Conflicts of interest in Twitter

We have previously shown that 79·5% of US-based haematologist-oncologists on Twitter have at least one financial conflict of interest (FCOI)[1] with the biopharmaceutical industry. However, we did not study whether conflicted physicians tweet about specific products for which they have a FCOI. Using our list of all US-based haematologist-oncologists on Twitter,[1] we focused on the subset of physicians with a FCOI of at least US$1000 in general payments in the year 2014, and at least 100 total tweets. We updated general payment information from the Open Payments website and updated their Twitter activity (number of tweets, followers, following). We excluded users who made their accounts private.

For accounts with less than 300 total tweets, we read all tweets. For accounts with more than 300 tweets, we calculated a "tweet rate" based on usage and read from a timepoint in the past that would approximate 300 tweets. Each tweet or retweet that mentioned an oncology drug with an FDA approval date later than 1996 was recorded.

Additionally, we randomly coded 100 tweets regarding drugs for which a conflict existed and 100 for which it did not. We coded these 200 tweets as positive, neutral, or negative. Our study was not submitted for Institutional Board Review as it concerned only publicly available data, and was conducted between Jan 7, to Jan 25, 2017.

We studied 156 physicians who tweeted a median of 584 times, with a 2014 median general payment totaling $13 600 (range 1000–444 100; table. Of these 156 physicians, 126 (81%) mentioned at least one drug from a company for which they had an FCOI. 137 (88%) physicians mentioned at least one drug for which they did not have an FCOI. Of 4358 total drug mentions, 2252 (52%) regarded conflicted drugs. Only two (1·3%) of the 156 individuals included disclosures of their payments, and these were in their 5-line twitter biography. When we compared 100 tweets about conflicted drugs with 100 tweets about non-conflicted drugs coded at random, conflicted tweets were more likely to be positive (66 *vs* 50; p=0·02), similarly likely to be neutral (35 *vs* 30, p=0·45), and less likely to be negative (4 *vs* 15; p=0·008).

Thus, we found that a majority of physicians on Twitter with significant financial conflict and frequent tweets mention specific drugs for which they have a conflict; and almost none disclose financial ties. Although these physicians also tweet about drugs for which they have no conflict, comparing these rates is a false equivalence. There are 371 biopharmaceutical companies in the world whose products could be discussed, but more than half of drug mentions refer to a median of six companies that pay these physicians. Moreover, doctors are more positive about drugs whose companies pay them.

Our results raise the concern that financial conflict of interest must be considered with the growing use of social media to discuss cancer products and practices,[1] as well as policies regarding disclosure, divesture, audit and recusal may be considered.

VP reports receiving royalties for his book Ending Medical Reversal. The other authors declare no competing interests.

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	Median (range; IQR) unless otherwise stated
Tweet & FCOI characteristics	
Number of tweets	584 (101–65000; 249–1853·5)
Number of accounts following	260 (14–17103; 115·5–592)
Number of followers	623·5 (19–43815; 289–1401·5)
Total general payments, 2014 (US$)	13 668·45 (1031·49–444 055·94; 4292·16–33213·47)
Number of tweets mentioning non-conflicted drug	8 (0–121; 3–18)
Number of tweets mentioning conflicted drug	7 (0–114; 1–20)
Number of companies from which they took payments	6 (1–30; 3–10)
Number of unique non-conflicted drugs mentioned*	4 (0–24; 2–7)
Number of unique conflicted drugs mentioned*	3 (0–36; 1–5)
Source and disclosures	
Range of date joined	7/22/2007–5/1/2016
Number of people who disclosed (%)	2 (1%)
Affiliation characteristics†	
MD Anderson	12
Cleveland Clinic	8
Memorial Sloan Kettering Cancer Center	8
Dana Farber Cancer Institute	6
University of Miami	5
Carolinas Health System	4
Duke	4
Emory	4
Cornell	3
Cancer Treatment Centers of America	3

FCOI=financial conflicts of interest. *All mentions of the same drug were counted only once. †Number of people with those affiliations.

Table: **Physician characteristics**

For the **Open Payments website** see https://openpaymentsdata.cms.gov

For a **list of pharmaceutical companies in the USA** see https://www.drugs.com/pharmaceutical-companies.html

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1 Tao DL, Boothby A, McLouth J, Prasad V. Financial conflicts of interest among hematologist-oncologists on Twitter. *JAMA Intern Med.* 2017; **177:** 425–27.

Research on Biosimilars: pivotal trials and principles

Biopharmaceuticals have been a fundamental part of modern oncology armamentarium. The registration of growth factor biosimilars (EPO and G-CSF) in Europe induced an immediate 30–40% price drop, decreasing the financial burden to health care and increasing access for patients. In 2017 the European Medicines Agency approved two biosimilars for rituximab, a monoclonal antibody essential in B-cell lymphoma therapy. Several biosimilars of other game changing biological drugs such as infliximab, etanercept, and adalimumab have been granted a marketing authorisation, and there are more to come (eg, bevacizumab, trastuzumab). Physicians should therefore get familiar with the principles of biosimilar development, which is fundamentally different from that of testing innovative compounds.

Two pivotal phase 3 trials[1,2] for biosimilar rituximab were published In *The Lancet Haematology*, and the results were put in perspective in a Comment by Shinichi Makita and Kensei Tobinai.[3] In their Comment, these authors argued that the two biolsimilar phase 3 trials did not have robust endpoints.

These trials were both part of an extensive similarity exercise, which is typical for the development pathway of biosimilars. This pathway is different from that of traditional innovative medicines. In this Correspondence, we will briefly explain the biosimilarity pathway as it has evolved over the past 10 years with great success in the European Union.

Biosimilarity is established in a stepwise approach. The proposed biosimilars are tested in preclinical studies up to beyond doubt as being almost indistinguishable to the originator biological in physicochemical characterisation (eg, primary structure, glycosylation, heterogeneity, post-translational modifications, and purity) and biological characterisation (for rituximab biosimilar: target and receptor binding, apoptosis, complement mediated cytotoxicity, and antibody-dependent cellular toxicity). It is followed by pharmacokinetics (PK) and pharmacodynamics (PD), toxicity, and efficacy studies done on animal models, confirming the similarity.

Subsequently, for the development of the rituximab biosimilar, clinical trials were done to confirm similarity in safety, PK and PD, and efficacy. First, a rather traditional bioequivalence trial confirmed bioequivalence and second, a phase 3 confirmatory trial showed the molecule did not behave differently from the reference product in patients. The endpoints were selected to be the most sensitive to show up any difference, in case there was one. Therefore, adequate endpoints may differ from innovator trials.[4] This research was done on the basic assumption that if the molecules are the same, they should have a similar effect on patients.

Rheumatoid arthritis is the best model for investigating PK and PD, because of the rituximab dosing schedule and the relatively low variability in peripheral blood B-lymphocyte counts. Efficacy in rheumatoid arthritis was assessed with disease activity score. Indication extrapolation is an important feature in biosimilar development.[5] In oncology, biosimilar trials have been done in follicular lymphoma, a well defined entity, for which the role of rituximab is undisputable, especially when combined with cyclophosphamide, vincristine, and prednisolone chemotherapy. The response rate chosen as a primary target is fully acceptable to confirm biosimilarity since it constitutes the most sensitive endpoint to compare the different molecules.

In our opinion it is rather disappointing that the special biosimilar development pathway was underexposed in the Comment[3] to the two largest biosimilar trials in oncology.[1,2] The problem is not about having a different opinion, and reading and interpreting clinical trial data differently; it is about having a new and different concept of drug development and of how to obtain evidence for similarity. It is important for clinicians to understand the scientific foundations of biosimilar development to appreciate the full potential for access to treatment and for great savings in health-care cost.

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1 Jurczak W, Moreira I, Kanakasetty GB, et al. Rituximab biosimilar and reference rituximab in patients with previously untreated advanced follicular lymphoma (ASSIST-FL): primary results from a confirmatory phase 3, double-blind, randomised, controlled study. *Lancet Haematol* 2017; **4:** e350–61.

2 Kim WS, Buske C, Ogura M, et al. Efficacy, pharmacokinetics, and safety of the biosimilar CT-P10 compared with rituximab in patients with previously untreated advanced-stage follicular lymphoma: a randomised, double-blind, parallel-group, non-inferiority phase 3 trial. *Lancet Haematol* 2017; **4:** e362–73.