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## Drug Marketing

# The whistleblowing drama behind Astellas's suspension from the ABPI

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*The Japanese drug company Astellas has had its knuckles rapped for wrongdoing four times in less than three years. Now **Deborah Cohen, Shai Mulinari, and Piotr Ozieranski** reveal fresh claims about the treatment of an employee who offered to help it clean up its act*

When Astellas was reprimanded by the Association of the British Pharmaceutical Industry (ABPI) in June 2016, for “deception on a grand scale which was appalling and shocking,” it received the harshest punishment ever levied by the membership organisation: two non-concurrent one year suspensions (see box 1).

### Box 1

#### MHRA, ABPI, and PMCPA

The UK's prescription drug marketing oversight system is formally a coregulatory arrangement involving the medicines watchdog the Medicines and Healthcare Products Regulatory Agency (MHRA), an executive agency of the Department of Health and Social Care, and the Prescription Medicines Code of Practice Authority (PMCPA).

The PMCPA was set up in 1993 by the Association of the British Pharmaceutical Industry (ABPI), a trade body, to administer the ABPI's code of practice.

The MHRA is formally tasked with investigating potential breaches of advertising and other relevant legislation, but it strongly recommends referral to the PMCPA for complaints about companies that have accepted the industry code.<sup>[1](#)</sup>

#### PMCPA sanctions

Companies in breach pay administrative charges to cover the costs of processing complaints. These are typically £3500 but increase to £12 000 if the ruling is unsuccessfully appealed.

In cases of serious wrongdoing the PMCPA can also publicly reprimand a company or require it to issue a corrective statement. For both sanctions the company pays £4000 towards the cost of advertising that fact in the medical (*The BMJ*), pharmaceutical (*Pharmaceutical Journal*), and nursing (*Nursing Standard*) press.

In severe cases the PMCPA can also undertake compulsory audit of a company, which costs £15 000 to £20 000 depending on complexity.

In extraordinary cases the PMCPA can ask the ABPI board to consider suspension or expulsion of the company from membership.

Heather Simmonds, PMPCA director, tells *The BMJ* that it is “very unusual for a company to get suspended. The longest sentence prior to Astellas was six months.” That case was also the last suspension before that of Astellas.

### **What an ABPI suspension means**

A suspended company temporarily loses membership benefits. This includes:

- Access to information on, and input into, industry-wide policy developments and cross industry initiatives
- Access to education and networking events
- Access to working groups and expert networks to keep up with developments, and
- A role in the Pharmaceutical Price Regulation Scheme conducted between the UK government and the ABPI.

The Japanese drug company’s offences included off-label marketing, a subsequent cover-up when the company was investigated, and a failure to mention certain adverse reactions in promotional material.

In the words of the Prescription Medicines Code of Practice Authority (PMCPA)—the self regulatory body that administers the ABPI’s code of practice—this was “one of the worst cases it had ever had to consider.” Astellas had prioritised “the bottom line” above all else, said the PMCPA. The case provides evidence of how Astellas used ostensibly scientific advisory boards to co-opt key opinion leaders in attempts to shape clinical decisions.

Now *The BMJ* can reveal new allegations that an employee who had raised an issue about off-label marketing was excluded and ignored, eventually leaving the company. If true, the employee’s claims raise wider questions about the role and protection of whistleblowers in investigating cases of corporate misconduct in Europe (see box 2).

#### Box 2

### **Protection for whistleblowers in Europe**

Protection for whistleblowers in Europe is patchwork. Some countries, such as Ireland, have robust laws in place, while others, such as Cyprus, have practically none. Sixteen EU member states have specific laws or provisions, and 10 of those adopted their laws in the past five years. Three other countries have at least partial legal protections for whistleblowers,<sup>6</sup> such as the UK’s 20 year old Public Interest Disclosure Act. In 2018 the European Commission proposed a new law to strengthen whistleblower protection throughout the EU:<sup>7</sup>

- Reporting system: whistleblowers will first have to use internal channels in their organisation before calling on external ones (set up by public authorities) and, eventually, going for public disclosure. However, the principle of a three step system includes

exceptions allowing a person to go directly for external or even public disclosures in some specific cases (such as manifest or imminent danger for the public interest);

- People protected by the new rules: these elements of the European Commission's proposal were kept, including a large number of profiles who could acquire information on breaches in a work related context, such as workers, including civil servants at national or local level, volunteers and trainees, non-executive members, and shareholders;
- Feedback obligations for authorities and companies: they will have to respond and follow up to whistleblowers' reports within three months (with the possibility of extending to six months for external channels in duly justified cases);
- Public disclosures: the European Council introduced an article setting out the conditions to be fulfilled for a person to be protected by the new rules if he or she publicly discloses information; and
- Scope of application: the European Council's position retains the wide scope as proposed by the European Commission and covers areas such as public procurement, financial services, prevention of money laundering, and public health.

Since the June 2016 reprimand Astellas has been the subject of three further adverse rulings by the PMCPA for serious misconduct in the UK (see box 3). The latest, announced in December 2018, concerned an inappropriate educational or service hospital payment for the use of Advagraf (tacrolimus) in kidney transplantation. As such, the case also raises questions about the effectiveness of the UK drug industry's self regulatory system.

#### Box 3

#### **Four PMCPA rulings against Astellas**

1. June 2016: for organising a meeting that was not a genuine advisory board and for paying UK health professionals to attend that meeting where Xtandi (enzalutamide) was promoted for an unlicensed indication, and for providing false information to the PMCPA
2. May 2017: for, among other things, its "wholly unsatisfactory oversight and control" over two patient support programmes that displayed "a lamentable lack of concern for patient safety"
3. June 2017: for producing a large number of promotional materials, which had been used for a number of years, that did not include the required prescribing information related to some serious or common adverse reactions, warnings, and precautions, for a total of eight drugs; and
4. December 2018: for a payment to a hospital in 2010 as a medical educational good or service, which did not meet the requirements of the code because it was inappropriately linked to the use of Advagraf (tacrolimus), and for providing incomplete and misleading information to the PMCPA.

Astellas was readmitted to the ABPI on 25 June 2018 and has recently been audited in "a very demanding process," the ABPI tells The BMJ. The findings are expected in the coming months. Despite the PMCPA recommending a five year suspension in its most recent ruling

from 2018 the ABPI said that patient safety had not been put at risk in the latest case and that the company had “made significant strides in improving the culture and processes within the organisation.”

A spokesperson for Astellas says, “We acknowledge that the mistakes in the past were not acceptable or reflective of our corporate culture, and we accepted the sanctions imposed upon us by the ABPI. Astellas has worked hard to improve the way we do business, and we continuously strive towards the highest standards of integrity and compliance.”

### “Advisory” meeting

One former employee has spoken to The BMJ on the condition of anonymity because they still work in the pharmaceutical industry. They had just started their job at Astellas Europe—whose headquarters are in the UK—when they were asked to attend a meeting in Milan in February 2014.

Over 100 oncologists and urologists from EU countries, as well as Turkey, Russia, and South Africa, had been invited to attend Astellas’s “Pan-European Uro-oncology Advisory Board Meeting.” All attendees were paid €1000 (£894; \$1139) except for those from southeastern Europe, who were paid €500, and two speakers who were each paid €1500.

The employee, who had worked in the drug industry for some time, quickly realised that all was not quite right. Astellas used the meeting to promote to prescribers the off-label use, for an additional indication, of its prostate cancer drug enzalutamide (Xtandi) and to assess the impact of potential promotional claims—despite the meeting’s purportedly scientific nature (box 4).

#### Box 4

##### **What the meeting in Milan was really about**

When first investigated by the PMCPA, Astellas said that the Milan meeting had been “non-promotional, scientific/medical-led . . . with an agenda focused on legitimate scientific exchange about the treatment of mCRPC [metastatic castration resistant prostate cancer]” and that doctors had been selected solely for their personal experience of treating patients with mCRPC and not for marketing purposes.

However, an internal document produced before the meeting detailed the “objectives for meeting.” These were clearly promotional:

##### **“Objectives for meeting**

- Increase Astellas’s profile in the field of oncology
- Communicate Astellas’s strategy and oncology pipeline to key target customers

- Communicate Xtandi [enzalutamide] and tivozanib [an unlicensed drug] data and common set of messages to EU affiliates' [national company branches'] key target customers
- Gain an increased understanding of the current landscape in RCC [renal cell carcinoma] and prostate cancer, and the challenges Astellas will face when launching Xtandi and tivozanib in the EU."

The document also detailed the target audience for the meeting:

#### **"Target audience for meeting**

- Mid-top level product OLs [opinion leaders]—those with the potential to be local product champions within the relevant EU markets
- Data-naive customers, ie those who have not been involved in any APEL [Astellas Pharma Europe Ltd] or national/local advisory board meetings prior to the pan EU ad board [advisory board] meeting
- 10 per affiliate [eg, Astellas UK]: five prostate/Xtandi and five RCC/tivozanib."

Internal emails show that, far from looking simply at "clinical expertise," the company's local affiliates selected participants who would fit Astellas's "customer criteria." These included a UK doctor they wanted to convert from prescribing Janssen's abiraterone, who had a reputation for being an "abi [abiraterone] man"; someone else who was a high prescriber of enzalutamide and would "respond well to such a meeting"; and another who they said would become nationally known "with time."

### **Raising concerns**

Initially, the employee claims to have raised concerns verbally, suggesting ways to become more compliant with the various codes and regulations governing the drug industry. These were ignored, they say.

Aware that the PMCPA had received a complaint about enzalutamide promotion at the Milan meeting from a UK healthcare professional who had attended, the employee then put their concerns in writing to a senior director at Astellas in Europe because "nothing had moved on or [been] taken seriously."

They wrote that the Milan meeting had been "highly suspicious and at the very least bordering on pre-licence promotional activity [marketing before marketing authorisation], which as you know is strictly banned by the MHRA [Medicines and Healthcare Products Regulatory Agency]."

The employee also expressed concern that Astellas would try to “deceive” the PMCPA by providing misleading and incomplete information about the true, promotional purpose of the Milan meeting in “an attempt to cover up the company’s activities.”

Soon after that the employee was excluded from meetings and was sent home after challenging this, they claim.

The BMJ put all of the employee’s allegations to Astellas, but the company did not respond directly to those about the employee’s exclusion.

An Astellas spokesperson says that the UK and European senior leadership has changed since the events the whistleblower describes. The company now uses an externally run website for employees to lodge concerns.

### **Whistleblower worries**

The two parties reached a financial settlement, but the former employee’s experience raises wider questions. The employee tells The BMJ that there is “no incentive for whistleblowers to come forward” in Europe. “It would take a very ballsy and courageous person . . . to potentially jeopardise their career, and hence the public could be less safe as a result.”

In the US, whistleblowers are entitled to a percentage of settlements and fines levied against a defrauding company. Settlements and fines can run into billions of dollars. This money helps the US’s publicly funded health system—Medicare or Medicaid—to claw back money erroneously spent on drugs.

For example, in 2014 Astellas agreed to pay back \$7.3m (£5.7m; €6.4m) for off-label promotion of Mycamine, an antifungal drug, for paediatric use. The federal government received \$4.2m, and state Medicaid programmes received \$3.1m.<sup>2</sup>

### **UK protection?**

The MHRA maintains that whistleblowers are also vital in the UK, saying that it recognises “the importance of whistleblowers and the role they can play in identifying and detecting wrongdoing.”

The agency tells The BMJ that it set up a dedicated, anonymous whistleblower service in 2014 and has received 318 reports since then. Only one of these related to promotion of medicines. A spokesperson says that “the relatively low levels of complaints that we receive suggest that this system is overall effective.”

But a low number of complaints may reflect that people are unwilling or feel unable to report, are unaware of what is happening, or do not trust that the MHRA will do anything or protect them.

Evidence from the US shows that people do not complain about complex cases to the federal Food and Drug Administration (FDA): most corporate activities uncovered by whistleblowers in the US were unknown to the FDA, having instead been reported to the Department of Justice.<sup>3</sup>

The number of complaints to the PMCPA, however, increased from 54 in 2015 to 76 in 2016,<sup>4</sup> but the former Astellas employee approached the PMCPA about their experience and now questions its ability to investigate serious allegations.

“These are not the people to take on big pharma,” says the employee. “The culture of the PMCPA is, ‘Send us complaints, we will investigate them, we’ll put a report online and that’s fine,’—that’s our self regulatory system. It doesn’t go any further than that.

“It’s time for a different approach, because it’s got to the point where both the volume and the complexity of the cases being brought to the [PMCPA] are unmanageable.”

Heather Simmonds, PMPCA director, tells The BMJ that the authority recommended the expulsion of Astellas from the ABPI in its fourth ruling against the company (see box 3), for a minimum of five years. However, the ABPI board decided that the previous two non-concurrent one year suspensions for the enzalutamide case were sufficient and that compliance was “an ongoing journey.”

## **Insufficient penalty**

Despite evidence of unethical and potentially unlawful activities that could jeopardise patient safety, and which Astellas has acknowledged, neither the MHRA nor any other European governmental drug regulatory authority has intervened in the case. The harshest punishment the company has faced is its temporary suspension from the ABPI.

Aside from “administrative charges” imposed on companies in breach—which for ABPI members can range from £3500 (€3921; \$4463)<sup>5</sup> to £12 000—the PMCPA says that the most important sanction available to it is adverse publicity (see box 1). The ABPI similarly tells The BMJ that the “Astellas case has resulted in high profile negative media coverage for the company.”

The suspension did receive media coverage, particularly in the trade press, and Astellas was ordered to pay for adverts in The BMJ, the Pharmaceutical Journal, and Nursing Standard saying that it had “brought discredit” on the pharmaceutical industry.



An ABPI spokesperson said, “We expect all companies to adhere to the highest standards of professional conduct, and our code of practice reflects and extends beyond UK law. Sanctions under the ABPI code include publication of detailed case reports in every case. Additional sanctions are imposed in serious cases.”

Astellas also had to send letters to the five UK healthcare professionals who attended the meeting in Milan, saying that “the arrangements did not meet the criteria for an advisory board and that UK health professionals had received payment to attend the meeting, which promoted Xtandi [enzalutamide] for an unlicensed indication.”

However, the reputational damage seemed not to translate into decreased sales or profits. In January 2016—coinciding with the PMCPA’s announcement that Astellas had provided “false and incomplete information regarding the selection criteria for attendees” at the Milan meeting to the PMCPA—enzalutamide was recommended by the National Institute for Health and Care Excellence for NHS use in England.

Nor is there evidence that the PMCPA’s rulings and the suspension had any impact on Astellas’s stock price. Indeed, in the weeks after the ABPI suspension in 2016 it increased steadily, reaching its fiscal year’s peak on 1 August, which coincided with the announcement of Astellas’s financial results for the first quarter.

## **Lack of action in Europe**

Although many countries in Europe were targeted at the Milan meeting, only the PMCPA and ABPI took any action. The Dutch drug industry body is the only other authority that found Astellas guilty of off-label promotion, on the basis of the PMCPA’s report. However, it decided that no action against the company was necessary considering the sanctions already levied by the ABPI.

It seems that only one of about 100 European healthcare professionals attending the Milan meeting complained to regulators: the UK doctor who complained to the PMCPA. Most doctors recruited by Astellas seem to have been either unaware of, or habituated to, the unethical promotional activities or to have been indifferent to being targeted with off-label promotion and being used—in what was essentially a market research exercise—to evaluate the likely success of promotional claims.

The European Federation of Pharmaceutical Industries and Associations (EFPIA) did not suspend Astellas Europe and has not publicly castigated the company. EFPIA says that the responsibility to process complaints about companies’ conduct rests with its member associations, such as the ABPI.

An EFPIA spokesperson tells The BMJ, “EFPIA convenes a network of [industry] code authorities from across Europe. Breaches of the codes are shared across the network with a view to ensuring that actions found in breach of a code in one country are not replicated in another country.”

### Footnotes

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