Drug scandals in France: have the lessons been learnt?

Despite some positive changes in recent years, much more can be done to prevent future drug scandals in France, say medical and legal experts. Barbara Casassus reports from Paris.

6 years after the scandal of Servier's antidiabetic drug Mediator (benfluorex) erupted, a number of French health professionals say the many "never again" declarations have not yet produced enough safeguards to ensure history does not repeat itself. "Conflict of interest remains rife, the pharmaceutical lobby is as powerful as ever, and doctors and patients are still under-informed", says Bernard Debré, urologist and Member of Parliament for the opposition party Les Républicains. In 2012, Debré and Philippe Even, a pulmonologist and founder of the Necker Institute in Paris, concluded in their book *Guide des 4000 Médicaments Utiles, Inutiles ou Dangéreux* (*Guide to 4000 Useful, Useless or Dangerous Medications*) that more is needed to avert further scandals.

The current government has acted to resolve some of the problems, but Debré says the book has not had the impact he and Even had hoped. "Like other countries in Europe, there is still so much connivance between health professionals and pharmaceutical companies in France that the sincerity of some people is questionable."

The amphetamine derivative Mediator was widely prescribed off-label as an appetite suppressant, and was finally withdrawn at the end of 2009 with a projected 1500–2100 deaths from valvular heart disease in France alone. Even though a number of alarm bells rang during Mediator's 33 years on the market, the scandal did not break into the open until pulmonologist Irène Frachon's book *Mediator 150 mg Combien de Morts?* (*How many Deaths?*) was published in June, 2010.

Fred Tanneau/Stringer

Irène Frachon

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Slow progress

Jean-Louis Montastruc, head of clinical pharmacology at the Toulouse University Hospital, is less alarmist than Debré. "We are going in the right direction, but it is a very long process partly because we still do not have a culture of clinical pharmacology in France", he says. "The rules on conflict of interest and off-label prescriptions are far from being fully respected, partly because they are not taught extensively enough in medical school or in further training." The European and national medicines agencies should consider market authorisation for important off-label drugs on a case-by-case basis, especially in paediatrics as these products "are often indispensable", he adds.

François Hirsch, head of the ethics office at the French biomedical research agency INSERM, agrees. "It is a question of education, and of declaring links of interest in order to prevent them from becoming conflicts of interest", he says.

Despite the risks of prescribing drugs off-label, doctors do not want to stop for fear of driving their patients away, and pharmaceutical manufacturers do not want it to stop because their sales would drop, Montastruc notes. "Young medical students and doctors arriving in hospitals see that conflict of interest is all around them, so find no reason not to behave the same way as their colleagues do", he adds.

Others put it differently. "We have made considerable progress in fighting conflict of interest, but we have not yet struck a satisfactory balance between public confidence and concern about drug toxicity that raises suspicion of conflict of interest", says François Rousselot, chairman of the practitioner-industry relations committee of the Conseil National de l'Ordre des Médecins (CNOM).

In March, the Paris Public Hospitals Authority recognised the problem was serious and advocated six measures to deal with it. So far guidelines have been issued on which extracurricular activities are acceptable or not, and how to obtain clearance to engage in them.

Court cases in progress

The fallout from the Mediator scandal continues. The Versailles Appeal Court recognised Servier's civil responsibility in April, 2016, when it upheld a first court ruling and ordered the company to pay €7650 in compensation to 68-year-old Esther Soulet. Earlier, the Paris Administrative Court was upheld in appeal on July 31, 2015, for recognising the government's responsibility in the affair, saying that the then national medicines agency AFSSAPS, the predecessor of the ANSM, should have withdrawn the drug 10 years earlier than it did based on the data at its disposal.

The 5 year criminal investigation ended this spring, but Servier is putting up so many legal obstacles that the case is unlikely to come to trial until 2019 at the earliest, according to Charles Joseph-Oudin, lawyer for 150 people who believe Mediator caused their valvular heart disease. "It is lost in limbo for the moment." In this case, AFSSAPS has been charged with involuntary manslaughter and unintentional injury as a result of negligence between 1995 and 2009. And the agency, Servier Companies, the group's partners, and about 20 individuals are accused of various other misdemeanours, including "aggravated deception".

Even then, the punishment might never fit the crime, since punitive damages do not exist in France, says Joseph-Oudin. "The French judicial system needs to be reformed—only if judges can act rapidly and forcefully will the system serve as a deterrent to future negligence", he adds. And France's new class action mechanism for health-related claims, which can only be filed by accredited associations, is unlikely to help. "It has just added another layer of complexity—pharmas laugh at it."

The compensation process has not always been smooth. Between Sept 1, 2011, and June 30, 2016, the National Office for Medical Accident Compensation (ONIAM) had received 9098 applications for cash compensation, of which it had accepted 2260 and rejected 4460. When ONIAM's independent committee of experts has given the go-ahead for compensation, it is up to the victims to lodge their claim with the drug manufacturer. If the latter is hesitant to pay, ONIAM pays and is reimbursed by the manufacturer. In the case of Mediator, ONIAM has had to step in for 34 claims, of which it has been repaid for 21; 13 are still pending.

On June 30, 2016, Servier says it had offered 2083 patients compensation of €38·4 million and paid out €25·5 million. But the debt could continue to rise since this year's health reform law will permit 1500 of the rejected cases to be re-examined by ONIAM's panel of experts now the latter have realised that aortic calcification or narrowing is not necessarily only age related, but can also be the result of drug toxicity, says Erik Rance, ONIAM director.

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The experts will probably recommend compensation in about 35% of the 958 cases re-examined so far, he adds. ONIAM might also reopen other cases if patients come forward with fresh evidence to back their claims, or their physical condition has worsened.

"Before there was a judicial as well as a public health scandal", notes Didier Jaubert, a Paris-based lawyer who represents the Association of Victims of Accidents from Medicines. "Now the burden of proof is on Servier instead of victims, and the presumption is that Mediator rather than anything else is the cause of valvular heart disease of patients who took the drug", he says.

But Frachon says many cash settlements are still too low and that she is "scandalised by Servier's hypocrisy and betrayal of its commitments to compensate victims. Despite its promises, the company is doing all it can to not pay up, and has convinced about 40 civil courts to suspend their hearings until a criminal trial is held, which might never happen, or at least not before many of the patients have died."

Laurent Boussu, Servier's risk management and insurance director, denied the allegation. "We ensure that patients receive compensation as quickly as possible once the independent experts and authorities have examined their cases", he said in an email to *The Lancet*. "Our greatest wish is for the trials to be over quickly."

"Bigger scandal"

Before Mediator could be consigned to history, sodium valproate drugs prescribed to pregnant women with epilepsy or bipolar disorder grabbed the headlines after the General Inspectorate of Social Affairs criticised the authorities and Sanofi in February for not reacting more rapidly after congenital malformations and development disorders were linked to the drug Dépakine. "This is a much bigger scandal, and could involve more than 14 000 youngsters born in France between 1976 [9 years after Dépakine was launched] and 2014", says Catherine Hill, senior epidemiologist at the Gustave-Roussy Institute in Paris.

Four complaints against Dépakine were filed with the Paris criminal court more than a year ago, but no date has yet been set for a hearing, says Joseph-Oudin, who has been contacted by 450 families on behalf of 800 children with possible valproate-linked congenital malformations and, in many cases, development disorders too. Nothing has been done about compensating the victims, and Sanofi is refusing to pay, for the moment at least, he says. "Several expert assessments are in progress", Sanofi said in an email to *The Lancet*. Until the responsibility of the different players and the intrauterine link with sodium valproate are established, it is up to ONIAM to look after the families concerned, the company added.

Enforcement problems

Whether the valproate case involves any conflict of interest remains to be seen. But Anne Chailleu, president of Formindep, an association promoting medical practitioners' independence, notes that the 2011 Bertrand law (named after the then health minister Xavier Bertrand), which was designed to prevent the conflicts of interest at the heart of the Mediator scandal, has never been applied in full. "Why do governments promote laws and then write application decrees that prevent the laws being enforced?" asks Chailleu.

After the Bertrand law was passed, Formindep and the CNOM alleged that the last government had abused its power by trying to water down a rule for the health ministry to make public the contracts with experts that drug companies post in the health ministry's database, Base Transparence Santé.

The Council of State ordered the government to rewrite the application decree in question, but this never happened. The upshot is that the measure surfaced in the health reform law that came into force in January, 2015, and is again awaiting enforcement. This should oblige drug and other companies to disclose details of the value and duration of the contracts they sign with health professionals, the work entailed, and the identity of the people behind the associations receiving the fees. These add to disclosures of gifts, training, and other incentives that are already covered by the Bertrand law.

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A book published in March, 2015, *Effets Secondaires, le Scandale Français* (*Side Effects, the French Scandal*), suggests that conflict of interest was behind the official position that no-one in France had side-effects or died of heart disease after taking Merck & Co's anti-inflammatory drug Vioxx (rofecoxib). The drug could have caused 2000 deaths in France during the 4 years it was on the market, according to Jaubert. "That is based on the 40 000 recognised Vioxx deaths in the US and the 500 000 people who took the drug regularly in France between 2000 and 2004", he says. "There is no reason to suppose that French hearts are more resistant than American hearts, but the medicines agency [AFSSAPS at the time] did not release the information it had to prove there was a problem."

Also in March, 2015, the public Court of Auditors said that "despite [the law's] ambition, the provisions on transparency contain major flaws—no control over declared information, criminal sanctions with no real impact, and a very restrictive interpretation of the perks industry gives health professionals". Verification of the introduction of the new rules in five public health agencies showed "frequent anomalies in respecting the declaration obligations, analysis of links of interest and management of conflicts of interest, publication of meetings proceeds, and the financial content of agreements with professionals", the report says. And this year's health reform law does not fill the gaps, the Court adds. The government should reorganise the central administration and health agencies, strengthen the independence and quality of health expertise, and create an independent body to audit declarations of interest, according to the Court.

Suggestions are that one of the five agencies audited by the Court, the French National Authority for Health (HAS), could take on the task of verifying declarations if its budget were increased, but one source who wished to remain anonymous dismissed the idea. "That is not the authority's role", she said. "The HAS is a scientific body, and was not set up to police the ethics of other health agencies. Besides, it has no investigative powers." Instead, each health agency is now required to have an ethics official, whose job is to ensure there is no cheating.

Even now, finding experts is difficult. "If practitioners are knowledgeable about something because they have worked with industry, they are immediately suspected of conflict of interest", says Rousselot. "We don't have the right solution to that." But on the positive side, at the beginning of this year, the anti-fraud department of the finance ministry nominated several inspectors to work exclusively on health issues, he adds.

Meanwhile, another source, who declined to be identified, is worried that public confidence in the French health system is being seriously shaken after having recovered from a contaminated blood scandal 25 years ago. The solution then was to create a public health administration, which currently compares well with others in Europe; but to restore public confidence now, "we will have to look for solutions elsewhere, which will be more complicated", the source adds.

Barbara Casassus