myth for controlled drugs

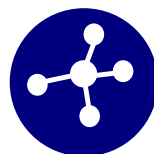
A common misconception amongst researchers is that the law allows the use of small amounts of a controlled substance for *in vitro* based lab work and research without appropriate controls or licenses. A typical use case might be having a few milligrams or microlitres of a controlled substance within larger chemical collection for *in vitro screening*, or building block for synthesis.

Researchers often believe that there is some form of “research exemption” for such small amounts. This incorrect view is further reinforced by R&D chemical suppliers often stating and asking scientists to confirm that anything bought is for research use only.

Although limited exemptions do exist in some countries, they tend to be heavily caveated and in general, the use of controlled drugs, even in small quantities for research is not exempt and must be treated as controlled substances.

Within the UK, the government issued specific guidance for research that states that for microtitre plate and sample replication

“...regardless of the destination plate amount, any source stock that contains more than 1 mg of a controlled substance would be considered controlled and require permits, and any replication of these would class as production...”



“At Scitegrity we have collated information on known research exemptions which you can read on our website¹”

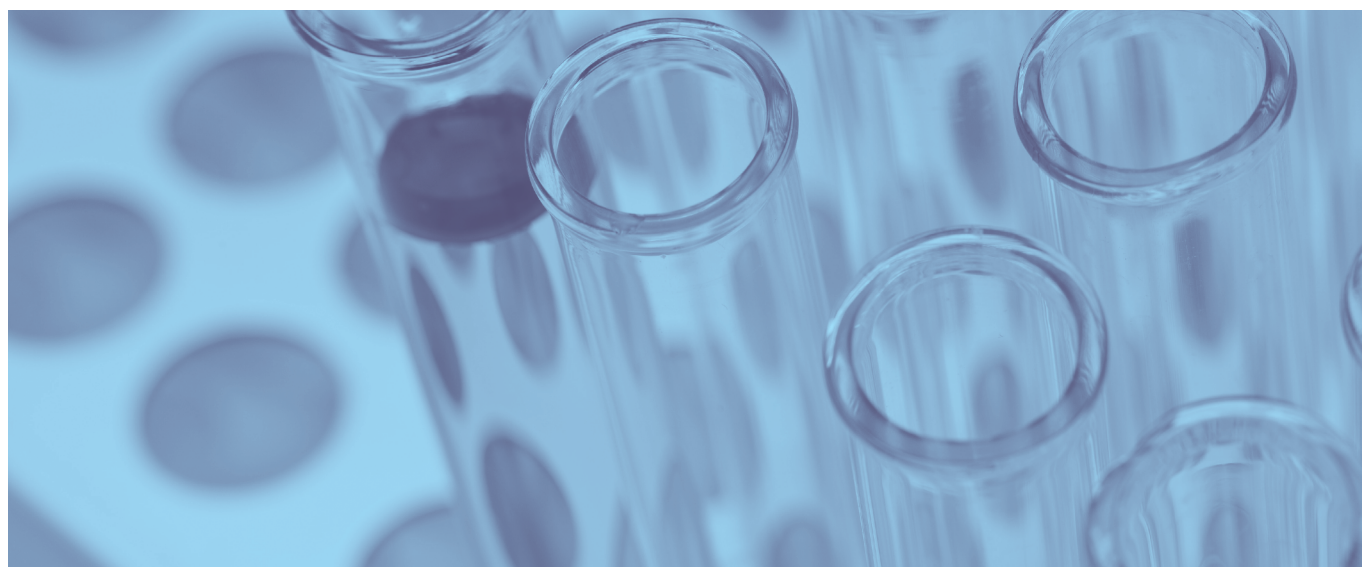
Common legislative approaches

Named substances. A named controlled substance. Often also covering all its ethers, esters, salts and stereoisomers. Used by all countries

Generic statements. Complex, but clearly defined areas of chemical space around a core structure that is considered controlled. Used by almost all countries

Analogues. All analogues of a named substance. The term analogues is left deliberately vague. Rejected as an approach in many jurisdictions, but used widely in the USA, Mexico and Canada.

Psychoactive effect. Not based around chemical structure. Instead it criminalises the act of supplying a substance with a psychoactive effect with the intent of, or knowing that the supply is likely to lead to someone consuming the substance. Meant as a “safety net” law to allow the control of completely novel substances before they are formally identified and controlled via the other approaches above.



Making compliance simple for sample managers, compliance officers, chemists and non-chemists

Although structure based chemical searching has been around for over 30 years and many companies have attempted to achieve regulatory compliance by implementing these techniques – the reality is that it is a difficult task. It requires a detailed knowledge of the legislation, chemistry, programming, chem-informatics, specialised programmatic tools kits and a lot of time. As legislation updates constantly it also requires constant monitoring and updating.

So in conjunction with a number of major pharmaceutical companies, we developed Controlled Substances Squared (CS²).

Each week Scitegrity's experts monitor and encode, chemically, all new legislation into the system. These updates are then used by the powerful CS² chemistry scanning engine to check all of a company's chemicals, alerting them to any that are, or have become regulated.

The simple to use interface requires no chemistry, scientific or regulatory knowledge, simply lookup a chemical by name, chemical ID or structure to see if its regulated. Any 'hits' are given in simple to understand terms, with detailed information for experts only a click away.

However, we believe the best levels of compliance are achieved when no user input is required. So CS² can easily be setup to automatically download updates and check all your chemicals each night, alerting the sample manager to any change in controlled status.

At the same time our API's allowing chemical ordering, registration and design applications to check in realtime if something is regulated and alert the end user, improving compliance and workflow efficiency.

As discussed, the legislative approaches taken vary greatly from country to country, all of which are encoded to ensure compliance. Terms used in legislation such as all salts, all stereoisomers, all ethers, all esters and analogues (via similarity searching) are all covered in CS² along with the generic statements.

Unfortunately, sometimes legislation is not entirely clear in its wording. So, we also work with our clients, academia, trade bodies and special interest groups of experts to engage with legislators on improving legislation, obtaining clarification of existing legislation and guidance in areas such as research exemptions. As part of this we alert clients to new legislation being proposed by legislators, to allow feedback from industry to legislators.



“CS² can easily be setup to automatically download updates and check all your chemicals each night, alerting the sample manager to any which change controlled status”

Input Structure	Matched Structure	Corporate ID	Jurisdiction	Controlled Status	Search Comments	Legislation / Rule Name	Legislation Title (English)	Comments	Control Code(s)
	 Generic structure match. Click here for details	131	Switzerland	Controlled	Generic structure match. Salt found. Legislation controls all salts.	CH Tryptamines	Regulation of EDI over the lists of narcotics, psychotropic substances, precursors and	Substances derived from tryptamine. DE - Von der Kontrolle ausgenommen ist die industrielle und die wissenschaftliche Verwendung. Der private Gebrauch ist nicht von der Kontrolle ausgenommen. EN - Excluded from the control is the industrial and scientific use. Private use is not exempt from the control.	Swiss Directory E
	 Generic structure match. Click here for details	131	United Kingdom	Controlled	Generic structure match. Salt found. Legislation controls all salts.	Tryptamine Derivatives	The Misuse of Drugs Act 1971 (Amendment) (No. 2) Order 2014	Updates the definition of tryptamine derivatives, the original being in the 1977 Modification Order.	UK Class A UK Schedule 1
	 Generic structure match. Click here for details	131	United States of America	Controlled	Exact match. Salt found. Legislation controls all salts.	Diisopropyltryptamine	Controlled Substances Act - Regulations 21 CFR, Part 1300-1399	On DEA ARCOS listing as a Schedule I, as DEA 7436. Dipropyltryptamine is also under DEA 7436 in ARCOS.	US ARCOS List US CSA Schedule I
	 Generic structure match. Click here for details	136	Switzerland	Controlled	Generic structure match.	Phenethylamine derivatives	Regulation of EDI over the lists of narcotics, psychotropic substances, precursors and	Substances derived from phenethylamine. DE - Von der Kontrolle ausgenommen ist die industrielle und die wissenschaftliche Verwendung. Der private Gebrauch ist nicht von der Kontrolle ausgenommen. EN - Excluded from the control is the industrial and scientific use. Private use is not exempt from the control.	Swiss Directory E

Key features

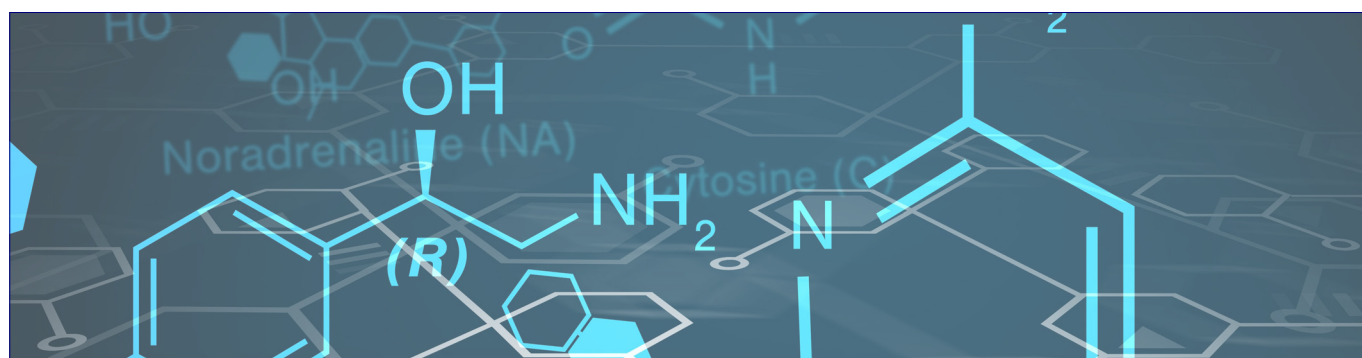
Controlled Substances Squared has been widely deployed by and is relied on by the pharmaceutical and chemicals industry. It's used by regulators, half the world's top 10 pharmaceutical companies, CROs, fine chemical suppliers and numerous specialist forensics standard companies

- On premise or fully hosted in the cloud.
- Covers legislation from over 28 countries and international conventions, including the UK, USA, EU and China.
- A simple web based user interface
- Clear, precise and accurate answers. No knowledge of chemistry or regulations are required.
- Detailed information to allow experts to understand how and why a substance is regulated
- Automatic nightly checks of all your compound collections, including newly registered compounds, with alerts when your compounds regulated status changes.
- Audit history of how the controlled status of your compounds have changed.
- Search via sdf, .mol, SMILES, InChI, common chemical names or draw a substance
- Search naturally using your own internal compound IDs and names
- Advanced webservices to automate checks. Integrations with Knime™ and Pipeline Pilot™
- Handles collections running into 10s of millions of chemicals
- Override context sensitive determinations with your own internal rules
- Legislation guidance, plus upload your own SOPs to display to users



“This software has had a great impact in helping us monitoring our controlled substances across multiple jurisdictions, which was for us a difficult process in the past.”

Director Research Informatics & Operations, LundBeck”



Case studies

Case study 1 - R&D organisation

During a regulatory investigation, a company identified that their R&D organisation had unknowingly been handling small quantities of scheduled substances. They were instructed by the authorities to ensure that all areas of the organisation were fully compliant with controlled drug legislation. As this involved checking millions of proprietary chemicals, they turned to Scitegrity to help. Against aggressive timelines Controlled Substances Squared was installed and integrated allowing the organisation's entire chemical inventory to be checked before the regulatory compliance deadline. This included automatic nightly checks of all chemicals they owned, along with proactive checking of chemicals planned for synthesis or purchase.



“Their expertise in the regulations has also been invaluable, as they provide alerts to regulatory changes and are available to answer specific queries that arise internally from scientists or management. I have been very pleased with the decision to work with Scitegrity and would endorse them, and their products, to others”

Controlled Chemicals Lead, Top 10 Pharma Company.”

Case study 2 - Chemical supplier

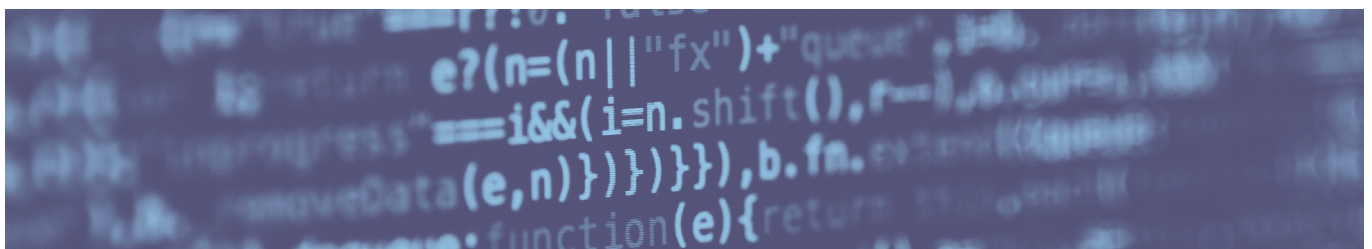
A supplier of chemicals to the forensics and research industries was finding it difficult to ensure compliance, primarily to controlled drug legislation, but also dual use, import export and chemicals weapons legislation when shipping internationally. This made it difficult to work with distributors and develop new overseas markets. By utilising Controlled Substances Squared and Scitegrity's expertise they have been able to dramatically reduce the time it takes to clear chemicals for shipping while also opening new markets.

Case study 3 - Regulatory engagement

In 2017 a major global pharmaceutical company discovered that a candidate in a clinical trial, despite having no narcotic activity, had recently become controlled under a new legislative amendment in the UK. This led to significant disruption and cost.

Working with Scitegrity they conducted an urgent assessment of their portfolio in order to identify any other regulatory issues. Scitegrity, in conjunction with regulators, trade bodies and other CS² customers then proposed amended technical wording to the legislation. This included running pre-emptive checks of research chemical collections to ensure the proposed wording avoided any further 'collateral' damage.

In 2019 this new wording was approved by the UK parliament, reducing the amendment's chemical space coverage by 90% and focusing it on narcotic chemical space.



About Scitegrity

For more information on Controlled Substances Squared please visit www.scitegrity.com

Founded in 2011 by former pharmaceutical scientists, chemists and data managers, Scitegrity specialises in allowing the searching of chemical regulations.

Our software solutions are relied on by dozens of chemical and pharmaceutical companies, CROs and regulators around the world, including half of the world's top-10 pharmaceutical companies.

Scitegrity also provides other related chemical legislation compliance services, such as Drug Abuse Potential assessments and Commodity / HS code classification and import duty calculations for the Harmonised Tariff Schedules of the EU, USA and China via our ExpediChem system.

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