Mediator° disaster: the damning appeal judgement

In late December 2023, the Paris appeal court found the pharmaceutical company Servier guilty of all the criminal offences of which it was accused: "*aggravated deception*", "*aggravated involuntary bodily harm and manslaughter*", "*fraud*" and "*improperly obtaining*" and subsequently renewing marketing authorisation for *benfluorex* (Mediator°, since withdrawn) (1). The company's former chief executive, Jean-Philippe Seta, was given a 4-year suspended prison sentence (with 1 year of house arrest under electronic monitoring), and Servier was ordered to pay a fine of over €9 million. The appeal court also ordered the pharmaceutical company to pay €420 million in reimbursement to mandatory and supplementary health insurance providers (2,3). The company and its former chief executive are contesting this judgement by appealing the decision to the supreme court (1).

Below, Prescrire has published excerpts from the 1101-page judgement, illustrating the position of the appeal judges on Servier's culpability (our translations), accompanied by Editors' notes to provide context where useful (2).

"(…) Mediator°'s appetite-suppressing properties were originally intended and claimed. The legal proceedings reveal, first, that *benfluorex* was originally developed in the context of the search for a drug that had appetite-suppressing properties, among other effects. In a note dated 26 April 1967 (…), Jean-Claude Le Douarec [Editors' note: then working at Servier as a pharmacologist] clearly explained that the research that had produced *benfluorex* was driven by the desire to find '*a new derivative of Pondéral°* [Editors' note: *fenfluramine*]', a drug marketed by Servier as an appetite suppressant, that did not have the same side effects. In one of her hearings, Brigitte Riveline [Editors' note: then working at Servier as a researcher] confirmed (…) that '*Benfluorex was intended to be an anorexiant* [Editors' note: appetite suppressant] *that did not have the sedating effects observed with Pondéral°*'. (…)

Second, it emerged that this [appetite-suppressing] property was originally claimed. For example, the (…) product sheet for *benfluorex*, a Servier internal document, stated that its '*likely therapeutic indications*' were '*analgesic/anorexiant*' (…). This was also the case with the product sheets for (…) two metabolites of *benfluorex*, metabolised in turn to norfenfluramine, a molecule known to have appetite-suppressing properties and to play a role in the appetite-suppressing effect of *fenfluramine* and dl-fenfluramine in its dl-norfenfluramine form. The same property was also claimed in the product sheet (…) for JP1513, a methanesulfonate salt of *benfluorex* (…).

Similarly, both the patent application filed on 5 April 1967 and the 'special drug patent' filed on 3 December 1967 mentioned *benfluorex*'s appetite-suppressing effect, among others. (…)

Finally, it emerged that, in 1970, as part of its international nonproprietary name application, Servier described the drug's claimed action as an '*obesity treatment*'.

Properties confirmed in both animal and human studies. (…) Above all, the court refers to the numerous clinical studies in humans, examined in the statement of facts, that demonstrated, both before and after submission of the marketing authorisation application, the existence of an appetite-suppressing effect resulting in sometimes substantial weight loss: from the 1968 study by Marcel Plauchu, followed by the study by Marcel Zara, through to the study by Asmal et al. published in September 1977 (…). Several of these studies compared the drug to other appetite suppressants marketed in the 1970s, such as Linyl° [*phentermine*], Insoral° [*phenformin*], and Pondéral°, and demonstrated similar effects. (…)

These appetite-suppressing properties were also supported, empirically, by the off-label use of Mediator° by a number of doctors 'specialising' in weight loss, generally for cosmetic purposes. Servier was aware of this, and the court notes that none of the various internal documents addressing this issue ever suggested that the decision of such practitioners to prescribe Mediator° off-label was medically unjustified, but it was merely seen as a threat to the drug remaining on the list of those eligible for reimbursement. (…)

Targeting a more attractive market. (…) In November 1969, Servier decided to banish use of the term 'anorexiant', and to entirely reposition *benfluorex* in the therapeutic area of lipid and carbohydrate metabolism disorders.

The various memos and internal documents from this pivotal year show that, although the drug's appetite-suppressing effect had been clinically confirmed at this time, and its magnitude discussed, its effect on metabolism remained highly hypothetical (…).

Yet while the minutes from a strategy meeting held on 29 December 1969 noted that (…) '*the biochemical clinical arguments we currently have are directly linked to weight loss…*' and that '*the most attractive arguments to establish would be… correction of lipid metabolism… effect on peripheral glucose uptake, improvement of diabetes control…*', the decision was taken to present *benfluorex* as a '*corrector of lipid metabolism*', in other words to prioritise an effect

that had not been demonstrated over one that had been observed clinically. The court notes that a few days earlier, in a memo dated 8 December 1969, Janine Servier [Editors' note: wife of Jacques Servier] had argued, in a reversal of scientific logic, that *benfluorex* had no future as an appetite suppressant and could only move forward as an adjunct to anti-diabetic treatment, an effect that had not yet been demonstrated. She suggested rapidly applying for approval and then intensifying '*a major research programme*' to confirm what was then merely a scientific hypothesis.

The various documents also indicate that Servier was not eager to develop a new appetite suppressant (a market sector for which it already had Pondéral®), but preferred to target a market that was more attractive given the prices commanded and the duration of therapy, obviously raising the subsequent issue of reimbursement.

In 1973, Servier therefore applied for marketing authorisation in three therapeutic indications in the area of metabolic disorders.

At the time it submitted this marketing authorisation application, Servier had detailed knowledge of the drug, its ultimate metabolism into norfenfluramine, its close similarity to the other fenfluramines, and its weight loss effects, albeit usually weak. (...)

Deliberate concealment of the appetite-suppressing properties. (...) While Servier was within its rights in deciding to restrict its marketing authorisation application to metabolic disorders, it was also careful to maintain total silence about the drug's appetite-suppressing effects, despite being well aware of them.

None of the studies explicitly referring to the existence of the appetite-suppressing effects of *benfluorex* in animals and humans were included in support of the initial marketing authorisation application. The company only provided studies that, if they referred to an effect on weight, did so without explicitly stating the origin of this weight loss effect.

This omission was not the only way in which the drug's appetite-suppressing properties were concealed.

Expert assessments signed by Dr Jean Charpentier [Editors' note: a pharmacologist who conducted studies for Servier at the time] included the results of the Schmitt study, but with the specific references to appetite-suppressing doses removed (...). Similarly, while these expert assessments included data from a study by Jacques Duhault [Editors' note: head of the Servier diabetes and obesity research laboratory from 1963 to 2000], the lines and tables concerning amphetamine had been carefully expunged (...). Finally, they included the data from an Iterc study [Editors' note: a Servier-funded study of the drug's 'behavioural and neurophysiological effects' in rats, mice and rabbits], but without the references to its appetite-suppressing effect.

The deliberate nature of the concealment was also confirmed during the criminal trial by Jean Charpentier, who stated that he and people at the company sought '*a weight loss mechanism that took the drug out of the amphetamine class*' (...).

The evidence presented also clearly shows that throughout Mediator®'s life cycle, Servier systematically failed to pass on studies that suggested appetite-suppressing properties. (...)

This continual preoccupation with concealing *benfluorex*'s appetite-suppressing properties was not solely driven by the desire of Servier and its founder to position Mediator® in the therapeutic area of lipid and carbohydrate metabolism. It was also necessary because they wanted to keep quiet about the role of norfenfluramine (which was responsible for the appetite-suppressing effect of both *benfluorex* and the fenfluramines) as the main metabolite of *benfluorex*.

By keeping quiet about these effects, Servier avoided any curiosity about their cause: curiosity that might have prompted questions about the role of norfenfluramine in Mediator®'s mechanism of action at an earlier stage, since the scale of this molecule's adverse effects had been apparent since the early 1960s, to the extent that clinical trials of this substance were abandoned.

Concealment of the similarities between the metabolism of benfluorex and fenfluramines. (...) While Servier never explicitly denied the presence of this common metabolite, it systematically maintained a level of ambiguity about the metabolism of *benfluorex* in its interactions with the regulatory authorities, which enabled it to conceal the similarities between the metabolism of *benfluorex* and fenfluramines, from both patients and doctors. (...)

This 'reluctance' to state the facts clearly is also illustrated by the communication problems surrounding the Gordon and Vis study conducted in 1993. (...) Jean-Philippe Seta also recognised (...) that '*the Gordon study clearly shows identical circulating levels of norfenfluramine following the administration of fenfluramine and benfluorex at therapeutic doses*'. (...)

The evidence presented also makes it clear that this study was not spontaneously reported to the regulatory authorities, in particular as part of the application to renew the drug's marketing authorisation submitted on 24 January 1997. (...)

This ambiguity enabled Servier to avoid including norfenfluramine as one of the metabolites of *benfluorex* in the drug's SmPC [summary of product characteristics], as it had done for Isoméride® [*dexfenfluramine*]. More broadly, it enabled the company to conceal the similarities between the metabolism of *benfluorex* and that of *fenfluramine* or *dexfenfluramine* from patients and doctors. (...)

Awareness of the risk of pulmonary arterial hypertension (PAH). The evidence presented primarily focuses on the case of PAH reported by the CRPV [Editors' note: Regional Pharmacovigilance Centre] at the Saint-Antoine Hospital in Paris in June 1999. But while this was the first reported case of PAH in which Mediator® was the only drug being

taken by the patient, it is clear that the drug had appeared in earlier reports since 1989.

It is true that each of these reports referred to the use of other drugs, including those with appetite-suppressing effects that could have played a role in the onset of the reported PAH. But from a pharmacovigilance perspective, the failure to ask questions about the possible role played by Mediator® is surprising, to say the least.

Firstly, the court notes that, at least in France, Mediator® featured in the reports as early as 1989, i.e. at a very similar point in time to Pondéral® and Isoméride®. Secondly, some of the reports noted that the patient had taken Mediator® longer or from an earlier date than Isoméride, a drug which they were also taking. Yet on each occasion, the various cases were judged to be primarily caused by Isoméride®, probably due to the fact that Mediator®'s market positioning meant it was not perceived as an appetite suppressant.

At this point, Servier not only did nothing to enlighten the health authorities about the scientific parallels that could be drawn between the fenfluramines and *benfluorex*, in particular due to the existence of a highly active common metabolite, norfenfluramine, but also, in contrast to its response in 1970, chose to avoid instigating any internal studies into *benfluorex* and the risk of PAH. The court notes that, in the meantime, the drug had been granted marketing authorisation and was bringing in substantial income. (...)

Awareness of the risk of heart valve disease. (...) The legal proceedings and evidence presented show that by 1995, at the very latest, Servier was fully aware of the risk linked to use of drugs of the fenfluramine class with regard to PAH, and by 1997, at the very latest, of the risk with regard to heart valve disease. (...)

Therefore, from 1995 and certainly from 1997, given the chemical similarity of the drugs that all belonged to the fenfluramine class, Servier should at the very least have informed the regulatory agency, doctors and patients of this risk, and recommended restrictions on use.

In 1999, the occurrence of two 'pure' cases (in which Mediator® was the only drug being taken by the patient) should have made the withdrawal of the drug inevitable, in line with the withdrawal of Pondéral® and Isoméride®, particularly since therapeutic alternatives were available (the same ones proposed in 2003 to '*justify*' the possibility of withdrawal from the Spanish market).

A systematic policy of denying the risks. (...) The legal proceedings show that every time scientific evidence implicated a fenfluramine drug, Servier reacted by repudiating the reliability or conclusiveness of the study in question. (...)

This systematic denial, including of results from studies carried out by the company itself, showed how Servier systematically chose to prioritise its economic interests over the safety of the consumers of its drugs.

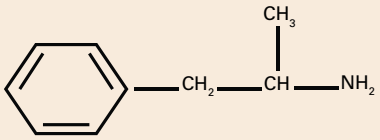
An obvious chemical relationship

As early as 1977, the French medical journal *Pratiques* pointed out (our translations) the "*obvious chemical relationship*" between *fenfluramine* and *benfluorex*.

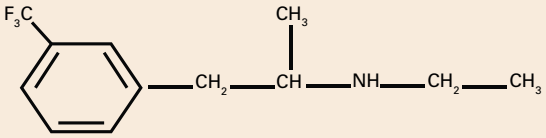
"*Servier says that 'Mediator® has taken us over a decade of research'... But why hasn't it been said that, in chemical terms, Mediator® is a derivative of amphetamine, and a derivative of another of the company's drugs, the appetite suppressant Pondéral®?*

We leave you to judge for yourselves:

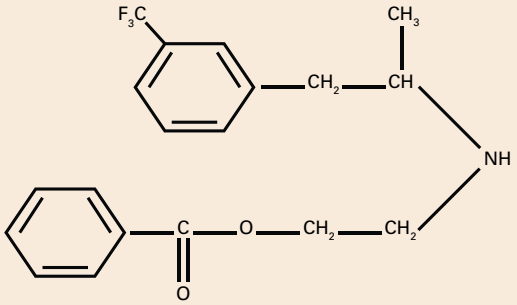
Amphetamine



Fenfluramine (Pondéral®)



Benfluorex (Mediator®)



In other words: Mediator® = Pondéral® + benzoic acid attached to the end of the chain" (1,2).

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1- "Les laboratoires Servier pour le Mediator®" *Pratiques, les Cahiers de la Médecine Utopique* 1977; (13): 28-31. **2-** Prescrire Rédaction "Le benfluorex démasqué dès 1977 dans la revue Pratiques ou les Cahiers de la médecine utopique" *Rev Prescrire* 2019; **39** (434): 946-947.

Keeping the drug on the market at all costs. (...) The evidence presented clearly shows that in the 2000s, far from considering any restrictions on the use of Mediator®, Servier positioned itself to develop the drug further. In the three-year strategic plan drawn up by Dr Denys Schutz [Editors' note: the marketing director at Servier responsible for

promoting Mediator°] dated 14 April 2008, Schutz wrote that he was revising the estimated sales of Mediator° for the current financial year upwards, and that '*time appears to be on our side, enabling us to get ready for the relaunch of its reputation as a diabetes drug, which is scheduled for spring 2008*'. He also hoped that the results of the first Moulin study and the awaited results of the Regulate study would support a re-evaluation of Mediator°'s indication in type 2 diabetes, '*culminating in a reassessment of the level of "actual clinical benefit"* [Editors' note: as determined by France's National Authority for Health (HAS)] *it provides in this disease, which will protect its price and eligibility for reimbursement*' (...).

The central role played by Jacques Servier. (...) The evidence presented reveals that it was Jacques Servier who made the decision in 1969 to reposition *benfluorex* as a diabetes drug, and to '*banish*' the use of the term 'appetite suppressant', even though at the time, as discussed above, its weight loss effects had been observed clinically, which was not the case for its effects on lipid and carbohydrate metabolism.

It was also Jacques Servier who, as the chief pharmacist, signed the marketing authorisation application for the drug on 29 November 1973, accompanied by studies in which references to any, even minor, appetite-suppressing effect had been carefully concealed. It was also he who, when responding to the requests for further information from the regulatory authorities as part of the assessment of this initial application, failed to mention norfenfluramine even though the company was asked about the chemical relationship between *benfluorex* and *fenfluramine*. (...) [see the inset "An obvious chemical relationship", p. 305].

Jacques Servier thus presided over not only the application to include Mediator° on the list of drugs eligible for reimbursement through the national health insurance system, but also the renewal applications in 1984, 1987, 1989 and 1992, and on each occasion approved the submission of documents that did not contain any information about the drug's appetite-suppressing side effects.

A clear intention to deceive consumers. (...) The company not only did nothing to prevent or limit the danger to patients but, at the same time, pursued a consistent policy, not of assessing the degree of risk by conducting safety studies, but of extending Mediator°'s indications and, at the very least, keeping Mediator° on the market despite the weak nature of the effects claimed. (...)

Warning signs of the harmful risks were thus purely and simply played down and treated as secondary to opportunities for development. (...)

It was thus demonstrated that Servier took a 'flexible' approach to the drug's indications, and was more concerned with developing 'benefits', in the financial sense of the term, rather than with risks, in this case, regrettably, in the scientific sense.

The serious nature of the crimes committed. (...) The extremely serious nature of the crimes for which the court has found Servier guilty hardly requires further explanation.

The first, and most tragic, reason for this is of course the physical consequences of taking Mediator°. (...) The many victims who gave evidence throughout the trial described, each in their own words, first, the agony of living with a sword of Damocles over their heads, and second, after the disease developed, a kind of slow descent into hell, characterised by increasingly limited mobility, ever greater suffering and, if they underwent surgery, enduring the difficult consequences of treatment that often enabled them merely to survive rather than thrive.

The second reason is, in addition to the direct consequences experienced by each victim individually, the suspicion this case has created towards everyone in the care pathway. Many of the victims, and others, felt they were up against a regulatory agency that was incapable of fulfilling its pharmacovigilance role, doctors who prescribed a potentially fatal drug without really caring about the molecule they were prescribing, and pharmaceutical companies that prioritised their financial interests over the interests of patients. This distrust of the health system as a whole represents a tragedy in itself, since it leads patients to systematically call into question messages about prevention and health care from the medical profession, at the risk of endangering their health and that of others when these messages concern the treatment of infectious diseases. (...)

The third reason is the duration and scale of the fraud, perpetrated not only on the health authorities, but most importantly on thousands of patients over a period of several decades. It is precisely this aspect that best characterises the conduct of the defendants.

Indeed, for all of those years, although they were aware of the deceit involved in bringing Mediator° to the market, the companies accused not only kept the drug on the market, but sought to develop it further, to the detriment of public health. Then, from 1995 onwards, they kept it on the market despite the harmful risks that had become apparent, thus putting their industrial and commercial interests first. (...)

The fourth reason is the financial impact of the marketing of the drug on the funding of the national health insurance system. By improperly pocketing large sums of money from this system, the company misappropriated the money of those who had paid into it, in other words almost all of French society. "

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Selected references from Prescrire's literature search

1- Prescrire Editorial Staff "Mediator° trial appeal: a judgement that better reflects the harm done" *Prescrire Int* 2024; **33** (261): 194.
2- Court of Appeal of Paris "Arrêt n° 629" 20 December 2023: 1101 pages.