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Published in:
Studies in History and Philosophy of Science Part A

DOI:
10.1016/j.shpsa.2025.102075

Publication date:
2025

Document Version
Publisher's PDF, also known as Version of record

Studies in History and Philosophy of Science 114 (2025) 102075

Contents lists available at ScienceDirect

Studies in History and Philosophy of Science

journal homepage: www.elsevier.com/locate/shpsa

A pink lie in French medicine

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A B S T R A C T

This paper sets to explain how one of the most prescribed and sold pharmaceutical drugs in France – Spasfon (phloroglucinol), introduced on the French market in the 1960s, became and remained so successful in the absence of solid scientific evidence. Integrating the epistemology of ignorance and a feminist approach to the history of medicine, my goal is to understand how this case of ignorance was initially constructed and how it has maintained itself to this day. I argue that sexism is one key factor explaining how ignorance was constructed around this very popular – and incidentally pink – pharmaceutical drug.

When citing this paper, please use the full journal title *Studies in History and Philosophy of Science*.

Introduction

Spasfon was born in France in the 1960s. It is the brand name for the chemical compound called phloroglucinol, a pharmaceutical drug available on the French market by prescriptions as well as over the counter. The drug was authorised on the French market in 1963 and subsequently commercialised by Laboratoire Lafon. Spasfon is often delivered in the shape of a round shiny pink pill. It is claimed to be an antispasmodic acting on smooth muscles in the body, such as those in the intestines, urinary bladder and uterus, and classified as such by the French health authorities (*Base de Données Publique des Médicaments*, 2024). Depending on the types of Spasfon (sugar-coated or freeze-dried tablets), the composition varies slightly: phloroglucinol only for freeze-dried Spasfon, phloroglucinol and trimethylphloroglucinol for the sugar-coated tablet version (this is the water-insoluble version of phloroglucinol). For simplicity's sake, I'll refer to 'phloroglucinol' or 'Spasfon' throughout the paper. Phloroglucinol is commonly prescribed and sold for a variety of abdominal, gynaecological, and urinary tract pains as well as to treat painful spasms during pregnancy. Spasfon is one of the most sold pharmaceutical drugs in France. It was the 5th most sold drug delivered over the counter in quantity in 2012 and 2013 (Cavalié, 2013, p. 24; Cavalié, 2014, p. 25). In 2013, Spasfon was more commonly sold than Nurofen, the most popular brand name for ibuprofen in the country (ranked 21st) (Cavalié, 2014, 25). Spasfon is a hugely popular self-medicating drug, but it is also broadly prescribed. Since 2014, prescriptions of Spasfon in all its different types and all its generic drugs have fluctuated between 23 million to almost 27 million units each year[1] (*Caisse Nationale de l'Assurance Maladie*, 2014-2024). When it is prescribed, it is partly reimbursed by the country's national health insurance, at a rate of 15 % for all indications except biliary pains (*Haute Autorité de Santé*, 2017).[2] Spasfon is thus a staple of the French pharmacy. Suffering with menstrual pain, you are more likely to self-medicate with this drug rather than with ibuprofen – even though non-steroidal anti-inflammatory drugs are recommended by international guidelines and systematic reviews for that indication (Burnett & Lemyre, 2017; Hickey et al., 2023; Iacovides et al., 2015; NICE Clinical Knowledge Summary, 2023).

Another key piece of information about Spasfon is that it is also disproportionately prescribed to women. In 2021, 72 % of prescribed phloroglucinol units were prescribed to women in France (*Caisse Nationale de l'Assurance Maladie*, 2014-2024).[3] This ratio goes up to 75 % for people between the age of 19 and 59. This gender ratio remains unbalanced even for patients after the age of 59, with 68.4 % of phloroglucinol prescribed to women, meaning that menstrual and obstetrical pains are not the sole explanation for such a difference.

In 2019, a team of medical researchers from Toulouse, France, published a humorous paper on the efficacy of phloroglucinol: 'Finally an evidence-based indication for injectable phloroglucinol!' revealing it is commonly used in French hospitals to remove iodopovidone stains and thus poking fun at the lack of evidence-based indication for the drug (Loussert et al., 2019). Indeed, as we shall see, the state of clinical

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[1] Units refer to boxes (pharmaceutical drugs are delivered in boxes in France).

[2] The evolution of this rate will be discussed in the third part of this paper.

[3] 71,68 % rounded up to 72 %.

https://doi.org/10.1016/j.shpsa.2025.102075

Received 2 May 2024; Received in revised form 12 August 2025; Accepted 12 October 2025

Available online 30 October 2025

evidence regarding phloroglucinol is lacking. However, this lack of knowledge about one of the most sold drugs in the country, heavily prescribed to women, is not exactly funny. My goal in this paper will be to examine the ignorance around Spasfon and phloroglucinol – how bad is it, how was it constructed, by whom and how harmful is it? To answer these questions, I suggest combining a presentist approach to the history of medicine with a feminist epistemology of ignorance (Chang, 2021; Tuana & Sullivan, 2006).

Presentism takes seriously the fact that even historians are stuck in the present; it argues that it is useful to write history from and for the present and that it is possible to do so without falling into the pitfall of a whiggish view of history: '[I]t is an "ism" in the sense of an ideology, a commitment to investigate history based on a clear and conscious engagement with our present, ultimately in order to improve that present' (Chang, 2021, p. 101). Hasok Chang's own favoured version of presentism investigates what he calls the 'loser's history' of science, moments of past science that present scientists consider as 'unimportant, outdated, or simply wrong' (2021, 107). Building on Chang's vocabulary, I suggest that in the case at hand – Spasfon – a 'winner's history' of medicine is needed to understand what mechanisms led the drug to become so successful despite the lack of evidence in its favour. In other words, I understand the other side of the coin of winners' history of science to be something like agnotology and the study of ignorance (Proctor, 1995; Proctor and Schiebinger, 2008). As it is specifically focused on identifying potential gender bias in the construction of ignorance in the case of Spasfon, my project can also be described as feminist epistemology of ignorance (Tuana & Sullivan, 2006). Feminist philosophy of science is a diverse field with a long history (Harding, 1986; Keller, 1995; Longino, 1990; Nelson, 1990). The ambition of this paper resembles what Sandra Harding has called feminist empiricism (Harding, 1986, p. 24; 1992, p. 439), an approach dedicated to identifying gender bias in science, without necessarily criticising the methodological norms involved. Indeed, a lot of issues in the case of Spasfon would be apparently resolved if evidence-based medicine was simply applied to the case at hand: phloroglucinol would be removed from the market and physicians would stop prescribing the drug to their patients. However, insufficient rigour in applying methodological standards is only one part of the problem, as the cause of that insufficient rigour should also be examined. As Nancy Tuana and Shannon Sullivan have argued, 'practices of ignorance are often intertwined with practices of oppression and exclusion' (Tuana & Sullivan, 2006). For this, the taxonomy of ignorance introduced by Tuana is particularly precious (Tuana, 2006). My goal will also be to understand the consequences of these practices of ignorance – in the case of Spasfon, understanding the harm done to women and patients in the country. Joining presentism with feminist epistemology of ignorance gives the necessary tools to identify the mechanisms behind ignorance and oppression which were both built in a historical context. Much like Chang's favoured approach, albeit with an opposite goal in mind, I find that a historical investigation can stimulate the production of knowledge to correct the ignorance that it identifies. As Chang writes, 'history-writing can and should serve the purpose of improving the present' (Chang, 2021, 112). This is the goal of my investigation on the history of Spasfon: improving pain management in France and notably that of women. Systematic reviews published in 2018 and 2020 were not able to change the status quo (Blanchard et al., 2018, 2020); my hope is that a feminist integrated history and philosophical investigation of ignorance will. Doing so, I hope to demonstrate how fruitful these approaches are.

I start the paper by examining the evidence about phloroglucinol for the indications for which it is prescribed in France. The lack of evidence is striking, especially for menstrual pain, for which no clinical trial can be found. In the second section, I turn to the investigation of the history of Spasfon. I review in detail the first clinical study on phloroglucinol, published in 1961 (Debray et al., 1961). Spasfon was not first thought as an antispasmodic, but as acting on bile production in the body, to cure illnesses such as migraines, 'biliary pains' and 'liver attacks.' All of these illnesses, according to Marie-Christine Pouchelle, were thought at the time to affect more predominantly women (Pouchelle, 2007, p. 4). I thus make the argument that Spasfon was, from the beginning, a drug for women. A peculiarity of this trial was its experimental design, which involved triggering harm in mostly female patients. I also examine the animal studies conducted on phloroglucinol before its market authorisation (Cahen, 1962; Cahen et al., 1962b). They illustrate further the uncertainty on the supposed mechanism of the drug. In the third section, I turn to scrutinise what I describe as regulatory apathy from the French health authorities. Based on 1960s documents from the administrative archive, I argue that ignorance about Spasfon was created in part by sexism. I then turn to review the health authorities' attitude towards Spasfon in more recent years. Here the concept of wilful ignorance introduced by Tuana is particularly useful to describe the apathy of the authorities (Tuana, 2006, p. 4). Finally, in the last section, I turn to consider the harms created by Spasfon's 'pink lie' in France: the impact on women's health, as well as ethical and epistemological harms.

1. Why you may have never heard of Spasfon

Despite what seems like a huge pharmaceutical success, you may have never heard of Spasfon or phloroglucinol as it is not available in every country. I am not going to attempt to give an exhaustive list of countries who currently are approving the drug on their market, as that would require checking each country's database. As of 2024, it does not seem to be authorised in the United States, Canada, the United Kingdom, Germany, or Austria, to cite just a few. Countries that market the drug seem to include Italy (Spasmex), South Korea (Flospan), as well as a large number of former French colonies in Africa. I have not attempted to investigate for each of those countries the scale at which phloroglucinol is used or whether the gender ratio is also skewed towards women. I will focus in this paper on the case of France, where the drug originated from in the 1960s and where it is popular. The situation of Spasfon and phloroglucinol in France seems to be especially striking, but other countries might be facing similar situations, and more research will be needed to understand the global journey of Spasfon.

One reason why the drug is not available worldwide may have to do with the weak state of the clinical evidence in its favour. My goal in this paragraph will be to give a precise as possible idea of where the clinical literature is currently standing regarding phloroglucinol's most common reimbursed indications in France (abdominal, gynaecological, urinary, and obstetrical pains, all broadly construed). Two systematic reviews have recently been published by the same team located in France, one on the abdominal indications and one on the gynaecological indications of the drug (Blanchard et al., 2018, 2020). Both systematic reviews conclude that there is not enough or adequate evidence for the use of phloroglucinol in these indications. Perhaps surprisingly, researchers were not able to track more than five randomised controlled trials on the drug in total. Out of the three trials reviewed for abdominal pain, only one trial declared significant results for IBS symptoms. That trial was published by a team of researchers from Cephalon, the pharmaceutical laboratory which owned Spasfon at the time (Chassany et al., 2007) and as such is at risk of bias. In the review on gynaecological pain, researchers were only able to track two randomised trials (Blanchard et al., 2020, p. 2). One trial evaluated the efficacy of phloroglucinol as a prophylactic painkiller before surgical abortion and found negative results. Another trial evaluated the efficacy of the drug in pain management during hysteroscopy – but results were only available in Chinese – and so it was not included in the review. The authors were not able to track trials on the efficacy of phloroglucinol in the more typical indications where it is prescribed in France, notably menstrual pain (Blanchard et al., 2020, p. 3). Since 2020, a few more trials have been published on the efficacy of phloroglucinol in its market indications. A small RCT published in 2020 by a South Korean team found ambiguous results, with both significant and nonsignificant results on the efficacy of the drug in IBS symptoms (the trial was conducted on 72 patients) (Shin

et al., 2020); phloroglucinol is commercialised in the country under the brand name Flospan by DAE HWA Pharmaceutical, which funded the study. An open-label trial conducted in 2022 in Italy (where phloroglucinol is commercialised under the brand name Spasmex) found positive results for the use of the drug for renal and biliary pains (the latter of which is an indication no longer reimbursed in France) (Corvino et al., 2023). Authors presented phloroglucinol in the introduction of their paper as a drug 'widely known in the world' and an 'effective' antispasmodic, notably citing the systematic review by Blanchard and al. from 2018 to support that statement, even though Blanchard et al. drew opposite conclusions (Corvino et al., 2023, p. 621). One of the authors of the study is listed as an employee of Scharper S.p.A, the pharmaceutical company commercialising Spasmex in Italy.

The state of the literature on phloroglucinol is inadequate: there are very few published randomised clinical trials; for some of the most common indications of the drug in France, there are no published trials at all; most of the studies report nonsignificant results; and the studies reporting significant results are at risk of bias. Furthermore, it is possible that further negative results have not been published. Publication bias – when negative results are less likely to get published compared to positive results – is a known problem in medical research.[4] It is likely that it has affected the current state of the literature on phloroglucinol. At least one trial on phloroglucinol conducted in South Korea and preregistered on the ClinicalTrials.gov platform does not seem to have led to the publication of any results (Lee, 2013).[5] The state of the literature on phloroglucinol contrasts with its staggering prescription numbers – 26.9 million in 2022 in France (*Caisse Nationale de l'Assurance Maladie*, 2014-2024). After the publication of *Pilules roses* in 2023, the current owner of Spasfon, Teva pharmaceuticals, faced media turmoil and sent a press release to journalists to defend the merit of Spasfon. In that press release, only one trial was cited: the Chassany et al., 2007 study on the efficacy of phloroglucinol on IBS.[6] In 2024, in a review of the 10 most prescribed drugs in France (totalling 21 medicines), the United Kingdom and the United States, Fournier and al. judged that phloroglucinol was one of three medicines with the worst quality of evidence in their favour (Fournier et al., 2024). No other painkiller fared as bad as phloroglucinol, and the drug was also the only one out of the 21 not available in these three countries.[7] It seems fair to describe this lack of sufficient knowledge about the efficacy of phloroglucinol – knowledge that should be there but is not – as ignorance. Today, pharmaceutical drugs need to show they have convincing evidence in their favour to be considered for introduction on a pharmaceutical market. As per the French public health code, the French medicine agency ANSM (*Agence Nationale de Sécurité du Medicament et des Produits de Santé*) is tasked with the mission of 'evaluating the benefits and risks of health products' (ANSM, 2022). However, some older drugs like Spasfon, on the market since the 1960s, have avoided such a minimum requirement on efficacy. This is why it is necessary to study the history of Spasfon to understand how this lack of knowledge came from and how it was allowed to remain.

2. Spasfon's not so rosy history

Alexandre Blondeau, a retired publicist, published in 1994 a history of French pharmaceutical companies, with the help of said companies (Blondeau, 1994, p. 191). The result is a triumphal account of the history of Laboratoire Lafon and its hit drug, Spasfon. It seems to be the only secondary literature about the history of the drug. The triumphal tone of the writing makes it the perfect start of my investigation on the supposedly 'success' of Spasfon.

2.1. The success story

Louis Lafon (1910–1992) – who will give the last syllable of his name to Spasfon[8] – studied pharmacy in Montpellier (1994, 154). According to Blondeau, in 1941, Lafon first became the owner of a pharmacy in Paris in 1941 and funded Laboratoire Lafon in 1951. His first commercial success was Higalex, a drug indicated for bloating. Blondeau writes that Lafon went door-to-door to medical practices to sell his remedies (1994, 155). Lafon quickly managed to sell 3000 units of Higalex every month. But it is the commercialisation of Spasfon in 1963 or 1964 that made the firm genuinely successful.[9] Blondeau writes that after a few years on the market, a million units of Spasfon were sold every month (1994, 157). In fact, by the end of the 1990, 40 % of Laboratoire Lafon's turnover –107 million euros – was achieved solely by Spasfon's sales (Flallo, 2001). In 1991, the firm received the prestigious French Galien prize 'for all its discoveries' (Prix Galien, 1991). Something Blondeau does not mention is that another success of the firm was modafinil, a popular wakefulness-promoting drug in the United States, where it was commercialised under licence by Cephalon.[10] This is perhaps what motivated Cephalon to buy Laboratoire Lafon in 2001, for 500 million euros (Flallo, 2001). Cephalon was then bought by Teva in 2011 for 6.8 billion dollars (Krauskopf, 2011). Blondeau concludes by praising Lafon, insisting on the 'the irrepressible idea of a humanist vocation', his 'creative genius' and his 'life of effort' (Blondeau, 1994, p. 161).

2.2. The first publication on the therapeutic use of phloroglucinol

The history of pharmacy is notoriously complicated by the lack of access to private business archives and the secretive nature of pharmaceutical companies. It is often necessary to make educated guesses around incomplete archives. The history of Spasfon is no different. I still tracked the first publications on phloroglucinol by collaborators of Laboratoire Lafon and much more. Lafon had built collaborations with Charles Debray (1907–1979), professor in gastroenterology at the Bichat hospital in Paris. The firm used this link to conduct human experimentation at the hospital (Blondeau, 1994, p. 157). In 1961, Debray and his two co-authors published the paper 'First therapeutic use of phloroglucinol' in collaboration with Laboratoire Lafon which supplied the authors with 'generous amount' of phloroglucinol (Debray et al., 1961, p. 982). This first publication is key to understanding why and how Spasfon came to be.

The main motivation for introducing phloroglucinol – a known chemical compound since the nineteenth century – in medicine was that researchers believed it to be similar in chemical nature to the sapwood of

[4] For a discussion of publication bias and documented examples, see Goldacre (2012, pp. 5–6).

[5] I reached out to the authors without success.

[6] The full version of the press release was sent to me by a journalist who wishes to remain anonymous. Since 2021, I have reached out several times to Teva pharmaceutical about phloroglucinol, the archives of Laboratoires Lafon, and Spasfon, but I was ignored.

[7] The two other medicines particularly lacking sufficient evidence and data according to the authors were levothyroxine and colecalciferol (a type of vitamin D).

[8] Other drugs commercialised by his firm shared a similar suffix: Valfon, Allergéfon, Derfon, Ulfon, Hypnofon, Lysofon, Olmifon … They all seem to have been removed from the French pharmaceutical market. On the analysis of drug names, see Faure (2018, 2022).

[9] Blondeau writes that the drug was introduced to the market in 1964. Yet Spasfon was approved by the French administration in 1963 (see part 3 of this paper) – I do not know whether Blondeau made a mistake or whether the firm waited a year to introduce the drug to the market after the authorisation.

[10] The history of modafinil was the object of an official investigation in France. It was profusely administered to French soldiers during the Gulf war before the market approval of the drug (Bordenave & Prieur, 2005; Salamon, 2004).

Tilia (lime[11]) (Debray et al., 1961, p. 978). In other words, herbal medicine was the first motivation for pursuing a therapeutic study of the drug. The sapwood of lime was described as acting on the bile production in the body, i.e. to be a 'choleretics' able to ease symptoms related to bile production and often simply referred to at the time as 'biliary pains' (Debray et al., 1961, pp. 978–87). According to anthropologist Marie-Christine Pouchelle, it was typical of French medicine of that time – which was still influenced by humoral medicine – to believe in a relation between bile production and a range of symptoms, from digestive disorders, nausea and vomiting to migraines (Pouchelle, 2007). Indeed, French doctors of the time, who referred to these symptoms as '*crise de foie*' (liver attacks) or 'digestive migraine', believed migraines were triggered by digestive symptoms and bile production. According to Pouchelle, Armand Trousseau (1801–1867) named the disease for the first time in the 19th century (Pouchelle, 2007, p. 2). Trousseau notably described the disease under the name '*coliques hépatiques et calculs biliaires*' in 1861 (Trousseau, 1861, p. 519), where he argued that dysfunction of the liver led to gallstones and then '*coliques hépatiques*', defined as the combination of intestinal pain, anxiety, nausea, vomiting and jaundice (1861, 519–20). The disease was believed to be more common in women than in men (1861, 519). In the middle of the 20th century, doctors tried to cure these symptoms by intervening on the gall bladder, sometimes surgically removed, or by prescribing spa treatments in the city of Vichy (Pouchelle, 2007, p. 8). Hysterectomies were also sometimes performed (Pouchelle, 2007, p. 5; Béraud, 1983, p. 23). However, Debray and colleagues admitted later in their paper that phloroglucinol and the sapwood of lime were in fact too dissimilar in chemical nature from one another (Debray et al., 1961, p. 986) and they were left to wonder about the mechanism of action of phloroglucinol. They cited the possible antispasmodic action of phloroglucinol – with some doubts (1961, 987). Finally, they wondered about other possible mechanisms: 'maybe the obtained success is caused by another mechanism?' (1961, 987). The authors mentioned old toxicity studies – some as old as the end of the nineteenth century – as well as animal studies concluding that phloroglucinol was not promising as a therapeutic (1961, 982). The paper then turned to describe three different experiments with phloroglucinol on a total of 14 patients. The experimenters decided on the dose of phloroglucinol 'after trial and error' (Debray et al., 1961, p. 982).

2.3. Triggering harm

In the first experiment, Debray and his colleagues – Hardouin, Vaille and Fablet[12] – used a 'technique' they had developed the previous year and which they called the 'choleretic-morphine trial' (Debray et al., 1960).[13] This consisted of injecting both a choleretic and morphine to a patient to trigger violent biliary pains, migraines – '*coliques hépatiques*' (1960, 1037). In the phloroglucinol paper, the authors described using this 'trial' procedure – basically, poisoning – for six patients, four of whom were women (Debray et al., 1961, pp. 983–85). These patients all suffered from the same biliary pains, headaches or digestive migraines. After the doctors successfully triggered painful symptoms, they administered phloroglucinol to the 'patients'; when it did not work, they gave a mixture of sapwood of lime. But this was not all. They then proceeded to give phloroglucinol a second time, this time as a prophylactic, before poisoning the patients again. It is mentioned in the paper that a larger number of patients were poisoned in this way, beyond the reported six cases. Patients were identified by their first name, initials, and age:

> On September 29, a 'choleretic-morphine trial' was performed: half an hour after the subcutaneous injection of morphine, pain in the left hypochondrium radiated to the right hypochondrium, where it became extremely violent half an hour later, i.e. one hour after the morphine. The patient writhes in his bed. He was then given 6 tablets of phloroglucinol; 40 minutes later, the pain had considerably diminished in intensity (…). (1961,12)

The effects of poisoning seemed to have lasted from a few hours to several days depending on the patient. One patient is described as an example of 'failure': the poisoning triggered a large variety of symptoms that lasted several weeks and phloroglucinol did not help – she was left with a fever, a rash, nausea, diarrhoea, and headaches. Despite this, she suffered the 'trial' twice like the other patients (Debray et al., 1961, pp. 983–84). Another patient was left so sick she was unable to return home (1961, 984). The pain triggered was so bad that another patient had to lay in her bed 'in a foetal position' (1961, 984). The authors did not say if patients consented to the experiment.

A whole other paper will be needed to analyse in detail and contextualise the human experimentation conducted in that paper.[14] The authors of the 1961's study on phloroglucinol explained that they had decided to use the 'choleretic-morphine trial' method to 'avoid as much as possible the subjectivity of therapeutic judgment' (Debray et al., 1961, p. 982), in other words, the goal was not straightforwardly therapeutic, but scientific. This scientific goal was also explicit in the first study on the 'choleretic-morphine trial', where authors concluded that the test, 'by recreating patients' painful symptoms', was very interesting from a physiopathological and pharmaceutical points of view (Debray et al., 1960, p. 1038). The 1961 experiment did not have a clear therapeutic value for the human subjects involved; it seemed to be necessarily harmful. The issue is that if this is correct, this experiment is difficult to reconcile with what we know about the history of medical ethics in France in the 20th century. Although the narrative about the rise of bioethics in the United States has become dominant (Baker, 2013; Rothman, 2003; Stark, 2012), it is ill fitted to understand the situation of France after World War II. There is no systematised history of experimental practices on human subjects in France to draw from either (Bonah, 2007, p. 74). However we know the medical ethics views expressed and published by medical elites of the time. Most historians agree that that before and after World War II, experimentations on human subjects which brought harm to subjects without a therapeutic goal were frowned upon in France (and in fact, illegal until the end of the 1980s[15]) (Amiel, 2011; Bonah, 2007; Fagot-Largeault, 1985; Weisz, 1990). At the international level, this was also one of the conclusions of the Nuremberg trials (1947) – consent and the minimisation of harm were at the heart of the text. Unfortunately, according to Amiel, the impact of this legal precedent was small in France (Amiel, 2011, p. 117).[16] We also know that the therapeutic goal of an experimentation could be used as a moral 'protective umbrella' (Bonah, 2007, p. 357) for risky tests of new therapeutics – like the injection of unproven vaccines, for instance. Yet it is difficult to fathom that such a protective umbrella would extend to the intentional triggering of pain in patients. As Bonah comments, '[t]he ethos of the corporation (…) conceived of and

[11] Lime, lime tree, or linden in American English. Sapwood designates the wood just under the bark, by opposition to heartwood.

[12] Fablet is not listed as a co-author of the 1961 study, but a footnote explains that he conducted several of the 'trials' reported in the paper (Debray et al., 1961, p. 983).

[13] In French, '*l'épreuve cholérétique-morphine*': '*épreuve*' can both mean trial, test or ordeal.

[14] Note that 'human experimentation' refers to any kind of clinical trials or experiments involving human subjects (by opposition to animal research), it is purely descriptive.

[15] In 1988, the Huriet-Sérusclat law legalised and regulated clinical research on human subjects in France. Amiel gives a fascinating account of the making of the law (Amiel, 2011, pp. 189–221).

[16] It also should be noted that the Nuremberg trials did not invent these criteria either. For a careful history of the ethics of experimentation in France, legal precedents and a comparative international approach on the question, see Amiel (2011).

admitted with difficulty the idea of deliberately causing harm' (2007, 357). More work will be needed to investigate this tension between what we know of medical ethics at the time in France and the experimental practices described in this 1961 paper on phloroglucinol.

2.4. Spasfon, migraineurs and women

The second experiment described in this 1961 paper on phloroglucinol was thankfully not as gruesome. It entailed the administration of phloroglucinol to a specific subgroup of patients: women suffering from 'biliary' symptoms – referred to as 'the biliary', '*les biliaires*' in French (Debray et al., 1961, p. 985). This section described four clinical cases of women suffering from headaches, migraines, and digestive issues. They had either previously been treated by sapwood of lime's mixtures or by spa treatments in Vichy.[17] Why only women? As already mentioned, at the time, 'biliary' symptoms, 'digestive migraine' or 'liver attacks' were believed to be more common among women and connected to their hormones, their period and sexual organs (Pouchelle, 2007, p. 5). One of the patients was described as a migraineur, 'hysterectomised at a young age' (Debray et al., 1961, pp. 985–86):

> Long-standing migraine, hysterectomised at a very young age. Headache attacks preceded by right subcostal pain, initially improved by a course of treatment at Vichy.
>
> On November 4, 1960, she was put on phloroglucinol: 6 tablets a day.
>
> She was seen again a month later with good results. Migraines were less intense, occurring only in the afternoon. Vomiting and bitter mouth sensation have disappeared, but this patient is very tired. (1961, 986)

Another patient was 'put on phloroglucinol for a month'. According to the experimenters, 'she feels better, suffers less, both less often and less violently. She sleeps better and is calmer' (1961, 986). This illustrates that Spasfon was thought from the start to be particularly useful to treat first and foremost women's symptoms. In fact, out of the 14 patients described in the paper, 10 were women.

In the third experiment, authors tested the chemical compound on patients suffering from renal colic, a disease unrelated to bile production. Four clinical cases were described. The authors of the paper admitted they did not have a clear hypothesis on why phloroglucinol could be effective for renal colic. They nevertheless concluded that the drug was a 'brilliant success' that had been 'confirmed' by urologists prescribing the drug in their private practice (1961, 988). Overall the authors concluded that phloroglucinol was an efficient drug to treat '*coliques hépatiques*' and renal colic (1961, 989).

2.5. The animal studies and the 'antispasmodic' hypothesis

Laboratoire Lafon published the first animal studies on phloroglucinol one year after the first clinical study, in 1962 (Cahen, 1962; Cahen et al., 1962b).[18] The laboratory's pharmacologist, Raymond Cahen, noted that phloroglucinol was previously considered as 'practically inactive' (Cahen, 1962, p. 311). Since 1917, the manual of pharmacology cited by Cahen considered 'phloroglucin' as 'inactive' (Sollmann, 1917, p. 470) or 'practically inactive' (1917, 484). Two animal experimentations were published by Cahen in a somewhat confusing order: the first paper published reevaluated the drug's supposed mechanism as an antispasmodic acting on smooth muscles (Cahen, 1962). The initial bile hypothesis was investigated on 33 or 34 dogs (the numbers given are conflicting) in a second animal study published by Cahen et al. later in that year (Cahen et al., 1962b).[19] The conclusion was that the choleretic nature of phloroglucinol was not very convincing. In the first paper reclassifying phloroglucinol as an antispasmodic, experiments were conducted on rats, guinea pigs, rabbits, and cat organs (Cahen, 1962, p. 311). Phloroglucinol was administered after experimentally induced contractions in various organs: the duodenum, the ileum, the heart, the ureter and the sphincter of Oddi. Cahen writes in that study that phloroglucinol's effect is 'highly selective', depending on how spasms were induced in animals or organs as well as depending on which organ was involved: it is 'outstanding on the ureter and on the biliary tract, but less on intestinal motility and vascular beds' (Cahen, 1962 p. 317). Nonetheless, based on a small number of animal data, he concluded that the results 'give evidence that phloroglucinol relaxes the smooth muscle both in vitro and in vivo' (Cahen, 1962, p. 316).

No additional mechanistic reasoning or evidence was given before Spasfon was approved and introduced to the French pharmaceutical market – this was normal at the time. However, almost no other animal experimentation seems to have been published to improve the solidity of this hypothesis since then. In fact, this 1962 study identifying phloroglucinol as an antispasmodic is still cited by contemporary clinical research working on the molecule. For instance, a study on phloroglucinol published in 2021 cites the paper as a basis to the following claim: 'It [phloroglucinol] suppresses spasms by normalising smooth muscle movement, which is excessively stimulated by acetylcholine' (Jung et al., 2021, p. 2). Another study (Shin et al., 2020) cites a 1996 French study describing a case of experimentally induced pain (Louvel et al., 1996). This study is also cited by Chassany et al. (2007) in their paper on IBS. It describes intracolonic injections of phloroglucinol on 10 patients (Louvel et al., 1996). None of these studies give mechanistic reasoning. In 2022, Yang et al. (2023) seem to have published one of the only recent animal studies on the mechanism of phloroglucinol; the authors motivated their study based on the fact that phloroglucinol is commonly clinically used despite little evidence of mechanisms. They experimented on rats and concluded that phloroglucinol could have an effect on smooth muscles. Searching for these mechanistic studies proved to be difficult and I may have missed some.[20]

Today, mechanistic reasoning or mechanistic evidence is ranked low in the hierarchy of evidence in medicine.[21] However, it is interesting to underline this additional layer of ignorance surrounding phloroglucinol, because the antispasmodic hypothesis seems to still play a role in science today, as demonstrated by the mechanistic rationale given in the few clinical studies on phloroglucinol. What exactly is mechanistic evidence and why is it different from a hypothesis? Mechanistic reasoning would need to demonstrate an 'inferential chain (or web) linking the

[17] Vichy is a city famous for its spa treatments. Debray has also extensively published on balneotherapy.

[18] The 1961 paper by Debray, Hardouin and Vaille was presented at the *Société française de Thérapeutique et de Pharmacodynamie* on November 15th, 1961; Cahen's 1961 paper was submitted on November 16th of the same year. This seems to suggest that human experiments were conducted before animal experiments.

[19] A toxicity study was also published at the end of 1962 (Cahen et al., 1962a). The chronology of these publications is hard to follow: the revaluation of phloroglucinol's mechanism was published before the paper testing the first mechanistic hypothesis and the toxicity study.

[20] I searched for such mechanistic evidence in the following way: first I checked all the main published phloroglucinol clinical studies' mechanistic rationale for a reference. This surprisingly led me to realise that some authors are citing the 1962 studies. The 2007 IBS study (Chassany et al., 2007) cites Louvel et al. (1996) which does not give mechanistic evidence. In 2008, on the HAL platform (the French public open science online archive) Louvel et al. have updated a different version of the paper which mentions unpublished data from animal studies. This new version is different from the final published version of the paper. Finally, I searched unsuccessfully for such published studies in medical databases.

[21] Some philosophers believe we should give more place to mechanistic evidence in medicine than we currently do (Clarke et al., 2014; Wilde, 2023).

intervention (…) to a patient-relevant outcome, via relevant mechanisms' (Howick, 2011, p. 929). However, this does not seem to be the case for phloroglucinol. At best, we can talk about an unsupported mechanistic story or hypothesis. This is especially blatant when we consider the wide range of indications of the drug that do not share the same mechanisms (for instance, menstrual pain is very different from urinary tract infections pain or IBS symptoms). Contrary to popular belief (in France at least), it could very well be that phloroglucinol is not an antispasmodic at all. As mentioned at the beginning of the paper, phloroglucinol is officially classified as an antispasmodic by the French health authorities (*Base de Données Publique des Médicaments*, 2024). It is not clear that health authorities realise this additional layer of ignorance about the mechanism of phloroglucinol; specifically, they do not seem to know that they do not know.

2.6. Spasfon's cradle of ignorance

When starting my historical investigation on Spasfon, I did not expect the scale of the ignorance it was born from. The first clinical study was unethical, as well as very anecdotal in nature. On top of this, animal experimentations – that never have been replicated or improved – did not give mechanistic reasoning about the drug. More importantly, the motivation for the drug relied on a now-defunct theory about 'bile' and its various effects on the body. In the 1961 paper on phloroglucinol, biliary symptoms were often listed alongside female patient's mood: patients were described as anxious and agitated, then calmer after taking phloroglucinol. In one of the clinical descriptions, the authors described the radiography of the gall bladder of a patient and suggested a causal connection with her 'extreme nervousness' (Debray et al., 1961, p. 986). How should we interpret these comments? Marie-Christine Pouchelle made the case that the French myth about 'liver attack' and 'biliary attacks' can be linked to the defunct nineteenth-century theory of hysteria (Pouchelle, 2007, p. 4). In fact, the case for this link with hysteria can be made even after Spasfon 'became' an antispasmodic. In his 1847's *Traité de l'hystérie*, Jean-Louis Brachet wrote the following:

> Since nervous mobility and the spasms or convulsions to which it gives rise are the dominant symptoms of hysteria, it is not surprising that people have always tried to stop them, and that they have put a great deal of faith in antispasmodics. Their vogue is not a passing one, but a reign of many centuries. (Brachet, 1847, 422)

It is tempting to read Brachet as prophesying about the future success of Spasfon. All of this, of course, does not explain how Spasfon was introduced on the French pharmaceutical market as well as how it was maintained through the decades even as the criteria for clinical evidence started to improve in France. For that, we must look at the regulating health authorities' decisions, and specifically, analysing what Robert Proctor has called in another context, 'public apathy and regularity impotence' (Proctor, 1995, p. 209). I first start with the regulatory decisions that led to the introduction to the market of phloroglucinol in the 1960s and to the extension of the drug's indication to obstetrics in the 1970s. I then turn to discussing the French health authorities' opinion of the drug in more recent years.

3. Who cares? Structural and regulatory apathy about Spasfon

3.1. Menstrual pain and Spasfon's market authorisation

In 1963, Laboratoire Lafon began the process for obtaining a market authorisation for Spasfon in France, a process known at the time as a 'visa.' The system of visas was instituted in 1941 (Chauveau, 2002, p. 174; Hauray, 2006, p. 39). To obtain a visa, pharmaceutical companies had to submit a scientific file showing the innovation and the safety of new medicines. According to Boris Hauray, it was at first mainly a protectionist administrative formality, as only medicines made in France could obtain such a visa (Hauray, 2006, p. 39; see also Chauveau, 1999, pp. 463–74). The scandal of the drug Stalinon, which killed 102 people in the country, led to new visa rules in 1959 (Hauray, 2006, p. 39). From this point on, pharmaceutical companies had to designate accredited pharmacology, toxicology and clinical experts (2006, 39) as well as demonstrate efficacy and not just safety in a detailed report of clinical trials (Chauveau, 2004, p. 106). In the case of Spasfon, these files have not been preserved. The archives of the ANSM – the current authority in charge of the pharmaceutical market in France – only contain the summaries of these scientific dossiers (ANSM, 1963). Only the first file on Spasfon 'as a tablet' and the file on Spasfon 'as a suppository' have been preserved. For the health authorities at the time, the purpose of the visa procedure was to control, to a certain extent, the safety of medicines, but also their therapeutic value (Chauveau, 2002, p. 173; 2004, 106). However, the methodological details were left to the discretion of the experts chosen by the pharmaceutical company (Chauveau, 1999, pp. 463–74). The administration did not deeply involve itself in the process and the new rules did not strengthen it (Hauray, 2006, pp. 39–40). 'The central state health administration was anaemic and did not have much power' (Gaudillière, 2013, p. 91). The regulating movement started by the thalidomide disaster at the beginning of the 1960s – a pharmaceutical drug which caused birth defects when taken during pregnancy – had not reached France yet at that time (Chauveau, 1999, pp. 474–75).[22] In what follows, I focus on the clinical expertise in the documents that have been preserved about Spasfon.

The file for Spasfon 'as a tablet' submitted in 1963 summarised the work of two appointed experts by the pharmaceutical firm. One of those experts – Hardouin – was one of the co-authors of the 1961 study (Debray et al., 1961). Each expert was appointed to study two indications for Spasfon: 1) pains related to urinary tract issues and 2) biliary pains. The document mentions clinical tests conducted on respectively 62 and 17 patients. Then, unexpectedly at the end of the summary of the first expertise, the following sentence mentions an additional test:

> In addition, 'Spasfon' proved to be a good medication for painful periods (out of 9 observations of dysmenorrhoea, the expert observed only one failure). (ANSM, 1963, 6)

The word 'dysmenorrhoea' was initially forgotten and added in curly brackets.[23] The second expert, Hardouin, also mentioned at the end of his expertise that he has tested Spasfon on menstrual pain on … one patient. There was no specific expert appointed to study the effect of phloroglucinol on menstrual pain. This is especially striking considering that menstrual pain was never mentioned in the previous published studies – whether the 1961 publication or the 1962 animal studies. And yet the summary of the drug indications *starts* by listing menstrual pain:

> At a dose of 3–6 tablets a day, this product is indicated for dysmenorrhoea, various forms of biliary pain (notably hepatic colic) and spasms of the urinary tract (renal colic, ureteral lithiasis, ureteral stricture, etc. (ANSM, 1963, 1)

A back and forth happened between the health authorities and Lafon and a first visa was granted in 1963, followed by an additional (but unnamed) indication in 1964. Another file found in the ANSM archives summarises the visa application for Spasfon 'as a suppository' in 1964 (ANSM 1964). The same experts mentioned clinical tests on 12 and 11 patients in total, for respectively urinary pains and biliary pains. No expert test was mentioned for menstrual pain, but dysmenorrhoea was nonetheless listed in the drug's indications. Spasfon suppositories were

[22] Chauveau writes that the scandal led to a reform in 1967 in France – however it did no change much compared to the 1959 reform (Chauveau, 1999, pp. 474–75). Trouvin identifies regulating changes following the thalidomide disaster, first at the level of the EU (1965) and much later in 1978 in France (Trouvin, 2010, p. 63).

[23] The document is handwritten.

approved by the health authorities five days after the visa application. In 1969, a brochure published by Laboratoire Lafon was recommending two suppositories of Spasfon a day, six days before one's period as well as during the first three days of it, therefore totalling 18 Spasfon suppositories a month for a person menstruating (*Laboratoire Lafon*, 1969).

The market approval procedure described for Spasfon was standard for the time (Chauveau, 1999, pp. 463–74; Hauray, 2006, pp. 39–40). However, these documents reveal a layer of ignorance about Spasfon specifically on the question of menstrual pain. The archives demonstrate that Lafon positioned Spasfon more explicitly towards women, even more than with the previous focus on 'biliary' symptoms. And Lafon did so seemingly based on almost nothing. No expert was specifically appointed to test Spasfon on menstrual pains. Experts only did so as what looks like an afterthought. In other words, Spasfon was born from weak evidence (which was standard at the time), but even weaker evidence was enough to introduce menstrual pain as the first indication of the drug – and to convince the health authorities that it was effective. It is haunting to consider that in 2025 still, millions in France are prescribed Spasfon for their menstrual pain based on anecdotal evidence from 10 women. Again, no randomised controlled trial exists to this day for this indication. Changing the mechanistic hypothesis of phloroglucinol from a choleretic to an antispasmodic allowed Lafon to position the drug for further types of pain and symptoms. Not only could the drug tackle urinary tract pains, but its indication could also be expanded to menstrual pains. In fact, 'spasm' became a powerful marketing tool in the pharmaceutical campaigns and the numerous documents the firm sent to medical doctors and medical schools (Blondeau, 1994, p. 61).[24] This will lead to the introduction of Spasfon to the realm of obstetrics in 1974.

3.2. Spasfon's introduction to obstetrics

In 1974, Spasfon's visa was replaced by an AMM ('market authorisation'), the new regulation procedure in place in France since 1967 (Chauveau, 1999, pp. 474–80; 2002, 174).[25] This new authorisation came with the extension of the indications of the drug to obstetrics. Interestingly, 'spasm' became ubiquitous in the medical vocabulary used in this document. 'Dysmenorrhoea' thus became 'spasmodic dysmenorrhoea'; obstetrics was introduced in the name of 'cervix spasms' (ANSM, 1963, 8).

The document does not mention the scientific dossier that was submitted for this new extension of the drug, so it is difficult to comment on that. A few years prior, in 1965, a small clinical trial had tested Spasfon in obstetrics (Masson et al., 1965). The authors insisted that their methodology was 'purely clinical' and not using a 'scientifically valid' process (Masson et al., 1965, p. 90). They also warned not to use phloroglucinol together with analgesics like morphine. The reasoning was that morphine generates spasms and thus phloroglucinol – a supposed antispasmodic – would not do well together with opioids.[26] The 1974's market authorisation mentioned this new contraindication, suggesting that the study may have played a role in the extension of the indications. In a brochure published by Laboratoire Lafon in 1969, research results were mixed with marketing content – as it was often the case at the time – to encourage the medical field to introduce the drug in obstetrics:

> Thanks to SPASFON
>
> A less unpleasant memory for the mother
>
> A completely normal birth for the baby.
>
> Saves time for the obstetrician and his staff. (*Laboratoire Lafon*, 1969, 27)[27]

3.3. The regulatory apathy about Spasfon since the 2000s

In his study of the social construction of medical ignorance, Proctor identified different mechanisms. One of them seems to have played a significant role in the 'success' of Spasfon: regulatory impotence. In *Cancer wars*, Proctor writes that '(t)he persistence of controversy is often not a natural consequence of imperfect knowledge but a political consequence of conflicting interests and structural apathies' (Proctor, 1995, p. 8). In the case of phloroglucinol, controversy does not seem to be at the heart of the construction of ignorance. It was (and still is) the lack of care for rigorous scientific evidence and arguably for health matters affecting women that allowed the creation of ignorance and its persistence for sixty years. Sometimes ignorance is intentionally created, to gain profits, for instance. What seems obvious, here, is simply that ignorance came about because of a structural lack of care for Spasfon's efficacy. I argue that based on the archives from the 1960s and the 1970s we have reasons to think this lack of care boils down to sexism. In plain words, nobody cared whether Spasfon worked, because it was and still largely is a drug prescribed mostly to women. In what follows, I review the state of this structural apathy in more recent years.

One question someone might first ask is why French health authorities are apparently not holding older drugs up to the same standards as newer medicines. Evidential standards for market approval became stricter over the years, including in France.[28] This process fastened under the work of health minister Simone Veil during her appointment between 1974 and 1979 (Hauray, 2006, p. 45; Amiel, 2011, p. 191). In 1976, a taskforce was created to reevaluate older drugs and started doing so at the beginning of the 1980s (Hauray, 2006, p. 45). This led to some medicines to be removed from the market. Hauray writes that 'for some products, which authorities did not want to remove, but for which available evidence was lacking, the leaflet states that their efficacy is possible, but not proven' (2006, 45). The French health authorities have always renewed Spasfon's market authorisation. In 2007, a new generic version of Spasfon was even approved on the French market; new scientific data was not needed as the pharmaceutical company only had to prove its drug was equivalent to Spasfon (AFSSAPS, 2007).

It is possible to follow the health authorities' opinion about phloroglucinol by looking at the available documents from the '*Avis de la Commission de la Transparence*' from the *Haute Autorité de Santé* (HAS henceforth).[29] Four main therapeutic indications have stayed basically the same since the 1990s: phloroglucinol is presented as a drug for treating symptoms: 1) in digestive and biliary tracts, 2) in urinary tracts, 3) spasms in gynaecology, 4) in obstetrics, as an 'adjuvant treatment for contractions during pregnancy, in association with rest' (HAS, 2008a, p. 2). The older publicly available documents from the HAS on Spasfon date from 2008. They mention without citing it a 1990s study that apparently tested Spasfon for menstrual pain and for pain management during IUD insertion on 70 women (HAS 2008b, 2; 2008a, 4).[30] The HAS

[24] I discuss this in more details in Ferry-Danini (2023, chapter 3).

[25] In French, '*autorisation de mise sur le marché*.'

[26] This counterindication still remains to this day, see (*Base de Données Publique Des Médicaments*, 2024): 'The combination of phloroglucinol with major analgesics such as morphine or its derivatives should be avoided because of their spasmogenic effect.'

[27] For extended discussions of the history of drug regulation in France see Chauveau (2002, 1999), Hauray (2011).

[28] For a history of how evidential standards in medicine evolved with time, both internationally and in the French case, see Bird (2019), Daly (2005), Amiel (2011), Ferry-Danini (2023).

[29] The HAS decides whether a drug is sufficiently useful to be reimbursed (and how much) by the French national health insurance scheme. It should not be confused with the national drug agency ANSM which grants market authorisations.

[30] One document focuses on the sugar-coated version of Spasfon and the other on the freeze-dried tablets. Later documents evaluate both at the same time.

explained that the study was sent by the pharmaceutical company – Cephalon – and that it was part of the 1990 market authorisation dossier for Spasfon. I could not find trace of this study in the scientific literature; I reached out to the HAS, but they could not provide the study or a reference for it. This could have been the only relevant clinical data about the efficacy of phloroglucinol on menstrual pain to date. This is important because ignorance is not just about failing to create knowledge, it is also about losing and forgetting knowledge (Tuana, 2006, p. 2), which seems to have happened here. It is also likely that the study was never published, which casts doubt on its results. In either case, it is again menstrual pain management that seems to suffer the worst from the carelessness of the pharmaceutical firm and the health authorities. Finally, nobody seemed to worry about this lost data in the subsequent documents from the HAS, which never mention the study again. The HAS still does not seem to be worried about the problem to this day, as they ignored my plea about the problem. On top of carelessness, this amounts to what Nancy Tuana have called wilful ignorance: health authorities know that they do not know yet fail to act on it. In other words, they do not care to know (Tuana, 2006, p. 4). This is similar to the wilful ignorance described by Tuana in the case of the male contraceptive pill, which historically did not attract as much scientific attention than the female contraceptive pill (Tuana, 2006, p. 4). For instance, potential loss of libido was a factor in the lack of research on the male contraceptive, while the same potential loss of libido was never deemed an issue for female contraceptives (Arditti, 1977; cited by Tuana, 2006, p. 4). Wilful ignorance means that one is not willing 'to engage in the research needed to know because such knowledge is not deemed important by those in the position to initiate (and fund) such research' (Tuana, 2006, p. 5). Here, the situation is slightly different, as it is the health authorities themselves which do not seem to care about the lack of evidence regarding phloroglucinol.

This wilful ignorance is apparent in a lot of passages from the '*Avis de la Commission de la Transparence*' over the years. In the 2008 report, they concluded that the 'medical usefulness' ('*service médical rendu*' in the administrative jargon) of Spasfon was 'insufficient' for biliary symptoms, citing the 'absence of clinical evidence'; they concluded that the usefulness of Spasfon was 'weak' for renal colic ('no specific evidence for this indication has been given by the pharmaceutical company') as well as for menstrual pain ('[n]o recommendations exist for antispasmodic use for pelvic pains whatever their cause'); they also concluded that the usefulness of Spasfon was 'weak' for contractions during pregnancy ('[n]o evidence for this indication has been brought forward by the pharmaceutical company') (HAS, 2008a, p. 6). On the basis of Cephalon's 2007 publication on the efficacy of phloroglucinol on IBS, they concluded that the medical usefulness for this use was 'moderate' (HAS, 2008a, p. 5). In the French administrative jargon, both 'moderate' and 'weak' medical usefulness means that it is useful enough to be reimbursed by the national health insurance. The health authorities thus decided to reimburse Spasfon at a rate of 35 % except for biliary pains, not recommended for reimbursement (HAS, 2008a, p. 8; 2008b, 2).

The HAS's 2011 report for Spasfon specifically reevaluated the usefulness of the drug for digestive symptoms, as 'weak' instead of 'moderate' (HAS, 2011, 5). The report did not clearly explain why the commission changed their mind about Cephalon's 2007 study. They concluded that 'it is not possible to identify a public health benefit for these medicines' (antispasmodic remedies); but still described them as 'first-line therapies, after compliance with lifestyle and dietary measures' (2011, 5). The commission decided to decrease the reimbursement rate to 15 % (2011, 7). A later report in 2014 was even harsher: it complained that the owner of Spasfon (Teva Pharmaceutical) sent clinical evidence unrelated to the authorisation for which the drug was approved in the country as well as 'methodologically dubious' evidence (HAS 2014, 4). The report also complained that it was sent a non-translated clinical trial written in Chinese (2014, 4). To this day, nobody has cared enough to translate this study. After 2011, all subsequent reports judged the usefulness of Spasfon for most of its indications as 'weak', maintaining a reimbursement rate of 15 % (HAS, 2014;2017; 2018). The only exception was the biliary indication, judged as 'insufficient' from 2008 onwards. In 2008 and 2014, the HAS wrote that there was no recommended use for antispasmodics to treat benign contractions during pregnancy, but that 'by their pharmacological effect on smooth muscles, they could attenuate uterine hypercontractility'[31] (HAS, 2008a, 8; HAS, 2014,7). This suggests that the antispasmodic hypothesis about phloroglucinol seems to play a role in the reasoning of health authorities. The last report published in 2018 on phloroglucinol did not cite the systematic review published by Blanchard et al., in 2018 (published earlier in the year in January). It should be added that those 'Transparency's commission' are not *transparent*; they do not mention authors, they do not always list a clear bibliography, and the methodology is also not explained.

3.4. Safety without efficacy?

Phloroglucinol has seemingly low numbers of side effects, mostly allergic reactions. The patient information leaflet for Spasfon *comprimé enrobé* states that 'in some cases, allergy can happen: spots and/or redness on the skin, itchiness; sudden swelling of the face or neck (angioedema); a sudden loss of consciousness caused by a drop in blood pressure (anaphylaxis).' Additionally, the leaflet states that 'at an indeterminate rate' Spasfon can trigger an acute dermatological reaction called AGEP.[32] Between 1995 and 2006, 62 serious adverse effects and serious allergic reactions have been reported for phloroglucinol – 11 anaphylaxis and 19 angioedema (Prescrire, 2010, p. 114). Historians have studied at length how pharmacovigilance has historically developed around risk management (for instance Kessel, 2015). Phloroglucinol, however, is not easily grasped within this framework. Some may argue that a medicine which does not lead to serious side effects should not necessarily be removed from the market, after all, what is the harm? In fact, it could be the 'philosophy' adopted by French health authorities and one important reason why Spasfon was never seriously criticised. Joséphine Eberhart has studied the way Di-Antalvic – a popular painkiller – was contested and then removed from the French market in 2011 after pressure from the European Medicine Agency (Eberhart, 2022). In 2009, the French health authorities of the time publicly responded to the EMA by recognising the lack of evidence in favour of the drug. Instead of focusing on efficacy, they argued for maintaining the drug on the market as it was safe and widely used by health professionals and patients (Eberhart, 2022, p. 43). Eberhart writes that the authorities were 'uninterested in documenting' the efficacy of the drug (2022, 49) and relied solely on the non-toxicity argument. Even the pharmaceutical company producing the drug – Sanofi – did not try to gather or produce evidence of efficacy (2022, 50). When contacted, the EMA has declined to discuss phloroglucinol and sent me back to the ANSM. However, when I contacted the ANSM about phloroglucinol's periodic safety report, the reply was that it was renewed in 2022 by the EMA and that I should contact them.[33] Both institutions are for now shifting responsibility on each other.

In December 2024, I received a response from the ANSM to the letter I sent the institution with questions about phloroglucinol, the lack of evidence in its favour and a potential gender bias. The ANSM's letter left many of my questions unanswered and it is difficult to judge whether to interpret it as a public relation exercise or a genuine description of their principles. Their explanations align well with my hypothesis regarding what could be the 'philosophy' of French health authorities: focusing on

[31] Highlighted in the original text.

[32] (*Base de Données Publique Des Médicaments*, 2024).

[33] Periodic safety reports are conducted by the EMA, and their goal is 'to present a comprehensive and critical analysis of the risk-benefit balance of the product, taking into account new or emerging safety information in the context of cumulative information on risk and benefits' (EMA, 2025).

safety to the detriment of efficacy. My main questions were whether the ANSM agrees that the scientific studies conducted in the 1960s are not adequate to evaluate the efficacy of phloroglucinol today; whether they are aware of any studies that can demonstrate that phloroglucinol is an antispasmodic beyond those; whether they are aware of the two negative systematic reviews published on phloroglucinol; whether they approve of phloroglucinol being heavily prescribed for menstrual pain in the absence of clinical studies; and simply put, why phloroglucinol is still on the market. Their response focused on explaining in length that phloroglucinol is a safe medicine, with the conclusion that they still consider the balance between risk and benefit for the drug to be positive: 'no new signals have been reported that would call into question the benefit/risk balance.' On phloroglucinol's antispasmodic properties, they agree that the only publications date back to the market authorisation during the 1960s: 'These studies are old, but to this day, the ANSM is not aware of new data that would question these properties.' The ANSM thus admit not having updated their evaluation of phloroglucinol after the criteria for such an evaluation were themselves updated. It is not clear if the ANSM considers phloroglucinol effective based on these old studies too, as the whole letter reads like an exercise to avoid talking about efficacy. As for my questions on gender bias and menstrual pain, they were simply ignored.[34]

One obvious problem with forgetting efficacy when evaluating a medicine is that balancing risk from benefit will necessarily lead to a negative balance. No amount of risk can be justified both epistemologically and ethically if a medicine is indeed inefficient. This tendency of focusing solely on the safety of medicines has been identified in other cases in the French context. For instance, in their study of how progestins became widely used in France, Ilana Löwy and George Weisz comment that '[t]he fact that progestins appeared in most cases to have few negative effects and that these were not life-threatening conditions, made the agents that much easier to prescribe' (Löwy & George, 2005, 2618). Interestingly, the authors also argue that the French 'uniqueness' of that prescription practice made it even harder to call it into question as 'there was relatively little foreign research' made about it (2005, 2618). Arguably, a similar phenomenon seems to be happening with the uncritical success of Spasfon in France. In the next part, I describe Spasfon as a 'pink lie' and argue that the harm of the mass prescription and use of phloroglucinol in France goes beyond possible side effects.

4. The harm of a 'pink lie'

The history of Spasfon helps in understanding why it is today disproportionately prescribed to women – at a ratio of 72 % in 2021 (*Caisse Nationale de l'Assurance Maladie*, 2014-2024). Spasfon's first intended purpose was to treat biliary pains and migraines, which were thought to be more typically found in women, in a way that is reminiscent of the diagnosis of hysteria. In fact, the first human experiment involving phloroglucinol was conducted on more women than men. The mechanistic hypothesis for the drug was initially thought to be related to bile production but was soon changed to the idea that it had an antispasmodic effect on smooth muscles. With this change in the mechanistic story came new indications, notably menstrual pain. Ten years later, obstetrical indications were added, suggesting that Laboratoire Lafon doubled down on women as the primary target patients for the drug. It is, however, difficult to say with certainty whether the choice to market Spasfon as a pink sugar-coated pill was an attempt to appeal to female patients. The pink dye – erythrosine – was present in the description of Spasfon's composition since its first market approval application in 1963 (ANSM, 1963). The white, freeze-dried version of the drug was introduced later. Pink started to be coded as a colour to market to women in the 1950s – think of Marilyn Monroe's pink dress in *Gentlemen prefer blondes* (1953). This coding phenomenon has been especially studied in the North American context (Grisard, 2017, pp. 86–87), less explicitly so in the European context, although Elsa Schiaparelli did introduce and popularise 'shocking pink' in high fashion in Paris as early as 1937 (Grisard, 2017, p. 87).[35] Other pink drugs existed at the time, such as Pepto Bismol and the 'Pink pills for pale people' which could have inspired Spasfon's pink hue. The latter seems to have been heavily advertised to women. 1930s French radio commercials for these 'pink pills' present fictional dialogues clearly destined to women:

> (Male voice) Simone looks at the fabric her mother has just bought her.
>
> - (Female voice) How do you like it?
>
> - (Girl's voice) Oh, not bad. But you know, I don't really want a new dress. I've got such a figure that I'd be ugly anyway. So …
>
> - Come on, darling, don't be silly! It's true that you look very tired. You need to pull yourself together. Starting tonight, you're going to start a course of Pink pills. And by the time your dress is finished, you'll look as good as new.
>
> (Male voice from above) Indeed, only Pink pills provide your blood with the oxygen it so badly needs. You'll be all revived when this life-giving oxygen flows through your veins. Pink pills: any pharmacy, 10 francs 60. (INA, 1936)

I was not able to find similar pharmaceutical commercials for Spasfon.[36] Without access to the private archives from Lafon Laboratory, it is not possible to confirm whether pink was indeed a gender-based decision. However, as we have seen, the administrative archives demonstrate that the indication uniquely targeting women – menstrual pains – was treated with less scientific rigour than the other indications of the drug – biliary pain and renal colic. For all of these reasons, I thus argue that sexism was a cog in the machine that created Spasfon and the scientific ignorance surrounding it.

Historians might worry about the risk of an anachronism when including a historical investigation in evaluating the evidence for phloroglucinol. However, in the absence of more recent evidence, it seems fair and even necessary to include that old evidence in the evaluation of Spasfon. It is also often said that the absence of evidence is not evidence of absence[37]: Spasfon could still be an efficient drug, it may be that nobody has bothered publishing the evidence. I am not satisfied with this answer. Over the years, pharmaceutical companies who owned Spasfon (Lafon, Cephalon and today Teva) had financial motivations to conduct and publish randomised controlled trials on phloroglucinol in the different indications of the drug: to secure higher reimbursement rates from the French health authorities as well as to earn new marketing authorisations in other countries. This strategy even paid off momentarily for Cephalon in 2008: after the publication of a clinical trial on phloroglucinol for treating IBS under its leadership (Chassany et al., 2007), Spasfon obtained a higher reimbursement rate for several years for abdominal pain in France (HAS, 2008a; 2008b). Other companies commercialising phloroglucinol did try to publish evidence in favour of

[34] For a more detailed analysis and the full text of this response, see Ferry-Danini (2025).

[35] Shocking pink is eerily similar to Spasfon's pink colour: a bright fuchsia, also known as 'hot pink.'

[36] I searched for 'phloroglucinol', 'Spasfon' and 'Lafon' in the *Institut national de l'audiovisuel*'s online archives. I went through 1960s medical journals and browsed unsuccessfully through their ads. I also went through Gallica. Finally, I went through online second-hand shops like eBay and leboncoin (the French equivalent). One interesting piece of marketing I was able to purchase was a parody of a 'war postcard' sent by Laboratoire Lafon to a doctor in the 1960s. In that 'postcard,' Spasfon is illustrated as a smiling woman exclaiming 'do not forget about me!' I discuss this card in relation to sexism in medical marketing between the postwar period and through the 1970s in France in Ferry-Danini (2023, p. 113).

[37] However, see Walton (1992) and Sober (2009).

phloroglucinol (Corvino et al., 2023; Shin et al., 2020). These pharmaceutical companies – especially Cephalon and Teva – clearly had the financial means to conduct these studies. As previously noted, one 1990 study also seems to have been left unpublished (HAS, 2008a, 4; HAS, 2008b, 2). It seems fair to infer that the reason why no additional randomised trials on phloroglucinol was published was because it was simply not possible to produce positive results, and therefore to seriously doubt the efficacy of Spasfon. In fact, it is possible that negative results were not published, as it is unfortunately common in the industry. If this inference to the best explanation is correct, it means that the roughly 25 million phloroglucinol units prescribed annually in France are akin to the mass prescription of what amounts to a placebo.[38] In fact, some sociological evidence suggests that some health professionals do view Spasfon as some sort of placebo. In a qualitative study of pain management during IUD insertion, prescription of Spasfon was routinely described (Clochey, 2015). When asked about the practice, doctors plainly stated to prescribing Spasfon as a placebo: 'When I prescribe an IUD, I always prescribe ibuprofen and Spasfon as a placebo' (2015, 37). Another practitioner explained that he prescribes ibuprofen 'for the princesses who are in pain' and Spasfon for the others.[39] Most were unsure about the drug's efficacy: 'I often give Spasfon (…). So, I don't know if it helps, to avoid spasms or contractions, I don't know' (2015, 37). Spasfon's 'pink lie' is therefore not always straightforwardly a lie. Practitioners prescribing Spasfon may genuinely believe the drug is efficient – they may simply be ignorant; they may not know whether it is useful and prescribe it nonetheless – they remain wilfully ignorant; they may know and believe it is not an efficient drug and prescribe it anyway – in which case, they lie. Remaining wilfully ignorant on whether a drug is efficient while not disclosing this information to the patient is also a form of lie. Whether the result of ignorance, wilful ignorance or lie, is the current mass prescription of Spasfon, however, harmless?[40]

Some might be tempted to reply that the lie or the ignorance – wilful or not – involved in prescribing Spasfon as a placebo is merely a white lie, a lie of no importance. Some might even be tempted to argue that people could even benefit from the placebo effect in this situation. One issue is that the placebo effect is often overrated and misunderstood by patients and health practitioners alike (Dahly & Rafi, 2020; Murray, 2021; A. Hróbjartsson & Gøtzsche, 2001; Asbjørn Hróbjartsson, & Gøtzsche, 2010).[41] At the ethical level, even seemingly harmless lies are today frowned upon in the clinical context. In this case, however, the lie is obviously not harmless: people prescribed with phloroglucinol without an alternative, are left suffering when their pain could be relieved. The harm *is* their pain. The sheer volume of prescriptions of phloroglucinol makes the 'white lie' argument absurd: lying daily to a huge proportion of the French population, on matter related to their health and not providing adequate pain management cannot be justified. The harm done to pain management in the country and especially for women is simply staggering. Another harm is epistemic: generalising deception in medicine normalises a harmful way of practising medicines, outside of the boundaries of informed consent and evidence-based medicine. At the same time, Spasfon's 'pink lie' is normalising the transgression of informed consent – thus normalising paternalism and the withholding of scientific information. This is also part of the ignorance created by Spasfon's 'pink lie': the scientific standards and ethical principles that medical practice should follow become blurred, for practitioners and patients alike. By creating ignorance, the situation also disempowers patients, in the case of Spasfon, especially, women. Prescriptions of pharmaceutical drugs as placebos are unfortunately commonplace (Nitzan & Lichtenberg, 2004; Tilburt et al., 2008). However, phloroglucinol is disproportionally prescribed to women. Importantly, phloroglucinol continues to be disproportionally prescribed to women over the age of 59. This means that menstrual pains, pregnancy, or contraceptive device monitoring cannot explain alone the gender unbalance in prescriptions. This is sexism in plain sight: women are more likely to be prescribed what would appear to be a placebo. Women are more likely to be subjected to unnecessary suffering; and their consent, autonomy, and trust, are more likely to be violated.

As already mentioned, phloroglucinol does not lead to frequent side effects. However, phloroglucinol is also commonly prescribed to women during pregnancy in France (Beyens et al., 2003, p. 508) and a pharmaceutical drug taken during pregnancy can lead to birth defects, as a quick glance at the history of medicine can sadly attest – namely, the thalidomide and diethylstilbestrol scandals (Knightly, & Potter, 1979; Stephens & Brynner, 2001; Daemmrich, 2004; Quirke, 2013; Löwy, 2017; Tournaire et al., 2014). The first epidemiological study about the safety of phloroglucinol during pregnancy was published in 2011, with reassuring conclusions (Lacroix et al., 2011). However, doubts have been recently investigated by a taskforce at the French medicines agency (ANSM), with the publication of two reports (Prescrire, 2023). In 2020, the first report noted that in a cohort of 135 576 pregnant women in France between 2004 and 2017, 22,7 % had received a prescription of phloroglucinol during the first trimester of pregnancy (ANSM, 2020a, 5). Babies of women who received such a prescription were at an increased risk of major deformity (2,8 % versus 2,4 %) (2020a, 5). Members of the taskforce, however, largely downplayed the significance of these numbers, listing different possible bias and confounding factors in the study, for instance that it was not possible to control whether women prescribed with phloroglucinol actually took the drug and vice versa, whether women were taking phloroglucinol over the counter (2020a, 5–6). They also argued it was not possible to acquire more data since phloroglucinol was 'only commercialised in France' (2020a, 7).[42] They recommended that the statistical analysis should be redone (2020a, 6). In the second report discussing these results, the exposition to phloroglucinol was this time studied during the first 10 weeks of pregnancy only (ANSM, 2020b, 5). No significant statistical difference was this time revealed. It is only during this second meeting that members of the taskforce discussed the question of whether phloroglucinol is clinically useful during pregnancy; members were 'split' on the question (2020b, 5), but they were forced to acknowledge that the ANSM has previously judged the drug to be clinically useful. Members voted to end the investigation (13 in favour, one abstained). In other words, despite acknowledging doubts about the efficacy and the safety of phloroglucinol during pregnancy, members of the taskforce did not attempt to revise the status quo about its use during pregnancy. Whether phloroglucinol increases the risk of birth defects is still in the end unknown, a disturbing fact considering the lacking nature of evidence regarding the efficacy of the drug in that context.

Finally, phloroglucinol has also become a 'pink tax' for women in France. Depending on whether the drug is partly reimbursed by insurance or bought over the counter, it is difficult to assess with certainty the scale of this 'pink tax', but phloroglucinol is certainly weighing on women's wallets in France.

5. Conclusion

The goal of my paper was twofold: I first aimed to investigate the history of phloroglucinol to understand how Spasfon succeeded despite the lack of convincing evidence. I also aimed to understand the role of sexism in the construction of ignorance in this story. I argued that several elements demonstrate the causal role of sexism in the

[38] More specifically, an impure placebo.

[39] In French '*les petites cocottes*' is both infantilizing and dismissive.

[40] It would be interesting to conduct a more thorough sociological survey of French health professionals and their reasons for prescribing Spasfon.

[41] I present a more detailed version of this argument in the last chapter of *Pilules roses* (Ferry-Danini, 2023).

[42] This is incorrect, as I explained in the first part of this paper. In the second report, the taskforce became aware that the drug is also commercialised in Italy.

construction of ignorance around Spasfon. Another important motor of ignorance was regulatory impotence: health authorities repeatedly failed at acting on the lack of evidence in favour of phloroglucinol.[43] What seem to prevail for French health authorities is instead the relative safety of the medicine. I argued that this is misguided, and I detailed the harms (beyond side effects) caused by this 'pink lie' in France: I identified medical, epistemic, and ethical harms all disproportionately affecting women in the country. Other older drugs are probably lacking quality evidence in their favour, and in that, the story of Spasfon is not unique. But it is special in that it is massively prescribed to women in France as a painkiller and thus it is damaging women pain management on a large scale without health authorities reacting. This case study on phloroglucinol adds to the literature on the gender-based prescription of medicines in France and beyond (Löwy & George, 2005; Bajos et al., 2014; Ortiz-Gomez, & Jesús Santesmases, 2016), illustrating how the lack of care for efficacy can also be a motor of injustice in medicine.

Funding

Earlier parts of this research was made possible by the support of FRS-FNRS.

Acknowledgements

I would like to thank anonymous reviewers for insightful comments and suggestions on earlier versions of this paper. I thank members of the *Séminaire Epistémologie Critique du Soin* at Université de Toulouse, as well as members of the research group Cermes3 (*Centre de Recherche médecine, sciences, santé, santé mentale et société*) at the Université Paris-Cité, members of the Gendhi (Gender and health inequalities) research group in Paris, members of the Max Planck Institute for the History of Science in Berlin and the London School of Economics philosophy department for giving me the opportunity to present earlier versions of this work and providing precious feedback and ideas. I especially want to thank Ilana Löwy and Jean-Paul Gaudillière for their reading suggestions. I am thankful to Liam Kofi Bright for calling the work in progress a 'banger': it kept me going. I would also like to thank Cassandre Terrier from the *Pôle Gestion Documentaire et Archivage de l'Agence Nationale de Sécurité et du Médicament et des Produits de Santé* who located for me all documents on Spasfon in the archives of the ANSM. I also want to thank the members of Cefises (Center for the Philosophy of Science and Society) at UCLouvain for their support and encouragement while working on earlier drafts of this work, especially Charles Pence. Finally, I would like to thank Mélie Chen for accompanying the writing of an earlier version of this work at Editions Stock.

Data availability

No data was used for the research described in the article.

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[43] French MP Clémentine Autain officially raised the matter to the government in a written question in November 2023, after the publication of *Pilules roses* (Autain, 2023, Question n°12729). Unfortunately, the French government is not required to reply to MPs' written questions, and no reply has been given on the matter. In June 2024, French president Emmanuel Macron dissolved the parliament and called for snap elections. This led all unanswered written question to be retired.

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