France's Mediator° trial reveals a cosy relationship between representatives of the French drug regulatory agency and an influential company

ABSTRACT

● **The court has given its verdict in the historic criminal trial involving the Mediator° (*benfluorex*) disaster, which was held in Paris from September 2019 to September 2020, ten years after this drug was withdrawn from the market in France. The company, Servier, and the French drug regulatory agency were both found guilty.**

● **The trial revealed how representatives of the agency, external experts charged with drug evaluation, and the company were constantly trying to come to a consensus, leading to a delay in the decision to withdraw Mediator° from the market.**

● **Some of the external experts, whose opinion was paramount, had a close relationship with the pharmaceutical industry. Several of them shared certain characteristics: naivety and a cavalier attitude towards conflicts of interest, coupled with inflated self-esteem leading to an unrealistic belief that they were immune from conflicts of interest.**

● **Some external experts also shared the pharmaceutical industry's overly positive view of drugs in general. As regards Mediator°, having failed to make the appropriate comparisons, most experts were left with an incomplete view of the drug's harm-benefit balance. Nor did they take a sufficiently critical approach to the company's data.**

● **These factors contributed to the unjustified, continued marketing of Mediator° for more than thirty years, and the resulting harms to patients.**

▶ Excerpt from *Rev Prescrire* **August 2021**
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Some key dates in the Mediator° disaster

1976. The company, Servier, markets the drug *benfluorex* in France under the brand name Mediator°. The drug's principal action is appetite suppression, but it is mainly presented as an antidiabetic and lipid-lowering drug.

1977. The French journal *Pratiques* questions the efficacy of Mediator° and points out its similarity to Ponderal°, another fenfluramine appetite suppressant manufactured by Servier. One year later, Henri Pradal carries out a similar analysis in his *Dictionnaire critique des médicaments*.

1997. Worldwide market withdrawal of Servier's other fenfluramine appetite suppressants, because they cause pulmonary arterial hypertension (PAH) and heart valve disease.

1997. *Prescrire* observes that "*there is currently no basis for treating noninsulin-dependent diabetics with benfluorex. The French health authorities should reconsider their decision to license and reimburse this product*".

1999. The first reported cases of PAH and heart valve disease associated with Mediator°.

2003, 2005, 2006, 2008 and 2009. *Prescrire* publishes reminders of the risks of PAH and heart valve disease linked to *benfluorex*, supported by data.

2009. Market withdrawal of Mediator° in France, following a pharmacovigilance safety alert.

2010. Publication of the book *"Mediator 150 mg, combien de morts?"* (Mediator 150 mg, how many deaths?) (Irène Frachon, éditions Dialogues). Servier initially obtained a court order censoring the subtitle "How many deaths?"

2011. A "drug safety" law is passed, in response to the Mediator° disaster. Among the measures, a new drug regulatory agency, ANSM, replaced the previous one.

2019-2021. The criminal trial relating to the disaster. An appeal will be heard, in 2022 at the earliest.

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EDITORS' OPINION

A trial to prevent a new disaster through understanding and dissuasion

The length of the Mediator° trial (seven months) makes it difficult to provide an exhaustive account of this trial. In its French edition, *Prescrire* chose to focus mainly on the part of the trial concerning the French drug regulatory agency and its experts, and less on the part about the company, Servier (1). The agency, as part of its public service mission, is supposed to defend the interests of patients. As France's "drug watchdog", it has a duty to monitor and control the actions of pharmaceutical companies, whatever their intentions, methods or business models might be. The agency should have withdrawn Mediator° (*benfluorex)* sooner.

From the specific to the general. Can one draw more general lessons about the functioning of the drug marketing system from the Mediator° case, as presented in the trial? *Prescrire* has chosen to anonymise those involved, in order to highlight established practices and views on drugs which were widespread at the time, rather than focusing attention on specific persons. The full article in our French edition only mentions two of the defendants by name: Jean-Michel Alexandre and Jean-Philippe Seta. Both had pivotal roles, one at the agency and the other in the company, both were convicted by the court.

During the trial, it also emerged that Servier was undoubtedly not like other companies, particularly in its relationship with the agency. It employed unorthodox methods, including exerting influence or even pressure, and going as far as intimidation and threats, according to some witnesses. The fact that it was a French company, with financial interests and a network of influence in France, also played an important role.

The company's conviction for *"deception"* and *"involuntary bodily harm and manslaughter"* did not surprise the Editors of *Prescrire*. We never believed that the company could have been unaware of the chemical similarity between *benfluorex* and the fenfluramines, the drug's metabolism, its appetite-suppressing properties, and its plausible (and later proven) role in causing pulmonary arterial hypertension and heart valve disease.

The Mediator° disaster is an extreme case. As is the opioid disaster in the United States and the many deaths linked to the excessive promotion of those drugs. But these extreme cases certainly provide examples which help raise awareness more generally of the risks incurred when there is a failure to separate the interests of stakeholders, such as experts, regulatory agencies, healthcare professionals and patient associations, from the very specific interests of pharmaceutical companies.

Sentences and fines too light. The judges, charged with deciding whether or not a given act amounted to an offense in the eyes of the law, acquitted several of the accused, either because of a statute of limitations, an absence of proof or because the accused had declared their personal financial interests at the time. However, such verdicts must not obscure the valuable contribution the trial has made by making certain things public. The statements made in court by defendants or witnesses revealed the context of industry-regulator relations in the Mediator° era, which led to patients being put in danger.

This verdict, which is subject to appeal, also raises questions as to the dissuasive nature of the penalties incurred. Will such penalties help prevent other disasters? At the end of the trial, Servier and its former second-in-command Jean-Philippe Seta, as well as the agency, were convicted of *"involuntary bodily harm and manslaughter"*. However, contrary to the prosecutors' request, no custodial sentence was imposed on the former second-in-command at Servier. This ruling was surprising, as was the acquittal of the company and its former second-in-command on the charge of *"fraud"* against the mandatory and complementary health insurance funders in France, which had reimbursed the prescriptions. The fines imposed on the company, its former second-in-command and the agency were the maximum allowed by the law in France at the time, but they are a pittance, when compared to the scale of the human disaster and to the profits Servier derived from the marketing of Mediator°.

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1- Prescrire Rédaction "Mediator°: procès d'un entre-soi entre des acteurs de l'Agence du médicament et une firme influente" *Rev Prescrire* 2021; **41** (454): 610-618.

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MARKETING AUTHORISATIONS

– Crizanlizumab to prevent vaso-occlusive crises in sickle-cell disease
– Fenfluramine and Dravet syndrome

ADVERSE EFFECTS

– Clopidogrel + a proton pump inhibitor: increased mortality

OUTLOOK

– DNDi: a collaborative research and development model focused on patients' needs