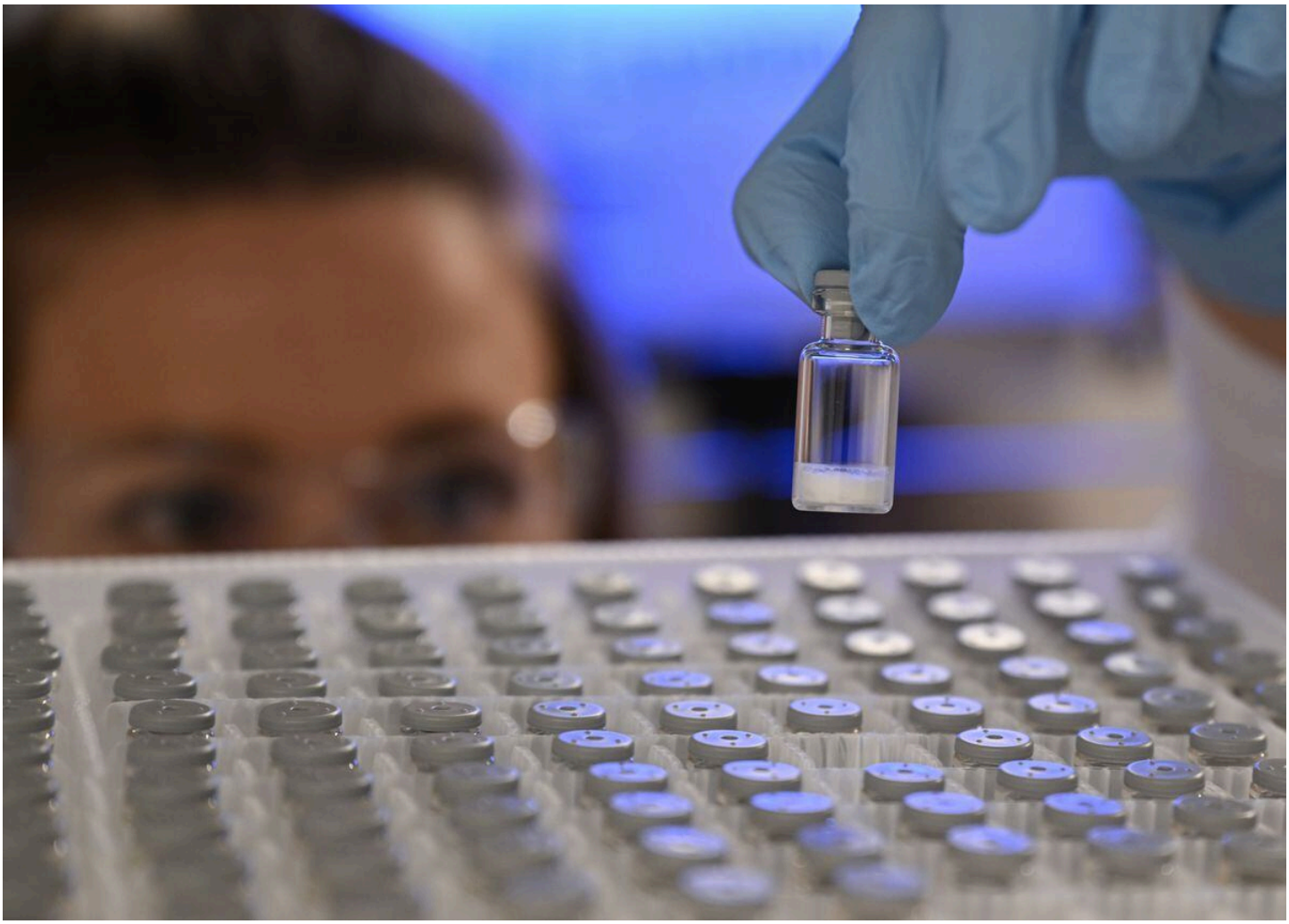
MEDICINES >

The enormous and unknown healing power of old medicines

The legislative reform being prepared by the EU plans to promote the use of already approved drugs for new ailments. This route allows to accelerate the approval of treatments and save costs in research



A laboratory technician manipulates a sample at a Merck pharmaceutical center in Darmstadt, Germany.
PICTURE ALLIANCE (DPA/PICTURE ALLIANCE VIA GETTY I)

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Nick Sireau was about to change his newborn son's diapers when he discovered a large, very dark reddish stain on them. It was a Sunday in October 2000 and the life of this aid worker, who was 27 years old at the time, was about to take a radical turn. “We went to the emergency room, but they didn't find anything. They told us that perhaps it was because of the color of the red cabbage that my wife had eaten, which could have passed into her breast milk and, from her, into her pee. We didn't know until later that what he really had was alkaptonuria,” he recalls. This ailment is a rare genetic disease that Sireau's second son also suffers from and that manifests itself with the darkening of some tissues and arthritis in the spine.

Almost 20 years later, on September 17, 2020, the European Medicines Agency (EMA) approved the first treatment for alkaptonuria. The drug is called nitisinone and it was not new, but had been used for many years for another condition (hereditary tyrosinemia type I). The research promoted by this Londoner in the search for a cure for his children served to demonstrate to the EMA that it was also effective against alkaptonuria. “It was a 20-year journey with ups and downs, but very rewarding. With other patients and doctors we managed to mobilize 20 million euros and promote two clinical trials. Fortunately, all this has helped my children and other people live much better today,” he adds.

The repositioning or reuse of medicines is the use in new ailments of therapies already approved for other diseases, something that the European Union plans to promote in the legislative reform it is carrying out in pharmaceutical matters. “It is an area with enormous potential and in which it is essential to advance. We have 7,000 rare diseases described, but less than 1,000 have a pharmacological treatment. Developing all these medicines from scratch would cost the equivalent of twice the GDP of Germany [about eight billion euros], something unaffordable. But if we take approved molecules, about which we already know a lot, and investigate their potential against other diseases, we will be able to reach the goal much sooner and for less

money," summarizes Adrian van den Hoven, director of Medicines for Europe, an association of manufacturers. of generics and biosimilars.

Van den Hoven and Sireau spoke this past week in Barcelona at the international congress Bridging Boundaries (Overcoming Borders), organized among other entities by REMEDi4ALL—a consortium financed by the European Union—and which met at the Historic Site of the Sant Pau Hospital. to 240 specialists from all over the world.

Nick Sireau, during his speech at the Bridging Boundaries conference, held last week in Barcelona.
ADIVA KOENIGSBERG

The prescribing of medications for ailments or indications other than those listed in the technical information sheet, also called off-label, is actually a common practice in medicine. But it is not ideal, experts agree. Firstly, because the knowledge on which the decision to do so is based is not comparable with the precision in efficacy, dosage and safety data provided by the trials required by agencies such as the EMA to approve a medicine.

And, secondly, for "equity," defends Donald Lo, director of drug development at EATRIS, a consortium of European research centers. "Off-label use can be very socially unfair. To benefit from it, you depend on your doctor to read all the scientific literature and be aware of the latest advances. And this happens more in large hospitals. 90% of patients are not treated there, so many may be left without the treatment they need. Approval by the EMA is the best guarantee that medical advances reach everyone," adds Lo.

Despite being desirable, achieving EMA approval is not easy, even when knowledge about the benefits of a drug is well established in a specialty. Experts point to two reasons that explain this. "It is a very technically demanding process. Evidence must be generated with very strict and expensive quality standards. This is something that pharmaceutical companies know how to do very well. But then we have a large amount of excellent academic research [from universities, public hospitals, research centers...] that, when push comes to shove, is not useful to achieve that approval," says Anton Ussi, director of operations at EATRIS.

The lack of incentives is the second big issue on the table. "Old medications are no longer protected by a patent and generic companies sell them very cheap. What pharmaceutical company will invest millions of euros in clinical trials if they are then going to be paid only a few cents per pill?" asks Ussi.

In reality, European regulations do contemplate some measures to encourage research in these cases, such as orphan drugs. The problem is that it is not applicable in many cases and when it is, it has often been involved in abusive practices. A famous example is that of the pharmaceutical company Leadiant Biosciences with chenodeoxycholic acid, a cheap medicine with decades of history (the pill was sold for 14 cents). After achieving marketing exclusivity for the drug thanks to its declaration as an orphan, the company multiplied its price by 1,000 without having invested a euro in carrying out new trials.

A possible solution to boost research would be the creation of a third category of medicines. "It would be something intermediate between new innovative therapies, much more expensive, and generics, very economical. The key question is: How to price repositioned medicines so that they are attractive to invest in and accessible?" asks Zsuzsanna Petyko of the Syreon Research Institute, a research center based in Budapest.

Making investment more attractive for the industry is only part of the solution. The other involves ensuring that all academic research accumulated in universities, hospitals and public research centers has easier access to EMA approvals. “We are not taking advantage of all this knowledge and it is an unaffordable waste. Fortunately, new opportunities are opening up for us. The legislative reform being carried out by the European Union plans to create a framework for the repositioning of medicines that will allow the two worlds, industry and academia, to a certain extent meet,” says Van den Hoven.

Sini Eskola, director of regulatory strategy at the EFPIA—the European association of innovative pharmaceutical companies—insists that “repositioning should not be seen as a substitute for the development of new drugs,” but rather as “a new opportunity for drugs that no longer have patent and a hope for patients suffering from conditions for which there are few or no medications.”

Several repositioning success stories were presented at the conference held in Barcelona. Rosie Lovett, head of the drug reuse program for the National Health Service (NHS) in England, gave the example of anastrozole, a treatment with 30 years of history against breast cancer — and, therefore, with the patent already expired. — which has been shown in clinical trials that, if used as a preventative, “reduces the incidence of the disease in postmenopausal women with a higher risk of suffering from it by almost 50%,” which can prevent 2,000 cases a year.

Heather Stone, from the United States Food and Drug Administration (FDA), highlighted the potential of nitroxoline—an antimicrobial with half a century of use in Europe and China, but not approved in the United States—against a rare type of encephalitis caused by the amoeba *Balamuthia mandrillaris*, fatal between 75% and 90% of cases. This specialist told how two patients with a very poor prognosis recovered in their country after being treated with the drug, which had to be imported exceptionally by the agency.

Stone, who works at the FDA's Center for Drug Evaluation and Research, explains how candidate molecules for repositioning are selected: “Potential treatments are usually identified through so-called high-throughput analyses, to which thousands of drugs are subjected. approved by the FDA and EMA for particular targets and mechanisms of action. But unfortunately, there is a huge amount of information that is *hidden* in clinical experience, scattered in

many sources and formats that are difficult to aggregate, or in experiences of doctors and patients that are never made public. All this is a valuable source of knowledge that should be taken advantage of," he says.

Claudia Fuchs, a neurobiologist who works in the alliance of patient organizations EURORDIS, gives another example: ketamine, originally an anesthetic that since 2019 has also been used against severe depression. "The repositioning of medications can be very useful in all medical specialties, but perhaps it is cancer and rare diseases where there are more ailments for which there are no treatments available or those that exist end up no longer effective," he says.

In the field of infectious diseases, the coronavirus pandemic – a new pathogen against which, therefore, there was no approved drug – demonstrated that, sometimes, repositioning is the only option. And it will continue to be so because "it is very likely that viruses of animal origin will continue to be transmitted to humans," so "a key component of preparing for a pandemic must be broad-spectrum antivirals widely available to the population," he defends. Denis Kainov, from the Norwegian University of Science and Technology. As explained in his presentation, the reuse of these antivirals against pathogens more or less similar to those already known would allow time to be gained until the development of specific vaccines and antivirals.

Eskola, of the EFPIA, defended for his part: "Although only a fraction of the drugs tested [in the early phases of the pandemic] were effective, the efforts demonstrated the great speed with which reuse can explore options of treatment in unknown territories. Technologies such as artificial intelligence, together with data sharing platforms, improve the efficiency of drug reuse."

César Hernández, general director of Pharmacy of the Ministry of Health and who also attended the congress, warns of the risks involved in not repositioning a drug in time. One is that they "disappear from the market when they still have real value for patients," something that has happened in the past with drugs such as ketoconazole. Another is "the re-entry of old drugs into the system as if they were new at a price that is difficult to justify," which is what happened in Europe with chenodeoxycholic acid.

Hernández highlights actions such as that carried out by the Spanish Agency for Medicines and Health Products (AEMPS) by "promoting together with a

small group of agencies and the EMA a pilot plan at the European level that influenced the European Pharmaceutical Strategy, where Spain promoted its inclusion, and in the legislative ones now underway." Within this project, the EMA is working together with non-profit organizations on the repositioning of 23 molecules.