

Mediator scandal rocks French medical community

A report into the events surrounding the “Mediator affair” has left French drug company Servier, regulators, industry, and the medical community reeling. Asher Mullard reports.

When French regulators withdrew Servier’s Mediator (benfluorex) from the market late in 2009, it hardly made a stir. For the past few months, however, the drug has been stealing unwanted headlines. According to some estimates, the drug—licensed as an add on for hyperlipidaemia and diabetes but also used off-label for obesity—caused between 500 and 2000 deaths during its tumultuous 33 years on the market. As stories of its safety profile and patchy history have emerged, many have questioned how such a scandal could happen. A startling 260-page report by the accountability organisation Inspection Générale des Affaires Sociales (IGAS) now provides a first independent account of the events.

“I was surprised because it showed the scandal was worse than I had expected”, says Irène Frachon, a chest physician CHU de Brest, France, whose research contributed to the decision to withdraw the drug in 2009 and whose book *Mediator 150 mg, combien de morts?* drummed up headlines in 2010. “Perhaps I am naive, but I thought at first that there had just been a mistake. I hadn’t realised that there were so many alarm bells and warnings during all those years.”

Few have emerged with their reputations untarnished by the IGAS report. Servier is accused of relentlessly marketing the drug “at

odds with its medical properties” and of applying undue lobbying pressure on regulators and on the medical community to ensure the successful commercialisation of its product. AFSSAPS, the French drug regulators, are deemed “inexplicably tolerant of a drug with no real therapeutic value”. They are also painted as an “overworked” bureaucracy “entangled in cumbersome and complex legal procedures”, and “restrained by fear of litigation”. The broader medical and scientific communities also take flak for irresponsible behaviour.

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Servier disagrees with the timeline, the events, and the conclusions laid out in the report. “Many facts are missing”, says Lucy Vincent, Servier’s general director of external affairs. And although IGAS interviewed hundreds of people for its report, she points out that Servier was not given the opportunity to present its case. AFSSAPS did not respond to *The Lancet’s* request for comment.

Ongoing legal challenges and parliamentary hearings will eventually provide further clarity on exactly how the events unravelled. But the regulatory and pharmaceutical communities are already shaken.

Jean Marimbert, who was head of AFSSAPS, resigned shortly after the publication of the report. The French association of drug makers LEEM, in an apparent attempt to distance itself from the furore, suspended Servier in January this year. “This decision [was] made to allow LEEM to be freely involved in discussions with public powers concerning the renovation of the system...and to enable Servier to organise their defence”, says Catherine Lassale, scientific affairs director at LEEM. Servier, in response, quit from the association.

More changes are sure to come, just as both culprits and scapegoats are sure to fall. French health minister Xavier Bertrand has promised reform of the regulatory landscape. Some believe that the scandal has unveiled the ugly underside of a broader problem—affecting not just France but also the rest of Europe—and that cross-border action may be needed. Although the drug was never approved in the USA, it was marketed elsewhere in Europe, Africa, and Asia. But before the French push through with hasty change, industry watchers want to ensure that they have first identified the real problems. Which brings back the key question that has been plaguing France: why was benfluorex left on the market for so long?

Benfluorex came onto the market in France in 1976. But to understand the

1976	1987	1995	1997	1998
Servier’s Mediator (benfluorex) first marketed in France, as add on therapy for hyperlipidaemia and for diabetes with obesity.	Under a European Directive, benfluorex (and all other drugs approved before 1976) is re-assessed, and approval in the diabetes setting is not upheld. A revised marketing approval is not issued.	The use of fenfluramine is restricted because of cardiovascular safety concerns. Benfluorex, a pharmacologically related molecule, is unaffected.	Fenfluramine is withdrawn, but benfluorex remains on the market. French drug regulator AFSSAPS revokes approval of benfluorex for diabetes in April, only to rescind the action 2 months later.	Benfluorex placed under “official” pharmacovigilance investigation in France, due to its “potential danger”. Italian regulators also raise concern.

history of the drug, IGAS went back to its early development days. In the 1960s, Servier was experimenting with derivatives of amphetamine, a molecule that was known to suppress appetite, in the hopes of developing new drugs. Their early hits included fenfluramine, dexfenfluramine, and benfluorex (later marketed as Mediator).

All three drugs are pharmacologically linked—in structure, in clinical effect, and in the metabolites they are broken down into. Yet, early on, Servier started to argue that benfluorex belonged to a distinct class from the amphetamines and fenfluramines. Fenfluramine and dexfenfluramine were marketed as anorexigens for obesity, under the respective trade names Ponderal and Isomeride. Servier argued that benfluorex might act on lipid and cholesterol metabolism, and so pushed to get the drug on the French market in 1976 as an adjunct to diet for hyperlipidaemia and for diabetes plus obesity. But the proposed mechanism of action in these two settings, says president of the Necker Institute Philippe Even, was “totally hypothetical and not scientifically demonstrated”. Its efficacy has also repeatedly been challenged.

Fast forward two decades, and the fenfluramines are under scrutiny over evidence that they increase the risk of pulmonary heart disease. AFSSAPS restricted the use of both fenfluramine and dexfenfluramine, and of all other appetite suppressant drugs, in the hopes of minimising harm. Benfluorex, despite its close relation with these drugs and its appetite suppressing properties,

had been approved in a different setting and so emerged unaffected by these developments. “This error of pharmacological reasoning will have serious consequences”, writes IGAS. 2 years later, fenfluramine was fully withdrawn from markets around the world, including France, because of its serious cardiovascular safety risk. Benfluorex, having shed its pharmacological origins, escaped unscathed in France and beyond.

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Servier is now facing legal charges of “deception” over its positioning of benfluorex. Vincent maintains, however, that IGAS have ignored key details in its account. The cardiovascular effects of fenfluramines were, for instance, in part thought to be due to combination use with the amphetamine drug phentemine. “It’s very easy for them to go back and rewrite today’s history”, she says.

Shortly after the withdrawal of fenfluramine, the agency missed another opportunity to ban the drug, says IGAS. This time, the report points to “serious failings” within the French pharmacovigilance system. In 1998, the drug was put under an official pharmacovigilance review in France. At the same time, Italian regulators started to question the safety of the drug and raised their concerns with the European Medicines Agency (EMA). These fears were heightened the following year, when French cardiologist Georges Chiche reported

a case of benfluorex-related valvulopathy and another team reported a case of serious pulmonary arterial hypertension in a patient taking benfluorex plus dexfenfluramine. Based on these cases, AFSSAPS pharmacovigilators called for an expedited review of the drug’s dossier.

In view of the two serious notifications in France, the European-wide discussion of the drug, and the known pharmacological properties of the drug, IGAS concludes that, “the decision to withdraw [benfluorex] should have been made in 1999”. Yet no restrictive action was taken.

A few years later, in 2003, Spanish regulators once again raised a red flag over the profile of the drug. That same year, Servier let its marketing licence for benfluorex lapse in both Spain and Italy (companies need to re-apply for drug approval in these markets every few years). “We decided not to renew the marketing authorisation because we were selling so little product in those countries”, says Vincent. Frachon speculates, however, that Servier might have chosen to pull the drug before any regulatory action was taken as a means of avoiding a forced withdrawal that could have impacted marketing authorisation elsewhere.

After nearly 33 years on the market, the scandal began to unravel in 2009. In part, this was down to Frachon’s research. While in training as a doctor, she had witnessed first hand the effects of fenfluramine 7 years before it was withdrawn from the market. “I was very shocked by the delay between medical evidence and the decision to withdraw the product”, she says. This

1999	2003	2007	2009	2010
Two cases of cardiovascular complications with benfluorex are reported in France. This is the year in which benfluorex should have been withdrawn, says the Inspection Générale des Affaires Sociales.	Spanish regulators report a case of cardiac valvulopathy to the European Medicines Agency (EMA). Servier withdraws benfluorex in Spain and Italy, by not re-applying for marketing authorisation.	AFSSAPS begins another review of benfluorex’s safety. Approval for hyperlipidaemia, but not diabetes, is revoked.	AFSSAPS suspends marketing of benfluorex in France, citing both efficacy and safety issues. Servier withdraws the drug worldwide.	EMA permanently revokes marketing approval. Judiciary investigations and governmental accountability reviews are planned.



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disappointment in the system stuck with her, and years later when she came across one case of pulmonary arterial hypertension and another of valvular heart disease in patients treated with benfluorex, she began to investigate.

After examining a set of hospital records, she was surprised to find that many benfluorex-treated patients had the characteristics of drug-induced valvular heart disease. "I realised that if there were so many patients just in Brest, there must be many more potential victims around France", she says. A case-control study confirmed her findings of increased suspicious cardiovascular disease with treatment.

At around the same time, Servier had completed a head-to-head trial of benfluorex versus the widely used antidiabetic pioglitazone, at the behest of the regulators. Safety data from the study showed that benfluorex treatment was associated with valvular anomalies. A third study by CNAMTS, the French national health insurance association, examined a database of more than 1 million diabetic patients and found that the relative risk of hospitalisation due to specific cardiovascular complications was about three times higher in patients treated with benfluorex than it was in those who had not been given the drug. "The signal was finally too strong to ignore", says Frachon. AFSSAPS suspended the drug in November, 2009, citing both efficacy and safety concerns, and the EMA fully withdrew it in July, 2010.

Servier—who says that annual sales of the drug have hovered around €20 million for the past 15 years—

continues to plead its innocence. Vincent points out that drug development is an inherently risky business, and that those involved have the difficult task of constantly trying to balance a complex set of risks and benefits in patients who may lose out by not taking a drug. "Knowing what we know today, of course we'd change the story", says Vincent. "But at every stage in the process, we did the best we could with the information that was available to us at the time. Of that I'm convinced."

IGAS, it seems, disagrees. It draws attention to aggressive marketing tactics, overly complex bureaucracy within AFSSAPS, fear of litigation, and unhealthy ties between industry and regulators as key culprits in the affair. It also points to a reverse precautionary principle—a view that drugs should only be withdrawn as a last resort—as effectively protecting drug firms rather than patients. With this perfect storm, says Even, a benfluorex-style scandal was inevitable.

There are also suspicions that Servier lobbyists have held too much weight even beyond the regulatory world. Frachon points for instance to a phone call that cardiologist Chiche received after contacting the authorities in 1999 from a local politician who argued that there was no link between the drug and the adverse events. "I think that Servier tried all the time to pressure cardiologists and authorities to ignore the signals", she says. Vincent says that concerns over the company's lobbying power are "overly exaggerated".

LEEM, for its part, argues that the benfluorex affair cannot be generalised across industry. "The events related in the IGAS report concern one company and one drug", says Lassale. Although she concedes that LEEM does have its faults, she also argues that the sector has taken great strides to improve pharmacovigilance over recent years.

Others, however, see clear signs of a systemic problem. "I am sure that there are many other chronic treatments that will cause as yet undetected severe complications", says Even.

AFSSAPS recently published a list of 77 drugs that it has placed "under reinforced surveillance" because of undesirable side-effects. But some still wonder how effectively the agency would be able to take action on these. "It would probably take the system 2 years to ban cyanide", says Even.

While court cases and parliamentary inquiries rumble on, IGAS is working on a second report outlining a set of recommendations for regulatory reform. It hopes to propose a system that is "entirely focused on the interests of patients and of public health". And everybody agrees that change is needed.

Frachon lists three main requirements of the new system: it needs to better separate pharmaceutical lobbyists from drug regulators; it needs to make better use of national insurance plan data; and it needs safeguards against political influence over regulatory decisions. LEEM says that there may be a need to develop better methods for picking out faint pharmacovigilance signals from large volumes of notifications.

Even suggests another, possibly more controversial, solution that he hopes might address the cause, rather than the symptoms, of the problem. The current patent protection landscape forces drug developers to churn out branded products every few years as a means of escaping profit erosion from cheaper generics, he argues. These market pressures, at least in part, drive companies to behave badly. If drug developers had longer patent protection for the products they created, he speculates, perhaps we could curb the development of unnecessary, and sometimes harmful, products.

Even has also managed to find a single silver lining from the scandal. "In spite of the sadness of the story, perhaps it will serve as a turning point, enabling the government to understand the risks that drugs can pose and facilitating a change in the regulatory system for the benefit of all citizens", he concludes.

Asher Mullard