The registry on pharmacoresistance in psychiatry: while awaiting the implementation of EU regulatory sandboxes, the work is on data useful to the regulator

Working document by Claudia Moretti, lawyer, Member of the General Council of the Luca Coscioni Association, for which she coordinates the campaign on psychedelic therapies

In December 2025, Europe approved the largest pharmaceutical reform in the last twenty years; among the novelties is the regulatory sandbox[1]. This is a protected regulatory environment in which innovative drugs and therapeutic protocols — those that do not conform to existing rules — can be developed with adapted requirements, under the supervision of competent authorities.

For psychedelic therapies, where the molecule is inseparable from the psychotherapy that accompanies it and standard trials get stuck on this reality, sandboxes are a promising tool. The problem is that they are not yet operational: the text still needs to be formally adopted to enter into force in 2026, with a transitional period extending to 2028. In the meantime, patients with treatment-resistant depression, chronic PTSD, and addictions that do not yield to ordinary treatments continue to wait.

A European instrument for drug data collection already exists: DARWIN EU[2], a federated network of 30 data partners in 16 European countries with access to data from approximately 180 million patients, fully operational since 2024. Catalogues of Real World Data already exist and the investigation system is already a European reality.

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[2] DARWIN EU — Data Analysis and Real World Interrogation Network — is the European real-world data network established by the EMA, fully operational since 2024. It coordinates 30 data partners including hospitals, primary care systems, insurance registries and biobanks in 16 European countries, with access to data from approximately 180 million patients. The technical principle on which it is based is the federated network: data do not move physically, they remain in local healthcare systems and are analysed locally, but are first translated into a common format — the OMOP model — which makes them comparable across countries. The EMA and national competent authorities can commission studies on this system whenever they need to answer regulatory questions about drugs already in use: safety, utilisation in real-world practice, disease epidemiology. It is not a tool open to researchers or associations: it is dedicated exclusively to supporting the decisions of EMA scientific committees. It works very well on what healthcare systems already collect as structured data — diagnoses, prescriptions, coded procedures. It cannot, however, capture what is never recorded in structured form: the clinical response to a treatment, the reason why a therapy was discontinued, the psychotherapeutic history of a patient. Not because of a technical limitation on its part, but because that data simply does not exist in the databases it interrogates.

[1] The term "sandbox" comes from computing: it is the "sandpit" in which children play without causing damage to the rest of the garden — an isolated environment where experimentation is possible without risk to the external system. In the pharmaceutical field, a regulatory sandbox is a temporary and controlled regulatory environment in which an innovative medicinal product or therapeutic protocol — which, due to its characteristics, cannot be developed following the ordinary rules — is tested with adapted requirements, under the direct supervision of competent authorities. It is not a derogation from safety: it is a derogation from standard procedures, with specific safeguards, for the time needed to generate the evidence that ordinary rules cannot produce. The new European pharmaceutical legislation, for which political agreement was reached in December 2025, introduces them for the first time in EU pharmaceutical law. The mechanism provides for the EMA to recommend to the European Commission the establishment of a sandbox, with a detailed plan specifying the product, the scientific and regulatory justification, the safety criteria and the patient population. The Commission establishes it in consultation with the Member States. For psychedelic therapies — where the drug is inseparable from the psychotherapy that accompanies it and standard trial models cannot evaluate interventions of this complexity — sandboxes are the most suitable regulatory tool that European law has ever conceived. Operational, however, not before 2028.

It is a tool that works well on what healthcare databases already contain as structured variables: prescriptions, International Classification of Diseases (ICD) diagnoses, hospitalisations. From its public catalogue emerge studies on prescribing trends for antipsychotics, on the risk of agranulocytosis from clozapine, and on prescriptions of ketamine and esketamine. All useful — the problem is that none of them concerns pharmacoresistance, because pharmacoresistance does not exist as a structured variable in any European healthcare system.

It is not an ICD code. It is a clinical trajectory — how many drugs has that patient already received, for how long, with what response, with what adherence — a trajectory that is not recorded anywhere in a comparable manner across countries. Querying DARWIN EU on pharmacoresistance in psychiatry today means searching for something that has never been archived.

There is also a second gap, even more problematic: even by building a catalogue of pharmacoresistance, we would know nothing about another equally important variable, namely the psychotherapeutic history of the patient. How many of these people have ever received structured psychotherapy? Of what type? For how long? In European administrative databases, that variable barely exists.

The OMOP model[3] on which DARWIN EU is based does not capture it. Yet for psychedelic therapies it is central: every serious researcher in the field recognises that the therapeutic response depends on the quality of the psychological preparation, the integration sessions, and the therapeutic alliance. In 2024, the Food and Drug Administration raised precisely this issue in its Complete Response Letter on MDMA for post-traumatic stress disorder (PTSD). The European sandboxes will also be born to answer this question; without data on the psychotherapeutic history of patients, however, there is a risk that they will respond in a vacuum.

The proposal that the Luca Coscioni Association is working on is to build a European Registry on pharmacoresistance in psychiatry: a shared minimum dataset — minimum mandatory variables, interoperable across different national healthcare systems — that collects what does not currently exist: shared operational definitions of pharmacoresistance for TRD, PTSD and substance use disorders; longitudinal therapeutic trajectories; relevant functional outcomes; and, above all, structured psychotherapeutic history.

A dataset that would become the source that DARWIN EU can query for evidence of unmet need that the Committee for Medicinal Products for Human Use (CHMP) of the EMA can use for opinions on compassionate use — the empirical basis on which HTA bodies will decide how to reimburse psychedelic therapies when authorisation arrives.

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[3] OMOP stands for Observational Medical Outcomes Partnership. It is a data model — that is, a standard schema that defines how to organise and name health information — originally developed in the United States and today used globally, including by DARWIN EU. The problem it solves is this: every hospital, every national health system, every insurance database collects patient data differently. In Italy a diagnosis of depression is coded in one way, in Germany in another, in the Netherlands in yet another. Drugs have different names, procedure codes are different, even the structure of medical records is different. This makes it impossible to conduct comparative studies across countries because you are comparing archives that speak different languages. OMOP is a common language. All data — diagnoses, drugs, tests, procedures, visits — are translated into shared standardised categories and codes. Once everyone speaks OMOP, you can ask the same question to thirty different databases in sixteen countries and obtain comparable answers. The categories that OMOP handles well are those that healthcare systems routinely collect as structured data: ICD diagnoses, pharmacological prescriptions, laboratory results, coded procedures. What OMOP cannot capture — not because of a limitation on its part, but because that data is simply not collected in structured form — is everything that remains in the clinician's head or in the free text of notes: the qualitative response to a drug, the judgement on the adequacy of a therapy, the psychotherapeutic history of the patient. Those things exist in medical records as prose, not as codes, and OMOP does not know what to do with them.

This work of reconnaissance and dataset construction could contribute to the need to address the ineffectiveness or failures of the drug-centric model in psychiatry, and to be able to do so not exclusively on the basis of opinions but on factual data.

To activate a sandbox, the EMA will need to recommend it to the Commission with a plan that includes the scientific justification, the definition of the patient population, and the safety criteria. Without European data on pharmacoresistance, that justification cannot be built.

The registry is not to be understood as an alternative, but as preparatory and complementary to the preparation for sandboxes, with the aim of accompanying a process of shared and usable knowledge. This is urgent work, to be started now so that when sandboxes become operational, they will find the evidence on which to rest.

Pharmacoresistant patients in psychiatry cannot wait for Europe to finish building its tools; the construction of the foundations must begin without delay so that those tools do not find a void beneath them.

To learn more and support the Luca Coscioni Association's campaign on psychedelic therapies: www.associazionelucacoscioni.it