COMMENTARY

Lotronex and the FDA: a fatal erosion of integrity

In March last year, *The Lancet* published the results of a randomised trial reporting that alosetron (Lotronex, GlaxoWellcome) "was well tolerated and clinically effective in alleviating pain and bowel-related symptoms" in women with irritable bowel syndrome.[1] Michael Camilleri and colleagues described their findings as "important". Indeed, irritable bowel syndrome, although not life threatening, can be severely disabling. Lotronex was an early example of a new class of drug for irritable bowel, the 5-HT_3 antagonists. This apparent pharmacological breakthrough has generated an explosion of new research interest in functional bowel disease.[2]

Camilleri and colleagues also found that one in ten patients taking Lotronex withdrew from the trial because of constipation, but they argued that this symptom was not "perceived as a negative consequence" of treatment. They concluded that "No serious drug-related adverse events or deaths were reported during the study". A single case of ischaemic colitis was, they wrote, misdiagnosed.

Lotronex was licensed by the US Food and Drug Administration (FDA) in February, 2000. By November, GlaxoWellcome had voluntarily withdrawn Lotronex from the market. At least five people had died after taking the drug. Yet many within the FDA's leadership now want to bring Lotronex back. An advisory committee meeting set up to do so is being planned for June or July. This story reveals not only dangerous failings in a single drug's approval and review process but also the extent to which the FDA, its Center for Drug Evaluation and Research (CDER) in particular, has become the servant of industry.

New drug application 21-107 (alosetron hydrochloride) was submitted to CDER on June 29, 1999, and assigned priority review. 7 months later, Victor Raczkowski, deputy director for the FDA's Office of Drug Evaluation dealing with Lotronex, wrote to inform GlaxoWellcome that, in the FDA's view, Lotronex was "safe and effective for use as recommended". He also reminded the company of its commitment to "A large, long-term (1 year) population risk trial to assess the incidence of colitis in patients receiving alosetron". The FDA was clearly anxious about the drug's risk profile. The printed labelling accompanying Lotronex warned about the possibility of acute ischaemic colitis but noted that such cases "resolved over several days to weeks without sequelae or complications".

Glossy six-page advertisements in specialist medical journals claimed that Lotronex had "a favourable safety profile and [was] generally well-tolerated". The advertisements did, however, mention the problem of ischaemic colitis, although the warning emphasised that a causal connection between the drug and this adverse event was uncertain. By July, 2000, concerns about the balance of risk and benefit were being voiced.[3] Between February and June that year, seven patients had developed serious complications of constipation, three of whom required surgery. Eight further cases of ischaemic colitis were reported. The FDA had an opportunity then to take stock of its earlier decision. The clinical data confirmed the substantial and potentially life-threatening risks hinted at during pre-approval review. But instead of withdrawing Lotronex and calling for more evidence, the FDA issued a medication guide designed to warn patients of escalating risks, while keeping the drug on the market.

This decision was to prove fatal. On Nov 28, GlaxoWellcome withdrew Lotronex from the market after the deaths of five patients taking the drug. There had been 49 cases of ischaemic colitis and 21 of severe constipation, including instances of obstructed and ruptured bowel. In addition to the deaths, 34 patients had required admission to hospital and ten needed surgery. A letter from Janet Woodcock, director of CDER, declared that the "FDA is committed to working with pharmaceutical sponsors to facilitate the development and availability of treatment options for patients with IBS". There was no word of sorrow or regret for the families of those who had died.

The course of these events can be followed through documents posted on the FDA's website (www.fda.gov). But what these press releases, talk papers, and letters do not reveal is the internal struggle and suppression of dissenting opinion that took place within the FDA once reports of serious complications and deaths began to come in. An evaluation of Lotronex's risk profile in the summer of 2000 found that the warning in the proposed medication guide was impracticable. The new guidance would be that women should stop taking Lotronex if they experienced "increasing abdominal discomfort". But since abdominal pain is a cardinal symptom of an irritable bowel, FDA scientists argued that it was unreasonable to expect either patients or their physicians to judge pain as an early warning of possibly fatal ischaemic colitis. This view was dismissed by FDA officials. The scientists who raised these issues felt intimidated by senior colleagues and were excluded from further discussions about Lotronex's future. Instead, the FDA preferred to support a series of epidemiological studies into ischaemic colitis and constipation. An independent review of these research protocols revealed profound flaws in their design. A more rigorous research proposal from one FDA scientist was ignored.

A memorandum dated Nov 16, 2000, and disclosed through the Freedom of Information Act by US Public Citizen's Health Research Group, shows the extent of FDA scientists' concern.[4] The company believed that the risk of Lotronex could be managed safely by looking for warning symptoms. But the note from FDA scientists to Lilia Talarico, director of the Division of Gastrointestinal and Coagulation Drug Products, explains that "Early warning of the dire side effects of this drug is clearly not feasible". The scientists state that "the sponsor [GlaxoWellcome] has not identified a subset of women who will respond to Lotronex therapy safely". Moreover, and crucially, given recent manoeuvres to reintroduce Lotronex, the report states that "a risk management plan cannot be successful that will eliminate deaths, colectomies, ischemic colitis, and complications of treatment that were never seen previously in the management of IBS".

This unambiguous conclusion was blurred by the time of

the key Nov 28 meeting between GlaxoWellcome and FDA officials. Rather than reject the company's risk-management proposal and withdraw Lotronex, the FDA offered several conciliatory options—eg, voluntary withdrawal of Lotronex, temporary suspension of marketing pending further discussion, and restricted marketing to specialists. Pleased and quite likely surprised by the FDA's desire to bargain over the terms of public access to Lotronex, the company pressed for a new advisory committee hearing and affirmed its view that risk management was feasible. The FDA's options were heavily criticised, the process was deemed unfair, and FDA scientists were accused of not taking irritable bowel syndrome seriously. There was stalemate, and the company blinked first.

Once GlaxoWellcome had withdrawn Lotronex, recriminations within the FDA began in earnest. In addition, Woodcock was swamped by e-mails from patients asking for the drug to be brought back. The company gave money to support groups for patients with irritable bowel syndrome to assist their research and educational programmes, according to Ramona DuBose, a GlaxoSmithKline spokeswoman. The FDA was brought under further pressure when the new Bush administration removed its Commissioner, Jane Henney, probably because of her support for the abortion-inducing mifepristone.

As arguments about Lotronex intensified, FDA officials took an increasingly hard line towards their own scientists. Yet new data acquired since the November withdrawal only strengthen the view that Lotronex should not be made widely available again. A further internal review of the incidence of ischaemic colitis among women taking Lotronex suggests that the company may have seriously underestimated the hazards of the drug. And additional adverse reports obtained by Public Citizen show rising numbers of cases of ischaemic colitis and severe constipation in women who continued to take Lotronex.

While the FDA held further internal discussions about how to respond to patients' groups and congressional pressure, private communications opened up between Woodcock and senior executives at the newly merged GlaxoSmithKline. The company was now worried that the open meeting it had proposed could produce a media circus, that committee members might disagree with a settlement made via these private communications, and that the entire process might be unduly prolonged. When I rang the FDA for a comment, I was told that the agency was "working with GlaxoSmithKline to discuss issues surrounding Lotronex and we are making progress". It is expected that the company will reluctantly agree to a few conditions for the reapproval of Lotronex—ie, there may be restrictions on which physicians can prescribe the drug and a requirement for signed patient-physician agreements. To ensure that the advisory committee does not overturn this privately determined decision, a senior representative of the company has asked the FDA about the composition of the committee. And the FDA has undertaken to work with the company to set limits to the meeting's agenda and questions.

This two-track process, one official and transparent, one unofficial and covert, is contrary to FDA's stated policy. According to Crystal Rice, an FDA spokeswoman, the correct procedure is for the company to write officially to the FDA replying to CDER's concerns and providing new data on safety. A full FDA review should then take place before an advisory committee meeting.

In the case of Lotronex, private communications appear to have subverted official procedures, while suppressed scientific debate has superseded a full and open review process. GlaxoSmithKline commented that "A team of FDA and GSK scientists have met on several occasions in an attempt to work out a risk management plan that would allow appropriate patients to receive benefit from the medicine while risks can be clearly understood and appropriately managed". This "effort is ongoing and no final decision has been made". The company also denied that there had been a back-channel for private communication between CDER officials and the sponsor. This claim was "untrue and very misleading", according to DuBose. "All meetings between GSK and the FDA have occurred primarily at the operational level between scientific teams". The FDA would "not comment on or discuss any details with regards to internal discussions between FDA and sponsors".

A further insight into the FDA's favourable attitude to industry was provided by a 1998 survey of FDA medical officers.[5] Many of these physicians reported that since the 1992 Prescription Drug User Fee Act (PDUFA), which enabled the FDA via direct industry funding ($329 million) to hire almost 700 more medical officers to review new products, standards for drug approval have declined. Many officers felt under greater pressure from FDA supervisors to approve new drugs; they received inappropriate calls from the sponsor about the drug under review; and they believed that the FDA too often interfered on the company's behalf in the drug-approval process. The Lotronex episode may show in microcosm a serious erosion of integrity within the FDA, and in particular CDER, whose operating budget now depends greatly on industry money.

Where next for Lotronex and the FDA? The clinical evidence indicates that, at most, Lotronex should be reclassified as an investigational new drug, with additional restrictions, thus limiting its use to experimental settings only.[4] Meanwhile, on this evidence the FDA urgently needs to re-establish the public's trust. First, all covert private communications between senior FDA officials and industry must be closed. Drug approvals and safety reviews should take place through accountable procedures. Second, greater weight should be placed on the epidemiological and statistical advice provided to advisory committees. Third, there should be an independent congressional audit of the FDA's drug-approval processes, including its priority reviews, since implementation of PDUFA. Fourth, pharmacovigilance should be removed from CDER's control. It is an impossible conflict for safety issues to be overseen by a centre that receives funding from industry to review and approve new drugs. Fifth, the culture within the FDA should welcome, not censure, differences of opinion about the impact of science on policymaking.

Finally, the FDA's new Commissioner should be an epidemiologically trained physician with substantial experience of conducting clinical trials, a person with a strong track record of institutional leadership, and, most importantly of all, someone who is demonstrably independent of the pharmaceutical industry.

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1 Camilleri M, Northcutt AR, Kong S, Dukes GE, McSorley D, Mangel AW. Efficacy and safety of alosetron in women with irritable bowel syndrome. *Lancet* 2000; **355:** 1035–40.
2 De Ponti F, Tonini M. Irritable bowel syndrome: new agents targeting serotonin receptor subtypes. *Drugs* 2001; **61:** 317–32.
3 McColl KEL. Alosetron in irritable bowel syndrome. *Lancet* 2000; **356:** 164.
4 http://www.citizen.org/hrg/PUBLICATIONS/1566.htm (accessed on May 14, 2001)
5 http://www.citizen.org/hrp/publications/fdasurvey.htm (accessed on May 14, 2001)