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# Conflicts and collaborations

**Claims of conflicts of interest concerning authorship of a scientific paper highlight the difficulties facing regulators participating in collaborations with industry.**



Back in mid-August, the US Department of Health and Human Services (DHHS) stated that it was investigating a conflict-of-interest allegation involving Janet Woodcock, the director of the US Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER). The investigation involves a complaint filed by Amphastar Pharmaceuticals that one of its competitors, Momenta Pharmaceuticals, had privileged access to Woodcock during the approval process for a generic version of Lovenox, a low-molecular-weight heparin (LMWH) product.

Amphastar claims to be hard-done-by because it was the first of the two companies to submit its abbreviated new drug application for enoxaparin sodium way back in March 2003. And although Amphastar's drug is yet to be approved, Momenta received approval for its product in July, even though it filed two years later in August 2005. In the meantime, Janet Woodcock and scientists at Momenta were co-authors on a scientific paper published in a high impact journal—an interaction that Amphastar lawyers have raised as one of the key pieces of evidence of the inappropriate closeness between FDA staffers and Momenta personnel.

At this point, we must also declare our interests. The journal in which the paper appeared was *Nature Biotechnology* (**26**, 669–675, 2008). The research dealt with analytical methods for assessing the potential presence of highly sulfated chondroitin compounds in preparations of heparin, contaminants that were responsible for 150 deaths in patients who experienced an allergic or hypotensive response after being exposed to the drug. The heparin in question was in products from Baxter produced using active ingredients sourced from a company called Scientific Proteins Limited (SPL), in China. Two of the authors on the paper, Robert Langer and Ram Sasisekharan, were not only directors of, and stockholders in, Momenta, but also advisors to SPL at the time of publication.

One of the realities in this affair is that, as a result of the adverse events arising from contaminated heparin, the approval applications of both companies—Momenta and Amphastar—were held up. Without access to the correspondence with FDA, little can be said about the reasons for the different timelines on the applications—further information may come to light following completion of the DHHS investigation that is still underway. However, on the broader question of conflicts arising from industry-regulator collaborations, much more can be said.

First, industry-regulator co-publication is not a new phenomenon. Although, until the mid-1990s, FDA-industry co-publications were quite rare—just three a year or fewer, from 1996 onwards—the number has steadily risen so that since 2003, between 20 and 49 co-publications have appeared per year. Many, but by no means all, are 'methods' papers, describing, for instance, the development of biochemical and cellular assays or the use of new animal models.

Although the growth in co-authored papers is hard to pin down to one factor, it seems likely to be associated with the passage of PDUFA legislation in 1992, which allowed FDA to levy user fees from industry. The association is certainly subtle: PDUFA fees allowed FDA to increase staffing levels, to become more efficient at processing applications and to add industry-standard 'competences'. Thus, a PDUFA-powered FDA has been able to participate in peer-to-peer discussion on matters such as mechanisms of action, potential side effects and the use of new categories of data applied to new types of interventions. And, in the interests of spreading their knowledge, FDA has published this work in the scientific literature. Indeed, FDA publishes a lot of journal articles—over 15,000 in the past 15 years, only 2% of which had industry co-authors.

These peer-to-peer discussions have entered into a new dimension with the arrival of R&D programs, such as the Critical Path Initiative in the United States or the Innovative Medicines Initiative (IMI) in Europe. Critical Path is a joint research program with an agenda set jointly by industry and the FDA and designed to anticipate some of the technical issues that hold back drug development. IMI is funded by the European Commission and (in kind) by a consortium of pharma companies. Industry sets the IMI agenda, but regulatory bodies participate in many of the consortia that IMI funds. Although the schemes are structured differently, both serve to bring industry and the regulators closer together.

The major issue—whether industry research collaborations increase the likelihood of conflicts of interests for agency staffers—has received relatively little attention in the wider media. Even so, the FDA has made efforts to compartmentalize responsibilities for regulatory oversight away from collaborative research. Thus, in the Predictive Safety Testing Consortium (PSTC), which is led by Critical Path, the regulators involved in assessing the scientific findings of the collaboration were different from those who worked with industry researchers on the experiments. And a different set of staffers again are involved in overseeing drug filings from the companies that are partners with FDA in PSTC. Such 'Chinese walls' guard against conflicts.

In the case of Janet Woodcock and Momenta, Amphastar went so far as to hire the private detective agency Kroll to collect details about her family, retrace the steps she made on business trips and file Freedom of Information Act requests for Woodcock's e-mails, phone records, voicemails, calendar and expense reports. These actions step over the line, but the FDA's response has also been less than satisfactory. Earlier in the year, FDA legal counsel Ralph Tyler announced "We've determined that there's no conflict here" and stated that Woodcock had stepped aside in 2009 from any involvement in the LMWH applications.

But the fact is, it was inappropriate for Woodcock to author a paper with a company filing products for review at CDER, where she is the director. The unfortunate reality is that these days, even the perception that a conflict might exist is sufficient to damage the reputation of an agency that already has fallen far in the public's estimation.