Evaluation of Serious Adverse Drug Reactions

A Proactive Pharmacovigilance Program (RADAR) vs Safety Activities Conducted by the Food and Drug Administration and Pharmaceutical Manufacturers

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**Background:** The Food and Drug Administration (FDA) and pharmaceutical manufacturers conduct most postmarketing pharmaceutical safety investigations. These efforts are frequently based on data mining of databases. In 1998, investigators initiated the Research on Adverse Drug events And Reports (RADAR) project to investigate reports of serious adverse drug reactions (ADRs) and prospectively obtain information on these cases. We compare safety efforts for evaluating serious ADRs conducted by the FDA and pharmaceutical manufacturers vs the RADAR project.

**Methods:** We evaluated the completeness of serious ADR descriptions in the FDA and RADAR databases and the comprehensiveness of notifications disseminated by pharmaceutical manufacturers and the RADAR investigators. A serious ADR was defined as an event that led to death or required intensive therapies to reverse.

**Results:** The RADAR investigators evaluated 16 serious ADRs. Compared with descriptions of these ADRs in FDA databases (2296 reports), reports in RADAR databases (472 reports) had a 2-fold higher rate of including information on history and physical examination (92% vs 45%; P < .001) and a 9-fold higher rate of including basic science findings (34% vs 4%; P = .08). Safety notifications were disseminated earlier by pharmaceutical suppliers (2 vs 4 years after approval, respectively), although notifications were less likely to include information on incidence (46% vs 93%; P = .02), outcomes (8% vs 100%; P < .001), treatment or prophylaxis (25% vs 93%; P < .001), or references (8% vs 80%; P < .001).

**Conclusion:** Proactive safety efforts conducted by the RADAR investigators are more comprehensive than those conducted by the FDA and pharmaceutical manufacturers, but dissemination of related safety notifications is less timely.

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**ADVERSE DRUG REACTIONS (ADRs) result in health care costs of $3.6 billion annually and are among the top 10 leading causes of death.** After product recalls for rofecoxib and cerivastatin, concern exists over the ability of the Food and Drug Administration (FDA) and pharmaceutical manufacturers to identify serious adverse events and to notify physicians about these findings. Serious ADRs can go unrecognized if initial safety signals are unclear. New approaches to identifying unexpected pharmaceutical toxic effects are needed.

One concern is that current pharmacovigilance efforts are hindered by low reporting rates, and when ADRs are reported the information is of variable quality. When pharmaceutical manufacturers and the FDA become convinced that an event represents a serious ADR, safety notifications are disseminated. Physicians may not be aware of serious ADRs if dissemination of these notifications is delayed, the safety notification is not comprehensive, or they do not read the notifications.

Academic researchers and nonprofit organizations have developed systems to identify and evaluate serious ADRs. As noted previously, surveillance efforts conducted by these groups differ from those of the FDA: the organizations focus on serious ADRs, and additional reports are obtained after queries to health care professionals who provide care for patients with the relevant toxic effects. The deputy director of the FDA proposed that adverse event reports obtained by proactive pharmacovigilance should be transmitted to the FDA and would augment existing pharmacovigilance systems. However, before augmentation can occur, comparisons of these pharmacovigi-
Research on Adverse Drug events And Reports (RADAR) project.14

**METHODS**

The RADAR project is a pharmacovigilance program that focuses on identification, evaluation, and dissemination of information describing serious ADRs, such as those resulting in death or severe organ failure or precipitating major therapeutic interventions. The RADAR project is funded by grants from the National Heart, Lung, and Blood Institute, the National Cancer Institute, the American Cancer Society, and the Department of Veterans Affairs. Pharmaceutical manufacturers do not provide support, although they are asked to provide relevant clinical information on each serious ADR.

The RADAR project is led by a hematologist-oncologist and health services researcher (C.L.B.) and consists of 23 investigators with training in internal medicine and the medical subspecialties of clinical pharmacology, epidemiology, statistics, and pharmacy. An investigation is initiated when a clinical event that represents a possible occurrence of a serious ADR is seen by a RADAR coinvestigator or reported by unaffiliated physicians. Senior members of the RADAR team review the indicator event, as well as associated literature and package inserts, to determine if the event represents an ADR. If further investigation of the ADR is meritorious, queries for additional case reports are submitted to the FDA and institutional review board approval is requested at collaborating institutions. The FDA reports are subject to a preliminary review to inform hypothesis generation and refine data collection tools. The case forms include demographics, source of information (eg, clinical trial or physician queries), medication history, event description (eg, date of the event, time elapsed between exposure and ADR event, event duration, other relevant history, physical findings, and study results), organ-specific history, and treatments. World Health Organization criteria are used to score causal associations between the suspect drug and the event. The RADAR investigators refine hypotheses about pathophysiologic features. Data elements and coding accommodate the range of data available in the FDA databases and address underlying causality hypotheses. Coding of the case classification form is designed to facilitate algorithmic analysis of case findings (Figure).14

**DATA SOURCES**

Initial sources for RADAR investigations are descriptions of single events of serious ADRs identified by a RADAR investigator, often originating with queries from health care workers, attorneys, or patients. The RADAR data sources for obtaining additional information include communications with clinical trialists or referral centers that treat large numbers of individuals with the given toxic effect. The FDA data sources for obtaining follow-up reports include spontaneous adverse event reports contained in MedWatch19 (for drugs) and the Manufacturer and User Facility Device Experience Database (MAUDE)20 (for drug-coated devices). Dissemination of RADAR findings occurs via published abstracts or articles. Dissemination of FDA and pharmaceutical supplier findings is made via “Dear Doctor” letters and package insert revisions.

**OUTCOME MEASURES**

Safety elements were abstracted onto syndrome-specific forms.21-32 These forms are based on the ADR systems of the World Health Organization33 and Naranjo et al.34,35 Data elements included history and physical examination, laboratory,
radiologic, and basic science findings; age and sex; clinical diagnosis for which the drug was being prescribed; duration and dose of the drug administered; use of concomitant drugs; relevant clinical and laboratory findings that supported the diagnosis of the adverse event; duration of clinical abnormalities; exposure-adjusted incidence rates; treatments and prophylaxis regimens; and references to relevant peer-reviewed articles. For each of the safety evaluations, completeness percentages were derived for individual case descriptions contained in the respective safety databases. Specific categories included history and physical examination findings, laboratory and radiologic test results, and basic science correlative studies. For each summary safety notification published as a peer-reviewed publication, Dear Doctor letter, or package insert revision, mean percentages were derived for frequency of inclusion in these reports of relevant clinical findings, estimated reporting and exposure-adjusted incidence rates, treatment and prophylaxis recommendations, and references to relevant peer-reviewed articles. A time to initial publication was derived for each summary notification, operationally defined as the time from FDA approval to publication (for RADAR notifications) or ADR notification via a Dear Doctors letter (for FDA or pharmaceutical supplier notification) or revised package inserts (for pharmaceutical supplier notifications).

STATISTICAL ANALYSIS

Overall unweighted mean percentages of completeness for inclusion of information from history and physical examinations, laboratory and radiologic tests, and basic science correlative studies were derived for clinical adverse event reports included in the FDA and RADAR safety databases. Statistical comparisons were made of completeness percentages for these individual data elements in FDA vs RADAR databases. With respect to dissemination, we reported mean completeness percentages for inclusion of relevant safety information in notifications from RADAR and the pharmaceutical manufacturers, as well as median time to publication of RADAR notification vs safety notifications from pharmaceutical manufacturers and/or the FDA. Statistical analyses were conducted using optimal discriminant analysis, a nonparametric exact statistic. The project received institutional review board approval from Northwestern University.

RESULTS

Between 1998 and 2006, the RADAR investigators published safety notifications for 12 unique serious ADRs associated with 14 drugs and 2 devices. The safety investigations were initiated after identification and reporting of a small number of serious individual clinical events by physicians conducting early-phase clinical trials (thalidomide- and lenalidomide-associated venous thromboembolism, gemtuzumab ozogamicin–associated sinusoidal obstructive syndrome, and gemcitabine hydrochloride–associated pneumonitis) or specialists who reviewed clinical and laboratory findings for individuals who experienced a likely drug- or device-related toxic effect (drug-eluting cardiac stent–associated hypersensitivity and erythropoietin-associated pure red blood cell aplasia) or provided care for individuals who experienced a probable drug-related toxic effect (ticlopidine hydrochloride– and clopidogrel bisulfate–associated thrombotic thrombocytopenic purpura, vardenafil hydrochloride– and tadalafl-associated optic neuritis, nevirapine-associated hepatotoxicity among health care workers not infected with human immunodeficiency virus [HIV], enoxaparin sodium–associated hemorrhage after cardiac angioplasty procedure, and bisphosphonate-associated jaw osteonecrosis; Table 1).

These clinical events required primarily intensive interventions, and occasionally patients died of the toxic effect. For each ADR, descriptions of additional detailed case information were obtained from health care professionals who conducted early-phase clinical trials, had referral practices that evaluated or treated patients with the relevant toxic effect, or directed specialty centers such as blood banks or leukemia referral centers. The number of individual event reports associated with each of the ADRs ranged from 3 to 1348. Overall, RADAR databases included 472 individual reports and FDA databases included 2296 reports.

Individual case descriptions were more complete in RADAR vs FDA databases (Table 1). The RADAR database had significantly higher mean rates of inclusion of history and physical examination information (92% vs 45%; P < .001) and a trend toward higher mean inclusion rates of basic science laboratory studies (34% vs 4%; P = .08). For laboratory and radiologic findings, reporting comprehensiveness rates were comparable (54% vs 46%; P = .61). Items frequently found in RADAR but not in FDA reports included physical examination findings, radiologic reports (venogram, computed tomogram, or magnetic resonance imaging findings), laboratory studies (hemoglobin level, creatinine level, and platelet count), pathologic findings (bone marrow aspirate, liver biopsy, bone biopsy, and autopsy findings), and antibody assay results.

Timing and completeness of safety notifications disseminated by pharmaceutical manufacturers and RADAR investigators differed (Table 2). Safety notifications were disseminated earlier by pharmaceutical manufacturers, usually as package inserts or Dear Doctor letters (median of 2 vs 4 years after FDA approval). For 4 ADRs (thrombotic thrombocytopenic purpura associated with clopidogrel, venous thromboembolism associated with thalidomide and lenalidomide, nevirapine-associated hepatotoxicity, and bisphosphonate-associated osteonecrosis of the jaw), RADAR safety notifications were the primary sources of summary safety information for the RADAR project, as well as for the related Dear Doctor letters and package insert notifications disseminated by pharmaceutical manufacturers. For 2 ADRs (fulminant hepatic failure with nevirapine that contained post-HIV-exposure prophylaxis regimens and enoxaparin-associated severe hemorrhages after invasive cardiologic procedures), safety notifications were made via RADAR publications but are not described in materials distributed by the pharmaceutical manufacturer because these toxic effects occurred in off-label settings.

Compared with notifications disseminated as pharmaceutical package insert revisions or Dear Doctor let-
tors, RADAR notifications were more likely to include reporting rates or exposure-adjusted incidence rates (93% vs 46%; \( P < .02 \)), outcomes (100% vs 8%; \( P < .001 \)), treatment and prophylaxis recommendations (93% vs 25%; \( P < .001 \)), and peer-reviewed references (80% vs 8%; \( P < .001 \)). Of note, for drug-eluting cardiac stents, a Dear Doctor letter issued on October 29, 2003, described rare instances of hypersensitivity when drug-eluting stents were placed in coronary arteries.\(^5\) One month later, a follow-up notification from the FDA indicated that these cases were most likely related to hypersensitivity to concomitantly administered drugs, primarily clopidogrel.\(^5\)

In 2004, a RADAR notification indicated that some instances of hypersensitivity appeared to be caused by the stents, since autopsies revealed eosinophilic infiltrates at the stent site for 4 patients and information in FDA notifications rarely supported clopidogrel as the cause.\(^2\) In this review of pharmacovigilance efforts associated with 16 serious ADRs, we found that clinical information ob-

### Table 1. Completeness of Reports Contained in RADAR Databases vs Completeness of Individual Case Reports Contained in FDA Data

<table>
<thead>
<tr>
<th>Drug (FDA Approval Year)</th>
<th>Source of Initial Signal</th>
<th>ADR (No. of Individual ADR Reports Contained in RADAR/MedWatch Databases)</th>
<th>History and Physical Examination, %</th>
<th>Laboratory and Radiologic Tests, %</th>
<th>Basic Science Correlative, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemtuzumab ozogamicin (2000)</td>
<td>Clinical trialists at MD Anderson Cancer Center, Houston, Tex (2000)</td>
<td>Sinusoidal obstructive syndrome (50/54)</td>
<td>90*</td>
<td>59</td>
<td>82†</td>
</tr>
<tr>
<td>Clopidogrel bisulfate (1997)</td>
<td>Active surveillance by the SERF-TTP Study Group, Chicago, Ill (1999)</td>
<td>Thrombotic thrombocytopenic purpura (13/13)</td>
<td>100*</td>
<td>23</td>
<td>100</td>
</tr>
<tr>
<td>Gemcitabine hydrochloride (1998)</td>
<td>Clinical researchers at the Dana Farber Cancer Institute, Boston, Mass (2003)</td>
<td>Pneumonitis (85/93)</td>
<td>89†</td>
<td>75</td>
<td>71</td>
</tr>
<tr>
<td>Paclitaxel (2004) or sirolimus (2003) coated cardiac stents</td>
<td>Cardiac pathologist at Walter Reed Hospital, Washington, DC (2004)</td>
<td>Hypersensitivity (6/263)</td>
<td>100†</td>
<td>45</td>
<td>0</td>
</tr>
<tr>
<td>Nevirapine (1996)</td>
<td>Infectious Disease Physician in Chicago, Ill (2000)</td>
<td>Hepatotoxicity (12/12)</td>
<td>100†</td>
<td>42</td>
<td>100</td>
</tr>
<tr>
<td>Nevirapine (1996)</td>
<td>Infectious Disease Physician in Chicago (2000)</td>
<td>Stevens-Johnson syndrome (5/7)</td>
<td>100†</td>
<td>29</td>
<td>0</td>
</tr>
<tr>
<td>Recombinant MGDF (not approved)</td>
<td>Lawyer (2004)</td>
<td>Lymphoproliferative disorder (3/0)</td>
<td>100</td>
<td>NA</td>
<td>100</td>
</tr>
<tr>
<td>Enoxaparin sodium (1998)</td>
<td>Invasive cardiologist in Chicago (2002)</td>
<td>Severe hemorrhage following invasive cardiology procedure (5/0)</td>
<td>100 NA</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Bisphosphonates (2006)</td>
<td>Dental professionals (2003)</td>
<td>Osteonecrosis of the mandible and maxilla (18/1467)</td>
<td>100*</td>
<td>45</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: ADR, adverse drug reaction; FDA, Food and Drug Administration; MGDF, megakaryocyte growth and development factor; NA, not applicable; RADAR, Research on Adverse Drug events And Reports; SERF-TTP, Surveillance Epidemiology and Risk Factors of Thrombotic Thrombocytopenic Purpura.

- *\( P < .005 \) for the comparison of completeness of the RADAR project vs the FDA.
- †\( P < .05 \) for the comparison of completeness of the RADAR project vs the FDA.
tained by the proactive RADAR program was of higher quality, but lower quantity, than that contained in the combination of spontaneous adverse event reports submitted to the FDA and adverse event reports submitted to the FDA by pharmaceutical manufacturers. Also, safety notifications from the RADAR investigators were more complete than those from pharmaceutical manufacturers or the FDA, although they were less timely. Our findings highlight differences between proactive pharmacovigilance efforts conducted by the RADAR group vs pharmacovigilance efforts conducted by the FDA and pharmaceutical manufacturers.55 In interpreting our findings, several factors should be considered.

Pharmacovigilance efforts of the FDA or the pharmaceutical supplier did not result in the initiation of investigations of any of the serious ADRs described herein. Indeed, none of the 5 ADRs for which more than 200 individual case descriptions resided in the FDA safety data database were investigated by the FDA or the pharmaceutical supplier. Thus, the RADAR investigators were more effective at identifying and investigating ADRs than were the FDA or the pharmaceutical suppliers.

Table 2. Completeness of ADR Reports Disseminated by RADAR vs Pharmaceutical Manufacturers

<table>
<thead>
<tr>
<th>Drug (FDA Approval Year)</th>
<th>ADR (No. of Individual ADR Reports Contained in RADAR/MedWatch Databases)</th>
<th>Incidence Rate</th>
<th>Outcome</th>
<th>Treatment or Prophylaxis</th>
<th>Where Summary Information Resides (Year Published)</th>
<th>References Included in Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine hydrochloride (1996)</td>
<td>Pneumonitis (85/93)</td>
<td>Yes No Yes No Yes No</td>
<td>Cancer (2006)</td>
<td>Package insert</td>
<td>Yes No</td>
<td></td>
</tr>
<tr>
<td>Nevirapine (1996)</td>
<td>Hepatotoxicity to health care workers (12/12)</td>
<td>Yes No Yes No Yes Yes</td>
<td>JAMA (2000)</td>
<td>Package insert (2001)</td>
<td>Yes No</td>
<td></td>
</tr>
<tr>
<td>Lenalidomide (2005)</td>
<td>Venous thromboembolism (75/3)</td>
<td>Yes Yes Yes No No No</td>
<td>JAMA (2006)</td>
<td>Package insert (2005)</td>
<td>Yes No</td>
<td></td>
</tr>
<tr>
<td>Recombinant MGDF (not approved)</td>
<td>Lymphoproliferative disorder</td>
<td>Yes NA Yes NA Yes NA</td>
<td>Br J Hematol (2005)</td>
<td>None</td>
<td>Yes No</td>
<td></td>
</tr>
<tr>
<td>Bisphosphonates (2001)</td>
<td>Osteonecrosis of the jaw (360/1467)</td>
<td>Yes Yes Yes No Yes Yes</td>
<td>Abstract (2007)*</td>
<td>Dear Doctor letter and package insert (2004)</td>
<td>Yes Yes</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ADR, adverse drug reaction; ARVO, Association for Research in Vision and Ophthalmology; MGDF, megakaryocyte growth and development factors; NA, not applicable (ie, no summary report was disseminated for the specific ADR); RADAR, Research on Adverse Drug events And Reports.

tabases were investigated before the initial reports of serious clinical events associated with these ADRs were published (Table 1). In contrast, each of the RADAR investigations was initiated when a serious clinical event that represented a potential serious ADR was identified by a RADAR investigator. As noted by others, despite having a large number of ADR reports in FDA databases, it is a difficult task to clearly identify a “signal” that suggests a new ADR has occurred versus “noise” associated with complex clinical settings.10

With respect to follow-up evaluations, the FDA receives more than 400,000 reports of serious and nonserious ADRs annually.56 It is impractical for the FDA to request follow-up information on most of these cases. However, in rare instances in which follow-up clinical information for an individual case report has been requested by pharmaceutical manufacturers or the FDA, health care professionals rarely comply with these requests.10 In contrast, health care professionals almost universally responded to follow-up queries from RADAR investigators. Although not paid for these efforts, participating physicians have subsequently contributed as coauthors to the summary RADAR publications that are disseminated in peer-reviewed medical journals.11 The end result is that large numbers of incomplete ADR reports are submitted by many health care professionals to the FDA and pharmaceutical manufacturers, whereas a small number of health care professionals submit fewer but more completely described safety reports to the RADAR program. It is the quality, not the quantity, of the case report information that primarily supports successful pharmacovigilance efforts. For 8 serious ADRs, RADAR summary reports were based on comprehensive review of a median of only 20 case reports for the individual toxic effect. Causality assessments, the most difficult and one of the most important aspects of pharmacovigilance studies, were included in several RADAR investigations, such as biopsy or autopsy findings or antibody test results for a small number of patients, but not in the pharmaceutical or FDA summary safety reports.

The RADAR notifications were disseminated a median of 2 vs 4 years after FDA approval. These notifications were disseminated primarily as peer-reviewed manuscripts, although some of the more urgent notifications were rapidly distributed as electronic preprints (clopidogrel-associated thrombotic thrombocytopenic purpura) or research letters (lenalidomide-associated thromboembolism) within 1 year of FDA approval of the relevant drug. The RADAR notifications, but not the FDA or pharmaceutical supplier safety notifications, included information on expected clinical outcomes, recommendations for treatment and prevention, and common strategies for diagnosis of the ADR. The recently released report from the Institute of Medicine’s Committee on Assessment of the US Drug Safety System recommended that the FDA be granted regulatory authority to affect the manner in which drugs are used or marketed when safety concerns are identified.57

After publication of the recent Institute of Medicine report on drug safety, experts proposed funding a consortium of nonprofit pharmacovigilance centers, such as the Centers for Education and Research on Therapeutics,10,56,58 Collaborations could build on the unique strengths of these centers. For example, the FDA may initially identify a weak safety signal by data-mining efforts and then issue a request for proposal to FDA-approved independent pharmacovigilance centers that have cooperative agreements. These centers might competitively bid on the proposed project, and the selected centers would then conduct proactive pharmacovigilance, identify additional reports of the serious adverse event, and obtain detailed case information on these individuals. The FDA and the selected pharmacovigilance centers would ultimately share safety information. Alternatively, the pharmacovigilance centers might identify signals of serious ADRs and present these findings to FDA officials at regularly scheduled meetings, similar to those that occur between the FDA and the Centers for Education and Research on Therapeutics. In addition, FDA data-mining efforts (application of statistical techniques to spontaneous ADR reports to identify potential associations between drug exposures and outcomes) would look for additional cases. Concise safety summaries may be prepared by pharmaceutical manufacturers with input from the FDA and the proactive safety centers, and dissemination may occur as revised package inserts and/or Dear Doctor letters. Academic investigators could prepare articles for submission to peer-reviewed journals that summarize reporting rates, outcomes, treatment, prophylaxis, and clinical and basic science findings. By tapping into the interests and expertise of safety centers while still maintaining control and focus, the FDA could highlight its strengths (sending rapid, nationwide feedback about new ADRs) while reducing bureaucratic burden.

Our study has limitations. First, additional sources of safety reports exist in databases maintained by institutional review boards, cooperative clinical trial groups, and insurance companies.59 Second, physicians frequently do not respond to Dear Doctor letters or black-box advisories.12,60-63 Third, the RADAR project focused primarily on ADRs related to drugs or drug-related devices (drug-eluting stents). In 2002, the Office of Devices and Radiologic Health of the FDA initiated the Medical Product Surveillance Network, a collaboration that resembles the proposed FDA-RADAR collaboration. However, the RADAR project, unlike the Medical Product Surveil-
Table 3. Safety-Related Actions Resulting Directly From RADAR Investigations

<table>
<thead>
<tr>
<th>Drug</th>
<th>Toxic Effect</th>
<th>Dissemination</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nevirapine</td>
<td>Severe hepatotoxicity when administered off label as prophylaxis for health care workers after HIV-exposure via needlestick</td>
<td>JAMA Letter to the Editor,24 Dear Doctor letter from the pharmaceutical supplier, and Morbidity and Mortality Weekly Report from the CDC</td>
<td>Nevirapine was no longer included as part of postexposure prophylaxis regimens recommended by the CDC and its use in this setting ended. Occupational health programs discontinued providing nevirapine to health care workers who required post-HIV-exposure prophylaxis.</td>
</tr>
<tr>
<td>Ticlopidine hydrochloride</td>
<td>Thrombotic thrombocytopenic purpura</td>
<td>Ann Intern Med brief report,25 Dear Doctor letter from the pharmaceutical supplier, and black-box warning in the package insert</td>
<td>Clinicians rapidly adopted the newer thienopyridine, clopidogrel, as the standard antiplatelet agent for persons with cerebrovascular or cardiovascular disease. Sales of ticlopidine in the United States decreased to less than $100,000 annually.</td>
</tr>
<tr>
<td>Clopidogrel bisulfate</td>
<td>Thrombotic thrombocytopenic purpura</td>
<td>Boxed warning added to the package insert</td>
<td>Unknown at this point.</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Venous thromboembolism</td>
<td>Abstract at the American Society of Hematology meeting; black-box warning added to the package insert</td>
<td>Connecticut Attorney General Richard Blumenthal filed a related Citizen’s Petition with the FDA outlining the RADAR project’s safety concerns (the first time that this approach has ever been used), requesting that the sponsor issue a Dear Doctor letter, add a related black-box warning to the package insert, and advise physicians to administer prophylaxis with low-molecular-weight heparin or warfarin sodium. He also requested that the sponsor conduct a postmarketing study evaluating alternative thromboembolism prophylaxis agents. Four of 6 requests outlined in this petition were endorsed by the FDA. Health care professionals routinely prescribe thromboembolism prophylaxis with thalidomide-dexamethasone treatment of multiple myeloma.</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>Venous thromboembolism</td>
<td>Abstract at the American Society of Hematology meeting; black-box warning included in the package insert</td>
<td>The pharmaceutical manufacturer preemptively included a black-box warning in the package insert, describing high rates of venous thromboembolism with off-label treatment of multiple myeloma with lenalidomide-dexamethasone.</td>
</tr>
<tr>
<td>Gemtuzumab ozogamicin</td>
<td>Sinusoidal obstructive syndrome develops if a stem cell transplantation is performed within 3 months of gemtuzumab administration</td>
<td>Publication in Cancer66; boxed warning included in the package insert</td>
<td>Health care professionals discontinued administering gemtuzumab within 3 months of an allogeneic stem cell transplantation procedure or in combination with hepatotoxic chemotherapeutic agents, and the FDA mandated that the sponsor initiate a comprehensive postmarketing registry looking for additional cases of this toxic effect.</td>
</tr>
<tr>
<td>Epoetin alfa</td>
<td>Pure red blood cell aplasia if the Eprex formulation is administered subcutaneously to patients with chronic kidney disease</td>
<td>Publication in the N Engl J Med26; safety alerts from national health registries in Europe and Canada, overview reports on Web sites for epoetin products, and boxed warning added to relevant package inserts</td>
<td>National regulatory authorities in Canada, Europe, and Australia mandated that administration of the Eprex formulation to patients with chronic kidney disease must be via the intravenous route. Estimated exposure-adjusted incidence of Eprex-associated pure red blood cell aplasia decreased by 95%. Manufacturers now maintain Web site information on pure red blood cell aplasia that is updated frequently.</td>
</tr>
<tr>
<td>Bisphosphonates</td>
<td>Osteonecrosis of the mandible and maxilla in patients with cancer and those without cancer who used intravenous and oral bisphosphonates</td>
<td>Safety alerts from national health registries in Canada and Australia and boxed warning added to relevant package inserts</td>
<td>National regulatory authorities in the United States, Canada, and Australia required prescriber notification and release of relevant safety publications.</td>
</tr>
</tbody>
</table>

**Abbreviations:** CDC, Centers for Disease Control and Prevention; FDA, Food and Drug Administration; HIV, human immunodeficiency virus; RADAR, Research on Adverse Drug events And Reports.

Finally, similar assessments of other nonprofit pharmacovigilance efforts, such as the Drug-Induced Liver Injury Network64 and the National Registry of Drug-Induced Ocular Side Effects, should be reported.65

In conclusion, our study identified differences in data quality for safety reports contained in databases obtained by proactive pharmacovigilance efforts conducted by the RADAR project vs the FDA, as well as in...
the completeness and timing of dissemination of safety notifications. Moving forward, collaborations could be developed that build on the strengths of independent non-profit organizations that proactively conduct pharmacovigilance efforts and of safety efforts of the FDA and pharmaceutical manufacturers.

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Author Contributions: Dr Bennett had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Bennett, Nebeker, Yarnold, Angelotta, and Belknap. Acquisition of data: Bennett, Edwards, Angelotta, Weitzman, Tallman, and Raisch. Analysis and interpretation of data: Bennett, Nebeker, Yarnold, Tigue, Dorr, McCoy, Edwards, Hurdle, West, Lau, Angelotta, Weitzman, Belknap, Djulbegovic, Tallman, Kuzel, Benson, Evans, Trifilio, Courtney, and Raisch. Drafting of the manuscript: Bennett, Nebeker, Yarnold, Dorr, Edwards, Angelotta, Belknap, Trifilio, and Courtney. Critical revision of the manuscript for important intellectual content: Bennett, Nebeker, Yarnold, Tigue, McCoy, Edwards, Hurdle, West, Lau, Angelotta, Weitzman, Belknap, Djulbegovic, Tallman, Kuzel, Benson, Evans, Trifilio, Courtney, and Raisch. Statistical analysis: Yarnold and Trifilio. Obtained funding: Bennett and Belknap. Administrative, technical, and material support: Tigue, Dorr, Hurdle, and Angelotta. Study supervision: Bennett, McCoy, Edwards, Angelotta, Belknap, and Evans.

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