is intended to encourage development of treatments for serious or life-threatening infections caused by bacteria or fungi. The term "qualified infectious disease product" (QIDP) refers to an antibacterial or antifungal human drug that is intended to treat serious or life-threatening infections. For certain drugs designated as QIDP, GAIN provides an additional five years of exclusivity. An application for a drug designated as a QIDP is also eligible for priority review and designation as a fast-track product.[8] The FDA has granted 47 QIDP designations representing 33 different antibacterial or antifungal drugs since the FDASIA was enacted in 2012.

Antibacterial drug development is challenging on many fronts. Although significant progress has been made in the past few years on designing scientifically sound and feasible clinical trials, more work remains to be done to make new therapies available to meet patient needs.

CONFLICT OF INTEREST
The authors declared no conflict of interest.

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See ARTICLE page 239

Use of Internet Search Logs to Evaluate Potential Drug Adverse Events

S Sarntivijai[1] and DR Abernethy[1]

Internet search logs provide an abundant source of data that can be explored for purposes such as identifying drug exposure–adverse event relationships. The methodology to rigorously conduct such evaluations is not well characterized, and the utility of such analyses is not well defined. In this issue, White and colleagues propose an approach using Internet search logs for this purpose and compare it to parallel analyses conducted using the US Food and Drug Administration's spontaneous reporting database.

It is gratifying to see that various approaches are under evaluation to improve detection and interpretation of clinical adverse drug events. At present, a mainstay for postapproval monitoring for adverse drug events is the US Food and Drug Administration's Adverse Event Reporting System (FAERS).[1] The strengths and weaknesses of the FAERS have been discussed extensively. Weaknesses include under- or overreporting of adverse events as a result of the voluntary nature of the system and the burden of completing reports. The latter may be less of an issue with Internet search logs, but that is unknown at this time. It should be noted that a FAERS report contains considerable detail about the patient, the drug, the underlying clinical condition, comorbid illness and concurrent drug exposures, and the temporal relationship between drug exposure and adverse event. This information would be lacking from Internet search log data.

When a disproportionately strong association between an adverse event and a drug exposure is noted during ongoing analysis of FAERS data, it can be viewed as generation of a hypothesis. Such a finding leads to careful examination of other data sources, the published literature, and the information in the reports themselves. Evaluation of the reports can lead to a reevaluation of the association if it becomes clear that there are duplicate reports or there is evidence of stimulated reporting (e.g., medical–legal activity, heightened awareness due to public-

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ity).[2] The hypotheses generated by use of Internet search logs could be viewed as yet another data source; however, much more experience and use of methods to increase confidence in their reliability as discussed below will be necessary before their utility can be placed into a meaningful context.

Use of patient-generated Internet data as described by White *et al.* in this issue represents the development of a potentially useful additional data source that may be complementary to evaluation of FAERS reports.[3] This can be viewed similarly to data sources such as the US Food and Drug Administration's Sentinel Initiative, electronic health records, reports from other regulatory jurisdictions, and other available sources, which are used to strengthen or weaken a potential signal for a drug–adverse event association.[4,5] In addition to these observational approaches, mechanistic plausibility for the drug–event association is a component of analysis that may strengthen or weaken a potential signal.[6]

Because of the limited experience in interpretation of Internet search log data and lack of efforts to confirm findings from Internet traffic patterns via evaluation of different platforms to obtain the same kind of data, many questions remain. Specific to the use of search logs to identify drug–adverse event associations, the methodology presented by White and colleagues reflects reasonable attempts to address potential confounding factors. They explain how use of the temporal association of the first mention of a drug and the first mention of a potential adverse event, the effort to exclude health-care provider Internet queries, and the effort to limit false positive reporting by limiting the area of the receiver operating characteristic curve may help to address their recent caution regarding the use of Internet search logs. In this caution, it is noted that the widely cited use of Google Flu Trends to forecast and analyze influenza-transmission patterns in real time appears to have overreported the transmission.[7] Lazer and colleagues note that use of Internet search logs has substantial limitations, in both the analytical search algorithms used, which are modified for various reasons over time, and the implicit assumption that the incorporation of more data into an analysis will somehow improve its accuracy.

White *et al.*[3] analyze signal-detection accuracy according to a set of what they call "gold standard" adverse events from the Observational Medical Outcomes Partnership and 181 drugs.[8] The four events are acute myocardial infarction, acute renal failure, acute liver injury, and upper gastrointestinal bleeding. Use of these drug–event associations allowed a comparison between parallel analyses of the publicly available FAERS data and this application of Internet search logs. Of more interest is the methodology presented to combine the use of the two data sources. This demonstrated that use of the combined data improved signal-detection accuracy for these well-known drug–event associations. This validation exercise is useful to demonstrate consistency across methods; however, it should not be used to imply the utility of Internet search logs for the detection of previously unknown drug–adverse event associations. It is not at all clear how Internet search behavior would differ between instances of well-known drug–event pairs (e.g., nonsteroidal anti-inflammatory drug–upper gastrointestinal bleeding) and potential pairs that have not been described in the news media and are not mentioned in available drug information sources. That analysis is essential and will require prospective study.

Another form of validation that will be critical at some point is individual case ascertainment. In a subset of appropriately informed and consented individuals, one must establish by individual interview the extent to which what was inferred using the Internet search log methodology is what actually happened. Such medical-record ascertainment is routine in other approaches to drug safety evaluation and is standard epidemiological practice.[9,10]

In conclusion, this application of Internet search log data to bring another data source to bear for the evaluation of potential adverse drug events seems a step in the right direction. At the same time, it should be seen as another form of hypothesis generation in an area where the "true" extent of a drug–adverse event association is often very difficult to define. Further investigations as outlined above are necessary to place into context the usefulness of this method for exploration of Internet search log data as a hypothesis-generating tool.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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