

Uncapping Conflict of Interest?

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The U.S. Food and Drug Administration (FDA) calls on advisory committees (ACs) to provide external expert advice and recommendations to “enhance FDA’s ability to protect and promote the public health and maintain the public trust” (1). The FDA Safety and Innovation Act (FDASIA) (2) was signed into law in 2012 primarily to reauthorize user-fee programs for drugs, devices, and biosimilars. We discuss concerns about how FDASIA also changes AC financial conflict of interest (COI) requirements.

Waivers may be granted so that experts with financial COIs can serve on FDA ACs. Generally, waivers are granted if one of the following is true: (i) the COI is unlikely to “affect the integrity of the services,” (ii) the “need for the individual’s services outweighs the potential for a COI,” or (iii) they will contribute “essential expertise.” Experts may not participate if financial COI is over \$50,000. COI disclosures and waivers must be publicly available on the FDA Web site (1).

In response to concerns of conflicted AC members influencing the objectivity and scientific scrutiny of the ACs (3, 4), the 2007 FDA Amendments Act (FDAAA) established “caps” on the number of COI waivers FDA can grant. The number decreased by 5% over 5 years to the 2012 limit of 11.5% of AC members each year (5). FDAAA also directed the FDA to recruit nonconflicted experts from academic institutions, professional societies, and patient and consumer groups (6).

A waiver-free AC does not mean it is necessarily conflict-free. The FDA only considers a member conflicted and requiring a waiver if he or she has a financial relationship within the past 12 months. Many institutions and journals require COI disclosure back 36 months (7, 8); the European Medicines Agency assigns experts a “risk level” based on declared COIs within 5 years (9).

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Amending COI Requirements

New provisions in FDASIA relax limitations on COI waivers and establish new priorities and mechanisms for recruiting AC members.

Waiver limitations. COI waiver caps were removed. Members must still disclose COIs and be granted a waiver, but an unlimited number of waivers may be granted.

Recruitment. Although AC recruitment will continue to target patient groups, disease advocacy organizations, professional societies, medical societies, academic organizations, and governmental organizations, the new legislation now calls for member referrals every 180 days to also include “product developers” but does not identify “consumer” or “patient safety” organizations.

Expertise. AC member selection criteria changed from including both expertise and financial disclosures to simply requiring “the most current expert advice.” COIs are not prioritized when evaluating potential AC members.

Annual report. In addition to reporting numbers of AC vacancies, nominees, and disclosures, the Annual Report on the FDA Advisory Committee Vacancies and Public Disclosures must now include the number of nominees who did not participate because of a disqualifying COI.

The 2012 scaling back of limits on FDA advisory panel financial conflicts had no clear basis and may have unanticipated impacts.

Reasons for Removing COI Caps

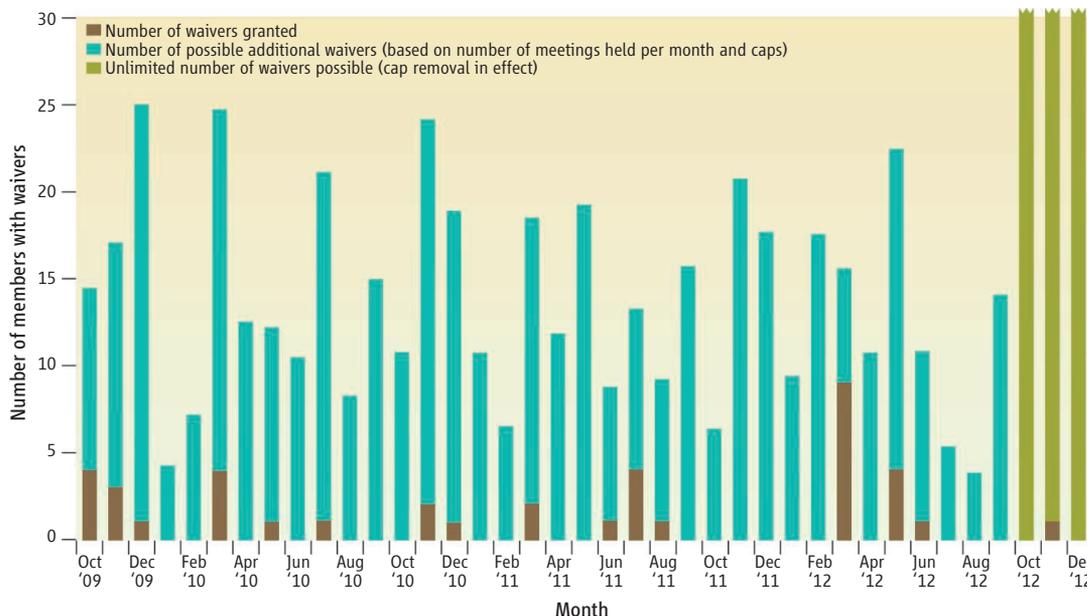
COIs may not affect voting patterns. A 2006 study did not show a statistically significant relation between conflict rates and voting patterns (10). An FDA-contracted study also found no statistically significant relation between disclosed COIs and voting outcomes (11).

Experts with COIs may have higher expertise. A 2007 FDA-contracted study created a composite expertise index combining number of publications, years of experience, and scientific productivity. AC members with COI waivers had a somewhat higher expertise composite (0.40) compared with nonconflicted members (0.31) (12).

Increased effort in finding nonconflicted members. The 2007 FDA study concluded “the ability to create a conflict-free panel is speculative,” arguing that it is more difficult to find highly qualified nonconflicted members and doing so would have negative impacts on FDA. It might worsen the high number of vacancies in ACs and could require additional recruiting efforts from the already burdened FDA, which could affect productivity (12). This argument has been made by pharmaceutical representatives critical of COI caps (13).

Support for Keeping COI Limits in Place

Scientific integrity. COI limitations were put



Conflict of interest waivers allowed and granted by month. Data from U.S. FDA. See SM for details.

in place by FDAAA in 2007 in part because of longstanding concern for the scientific validity and objectivity of the ACs; the FDA Science Board concluded “science at the FDA is in a precarious position” (3). A 2009 Institute of Medicine report determined that COIs “threaten the integrity of scientific investigations, the objectivity of medical education, and the quality of patient care, ... [and] jeopardize public trust in medicine” (14). Other studies have identified that AC members “describe pressure to conform and to recommend approval” (4), which compromises the integrity of the recommendations.

COIs may affect AC decisions. Although detecting a direct impact of COIs on voting patterns is difficult (10, 11), specific cases have raised concerns. An AC voted 15 to 11 that the risk of blood clots from Yaz and Yasmin contraceptives was outweighed by benefits. Four members of the AC had undisclosed COIs, enough to change the voting outcome (15). In separate votes on painkillers Celebrex, Bextra, and Vioxx, 93% of votes cast by the 10 conflicted AC members favored the drugs’ approval, compared with 56% of votes by the 22 nonconflicted members (16, 17).

Vacancies are decreasing, and FDA productivity is increasing. Public FDA data show that vacancies in AC positions have decreased or remained stable, despite the caps [see fig. S1, supplementary materials (SM)]. The FDA’s goal is to have 10% or less of AC positions vacant. December 2012 vacancy rates were 22% versus 33% in October 2009.

FDA approval of new drugs is not declining, contrary to claims that COI caps would slow FDA functionality. As one measure of productivity, in fiscal year 2011, the FDA Center for Drug Evaluation and Research (CDER), with a workload of 39 applications, approved 30 new molecular entities, similar to approval rates since 2002 (18). Within the FDA, CDER has the highest number of AC members and most meetings each year (19).

Caps have never been reached. Since their establishment, financial COI waiver caps have never been reached, which implies that conflicted experts identified through the waiver process have not been denied membership solely because of waiver limitations. According to FDA data from October 2009 to December 2012, the average percentage of AC members granted waivers each month was only 0.78%, of the allowable 11.5 to 13.0% (see SM). From October 2009 until September 2012 (the date the caps were removed), an additional 455 waivers could have been granted, which would have allowed FDA to fill vacant positions with conflicted members while remaining well within FDAAA

waiver limits (10) (see the chart). This is not to argue that the FDA should use more conflicted members to fill vacancies or that the caps serve no purpose. Rather, there is no reason to proactively remove the caps if they are not being reached. Caps can provide protection from overly conflicted ACs, while allowing waived, conflicted experts to serve.

Nonconflicted experts are out there. A 2009 study of academic life science researchers found that 47.2% declared no relationship with industry. The study concluded that “it is difficult, but not impossible, to find academic scientists without industry relationships to serve in advisory roles for organizations such as [FDA] ...” (20). With roughly 139,000 faculty at U.S. medical, pharmacy, and public health schools (21–23), there is capacity to fill AC positions with nonconflicted experts.

Support for a nonconflicted FDA. A 2012 U.S. public poll found that 92% of respondents expressed some concern, and 66% expressed high concern about “recommendations made by expert committees that included doctors who had current financial relationships with medical device makers” (24). In 2010, FDA Commissioner Hamburg wrote “it is clearly better for the agency in fulfilling its public health mission when advisors have no [COI]” (25). In 2011, she supported weakening COI regulation, but reaffirmed her original position in 2012: “...we are not bumping up against our cap in terms of waivers, and we have actually been making an aggressive effort to fill empty slots on our advisory committees and have made progress... We don’t at the moment see major areas where a legislative fix is required” (13).

Appearance of a Threat to Integrity

Evidence we have identified does not support the need to remove the COI limitations. Removal of the caps weakens the system for managing COIs and creates potential for an unlimited number of conflicted AC members. At a minimum, this could create the appearance of a threat to scientific integrity.

Removing the 2007 COI restrictions did not occur by accident but in response to advocacy by interested parties. Long-term impacts of this legislation could include more conflicted members voting on FDA recommendations, with unforeseen consequences on the safety and efficacy of FDA-regulated products and, thus, on the health of consumers. Reauthorization of FDASIA is scheduled for 2017, with discussions beginning much sooner. Increased engagement of the scientific and medical communities is crucial to ensure a strong and effective FDA advisory system.

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Supplementary Materials

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10.1126/science.1231955

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Science **340** (6137), 1172-1173.
DOI: 10.1126/science.1231955

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