WORKING DOCUMENT — APRIL 2025

Psychedelic therapies and treatment resistance: a European proposal for the right to hope

How the European Union can begin today to build the conditions for fair, safe and monitored access to psychedelic therapies in treatment-resistant psychiatric conditions

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1. A crisis that cannot wait

In Europe, over 30 million people suffer from major depression. Around 30-40% do not respond adequately to authorized pharmacological treatments: these are people with treatment-resistant depression (TRD). To them must be added tens of millions of people with post-traumatic stress disorder (PTSD) and substance use disorders (SUD), for whom the therapies available often prove insufficient or wholly unsatisfactory. This population — invisible in aggregate statistics, excluded from innovation, abandoned by ordinary therapeutic pathways — constitutes one of the greatest silent scandals in European healthcare.

Scientific evidence of possible therapeutic responses exists. Psychedelic-assisted therapies — psilocybin, MDMA and related compounds — have shown promising results in controlled clinical studies, including phase 2 and phase 3 trials, in TRD, PTSD and SUD. Australia authorized the therapeutic use of MDMA and psilocybin in 2023. The U.S. FDA granted both molecules Breakthrough Therapy designation. In the Netherlands, Switzerland and Israel, structured clinical programs already exist. Yet Europe still has no shared regulatory framework governing access to these therapies for those who could benefit from them today.

2. The European tools: they exist, so why are they not being used?

The European Union already has the necessary legal mechanisms. **Article 83 of Regulation (EC) No 726/2004** allows the EMA's CHMP to adopt opinions on the conditions for compassionate use[1] of medicinal products not yet authorized, with the explicit aim of promoting a common approach among Member States. EMA guidelines specify that "an approach as common as possible" is the founding principle of the system.

This principle has not yet been applied in psychiatry to psychedelic-assisted therapies. No Member State has ever formally requested a CHMP opinion on compassionate access to psilocybin or MDMA for treatment-resistant TRD, PTSD or SUD. The Article 83 CHMP opinion procedure has been activated only six times in the entire history of the system — for medicines

[1]Compassionate use under Article 83 of Regulation (EC) No 726/2004: a mechanism that allows one or more Member States to make an as-yet unauthorized medicinal product available to patients with a serious, chronic or life-threatening illness for whom no satisfactory therapeutic alternatives exist. The Committee for Medicinal Products for Human Use, CHMP, may adopt an opinion on the conditions of use in order to promote a common approach among Member States. It is not binding, but Member States are required to "take it into account".
https://www.ema.europa.eu/en/human-regulatory-overview/research-development/compassionate-use — EMA official page on compassionate use
https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-compassionate-use-medicinal-products-pursuant-article-83-regulation-ec-no-7262004_en.pdf — CHMP guidelines under Article 83

against COVID-19, hepatitis C and influenza. The gap in psychiatry is not technical: it is a matter of political will.

An indirect signal, however, comes from existing authorizations: EMA and AIFA have authorized esketamine (Spravato) for TRD, thereby formally recognizing treatment-resistant depression as a condition of *unmet need* within the European regulatory system. This precedent does not exhaust the problem — it leaves uncovered a large share of the TRD population that does not respond even to esketamine — but it provides a definitional and political anchor to build on. There is also a Reflection Paper[2] by the EMA (EMA/CHMP/761905/2013) on TRD as an *endpoint* in clinical trials: the direct methodological precedent on which to base a request for a new document addressing the conditions for compassionate access.

3. The European pharmaceutical reform: a window opening

In December 2025, the European Parliament and the Council of the EU reached political agreement on the most significant reform of European pharmaceutical law in the last twenty years. Among the developments most relevant to this initiative: the introduction of *regulatory sandboxes*[3] — protected regulatory environments in which medicines and innovative protocols that do not fit existing rules can be developed with adapted requirements, under the supervision of the competent authorities — and stronger incentives for orphan medicines, with market exclusivity of up to eleven years for "breakthrough" products in indications for which no therapies are available.

For psychedelic-assisted therapies, *sandboxes* are the most suitable regulatory instrument that European law has ever conceived. These therapies present a feature that unsettles standard evaluation models: the molecule is inseparable from the psychotherapy that accompanies it, and traditional clinical trials struggle to assess interventions of such complexity. The problem has already emerged concretely: in August 2024, the FDA responded to the application for approval of MDMA for PTSD by requesting a new phase 3 trial and raising methodological questions precisely on these variables — therapist competence, the quality of the therapeutic alliance, and the consistency of the psychotherapeutic protocol across different trial sites.

The issue is crucial. How do we evaluate a therapeutic intervention in which the response depends not only on the molecule but on the quality of the therapeutic relationship? European

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[2]The EMA Reflection Paper on treatment-resistant depression as an endpoint in clinical trials is the key EMA methodological document that first formally framed the concept of TRD at European regulatory level for the purposes of evaluating clinical studies. It is the direct precedent on which the request for a new Reflection Paper can be based, one that includes the compassionate-access dimension and the operational conditions for psychedelic-assisted therapies.

[3]Pharmaceutical regulatory sandbox: a temporary and controlled regulatory environment, introduced for the first time into EU pharmaceutical law by the December 2025 reform, in which medicinal products or innovative protocols that do not fit ordinary rules can be developed with adapted requirements, under the direct supervision of the competent authorities. The European Commission establishes it on the recommendation of EMA. For psychedelic therapies — where the molecule is inseparable from the psychotherapy that accompanies it — it is the most suitable regulatory instrument ever conceived by European law. It will not become operational before 2028.
https://www.ema.europa.eu/en/news/ema-welcomes-political-agreement-new-eu-pharmaceutical-legislation — EMA press release on pharmaceutical reform (11 Dec. 2025)
https://www.europarl.europa.eu/news/en/press-room/20251209IPR32110/deal-on-comprehensive-reform-of-eu-pharmaceutical-legislation — European Parliament press release on the reform
https://www.ema.europa.eu/en/about-us/what-we-do/reform-eu-pharmaceutical-legislation — EMA page on implementation of the reform

sandboxes will also be created to answer this question. But without data on patients' psychotherapeutic history — that is, without knowing how many of them have ever received structured psychotherapy, what type, for how long, and with what outcome — there is a risk that the sandboxes will find emptiness beneath them.[4] The work on data must begin before the instruments become operational.

4. The data problem: what does not exist and why it matters

4.1 DARWIN EU and its structural limits

Europe already has an advanced health data infrastructure: DARWIN EU[5] — Data Analysis and Real World Interrogation Network — is the federated network established by EMA, fully operational since 2024, with 30 data partners in 16 European countries and access to data from around 180 million patients. The data remain physically in local health systems and are analyzed on site, but they are translated into the common OMOP[6] so that they can be compared across countries. The public catalogue of DARWIN EU studies already includes research on antipsychotics, clozapine and, significantly, prescribing trends for ketamine and esketamine.

But DARWIN EU works well on what health databases already contain as structured variables: International Classification of Diseases (ICD) diagnoses, drug prescriptions, hospitalizations, codified procedures. The system queries well-ordered archives. The problem is that psychiatric treatment resistance is nowhere stored in structured form.

4.2 Treatment resistance does not exist as data

Treatment resistance in psychiatry is not an ICD code. It is a clinical trajectory: how many medicines that patient has already received, for how long, at what dose, with what response, and with what adherence. It is a trajectory that clinicians and psychiatrists know very well in daily practice, but that is not recorded in any European health system in a way that is comparable across countries. Querying DARWIN EU on treatment resistance in psychiatry today means looking for something that has never been stored. This is not a technical limitation of the system: it is data that simply do not exist.

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[4]FDA Complete Response Letter on MDMA-PTSD (August 2024): the Food and Drug Administration's response to the application for approval of MDMA for PTSD submitted by Lykos Therapeutics (formerly MAPS PBC), in which the FDA requested a new phase 3 trial, raising methodological questions regarding the adequacy of blinding, the quality and consistency of psychotherapy across different centres, and variables concerning therapist competence and therapeutic alliance. It is not a definitive rejection: it is a request for better data on variables that standard trials were not designed to measure.

[5]DARWIN EU (Data Analysis and Real World Interrogation Network): a federated network of 30 data partners in 16 European countries, fully operational since 2024, created by EMA and the European regulatory network to generate real-world evidence in support of decisions by EMA scientific committees. Data remain in local health systems (the federated principle) but are translated into the common OMOP model so that they can be compared. It has access to data from around 180 million patients. It is not a tool open to researchers or associations: it is reserved exclusively for supporting EMA's regulatory decisions.
https://www.ema.europa.eu/en/about-us/how-we-work/data-regulation-big-data-other-sources/real-world-evidence/data-analysis-real-world-interrogation-network-darwin-eu — DARWIN EU official page on EMA
https://catalogues.ema.europa.eu/network/49628 — DARWIN EU study catalogue (including studies on ketamine and esketamine)

[6]OMOP (Observational Medical Outcomes Partnership): a standard data model, originally developed in the United States and now adopted globally — including by DARWIN EU — that translates diagnoses, prescriptions, procedures and laboratory results into a common format comparable across different national health systems. It solves the Babel problem of medical records: a diagnosis coded differently in Italy, Germany and the Netherlands becomes comparable. Structural limits: it does not capture variables that are not routinely coded — qualitative response to a drug, the patient's psychotherapeutic history, the social context — because those data exist as free text in clinical notes, not as structured codes.

Yet operational definitions of TRD do exist in the clinical literature, and some have already been incorporated at regulatory level: EMA and AIFA, in assessing and authorizing esketamine, formally defined TRD as failure to respond to at least two adequate antidepressant treatments. The definitional threshold exists. What is missing is systematic collection and correlation with concurrent treatments, the settings chosen, and the conditions that shape care: no one cross-references this definition with patients' real trajectories, either nationally or at European level.

4.3 The biggest gap: psychotherapy and social determinants

There is, in fact, a second gap, even deeper and almost never named in the regulatory debate: even if we built a register of treatment resistance based on pharmacological trajectories, we would still remain in the dark about another variable that matters at least as much: the patient's psychotherapeutic history and the social determinants of their mental health.

How many of the patients classified as treatment-resistant have ever received structured and adequate psychotherapy? Of what kind — cognitive-behavioural, psychodynamic, EMDR, systemic? For how long, with what frequency, with what therapeutic alliance? How many live in conditions of social isolation, economic precarity, exposure to violence or trauma? In European administrative databases these variables scarcely exist. The Observational Medical Outcomes Partnership model, OMOP, does not capture them. Yet every serious researcher in the field of psychedelic therapies acknowledges that therapeutic response depends significantly on the quality of psychological preparation, integration sessions, the therapeutic alliance, and the patient's living context.

How will we one day be able to assess the pharmacological trajectories of psychiatric patients — and decide who is truly "resistant" to treatment — if we do not have data that genuinely intersect with what determines or heals mental health? Can a patient who has never received adequate psychotherapy be said to be treatment-resistant, or is that a patient who has not received a decisive part of care? Confusing such a patient with one who has failed every possible treatment is not only a clinical error: it is a regulatory error with consequences for the rights of the people concerned.

The future of evaluating psychedelic therapies — and, more broadly, any integrated therapy — runs through this point. European sandboxes, when they become operational, will have to assess protocols in which drug and psychotherapy are inseparable. Without structured data on psychotherapeutic history and social determinants, that evaluation will be blind in one eye.

5. The three priority actions identified by ALC

5.1 CHMP opinion and Reflection Paper on compassionate use in psychiatry

The first action is to put to the CHMP a question that no one has yet formulated in a coordinated way: a **formal opinion,** under Article 83, on the conditions for compassionate use of psilocybin and MDMA for the indications of TRD and treatment-resistant PTSD, preceded by a **paper** that operationally defines treatment resistance and the minimum conditions of *setting*, professional qualification and data collection for the safe delivery of these therapies.

This path requires building a European legal and regulatory network among those Member States — first and foremost the Netherlands, Germany, Portugal, Italy and the Czech Republic — where clinical experience or experimental programs already exist, in order to formulate a joint or coordinated request to the CHMP.

5.2 The European register on treatment resistance in psychiatry

The second — and in some respects the most urgent — action is to build the empirical foundation on which everything else rests: a **European register on treatment resistance in psychiatry**, bringing together what today does not exist except in fragmented and disaggregated form, and is therefore of no use for decisions concerning the approval of therapeutic pathways. What is needed is a shared minimum dataset — mandatory minimum variables, interoperable across national health systems — including: shared operational definitions of treatment resistance for TRD, PTSD and SUD; longitudinal therapeutic trajectories (pharmacological and psychotherapeutic); relevant functional outcomes; and, in structured form, the patient's psychotherapeutic history and the main social determinants of mental health.

This dataset would become the source that DARWIN EU itself could query to investigate evidence of unmet need, the empirical basis on which the CHMP and national regulators could ground their opinions on compassionate use, and the starting point for the scientific justification that EMA will have to produce in order to recommend that the European Commission establish a regulatory sandbox. Without European data on treatment resistance and on patients' integrated therapeutic history, that justification cannot be built.

The register is not an alternative to the tools that European pharmaceutical reform is building: it is preliminary and complementary to them. It is the work that must be done now so that the sandboxes — when they become operational in 2028 — will find evidence to stand on, not a void.

5.3 A European legal network for coordinating early access

The fourth action is to build a European network of jurists and lawyers specializing in those Member States where early-access programs for psychedelic-assisted therapies already exist or are being developed. The objective of the network is to coordinate national actions within the framework of European compassionate-use law, to train therapists in advance of the arrival of medicinal products on the market, and to define access protocols for medicines in the experimental phase that are consistent with minimum European requirements — thereby preparing the ground so that future CHMP opinions will encounter national systems already aligned.

6. Why now

European pharmaceutical reform has opened a window that did not exist before. *Regulatory sandboxes* and the strengthening of the PRIME programme[7] for priority medicines, for example, are instruments designed precisely for situations in which scientific innovation has outpaced the regulatory framework's ability to assess it. Psychedelic-assisted therapies fit squarely within this category.

At the same time, the international context has changed. The Australian authorization, FDA designations, and phase 3 trials underway in Europe: the scientific evidence currently available is already sufficient to begin a serious regulatory conversation. Not to authorize products without safeguards, but to build the framework within which a safe and monitored authorization can become possible — and, in the meantime, to guarantee a governed compassionate-access pathway for those who cannot wait.

[7] PRIME is a programme run by the European Medicines Agency (EMA) to enhance support for the development of medicines intended to address unmet medical needs. It is based on early dialogue with companies in order to optimize development plans and speed up assessment.

Treatment-resistant psychiatric patients cannot wait for Europe to finish building its investigative tools while science advances by leaps and bounds. In the short term, early access must be harmonized with the regulatory instruments already in place and, in the medium term, the regulatory process of the near future must be supplied with useful real-world data, shared definitions, and a coordinated institutional request.

The work proposed by ALC and EUMANS aims to help, today, those who are suffering and those who still hope for treatment, while preparing in time for the therapies of tomorrow by bringing together experience and expertise at European level.

To learn more and support the campaign

Psychedelic therapies campaign — Associazione Luca Coscioni:
www.associazionelucacoscioni.it/psichedeliche
EUMANS: **www.eumans.eu**

Main legal references: Article 83 of Regulation (EC) No 726/2004 (compassionate use); Regulation (EC) No 141/2000 (orphan medicines); Article 35 of the Charter of Fundamental Rights of the European Union (right to health); Ministerial Decree of 7 September 2017 and Legislative Decree No 219/2006 (Italian system); Political agreement on EU pharmaceutical reform, 11 December 2025; EMA/CHMP/761905/2013 Reflection Paper (TRD as an endpoint).