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EDITORIAL

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Medical experts are regularly solicited by national and international scientific and professional societies to contribute to clinical recommendations and management guidelines. Quite likely, and for the very same reasons, these experts are often involved in collaborations with the healthcare industry, for example the clinical trial conduct (both investigator- and industry-initiated), the participation to drug safety monitoring or advisory boards, consultancy agreements and the organization of symposia and other educational or promotional events. These collaborations may entail financial or in-kind compensations, often paid totally or in part to the experts themselves, unless their institutions have established otherwise. As a consequence, such experts find themselves confronted with a situation entailing a typical conflict of interest (CoI).

Legally, a CoI mostly arises when individuals have a ***financial incentive*** to breach their statutory, professional or moral obligations. Not all CoI imply a monetary reward, of course. Indeed, this is merely a special case of a wider set of situations where any kind of 'personal consideration may present the potential to compromise or bias professional judgement and objectivity' (see a tentative list in the Table 1),[1] although it is a matter of debate whether having a non-financial interest might pose a CoI.[2] The most common case scenario involves medical practitioners, who—in the course of their profession—are expected to provide patients with the most appropriate treatment, that is, based on the available scientific evidence. Here, financial advantages offered by a pharmaceutical company may unduly influence the doctor's choices (eg, favouring one medicine over another one, irrespective of their safety and efficacy profile) with potential detrimental effects either on the patients themselves or on the competing drug companies. The untoward consequences of such biased judgement encompass the risk of inflicting harm and/or losing credibility, both one's own and that of an entire professional category. On the other hand, it must be made clear that having a CoI does not necessarily lead to a biased decision: experts may have a CoI and, at the same time, provide a fully independent and objective advice, thus fulfilling their own obligations. In other words, although a CoI is a situation at risk, it is not automatically tantamount to a breach of conduct. Experts should not be presumed guilty until proven innocent.

In a provocative article published in *Liver International*,[3] Kida and collaborators analysed the financial contributions provided by the pharmaceutical industry in 2016 and 2017 to the 17 authors of the Hepatitis C Clinical Practice Guidelines (CPG) published by the Japanese Society of Gastroenterology (JSH). The JSH is a large scientific society, strong of more than 12 000 members. The choice was dictated by the introduction, in 2014, of direct-acting antiviral (DAA)-based regimens to treat Hepatitis C into the Japanese market. Although DAA undoubtedly represented a quantum leap in terms of efficacy and safety in the treatment of hepatitis C, they were also immediately singled out and blamed for their staggering market prices. As a result, the initial returns on investments have been stellar, with worldwide global DAA sales totalling about 70 billion USD during the first 4 years from marketing. Gilead blockbuster sofosbuvir alone (marketed as monotherapy under the trade name Sovaldi™ and in combination with ledipasvir as Harvoni™) accounted for 55 billion USD in sales during the same period (2014-2017), although in more recent years this trend has suffered from a downturn.[4]

Thus, payments (speaking, consulting and writing fees) paid by all pharmaceutical companies belonging to the Japan Pharmaceutical Manufacturers Association (JPMA) to the CPG authors were recorded. Of the 17 authors (incidentally, all males), four were members of the JSH board and eight were University professors. All 17 had received at least one payment from the industry in 2016 or 2017. The largest amount received by a single author during the 2 years was USD 272 053, although this was an outlier. Mean and median payments were USD 66 979 and 46 033 respectively. Most (~80%) of the fees were given for speaking at conferences and other events. The top three companies making payments, not unsurprisingly, were also the ones manufacturing DAAs (AbbVie, MSD and Bristol-Myers Squibb). Ironically, Gilead, a leading manufacturer of DAA, does not belong to JPMA and therefore did not disclose any payment.

The JSH stipulates that all CPG authors must disclose payments above a certain threshold (USD 4596 for speaking and writing tasks, and USD 9191 for consultancy agreements) received from the pharmaceutical industry that may be perceived as a CoI. The details of each payment are not compulsorily public, and thus are not included in the CPG publications, which only list the companies that made the payments to the authors but not their names, at variance with policies followed in the United States[5] and other countries. The authors concluded by stating that for the first time the financial relationships between the Hepatitis C JSH CPG authors and the pharmaceutical industry had been clarified, showing also how the highest payments had been made by the manufacturers of Hepatitis C DAA. They also stated very clearly that the system as a whole, rather than the CPG authors, should be blamed, and that draconian rules should possibly be adopted preventing authors from receiving any financial benefit from the companies whose products are to be evaluated in the setting of management recommendations. Lack of transparency by the

TABLE 1 List of situations potentially involving a conflict of interest

Academic conflict of interest (eg, interference with the peer-review process or unduly delaying dissemination of scientific results motivated by personal gain)
Conflict of commitment/obligation (eg, when the time spent on accessory activities interferes with the time that should be committed to the service to the primary employer)
Conflict of conscience (ie, when personal beliefs—religious, ideological, political—affect scientific objectivity, including when belonging to schools of thought or advocacy/policy groups and organizations)
Intellectual passion overtaking ethical obligations of research
Desire of glory/career advancement
Personal relationship with persons having the disease under study

Note: Adapted from Ref. [2].

JSH was also pointed out, although, ironically, many CPG authors were also members of the JSH board, that is the same society that should improve such transparency rules.

Many solutions have been proposed.[6] Regulation of CoI is currently the preferred course of action. Disclosure is almost universally requested by all stakeholders, and involves not only payments for consultancies or participation into industry speakers' bureau, but also ownership of stocks, patents and other intellectual properties, research grants, in-kind gifts and other forms of financial support (eg, travel and conference participation grants). Although experts and physicians with the possibility to prescribe medicines are required in most countries to divulge the above financial relationships with the industry, full transparency may not be sufficient to dispel the perception of bias, and may even create false trust. Members of advisory boards may be recused from voting, especially if the financial benefit coming from the industry goes above predefined thresholds, or the scope of their activity may be restricted, and/or supervised by third parties. Board chairs may pick a majority of advisors without CoI, that is outnumbering those with a financial relationship with the industry. Alternatively, when applicable, the financial interests (eg, ownership of shares or other financial instruments) may be placed in a blind trust for the whole period of collaboration. It must be stated, however, that whenever the above measures do not involve the complete divestment of the financial interest, the CoI will remain unchanged. Thus, the ultimate solution to abolish the CoI should be to terminate the conflicting relationship, at least for the whole duration of the participation, for example to a CPG panel, or to an advisory board, especially in the setting of collaborations with governments or high-profile non-governmental institutions (eg, the World Health Organization or Doctors Without Borders).

The heated discussions about treatment and prevention of COVID-19 have shown how the debate surrounding the perceived CoI in the healthcare industry is today striking a chord with everyone. The accusations of collusion of the healthcare sector with the pharmaceutical industry have become an inescapable ingredient of the political and media discourse. The latest example is probably the recent appointment of Vivek H. Murthy as US Surgeon General, which elicited virulent remarks, as reported even in the mainstream media, where Murthy was accused of 'the most financial entanglements of any surgeon general pick in recent history'.[7] All stakeholders should take the utmost care to avoid the slightest perception of bias, otherwise any decision may be tainted by suspicions of collusion, entailing the risk of jeopardizing the credibility not only of the involved actors, but also—and this would lead to potentially irreparable damage—of the entire system.

KEYWORDS

conflict of interest, conflict of loyalty, healthcare industry, pharmaceutical industry

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CONFLICT OF INTEREST

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