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Psychedelic Drugs in Psychiatry - A European Regulatory Perspective

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Disclaimer

- As member of a NCA and governement employee I have **no Conflicts of Interest** to declare.
- **All information** presented here **is publically available**.

Content

1. Unmet medical need for treatment of mental disorders and increasing interest in psychedelic research
2. Regulatory (clinical) background - **High level**
3. **Main scientific and regulatory challenges for psychedelics**
4. What can be offered – European regulatory framework?
5. Conclusions with a view to the future
6. Questions

Unmet medical need and increasing interest in psychedelic drugs

Psychiatric Diseases - Unmet medical need

- In the EU, mental health problems affect more than 1 in 6 people (17,3% or 84 million).
- Economic costs exceed 4% of gross domestic product (~ 600 billion EURO).
- Sharp increase of mental diseases due to the COVID-19 pandemic
- **Major Depressive Disorder** (MDD) is the leading cause of disability worldwide according to WHO.
  - > 300 million individuals worldwide, including 40.2 million in Europe and 17.5 million in the US
  - Affects core aspects of life – eating, sleeping, energy level, self-worth, intellect, and the desire to live
  - MDD is associated with a reduction in life expectancy by 10 years.
  - Up to 20% are considered non-responders to standard antidepressants.

https://www.cdc.gov/mmwr/volumes/69/wr/mm6932a1.htm;

https://www.oecd.org/health/health-at-a-glance/;

https://www.who.int/publications/i/item/depression-global-health-estimates

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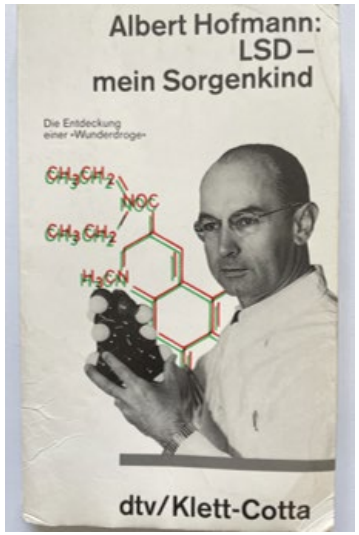
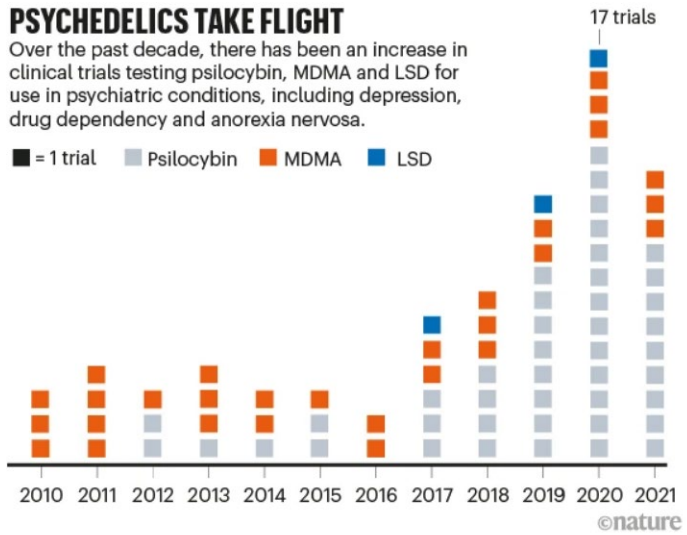
Evolving landscape of psychedelic research





- **1938** Albert Hofmann discovers LSD
- **1971** "War on drugs" coined by President Richard Nixon
- **2010 -->** Psychedelics take flight https://www.nature.com/articles/d41586-021-00187-9
- **January 24, 2024** **Horizon Europe: € 6.5 million EU program**
  EU funds first psychedelic study in **patients with incurable diseases**:
  COPD, MS, ALS, atypical PD

https://www.politico.eu/article/eu-funds-first-psychedelic-study-in-patients-with-incurable-diseases/

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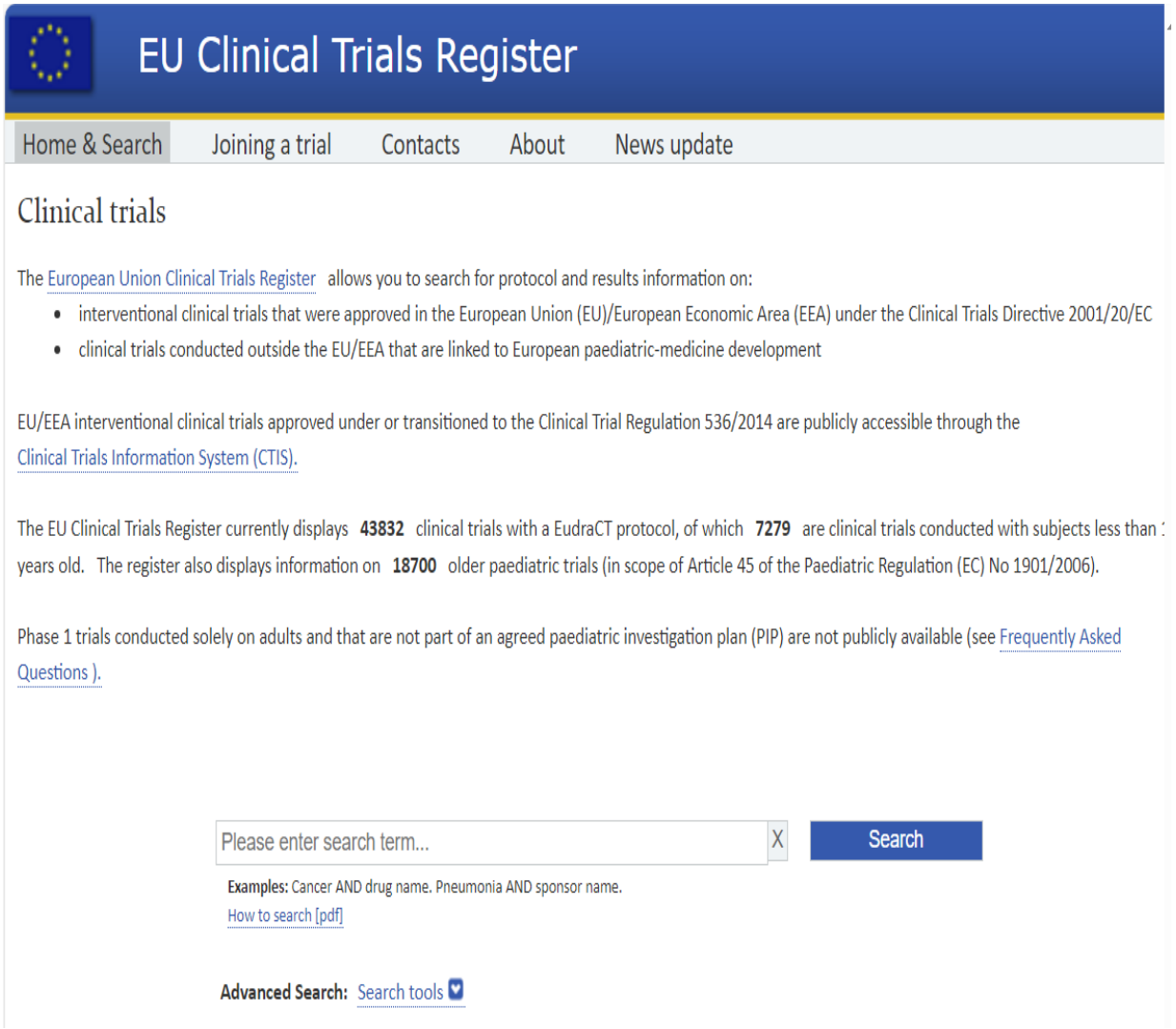
From stigmatisation to EXPECTATION

EU Clinical Trial Register (17 Feb 2023 → 02 Apr 2024)

EU Clinical Trials for Various CNS conditions (and increase in ~13 months):

- 11→19 ongoing clinical trials in EU with psilocybin
- 4→7 trials ongoing with MDMA
- 1→3 trial with LSD



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Recent activities from EU regulators

Publications and conferences

- **The therapeutic potenital of psychedelics: the European regulatory perspective**

Butlen-Ducuing F, McCulloch DE, Haberkamp M, Mattila T, Bałkowiec-Iskra E, Aislaitner G, Balabanov P, Lundberg J, Stenbæk DS, Elferink A, Knudsen GM, Thirstrup S. The therapeutic potential of psychedelics: the European regulatory perspective. Lancet. 2023 Mar 4;401(10378):714-716. doi: 10.1016/S0140-6736(23)00264-7. Epub 2023 Feb 10. PMID: 36780909.

- **ECNP New Frontiers meeting; Nice March 2023**
- **Knowledge gaps in psychedelic medicalisation: Clinical studies and regulatory aspects**
  https://doi.org/10.1016/j.nsa.2024.103938
- **Regulatory workshop Insight Conference, Berlin, 31.08.2023**
- **EMA Depression Guideline, Revision 3**
- **The new European Medicines Agency guideline on antidepressants: a guide for researchers and drug developers**

Butlen-Ducuing F, Haberkamp M, Aislaitner G, Bałkowiec-Iskra E, Mattila T, Doucet M, Kollb-Sielecka M, Balabanov P, Leuchs AK, Elferink A. The new European Medicines Agency guideline on antidepressants: a guide for researchers and drug developers. Eur Psychiatry. 2023 Dec 15;67(1):e2. doi: 10.1192/j.eurpsy.2023.2479. PMID: 38098366; PMCID: PMC10790230.

Updated EMA Draft Depression Guideline, Revision 3

It was timely to come forward with an update

- Revison 2 from 2013
- Section on Rapid acting antidepressants (RAADs) based on what we have learned from approving Spravato (esketamine) for treatment resistant depression (4.3.2.3)
- Section on psychedelics (4.3.2.4)

1 September 2023
2 EMA/CHMP/185423/2010, Rev.3
3 Committee for Medicinal Products for Human Use (CHMP)

4 Guideline on clinical investigation of medicinal products in
5 the treatment of depression
6 Draft

Draft agreed by CNSWP	1 September 2023
Adopted by CHMP for release for consultation	4 September 2023
Start of public consultation	15 September 2023
End of consultation (deadline for comments)	31 March 2024

7
8 This guideline replaces "Guidance on clinical investigation of medicinal products in the treatment of
9 Depression' (EMA/CHMP/185423/2010, Rev. 2)
10

Comments should be provided using this EUSurvey form. For any technical issues, please contact the EUSurvey Support.

11
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Keywords	***major depression, major depressive episode, partial response, treatment resistance, suicidal thoughts, suicidal behaviour, suicide, acute treatment, maintenance treatment, recurrence prevention***

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EMA Guidelines - Clinical efficacy and safety: nervous system

Guidelines

- Clinical development of medicinal products for the treatment of autism spectrum disorder (ASD)
- Clinical development of medicinal products intended for the treatment of pain
- Clinical investigation of medicinal products for the treatment and prevention of bipolar disorder
- Clinical investigation of medicinal products for the treatment of amyotrophic lateral sclerosis
- Clinical investigation of medicinal products for the treatment of attention deficit hyperactivity disorder (ADHD)
- Clinical investigation of medicinal products for the treatment of Duchenne and Becker muscular dystrophy
- Clinical investigation of medicinal products for the treatment of multiple sclerosis
- Clinical investigation of medicinal products for the treatment of obsessive compulsive disorder
- Clinical investigation of medicinal products for treatment of migraine
- Clinical investigation of medicinal products in the treatment of depression
- Clinical investigation of medicinal products in the treatment of epileptic disorders
- Clinical investigation of medicinal products in the treatment of Parkinson's disease
- Clinical investigation of medicinal products indicated for generalised anxiety disorder
- Clinical investigation of medicinal products indicated for panic disorder
- Clinical investigation of medicinal products indicated for the treatment of social anxiety
- Clinical investigation of medicinal products, including depot preparations in the treatment of schizophrenia
- Development of medicinal products for the treatment of alcohol dependence
- Development of medicinal products for the treatment of post-traumatic stress disorder

Development of new medicinal products for the treatment of smoking

Clinical investigation of medicines for the treatment of Alzheimer's disease

Medicinal products for the treatment of insomnia

Treatment of premenstrual dysphoric disorder

[FDA Accepts, Grants Priority Review of NDA for MDMA-Assisted Therapy for PTSD (MAPP1 and MAPP2)]

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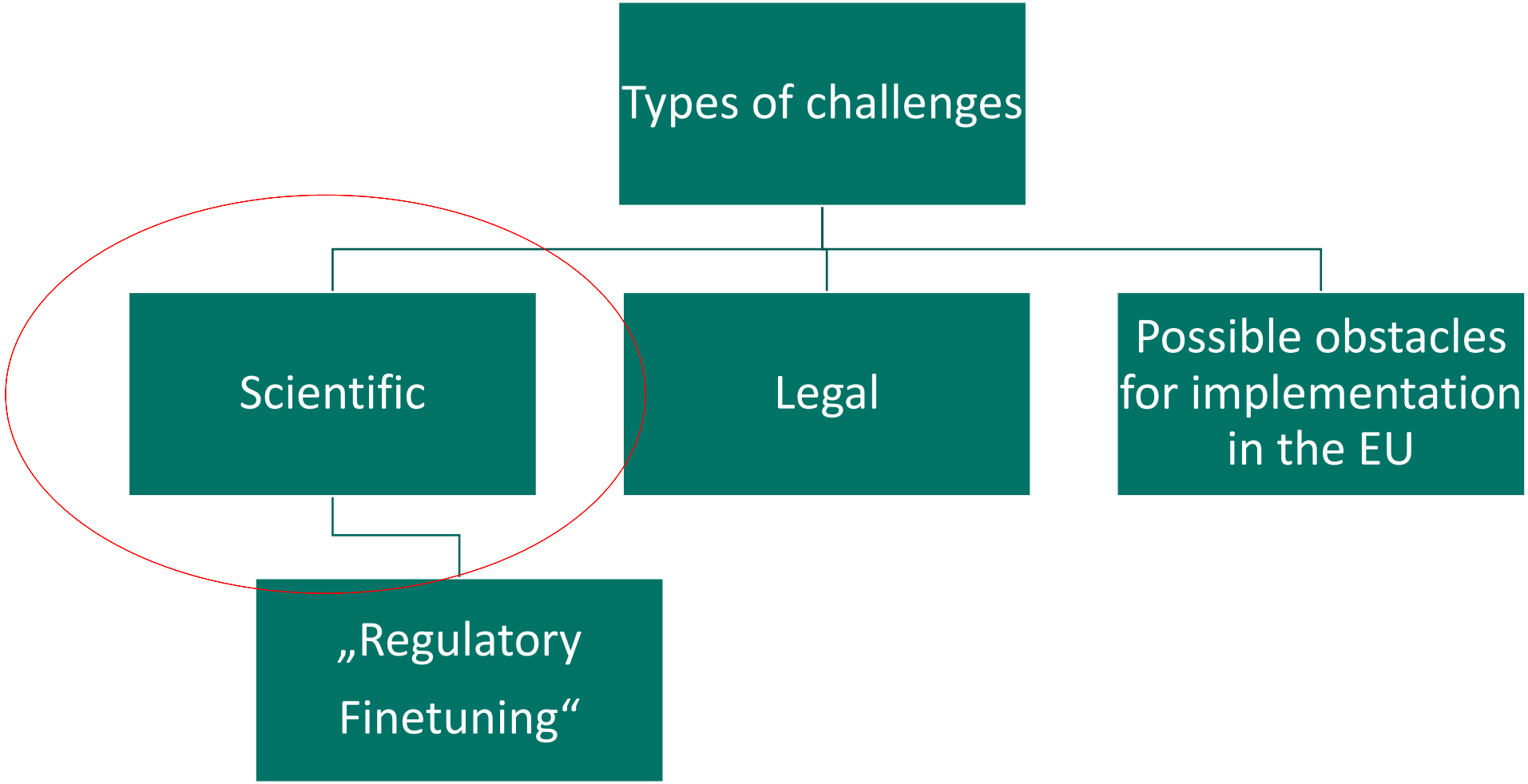
Scientific and regulatory challenges for psychedelics



Psychedelics (e.g. Psilocybin, LSD, MDMA)

- Several studies with psychedelics in the field of depression are currently ongoing. [Psilocybin is starting phase 3 for treatment resistant depression (TRD)].

- As with all other antidepressants, to establish a positive benefit/risk randomized, **double-blind placebo-controlled short-term trials** are needed, as well as trials to determine the **maintenance of effect**.

- Due to the safety profile and challenging study setup and execution, it is recommended to **start development in a more severely affected population**, such as patients with **TRD** (section 4.4.1.).

- The psychoactive effects of currently investigated psychedelic agents present several challenges for the design, conduct, and interpretation of clinical trials:

Main challenges

- Placebo and/or comparator issue and maintaining the double blind
- Expectancy bias (positive and negative): low dose or active placebo
- Dose finding and justification of the adequate therapeutic dose
- Maintenance of effect: endurance and need for recurrent dosing
- Psychotherapy and psychological support as integral part of the therapy?
- Setting and training need to be standardized
- Safety (anxiety with derealisation, negative trips, addiction, cardiovascular effects)
- HTA and post approval considerations

How to regulate psychedelics?

➢ Establishment of a positive benefit/risk balance

"The findings are both intriguing and sobering." "Longer and larger trials are needed…"
https://www.nejm.org/doi/full/10.1056/NEJMe2210975
https://www.nejm.org/doi/pdf/10.1056/NEJMoa2206443?articleTools=true

➢ Combination with psychological support and/ or psychotherapy

➢ Depending on the mechanism of action, safety and the potential for addiction should be carefully evaluated.

➢ Regulatory tools:

- SmPCs, RMP, PASS studies
- Additional risk minimisation measures,
  i.e. educational materials, training , controlled access programs
- Legal status, Restricted Medical Prescription,
  e.g. "XX should only be prescribed by physicians experienced in psychedelic assisted therapy"

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What can be offered?

European regulatory framework

What can be offered?

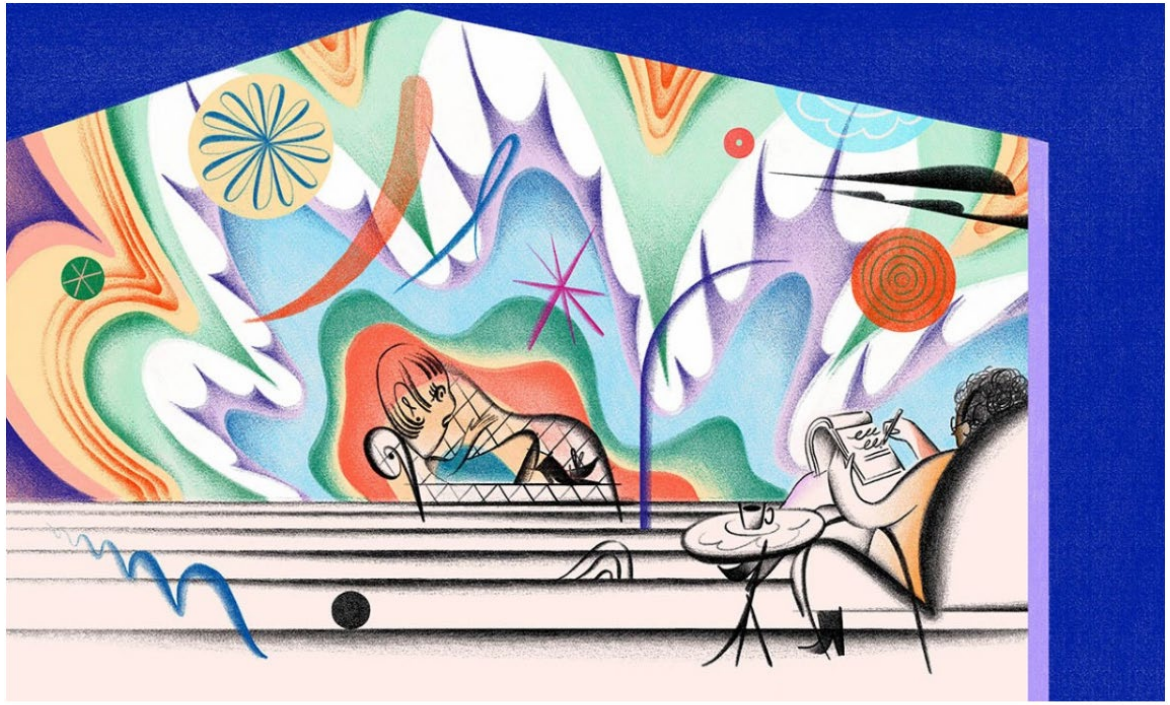

Illustration by Gizem Vural

https://www.nature.com/articles/d41586-021-00187-9

➢ **Early involvement of regulators**:

- at **Innovation Task Force (ITF)** or
- Scientific Advice Working Party (**SAWP**) for **Scientific advice**
- Specific **SAWP qualification procedures** on assessment instruments, methods, and study design
- Consultations **in parallel with HTA**
- **Regulatory Guidelines**

➢ The new EMA **clinical Trials Regulation**

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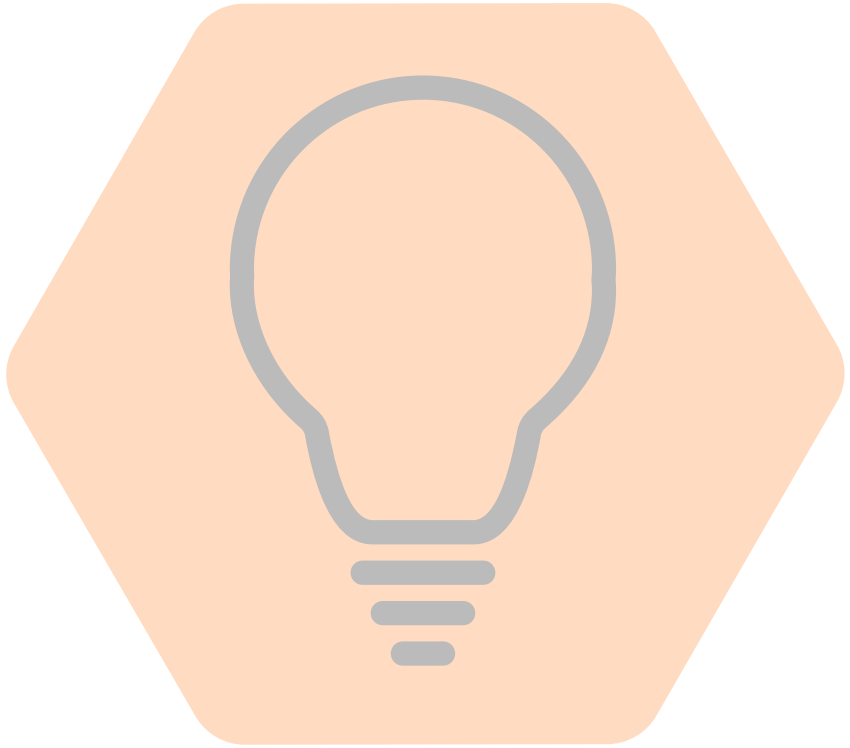
Conclusions
with a view to the future

Conclusions with a view to the future



1. Psychedelics need to be regulated according to general standards for drug approval. The field is dynamic and constantly evolving.
2. Regulatory Guidelines are constantly adapted if scientifically reasonable.
3. Appropriate risk evaluation and mitigation strategies supported by data need to be developed.
4. Scientific Advice and early dialogue is recommended and is probably helpful.
5. Targeting the “hallucinogenic” 5-HT2A receptor without eliciting hallucinations may be achievable?? Subjective experience needed for therapeutic benefit?

https://www.nature.com/articles/s41586-022-05258-z

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Thank you very much for your attention!

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Back-up

Several psychedelic drugs are currently under focus

Classical psychedelics (5-HT2A receptor agonism)	Atypical psychedelics
Mescaline Dimethyltryptamine (DMT) **Lysergic Acid Diethylamide (LSD)** **Psilocybin**	3,4-methylendioxymethamphetamine (**MDMA**, ectasy) **Ketamine, Esketamine**

https://www.prnewswire.com/news-releases/global-psychedelic-drugs-markets-2022-2025-emergence-of-psychedelic-assisted-psychotherapy-pap--rising-approval-for-additional-psychedelic-drugs--growing-popularity-of-psilocybin-301510800.html

- Single-Dose Psilocybin for a Treatment-Resistant Episode of Major Depression
  https://www.nejm.org/doi/pdf/10.1056/NEJMoa2206443?articleTools=true

Are the Narcotic Acts/Laws an obstacle from a regulatory perspective? → Opening

- **Break-through designation FDA 2017 and 2019 for psilocybin and MDMA**

- **Australian TGA down-listed psilocybin and MDMA** from prohibited (schedule 9) to controlled (schedule 8) to enable prescribing by specifically authorized psychiatrist February 2023, starting July 1st

- Indications TRD and PTSD

➢ National regulations may have to be adapted, which is possible without violating the convention. E.g. Down-listing from Annex I (prohibited) to Annex III (controlled) in Germany

➢ In the medium term, the schedules should be reclassified and the evaluation process initiated at an early stage.

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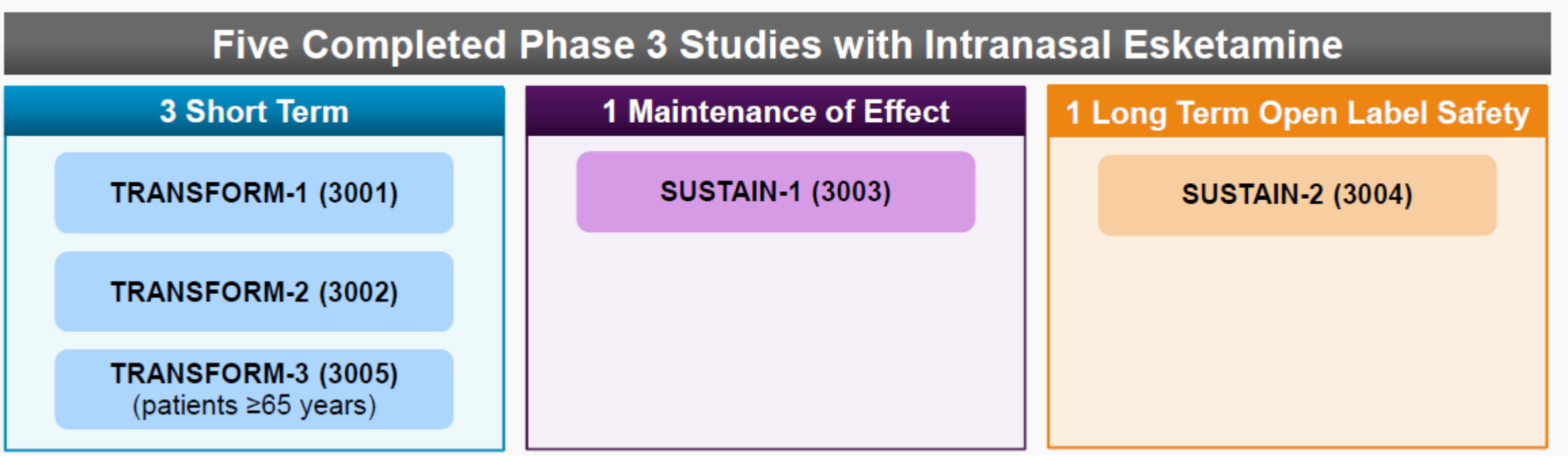
Studies for licensing of Esketamine

TRD

Five Phase 3 clinical studies in adult patients (18 to 86 years) with treatment-resistant depression (TRD) who met DSM-5 criteria for major depressive disorder and were non-responders to at least two oral antidepressants (ADs) treatments, of adequate dosage and duration, in the current major depressive episode. n = 1833 patients



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EMA Depression Guideline is currently being updated

Work in progress by CNS Working party at EMA

Clinical investigation of medicinal products in the treatment of depression

Share

Current effective version	Revision 2 - Adopted guideline
Reference number	CHMP/185423/2010 Rev. 2
Published	30/05/2013
Effective from	01/12/2013
Keywords	Major depression, major depressive episode, partial response, treatment resistance, suicidal thoughts, suicidal behaviour, suicide, acute treatment, maintenance treatment, recurrence prevention
Description	This document provides guidance on the development of medicinal products for acute and long-term treatment of major depressive disorder

Document history

Revision 3 *In progress*	Concept paper	Published: 18/11/2016 Deadline for comments: 28/02/2017
Revision 2 *Current version*	Adopted guideline	In operation: 01/12/2013–present
	Draft guideline	Published: 11/10/2011
	Concept paper	Published: 19/02/2009
Revision 1	Adopted guideline	In operation: 01/10/2002–30/11/2013

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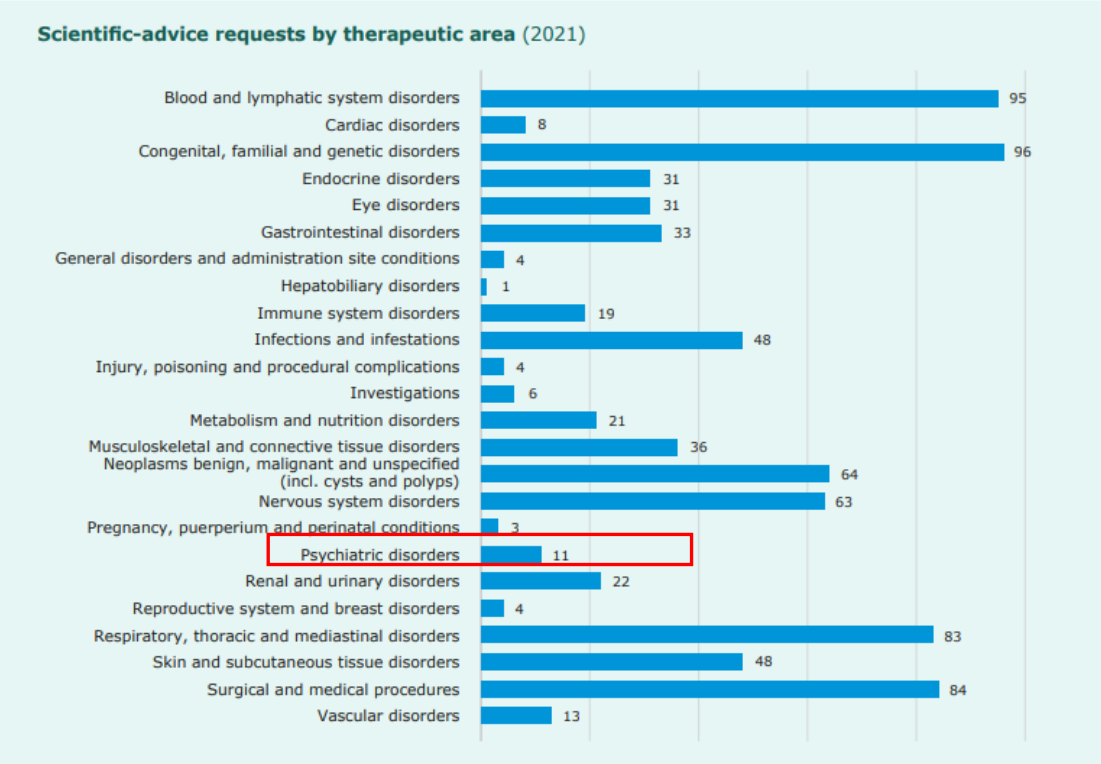
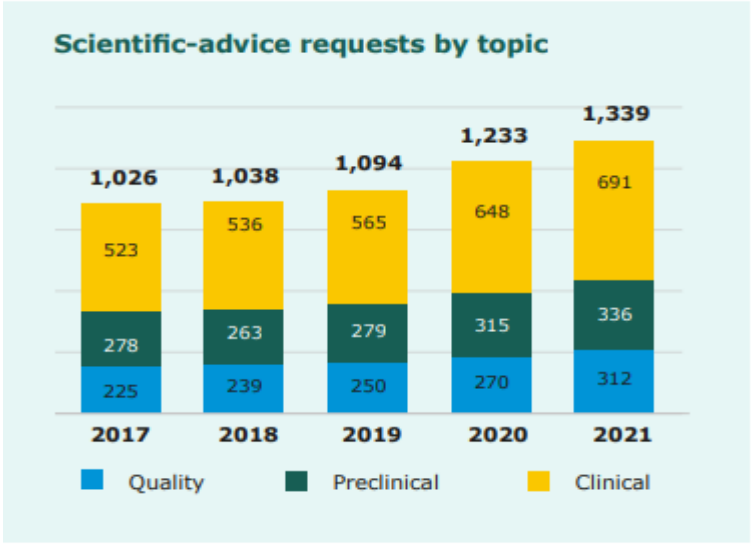
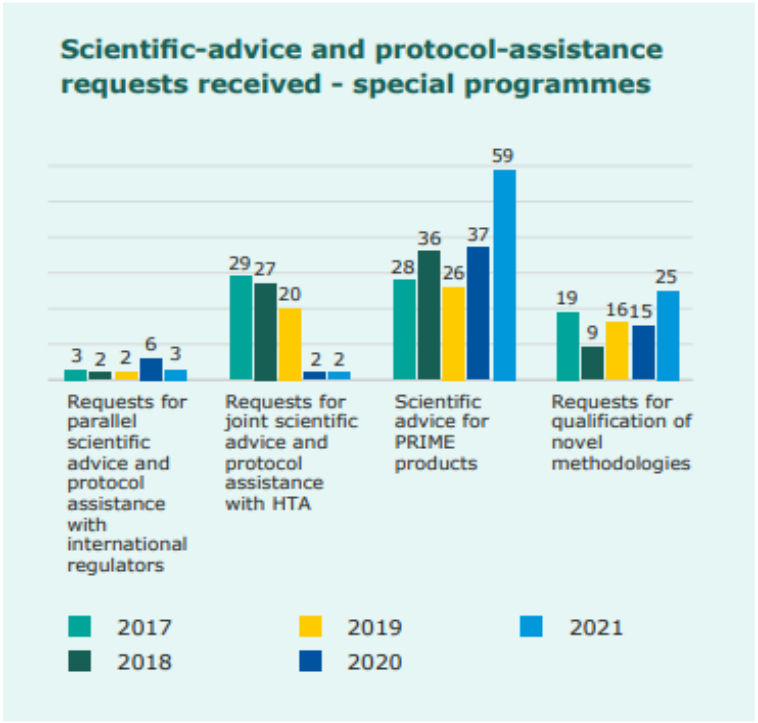
Scientific Advice at EMA – statistics (2021)



22% of the total number of requests came from SMEs.





https://www.ema.europa.eu/en/documents/annual-report/2021-annual-report-european-medicines-agency_en.pdf

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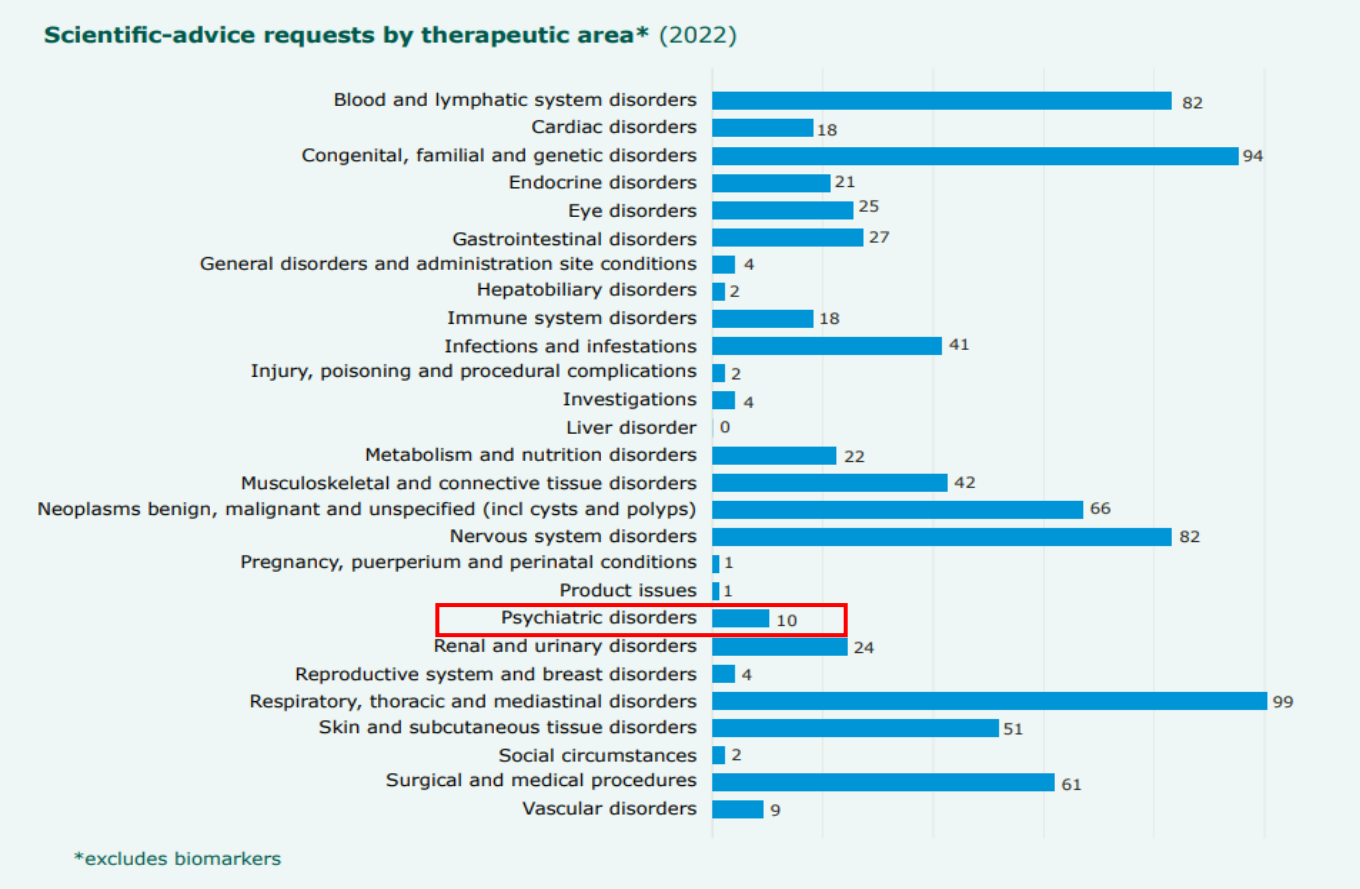
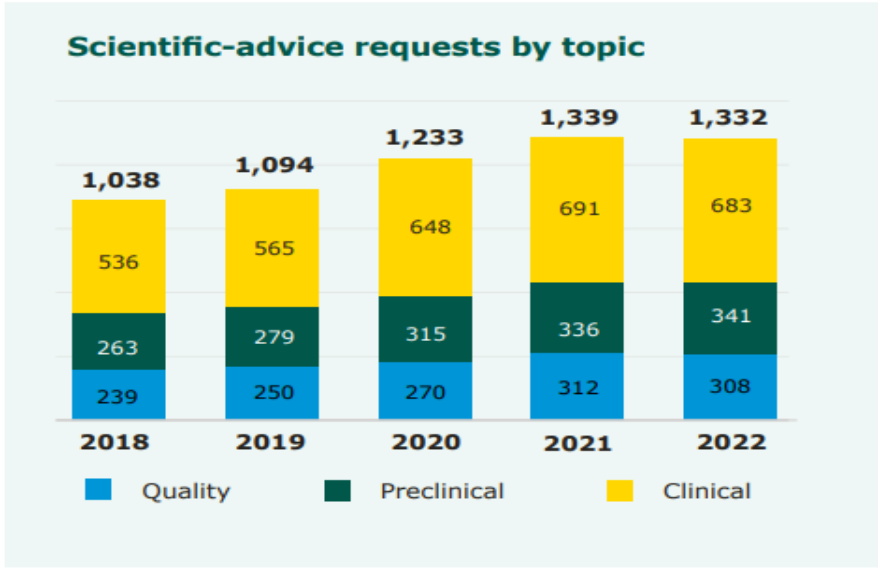
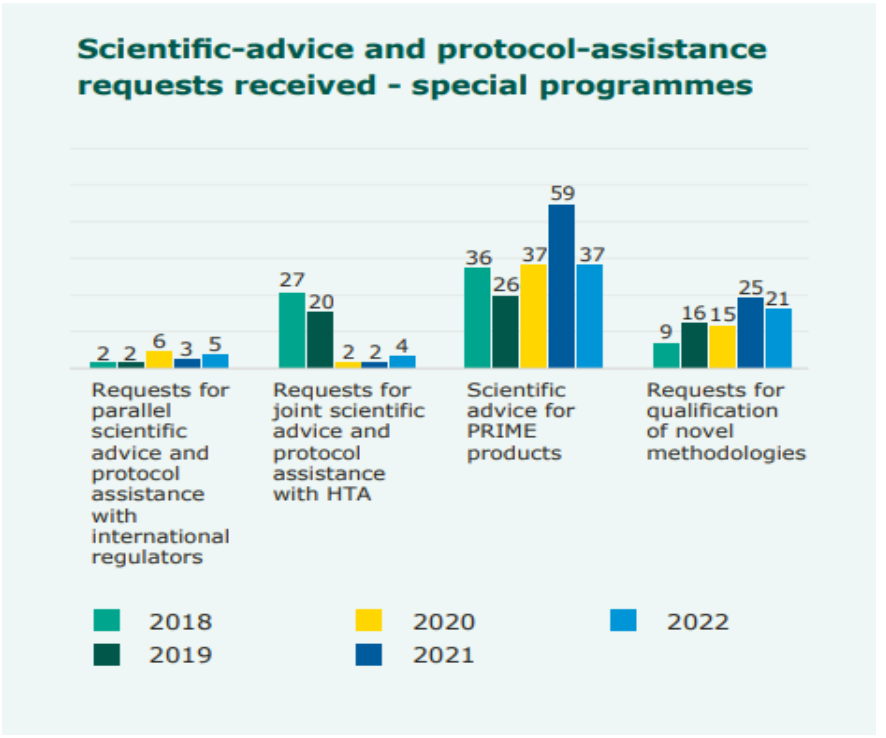
EMA Multi-stakeholder workshop on psychedelics, April 2024; 27

Scientific Advice at EMA – statistics (2022)







https://www.ema.europa.eu/en/documents/annual-report/2022-annual-report-european-medicines-agency_en.pdf

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