



UGM Boston
Oct. 4th 23
 Chemaxon

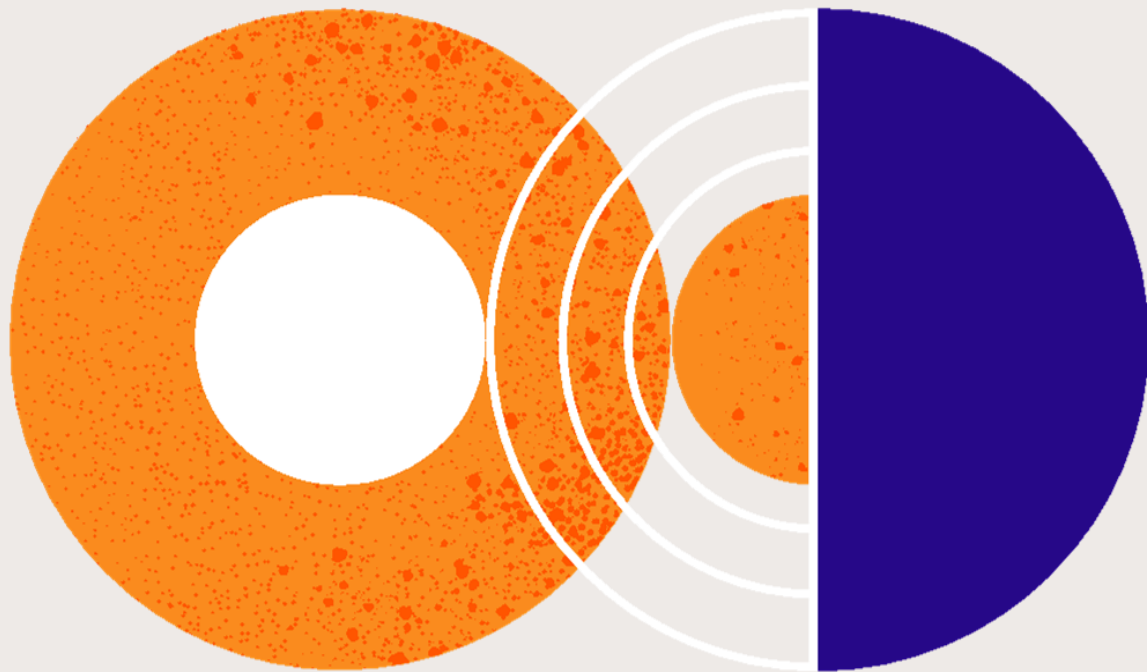
Advocating Change: One Synthetic Cannabinoid at a Time

Zofia Jordan
Compound Compliance Consultant,
formerly of GSK

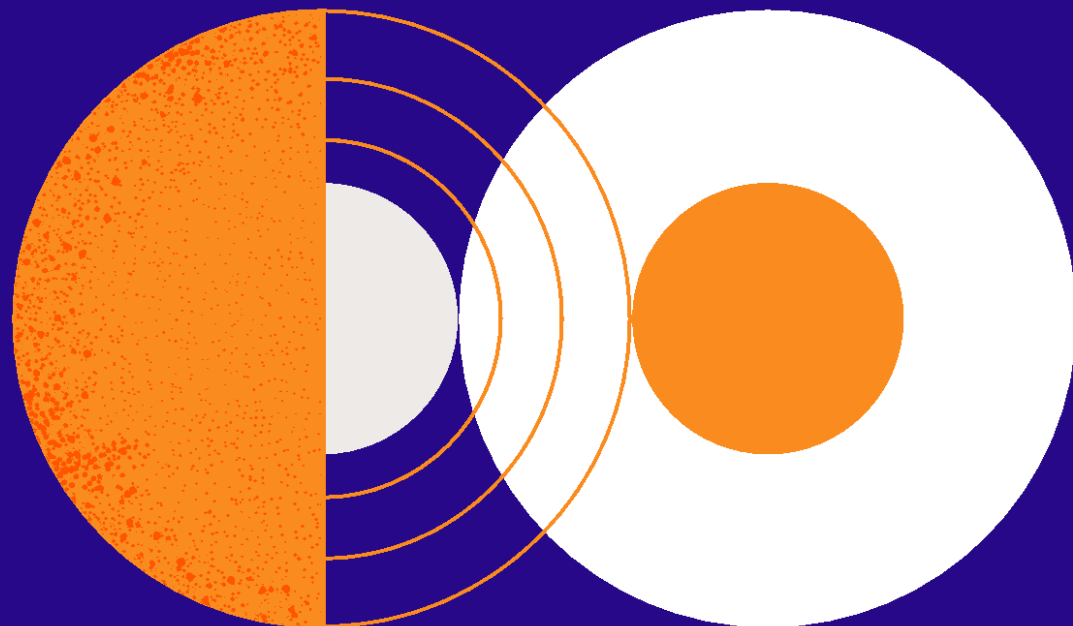
Advocating Change: One Synthetic Cannabinoid at Time

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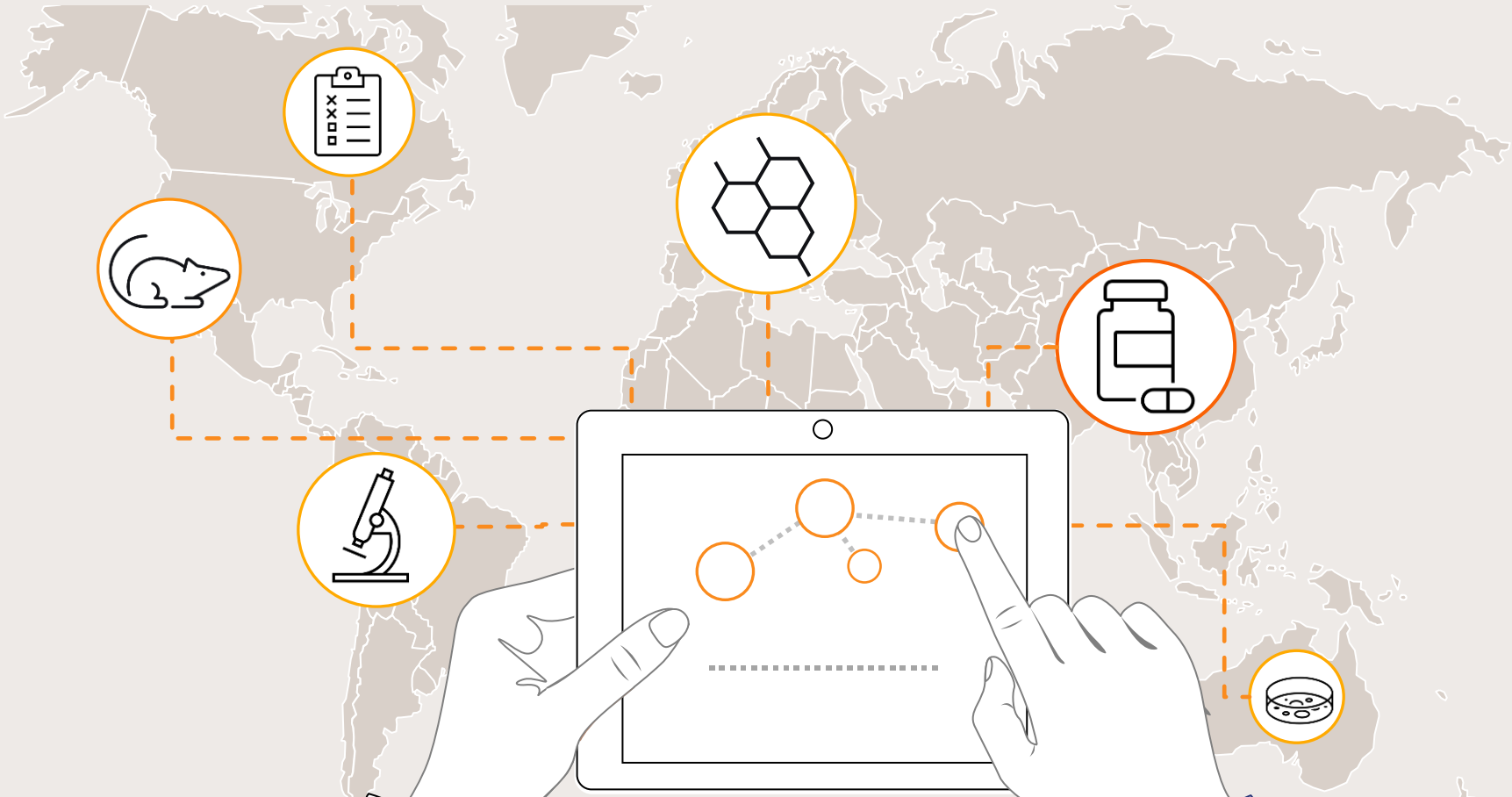
Zofia Jordan
Compliance Consultant
ScjBiopharm Ltd



Introduction: Global Nature of R&D

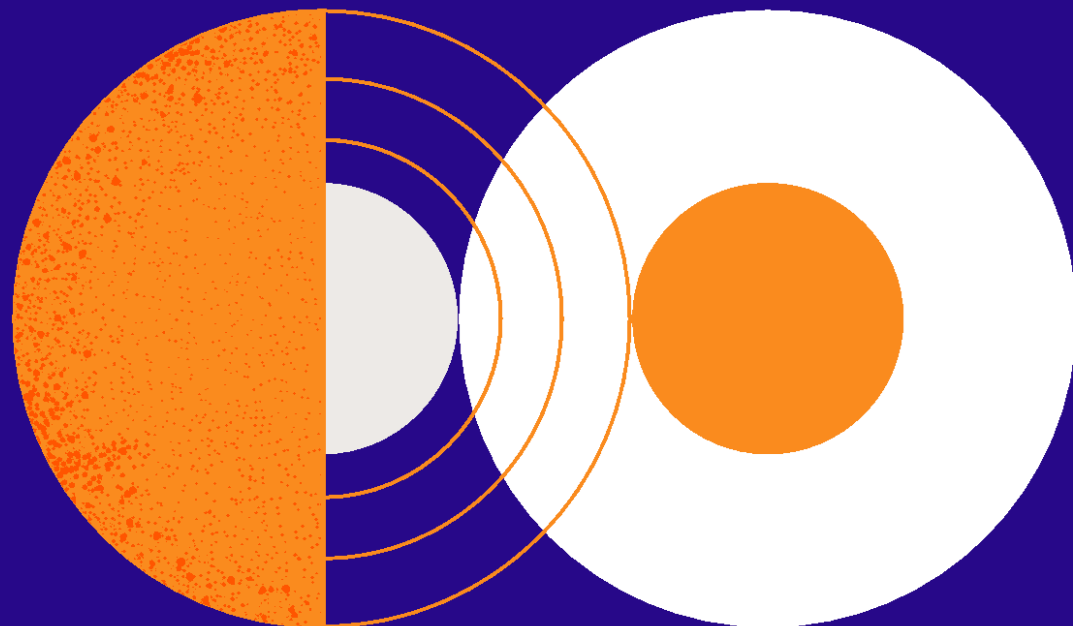


Global Nature of R&D



Misuse of Drugs Act:

Third Generation Synthetic
Cannabinoids



Myriad of legislation

Controlled Substances Act

United States anti-drug law



The Control
the statute
which the n

Federal and Health

Belgian governm



The Federal Age
Belgium is resp
new medication
Xavier De Cuype

Misuse of Drugs Act 1971

UK legislation



German Federal Narcotics Act

Drug law in Germany are covered by the German Federal Narcotics Act [1](#) [2](#) [3](#) The act defin trade an

European Medicines Agency

smittel,
and Hilfschemikalien



Arrêté du 22 février 1990 fixant la liste des substances classées comme stupéfiants

i Dernière mise à jour des données de ce texte : 23 mai 2021

NOR : SPSM9000498A

▸ [Accéder à la version initiale](#)

It was all going so well

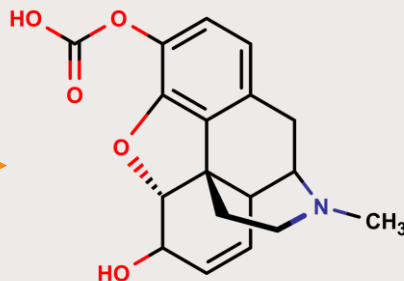
In the past



Legislation was based around specific structures and some small generic examples.

Examples has to be interpreted and transformed from legal wording into scientific nomenclature to be useful,
i.e. words into chemical structures

morphine



Misuse of Drugs Act 1971 (UK)

1977

the very first generic legislation
amphetamine derivatives and substituted tryptamines





1986

fentanyl and pethidine derivatives

2000

mescaline derivatives



2008

The first detection a synthetic cannabinoid *

JWH-018, in a product sold under the brand name 'Spice',
Germany, Austria



2008

The first detection a synthetic cannabinoid *

JWH-018, in a product sold under the brand name 'Spice',
Germany, Austria

2009

First generation synthetic
cannabinoid legislation



2013

Second generation synthetic
cannabinoid



2013

Second generation synthetic
cannabinoid

2014

ACMD Report on 'Third
Generation' synthetic
cannabinoids

ACMD Report

Addresses 'Third Generation' synthetic cannabinoids
An expanded generic definition...

'Simply increasing the number of generic controls to cover the broad range of psychoactive cannabinoid structures which are being identified using a similar approach to the existing controls **would require an extremely long list** of additional paragraphs. It is therefore proposed to adopt a different approach, based on defined modifications of a 'model' compound, 1-pentyl-3-(1-naphthoyl)indole ('JWH-018')

<https://www.gov.uk/government/publications/third-generation-synthetic-cannabinoids>

* ACMD: Advisory Council on the Misuse of Drugs





2013

Second generation synthetic
cannabinoid

2014

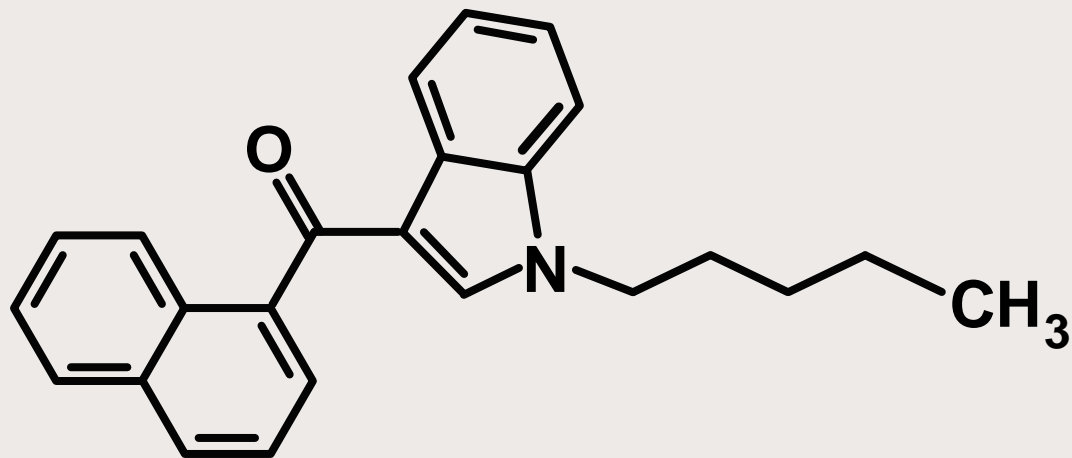
ACMD Report on 'Third
Generation' synthetic
cannabinoids



2016

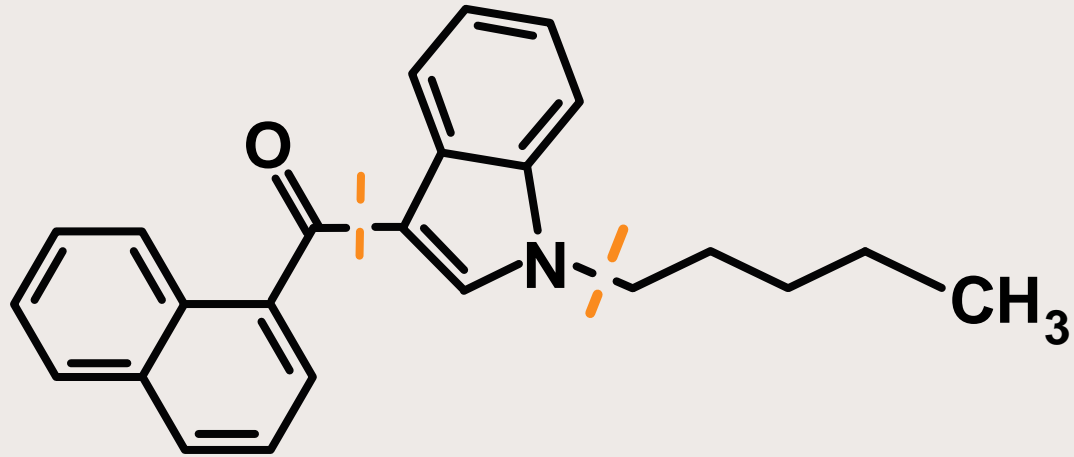
Third generation synthetic
cannabinoid

JWH-018



JWH-018

core structure



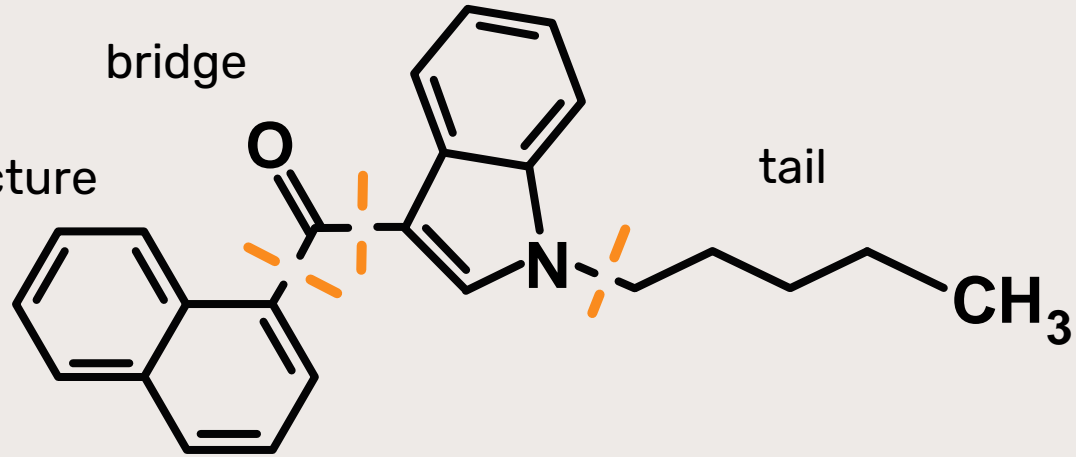
JWH-018

core structure

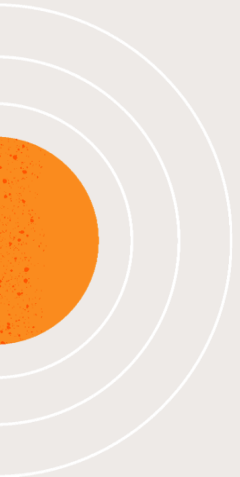
bridge

secondary structure

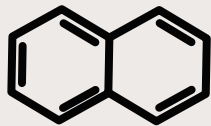
tail



JWH-018



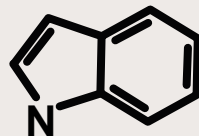
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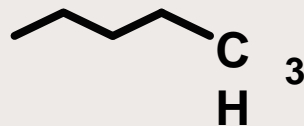
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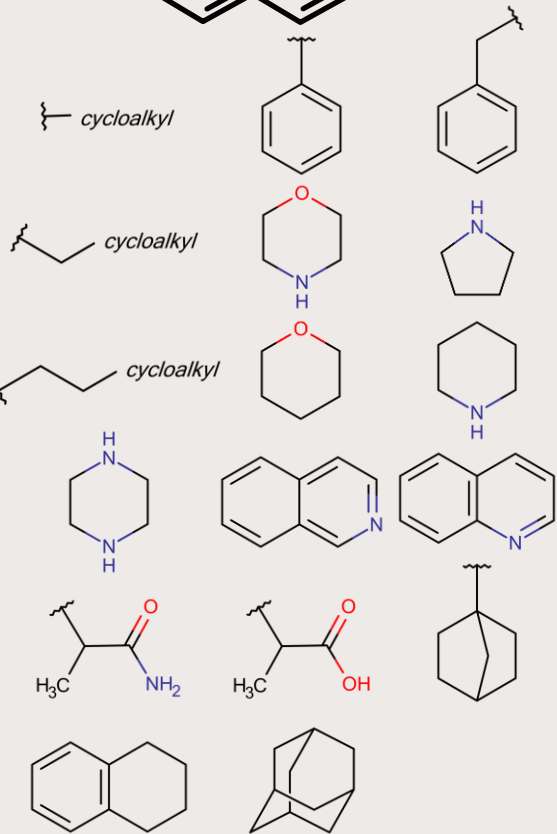
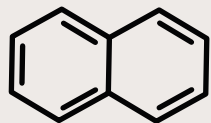
core structure



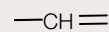
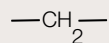
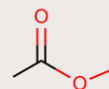
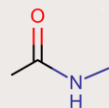
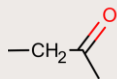
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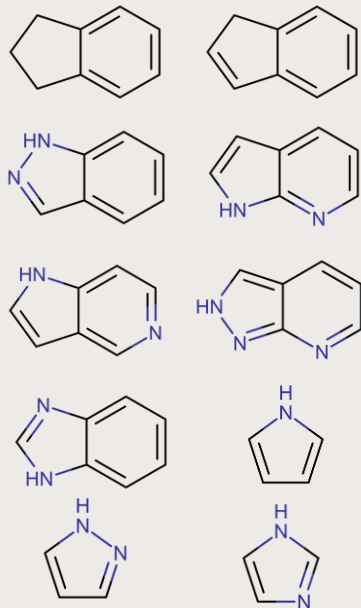
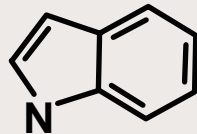
secondary structure



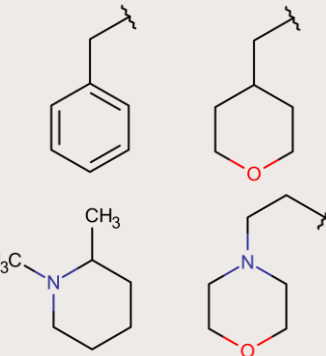
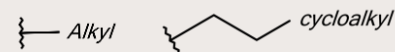
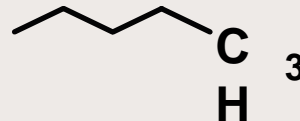
bridge



core structure



tail

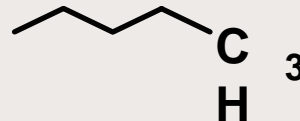
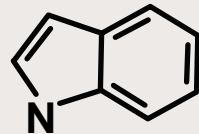
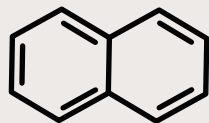


secondary structure

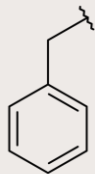
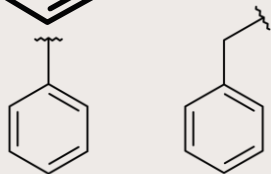
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core structure

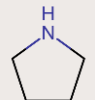
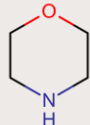
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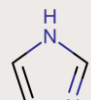
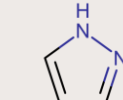
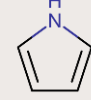
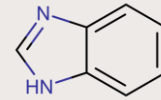
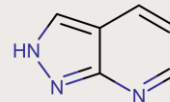
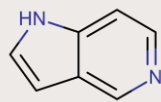
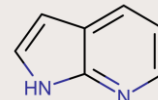
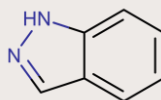
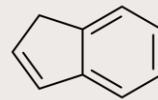
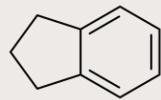
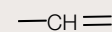
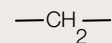
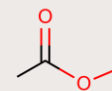
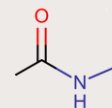
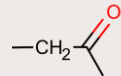
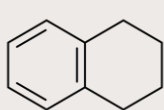
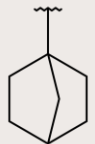
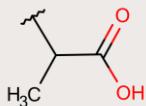
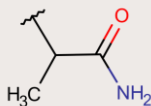
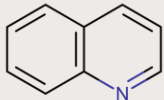
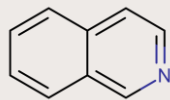
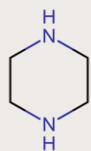
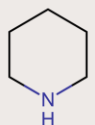
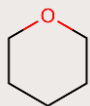
cycloalkyl



cycloalkyl



cycloalkyl

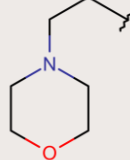
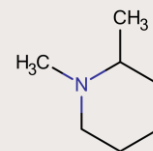
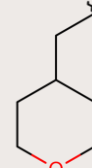
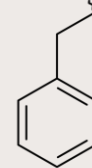


Alkyl

cycloalkyl

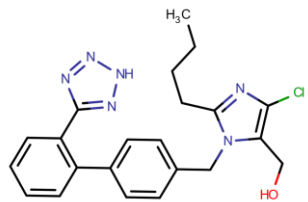
Alkenyl

cycloalkyl

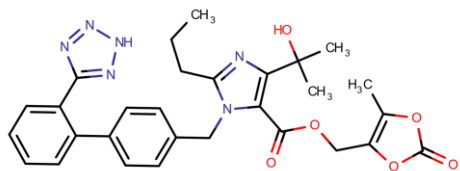


and whether or not substituted in any of the linked sub-structures with one or more univalent substituents

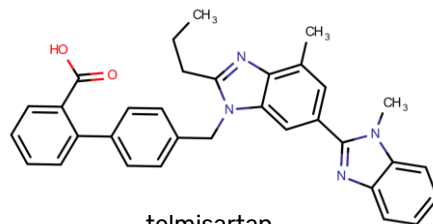
**Exempted
molecules**



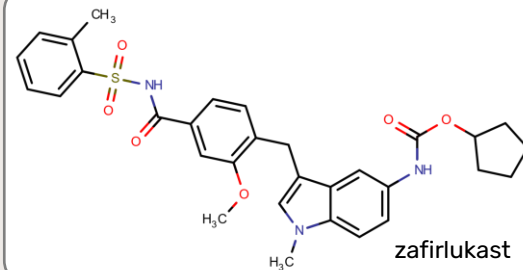
losartan



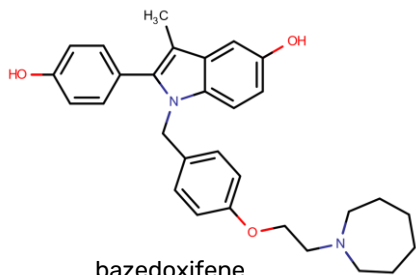
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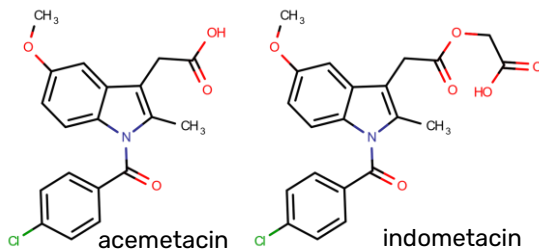
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zafirlukast

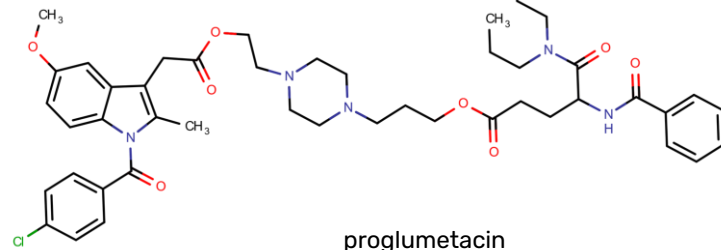


bazedoxifene

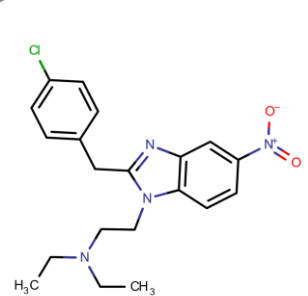


acetaminophen

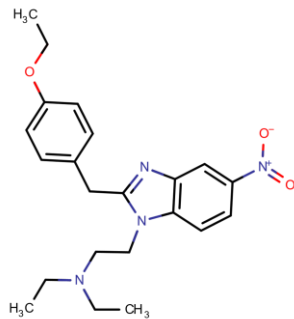
indometacin



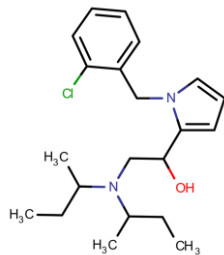
proglumetacin



clonitazene

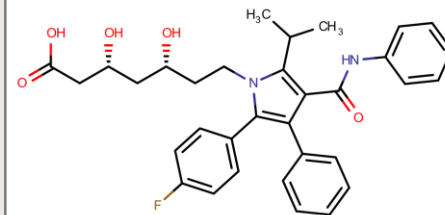


etonitazene

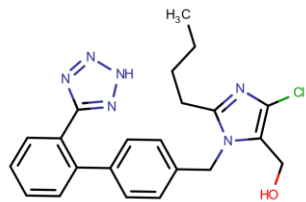


viminol

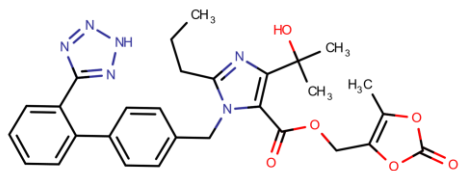
**Exempted
molecules**



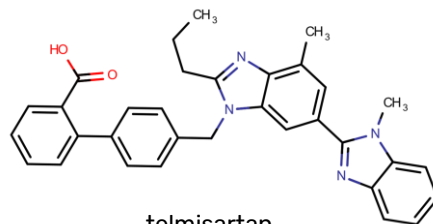
atorvastatin



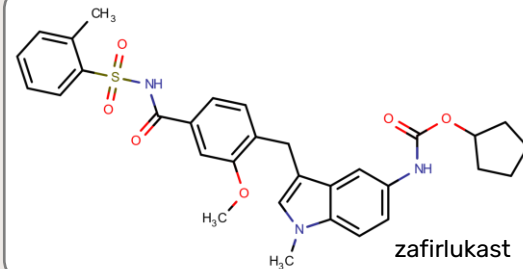
losartan



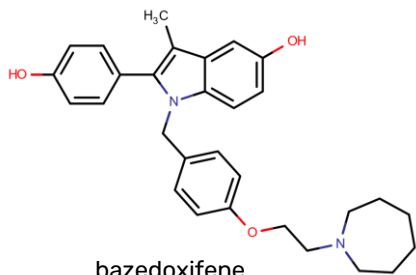
olmesartan,



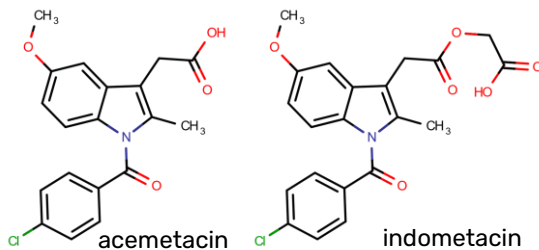
telmisartan



zafirlukast

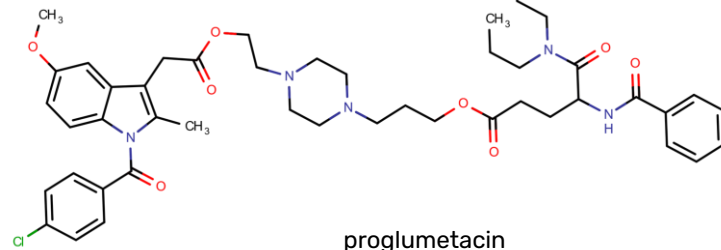


bazedoxifene

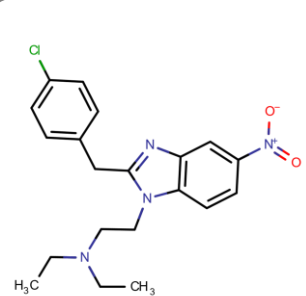


acetaminophen

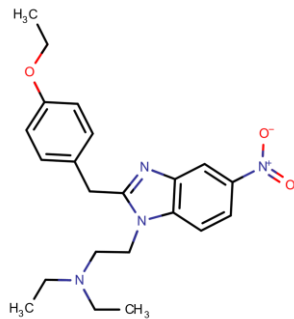
indometacin



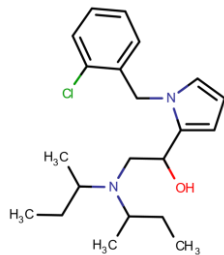
proglumetacin



clonitazene

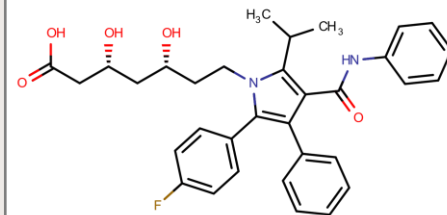


etonitazene



viminol

**Exempted
molecules**



atorvastatin

losartan olmesartan, telmisartan	angiotensin II receptor antagonist	hypertension
zafirlukast	leukotriene receptor antagonist	asthma
bazedoxifene	estrogen receptor modulator	postmenopausal osteoporosis
acemetacin indometacin proglumetacin	COX inhibitor	osteoarthritis, rheumatoid arthritis
clonitazene etonitazene viminol	opioid agonist	
atorvastatin	inhibitor of HMG-CoA reductase	hypercholesterolemia

An Unprecedented Change

From

To

Listing substances on a named basis



Structure based generic definition

Clarity & manageable licensing process



Uncertainty & unprecedented scale

Industrial strategy: efforts to improve UK environment



New barrier to investment and research



Identifying the newly controlled structures

- Commercial packages are available to allow compound inventories to be checked against legislation
- Compliance Checker from Chemaxon screens chemical structures efficiently against controlling legislation across a number of countries as well as overarching UN conventions

The screenshot displays the Chemaxon Compliance Checker interface. On the left, a search box contains the word "cocaine" and shows a chemical structure of cocaine. Below the search box, there is a "Regulation categories" section with a grid of country buttons: Austria, Belgium, Canada, China, Denmark, France, Germany, India, Ireland, Italy, Japan, Netherlands, Singapore, Spain, Sweden, Switzerland, and United Kingdom. A "United States of America" button is also visible. A "Switch to category groups" link is at the bottom of the grid. A blue "Compliance check" button is located below the grid.

On the right, the "Single check summary" panel shows the checked structure (cocaine) and the following details:

- Checked structure: cocaine
- Against countries / category groups: ALL
- Date of regulations: Aug 16, 2023
- Max atom count: 200
- Checked at: Aug 16, 2023, 2:28:19 PM
- Knowledge base version: 23.08.10.0

Below the summary is a table with the following columns: #, Regulation, Match details, Example, CAS #, and DEA #.

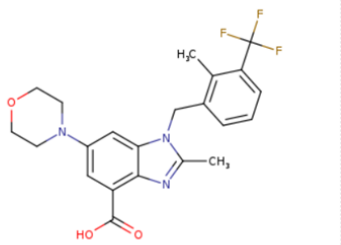
#	Regulation	Match details	Example	CAS #	DEA #
1	AT Suchtgiftverordnung Anhang I (litf1)	More...		50-36-2 53-21-4	9041
2	AT Suchtgiftverordnung Anhang I (litf1)	More...		461-37-6 5796-31-4	9180
3	BE Arrêté royal de 6 septembre 2017 réglementant les substances stupéfiantes et psychotropes Annexe I (litf1)	More...		50-36-2 53-21-4	9041

Identification of Controlled Compounds

Compliance Checker | Single check | File check | HS single check | HS file check | Administration | zjordan@chemaxon.com

Single check

1372540-25-4



Regulation categories All countries

Countries:

Austria Belgium Canada China Denmark
France Germany India Ireland Italy
Japan Netherlands Singapore Spain
Sweden Switzerland United Kingdom
United States of America

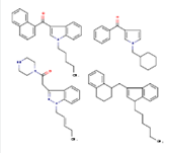
Switch to category groups

Compliance check

Single check summary

Checked structure: 1372540-25-4
Against countries / category groups: ALL
Date of regulations: Jan 1, 2017
Max atom count: 200
Checked at: Aug 16, 2023, 2:48:04 PM
Knowledge base version: 23.08.10.0

Generate

#	Regulation	Match details	Example	CAS #	DEA #
1	UK Third Generation Synthetic Cannabinoids (Ref1,Ref2,Ref3,Ref4)	More...			

By File

Compliance Checker Single check File check HS single check HS file check

File check

Checks all molecules or text entries in a file at once.

SMILES_Header.csv

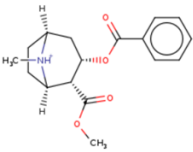
ComplianceChecker Report

Check finished at: 2023.08.16 16:18:02 (GMT+02:00)
Report generation started at: 2023.08.16 16:18:07 (GMT+02:00)
Document ID: 1692195482631
User: zjordan@chemaxon.com
Country / category group: Germany
Date of regulations: Aug 16, 2023
Content: error and hit
Similarity categories: highly similar

Select molecule format:
Auto-recognize

Regulation categories

Countries:
Austria Belgium Canada
France Germany
Japan Netherlands Singapore
Sweden Switzerland United States of America

Input #	Input molecule image	Synonyms
3		(-)-3-beta-benzoyloxytropan-2-beta-carbonzure methylester, Benzoylegoninmethylester, Coca, Cocain, Cocaine, Cocainum, Cocaina, Crack, Erythroxylo, Kokain, Methyl benzoylegonine, Methyl(3β-(benzoyloxy)tropan-2α-carboxylat), Methyl(3β-(benzoyloxy)tropan-2β-carboxylat), Metylestrar av bensoylekgonin, benzoylimethylegonine,
		(-)-3-beta-benzoyloxytropan-2-beta-carbonzure methylester, Benzoylegoninmethylester



International Narcotics Control Board

Yellow List

Annex to Forms A, B and C
52nd edition, December 2013

LIST OF NARCOTIC DRUGS UNDER INTERNATIONAL CONTROL

Prepared by the

INTERNATIONAL NARCOTICS CONTROL BOARD*

Vienna International Centre
P.O. Box 500
A-1400 Vienna, Austria
Internet address: <http://www.incb.org/>

in accordance with the

Single Convention on Narcotic Drugs, 1961**

Protocol of 25 March 1972 amending the Single Convention on Narcotic Drugs, 1961

Customisation

The screenshot shows a user interface for customising settings. It is divided into three main sections:

- Regulation categories:** Shows selected countries: Germany and United Kingdom. Other available countries include Austria, Belgium, Canada, China, Denmark, France, India, Ireland, Italy, Japan, Netherlands, Singapore, Spain, Sweden, Switzerland, and United States of America. A "Switch to category groups" button is at the bottom.
- Report formats:** Shows selected formats: HTML and PDF. Other available formats include SDF, MRV, XLSX, and CSV.
- Report content:** Shows a "Report template" dropdown set to "Default". Below are four checkboxes:
 - Controlled structures:
 - Highly similar structures:
 - Similar structures:
 - Non-controlled structures:

At the bottom, there is a blue button with a logo and the text "Compliance check".

- Regulation Categories: User defined at country or specific regulation level
- Reports: Number of formats available
- Report Content: Customisable
- Note: Highly Similar Structures option
For shipping to US, structures must be checked for Highly Similar to Controlled Substances



Customisation

The screenshot displays a user interface for customizing regulatory categories and report settings. It is divided into three main sections:

- Regulation categories:** Shows a dropdown menu currently set to "Germany, United Kingdom". Below it, a "Countries:" section lists various countries in button format: Austria, Belgium, Canada, China, Denmark, France, Germany (selected with a blue checkmark), India, Ireland, Italy, Japan, Netherlands, Singapore, Spain, Sweden, Switzerland, United Kingdom (selected with a blue checkmark), and United States of America. A "Switch to category groups" button is located at the bottom of this section.
- Report formats:** Shows a dropdown menu currently set to "PDF, HTML". Below it, a row of buttons lists report formats: HTML (checked), PDF (checked), SDF, MRV, and XLSX. A "CSV" button is visible below this row.
- Report content:** Shows a dropdown menu currently set to "Default". Below it, a "Report template:" dropdown is also set to "Default". At the bottom of this section, there are four checkboxes: "Controlled structures" (checked), "Highly similar structures" (checked), "Similar structures" (unchecked), and "Non-controlled structures" (unchecked).

At the bottom of the interface, there is a large blue button labeled "Compliance check" with a small icon to its left.

- Regulation Categories: User defined at country or specific regulation level
- Reports: Number of formats available
- Report Content: Customisable
- Note: Highly Similar Structures option
For shipping to US, structures must be checked for Highly Similar to Controlled Substances



Customisation

The screenshot displays a user interface for customizing report generation. It is divided into three main sections:

- Regulation categories:** Shows selected countries: Germany and United Kingdom. A grid of other countries is visible, including Austria, Belgium, Canada, China, Denmark, France, India, Ireland, Italy, Japan, Netherlands, Singapore, Spain, Sweden, Switzerland, and United States of America. A 'Switch to category groups' button is at the bottom.
- Report formats:** Shows selected formats: HTML and PDF. Other available formats are SDF, MRV, XLSX, and CSV.
- Report content:** Shows a 'Report template' dropdown set to 'Default'. Below are four checkboxes: 'Controlled structures' (checked), 'Highly similar structures' (checked), 'Similar structures' (unchecked), and 'Non-controlled structures' (unchecked).

A blue button at the bottom left contains a logo and the text 'Compliance check'.

- Regulation Categories: User defined at country or specific regulation level
- Reports: Number of formats available
- Report Content: Customisable
- Note: Highly Similar Structures option
For shipping to US, structures must be checked for Highly Similar to Controlled Substances



Customisation

The screenshot displays a user interface for customizing report generation. It is divided into three main sections:

- Regulation categories:** Shows a list of countries with checkboxes. 'Germany' and 'United Kingdom' are selected. A 'Switch to category groups' button is at the bottom.
- Report formats:** Shows a list of report formats with checkboxes. 'HTML', 'PDF', 'SDF', 'MRV', 'XLSX', and 'CSV' are visible. 'HTML' and 'PDF' are selected.
- Report content:** Shows a dropdown for 'Report template' set to 'Default'. Below it are four checkboxes: 'Controlled structures' (checked), 'Highly similar structures' (checked), 'Similar structures' (unchecked), and 'Non-controlled structures' (unchecked).

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Problems

R&D

Pre-
clinical

Clinical
trials

Regulatory
update
and scale up

Problems

**~ 100,000
controlled
substances**

International research collaborations (shipping restrictions)

Increased use of non-UK based CRO services

Activities moved out of the UK

Compounds removed from trials

Exclusion of UK trial sites

Exclusion of non-UK trial sites

Increased cost to trial sites

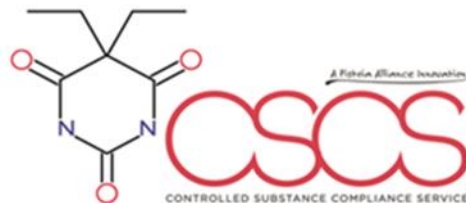
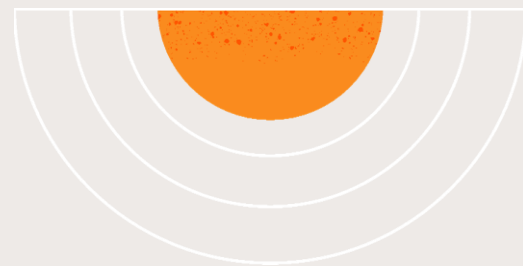
R&D

Pre-clinical

Clinical trials

Regulatory update and scale up

Tackling the Issue: Working with our Partners



We are a global, not-for-profit organization focused on driving innovation in life sciences.

Controlled Substance Compliance & Shipping Expert Community to

**The Association of the
British Pharmaceutical
Industry**



**BRITISH
PHARMACOLOGICAL
SOCIETY**



R&D

Pre-clinical

Clinical trials

Regulatory update and scale up

**End to end
research
exemption**

Solution

International comparison

Germany

Research exemption:

“the usage of a new psychoactive substance for industrial, commercial or scientific purpose according to the current scientific knowledge and technique”

Initial Proposals to Advisory Council on the Misuse of Drugs (Dec 2017)



Initial Proposals to Advisory Council on the Misuse of Drugs (Dec 2017)



Generic definition: A revision for synthetic cannabinoids in order to reduce the scope



Exempt product definition: utilised or further developed to cover multi-well screening plates



Compound specific exemption: to apply to the Home Office for a compound-specific exemption



Clinical trial schedule: with reduced requirements for trials with HRA ethical committee approval.



Import/export licences: proposed measure may be the extension of the import/export licence validity period.



Guidance for researchers: aimed at the research community to clarify the Schedule I licensing requirements (Completed November 2019)



Generic Definition



Following conversations:

New proposed definition was proposed by the ACMD and accepted by the Home Office to take to Parliament

- Discussions had between:
- ACMD Technical Committee, Full ACMD, Drug and Alcohol Licensing Unit, Chief Scientific Advisors for the Home Office and Home Office lawyers
- Parliamentary time had to be bid for, which was difficult to score due to other demands (Brexit)

Time taken to reach this point ~ 2 years.

Generic Definitions



Generic definition: A revision for synthetic cannabinoids in order to reduce the scope

2016

any of the sub-structures have been modified, and whether or not substituted in any of the linked sub-structures with one or more **univalent** substituents

2019

whether or not substituted in any of the linked sub-structures with a **benzyl or phenyl** group and whether or not such compound is further substituted to any extent with **alkyl, alkenyl, alkoxy, halide, haloalkyl or cyano** substituents

Initial Proposals to Advisory Council on the Misuse of Drugs (Dec 2017)



Generic definition: A revision for synthetic cannabinoids in order to reduce the scope



Exempt product definition: utilised or further developed to cover multi-well screening plates



Compound specific exemption: to apply to the Home Office for a compound-specific exemption



Clinical trial schedule: with reduced requirements for trials with HRA ethical committee approval.



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How Drafting Legislation works in the UK



ACMD



Home
Office



Parliament



2016

Third generation synthetic
cannabinoid



2016

Third generation synthetic
cannabinoid

2017

ACMD
Legitimate use of controlled drugs:
research and healthcare



2016

Third generation synthetic
cannabinoid

2017

ACMD

Legitimate use of controlled drugs:
research and healthcare

2019

(Amendment) Order 2019



2016

Third generation synthetic
cannabinoid

2017

ACMD

Legitimate use of controlled drugs:
research and healthcare

2019

(Amendment) Order 2019

The House of Commons and the House of Lords



Dangerous Drugs
Supply and Appropriation (Main Estimate)
Commons at 3:49 pm on 3rd July 2019

Alert me about debates like this



Nick Hurd The Minister of State, Home Department

I beg to move,

That the draft [Misuse of Drugs Act 1971](#) laid before this House on 4 June, be approved.

I am sure that [Members of the House](#) will be made by the draft order is based on scientific evidence and is therefore distinct from other amendments which have recently been brought forward for debate. I would like to record my thanks to the [Advisory Council on the Misuse of Drugs](#) for its advice on the matter and for its continued support of the draft order.

STATUTORY INSTRUMENTS

2019 No. 1323

DANGEROUS DRUGS

The Misuse of Drugs Act 1971 (Amendment) Order 2019

Made - - - - 8th October 2019

Coming into force - - 15th November 2019

At the Court at Buckingham Palace, the 8th day of October 2019

Present,

The Queen's Most Excellent Majesty in Council

In accordance with section 2(5) of the Misuse of Drugs Act 1971(a), a draft of this Order has been laid before Parliament on the recommendation of the Advisory Council on the Misuse of Drugs and approved by a resolution of each House of Parliament.

(Amendment) Order 2019

15 July 2019
Volume 799

(Amendment) Order 2019.

Committee

(Amendment) Order 2019

Misuse of Drugs Act 1971 in that it is based on

introduce further controls on compounds

The new generic had been run through compliance software and shown to decrease the numbers by ~ 90%

Companies are freed up from the burden of Schedule I constraints

Worldwide research can more easily be carried out



R&D

Pre-clinical

Clinical trials

Regulatory update and scale up

**End to end
research
exemption**

Solution

And it was all going so well (Part II)



2019

(Amendment) Order 2019



2019

(Amendment) Order 2019

2021

Cumyl-PeGaClone -
Convention on Psychotropic
Substances



2021

Cumyl-PeGaClone -
Convention on Psychotropic
Substances

2022

Home Secretary

2023

ACMD
Cumyl-PeGaClone and other recently
encountered synthetic cannabinoid
receptor agonists

Title

	In force	Proposed	Increase
ChEMBL33	3912	3325	85%
Pharma	7041	8518	121 %

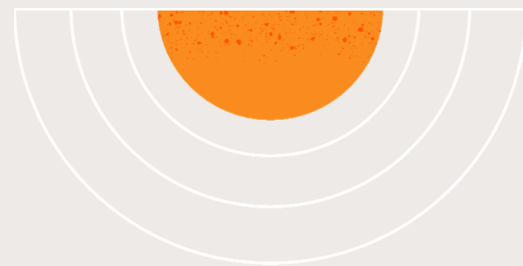
Note:

Most of the hits are against one of the generic structures

ChEMBL analysis showed assay data for ~270 new hits, around 50 being active
Pharma: Compounds in late stage with no activity

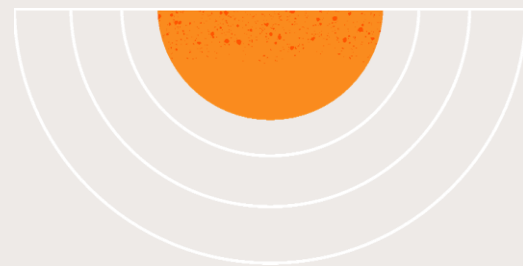
ACMD states that no commercial compounds have been captured - 4
Clotrimazole - Lotrimin - Canesten

Wrap up



- Anyone carrying out research or involved with moving compounds needs to have access to compliance software
 - Generic definitions make it impossible to manage research otherwise
- Through legislation watches carried out by systems used to detect controlled substances such as Compliance Checker, future changes to law can be anticipated and discussions started if needed...
 - Cumyl-PeGaClone generic amendment

Thanks



- ACMD for giving me this opportunity
- GSK for letting me run with it
- Chemaxon for inviting me to present
- Especially Nikki Mihala for help with the slides

Thank you

Zofia Jordan

zofiajordan@Scjbiopharm.com

