Mediator° trial appeal: a judgement that better reflects the harm done

● French appeal court finds Servier guilty of four charges, handing down sentences more respectful of the victims of decades of constant, organised deception.

In March 2021, following the initial criminal trial over the Mediator° (*benfluorex*) disaster in France, the pharmaceutical company Servier and its former chief executive, Jean-Philippe Seta, were convicted of "*aggravated deception*" and "*involuntary bodily harm and manslaughter*". But they were not found guilty of "*fraud*" against the mandatory and supplementary health insurance providers that reimbursed prescriptions of Mediator°, nor of "*improperly obtaining marketing authorisation*", and no custodial sentences were handed down (1,2). The judgement on an appeal pursued to challenge these acquittals was delivered on 20 December 2023 (2-4).

The appeal court judge set out in extensive legal and scientific detail how the court had reached its judgement on the four charges: aggravated deception; involuntary bodily harm and manslaughter; improperly obtaining marketing authorisation (MA) and fraudulently obtaining MA renewals; and defrauding health insurance providers (1,2,4).

It has been proven that in order to obtain marketing authorisation for Mediator° in 1974, Servier took the risk of developing and promoting a new amphetamine drug, concealing its appetite-suppressing effect and misleading people about its metabolisation to norfenfluramine, the cause of the drug's adverse effects on heart valves in particular. Over the decades that followed, Servier not only denied that the drug had serious adverse effects, but sought to expand its indications, even though it would have been withdrawn from the market had the pharmaceutical company not hidden what it knew from patients, health professionals and the regulatory authorities (2-4).

The appeal court found that Servier's actions illustrated a peculiar concept of the harm-benefit balance: "*financial benefit for the company, deadly harm to patients*" (our translation) (2,4). It went further than the original court in its judgement, finding Servier guilty on all counts (2-5). 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. It also ordered the pharmaceutical company to pay €420 million in reimbursement to health insurance providers (2,3).

This judgement, which Servier and its former chief executive are once again contesting by appealing the decision to the supreme court, better reflects the harm caused.

The appeal court was highly critical of Jacques Servier, who died in 2014, finding that he acted in a deliberately deceitful manner over a period of several decades. Let us hope that this judgement sends a message not only to other pharmaceutical companies, but also to the many health professionals and policy makers who put too much trust in Servier and the "big man" at the top.

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Selected references from Prescrire's literature search

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.

2- "Notes d'audience prises par deux rédacteurs de Prescrire" 21 December 2023: 2 pages.

3- APM "Mediator°: condamnation aggravée en appel de Servier et son ancien numéro 2 Jean-Philippe Seta" 20 December 2023: 3 pages.

4- APM "Mediator°: l'escroquerie de Servier à l'assurance maladie et aux mutuelles était "parfaitement caractérisée" (cour d'appel)" 20 December 2023: 3 pages.

5- APM "Mediator°: une sanction "exemplaire" pour restituer les "fonds escroqués" par Servier au système de santé" 20 December 2023: 3 pages.

New data after marketing authorisation: European Commission consultation

● Prescrire has contributed to a public consultation on the proposed revision of the rules governing variations to marketing authorisations, submitted to take into account new data, for example on efficacy or a new adverse effect.

In September 2023, Prescrire responded to a consultation organised by the European Commission prior to revising the "variation framework", which sets out the required procedures for updating marketing authorisations when new data become available, for example on adverse effects, efficacy or use in children (1).

The Commission's initial call for evidence stated that it wants to increase the efficiency of the current regulatory framework for post-authorisation changes. It is aiming to reduce the administrative burden for marketing authorisation holders and authorities, and to free up some of the resources currently needed to process the large number of post-authorisation changes. Its proposals

include potentially increasing the proportion of variations subject to less stringent requirements, and thus less oversight (2).

In Prescrire's opinion, it would appear logical and inevitable for the workload associated with post-authorisation management of drugs to increase year on year, because new drugs are authorised every year, while existing drugs are rarely withdrawn from the market.

In order to ensure an acceptable level of patient protection, Prescrire called on the Commission to allocate sufficient resources (both human and financial) to the European Medicines Agency (EMA) to enable it to fulfil its obligations regarding the oversight of an ever-increasing number of authorised drugs.

In Prescrire's view, there is nothing inherently wrong with simplifying and rationalising administrative tasks, provided that this does not have a negative impact on the surveillance of drug efficacy and patient safety. Prescrire called on the Commission to set stricter standards for the clinical evaluation of drugs prior to authorisation (in order to reduce the number of drugs to be monitored that are not useful to patients), and to strengthen the requirements for post-authorisation evaluation.

Prescrire also urged the EMA to reduce its workload by reviewing the need to keep drugs on the market that have no real clinical utility or that are more dangerous than beneficial.

Finally, Prescrire also stressed the urgent need for more transparency about variations concerning efficacy and adverse effects, and to make more post-authorisation evaluation documents systematically available to the public (1).

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References 1- Prescrire Editorial Staff "Prescrire's response on a call for evidence of the European Commission on the Revision of the variation framework for medicines" 20 September 2023: 2 pages. **2-** European Commission "Call for evidence: Pharmaceuticals – changes to marketing authorizations (revision of the variation framework for medicines)" 29 August 2023: 4 pages.

Non-comparative trials for marketing authorisations: EMA consultation

● Prescrire has contributed to a consultation on the use of non-comparative clinical trials to obtain marketing authorisation.

In September 2023, Prescrire submitted its response to a public consultation organised by the European Medicines Agency (EMA) on the use of non-comparative clinical trials as the main ("pivotal") evidence of efficacy in marketing authorisation applications (1,2).

Prescrire considers that the reflection paper rightly highlighted the methodological weaknesses of non-comparative trials in evaluating the potential efficacy of a drug. It is because of these weaknesses that, with a few rare and substantiated exceptions, marketing authorisations should not be based on such trials. Prescrire felt it was regrettable that the EMA's preparatory document:
– Does not clearly spell out what these trials can do (generate hypotheses) and what they cannot do (demonstrate a causal relationship between the treatment and the outcomes observed);
– And does not define, from the outset, the handful of exceptional situations in which the use of a non-comparative trial might be considered an acceptable basis for marketing authorisation.

Drawing on concrete examples, Prescrire expressed its concern about the fact that, despite the known weaknesses of non-comparative trials, the EMA is increasingly accepting them as the sole basis for marketing authorisations (2).

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References 1- EMA "Reflection paper on establishing efficacy based on single-arm trials submitted as pivotal evidence in a marketing authorisation" 17 April 2023: 15 pages. **2-** Prescrire Editorial Staff "Final Prescrire response to EMA consultation guideline single arm trials" 20 September 2023: 9 pages.

Drug shortages: Prescrire calls for transparency

In October 2023, ahead of the publication of a Communication from the European Commission on addressing medicine shortages in the European Union (EU), a joint letter was sent to the Commission by Prescrire, the European Public Health Alliance (EPHA) and the patient rights umbrella organisation France Assos Santé (1,2).

The Commission is in favour of introducing a "Voluntary Solidarity Mechanism" across EU member states to address drug shortages. The cosignatories of the letter emphasised that transparency about drug stocks will be needed if such a mechanism is to work. They urged the Commission to call for the introduction of requirements for manufacturers and wholesalers that provide information on stock levels to the EU's national drug regulatory agencies.

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References 1- European Commission "Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions": 19 pages. **2-** EPHA-FAS-Prescrire "Lettre conjointe" 17 October 2023: 1 page.