Servier and French drug regulatory agency on trial

ABSTRACT

- **The criminal trial relating to the Mediator° disaster began in September 2019 in Paris. It is expected to last for six months.**

- **Individuals and corporate entities are facing charges for various offences, notably "*involuntary bodily harm and manslaughter*".**

- **The company, Servier, is accused of concealing the anorexic effects of the drug and some of its adverse effects, and the French drug regulatory agency of having delayed suspension of its marketing authorisation.**

In France, ten years after the market withdrawal of Mediator° (*benfluorex*), an amphetamine-like drug which caused several hundred deaths, the trial relating to the criminal aspects of this disaster began at the Paris High Court in September 2019 and is expected to last for six months (**a**)(1). Who are the defendants? What charges have been brought against them?

The following account is based on the indictment signed by the examining magistrates.

Charges against corporate entities

The parent company, Servier, and nine of its subsidiaries, as well as the French drug regulatory agency (Afssaps at the time), are being charged (2).

The company, Servier. Ten companies in the Servier group are being prosecuted on various counts (2). *"Obtaining unjustified authorisation"* refers to their having obtained a renewal of marketing authorisation (MA) for *benfluorex* for indications related to metabolic disorders, in particular diabetes, while concealing its anorexic effects. The company will also have to respond to the charge of *"deception concerning the essential qualities of Mediator°, and the risks inherent in its utilisation, with endangerment to life"*. It is also on trial for *"involuntary bodily harm and manslaughter, through clearly deliberate violations"*, notably for not having informed patients and doctors about all the adverse effects of *benfluorex*, while the dangers were known and cases of heart valve disease and pulmonary arterial hypertension linked to its use had been reported (2,3). Servier is also being prosecuted for *"fraud"*. It is accused of having deceived the mandatory and supplementary health insurance funders in France, regarding reimbursement of the proprietary drug Mediator°. Another accusation, *"influence peddling"*, refers to the payment of a scientist who, according to the inquiry, lobbied a senator with a view to influencing a Senate inquiry into the Mediator° disaster (2).

The French drug regulatory agency. The agency is accused of *"manslaughter through negligence"* and *"involuntary bodily harm through negligence"*, notably for having delayed suspension of the marketing authorisation for *benfluorex* and not having warned patients and doctors about its anorexic effects and adverse effects. According to the inquiry, by not taking the necessary measures to prevent the situation, the agency involuntarily caused bodily harm and death (2).

Charges against individuals

These are principally senior officers of the company and members of the French drug regulatory agency at the time the events occurred.

Responsible officers at Servier. Two senior representatives of the group have been sent for trial: one (Jean-Philippe Seta) for the same reasons as the company, mentioned above, and the other (Christian Bazantay) for complicity in an offence in which a director of drug evaluation from the regulatory agency has been accused (2). Jacques Servier, founding president of the group, who was also charged, died in 2014. (2).

Members of the French drug regulatory agency. A former director of evaluation at the French drug regulatory agency (Jean-Michel Alexandre) is charged with *"illegal involvement of a civil servant in a previously inspected company"*, for having been paid for advice by Servier less than three years after leaving the agency, where he was responsible for inspecting pharmaceutical companies, including Servier. The former chairman of the marketing authorisation committee of the agency (Charles Caulin) is facing the same charge. Three former experts from this same MA committee (Jean-Roger Claude, Michel Detilleux and Bernard Rouveix) are being prosecuted for *"illegal acquisition of benefits"* because of their links with Servier

***a-** Civil proceedings have also begun, through the Administrative Courts as well as the French National Office for Medical Accident Compensation (ONIAM) (refs 2,4-6).*

as consultants (2). A former drug evaluation official (Eric Abadie) was charged with the same offence, but died in 2019.

Other members of health authorities. A former member of the French National Authority for Health (HAS) and the "Direction générale de la santé" (the French government Health Department), Jacques Massol, is accused of *"illegal involvement of a civil servant or representative of a public authority, during this period, in a previously inspected company"* and of *"illegal acquisition of benefits"*, as a result of having provided advice to Servier less than three years after carrying out a public service mission (2). As a result of providing similar services, François Lhoste, a former project manager for the French pharmacoeconomic committee for health products (CEPS) is also being charged with *"illegal acquisition of benefits"* (2).

Companies in the Servier group and other individuals are also being put on trial for having been complicit in or having concealed the offences for which members of the health authorities or drug regulatory agency are being accused (2).

A scientist and a senator. A former director general of INSERM (Claude Griscelli) is on trial for *"influence peddling"* as a result of having sent information to a senator (Marie-Thérèse Hermange) which could have altered the interpretation of a senate inquiry into Mediator®. At the time, he was being paid by Servier as a consultant (2). The ex-senator will face a charge of *"complicity in the offence of influence peddling"* (2).

In summary. The examining magistrates point out that there is a *"major difference"* between the *"deliberate misconduct"* of the company, Servier, and the allegations against the regulatory agency, which fall into the category of *"unintentional negligence"* (2). As with all trials, the hearings will have to establish individual responsibilities. More than 4100 plaintiffs are waiting for answers (2).

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Selected references from Prescrire's literature search

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3- Prescrire Editorial Staff "Benfluorex: adverse effects reviewed, 1976-2015" *Prescrire Int* 2017; **26** (179): 47.

4- "Nouvelle procédure de recouvrement de l'Oniam: plus de 30% de créances recouvrées fin 2018 (rapport d'activité)" APMNews 26 June 2019: 2 pages.

5- "Mediator®: Servier finalement condamné à indemniser l'intégralité du préjudice malgré un antécédent de rhumatisme articulaire aigu" APMNews 4 July 2019: 2 pages.

6- "Mediator®: Servier demande à l'État de rembourser 30% de toutes les indemnisations versées aux victimes" APMNews 15 February 2019: 2 pages.

Diseases still being neglected

Research into a range of diseases affecting poor countries was better funded in 2017, but funding is still inadequate.

Neglected diseases are those for which research and development efforts are inadequate, not because they are rare (those are referred to as orphan diseases), but because a large number of people affected are poor. Most are so-called tropical diseases and those which disproportionately affect poor countries, such as malaria, tuberculosis and AIDS (1,2).

Funding of research and development for these diseases reached a record high in 2017: about 3.6 billion dollars (2,3).

Significant new drugs were introduced to the market in 2017, including: *fexinidazole*, the first short-course oral treatment for both stages of sleeping sickness (African trypanosomiasis); *moxidectin*, the first new drug in 20 years for combatting river blindness (onchocerciasis); and *tafenoquine*, the first single-dose treatment for *Plasmodium vivax* (2,3).

Public sector funding of research into these neglected diseases reached 2.3 billion dollars. The three main contributors (in descending order) were the US, the UK and the European Union. Private foundations contributed 700 million and commercial companies 600 million dollars (3). Although relatively high, these amounts fall far short of the level recommended by the World Health Organization: 0.01% of countries' gross domestic product (GDP) (2,3). The USA and the UK came closest, allocating respectively 0.008% and 0.007% of their GDP to this research; no other country reached 0.005% (3).

By way of comparison, the total global research and development spending of pharmaceutical companies was estimated at 150 billion dollars in 2015 (4).

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Volume 39 N° 430 • Page 627

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