The Research on Adverse Drug Events and Reports (RADAR) Project

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ADVERSE DRUG AND DEVICE REACTIONS (ADRs) account for as many as 100,000 deaths annually. Prior to US Food and Drug Administration (FDA) approval, drugs are evaluated in well-designed and carefully monitored clinical trials. Only half of newly discovered serious ADRs are detected and documented in the Physicians’ Desk Reference (PDR) and traditional pharmacovigilance systems. Postmarketing surveillance may supplement existing regulatory surveillance systems and improve patient safety.

Context In 1998, a multidisciplinary team of investigators initiated RADAR (Research on Adverse Drug events And Reports), a clinically based postmarketing surveillance program that systematically investigates and disseminates information describing serious and previously unrecognized adverse drug and device reactions (ADRs).

Objective To describe the structure, operations, and preliminary findings from the RADAR project and related dissemination efforts by pharmaceutical suppliers and the US Food and Drug Administration (FDA).

Design After identifying a serious and unexpected clinical event suitable for further investigation, RADAR collaborators postulated clinical hypotheses and derived case series and incidence estimates from physician queries, published and unpublished clinical trials, published case reports, FDA databases, and manufacturer sales figures.

Results RADAR investigators identified 16 types of serious ADRs among 1699 patients, of whom 169 (10%) died as a result of the reaction. Initial cases were identified by 7 RADAR investigators, 4 collaborating physicians, 2 attorneys, and by reviewing 3 published reports. Additional sources included queries of occupational health programs and medical directors of interventional cardiology laboratories (3 types of ADRs), published manuscripts and clinical trials (11 types of ADRs), review of medical records at a RADAR site (2 types of ADRs), unpublished clinical trial reports (3 types of ADRs), and reports from attorneys, family members, or patients (4 types of ADRs). Incidence estimates, ranging from 0.4% to 33%, were derived from 5 clinical trial reports, 2 physician queries, and 2 observational databases. Laboratory support for hypotheses included identification of 3 neutralizing antibodies and 3 histopathological findings. ADR reports were disseminated as 8 revised package inserts, 7 “dear doctor” letters, and 9 peer-reviewed articles.

Conclusion A new, clinically based, hypothesis-driven approach to postmarketing surveillance may supplement existing regulatory surveillance systems and improve patient safety.

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miologic analyses of large numbers of ADRs, and review of voluntary case reports submitted to the Adverse Event Reports System (AERS) or the Manu-

ufacturers’ User and Device Experience (MAUDE).3 Ranging from 100 to several thousand patients, the size of many licensing clinical trials is often too small to identify rare but potentially serious ADRs. Additionally, selective study sample characteristics of premarketing trials and small sizes of clinical trials that support accelerated approval of new drugs limit opportunities to identify many common ADRs. The poor quality and low submission rate of ADR reports outside of the clinical trial setting limit the usefulness of the MedWatch system.4 No clear mechanisms exist for routine synthesis and analysis of postmarketing and regulatory reports describing potentially serious ADRs.7,8

The recently initiated Research on Adverse Drug Events And Reports (RADAR) project is funded independently of the pharmaceutical industry. It seeks to describe previously unrecognized, serious ADRs and to identify new patient populations at high risk for previously identified serious ADRs. Many RADAR reviews have led to publication in medical journals and dissemination by manufacturers through “clear doctor” product warnings and labeling changes.9-33 Herein, we describe the RADAR project’s funding, organization, and methods; review subsequent safety measures taken by the FDA and pharmaceutical suppliers; and discuss the implications of incorporating lessons learned from this collaboration into future postmarketing surveillance efforts.

**BACKGROUND**

The RADAR project focuses on identification, evaluation, and dissemination of information describing serious ADRs characterized as those resulting in death, severe organ failure, or precipitating major therapeutic interventions (such as cardiopulmonary resuscitation, intubation and mechanical ventilation, plasmapheresis, frequent transfusion of blood or blood products, or organ transplantation).34 The RADAR project does not focus on ADRs that only prolong hospitalization, although these would be included in the FDA’s criteria for a serious ADR.35 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 (VA). Pharmaceutical manufacturers or suppliers do not provide financial support, although they are asked to provide relevant clinical information on each serious ADR.

The RADAR core team is led by a hematologist/oncologist/health services researcher (C.L.B.) and consists of 25 core investigators with training in internal medicine and various medical subspecialties (geriatrics, cardiology, infectious disease, neurology, dermatology, hematology, and oncology), clinical pharmacology, epidemiology, statistics, and pharmacy. Core investigators are located at VA and academic medical centers in Chicago, Ill; Albuquerque, NM; San Antonio, Tex; Salt Lake City, Utah; and New Orleans, La. Additional co-investigators with expertise relevant to particular types of ADRs participate in specific RADAR investigations. The RADAR team holds weekly operational meetings in Chicago for local investigators, with access to collaborating off-site investigators via conference call.

An investigation is initiated when a clinical event that represents a possible occurrence of a serious ADR is seen by a RADAR co-investigator or reported to a RADAR co-investigator by unaffiliated physicians. Senior members of the RADAR team (C.L.B., M.H.S., D.W.R., M.S.T., T.M.K.) review the indicator event and oversee a review of the published literature and relevant package inserts to determine if the event represents an instance of a severe and previously unreported type of ADR (FIGURE). If senior members of the RADAR team agree that further investigation of the ADR is meritorious, then queries for additional case reports are submitted (D.W.R.) to the FDA, a more extensive literature review is initiated, and institutional review board (IRB) approvals are requested at the collaborating institutions.

FDA reports, usually received within 3 weeks of the inquiry, are subject to a

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**Figure. Flowchart of RADAR Investigations**

RADAR indicates Research on Adverse Drug events And Reports; ADR, adverse drug and device reaction; FDA, US Food and Drug Administration; IRB, institutional review board.
preliminary review to inform hypothesis generation and refine data collection tools. At a weekly conference, assigned investigators adapt case classification forms to the event under study. The case classification forms include generic core data elements that relate to patient demographics (eg, age, sex), the source of the information (eg, clinical trial, physician queries), concomitant medication history, event description (eg, date of the event, time elapsed between exposure and ADR event, event duration, other relevant history, physical finding, study results), organ-specific history, and treatments (eg, hospitalization, medications). World Health Organization criteria are used to score causal associations for each case between the suspect drug and the event. After reviewing a sample of cases (from fifty to several hundred), the RADAR team meets to refine hypotheses about the pathophysiology of the candidate ADR. These hypotheses and experience from the preliminary case review inform the refinement of ADR case classification forms that are specific to the syndrome under investigation. Data elements and coding are chosen to accommodate the range of data available in the FDA reports and also to address the underlying hypotheses about the specific type of ADR. Coding of the case classification form is designed to facilitate algorithmic analysis of case findings and case-based causality assessments.

Next, the RADAR team identifies additional data sources that include information on individual cases or a series of patients with the suspected ADR. Data sources include abstracts or peer-reviewed manuscripts that describe published clinical trials (identified by a MEDLINE search with appropriate search terms) and queries of physicians at medical centers that treat large numbers of patients who receive the relevant drug or who receive treatment for the suspected ADR. In addition, representatives of clinical research and drug safety at the relevant pharmaceutical firms (primarily for safety reports from both unpublished and published studies) and safety officials at the FDA, Centers for Disease Control and Prevention, and other federal organizations are asked to provide case reports. For example, cases of drug-associated thrombotic thrombocytopenic purpura (TTP) were identified by queries of physicians in large metropolitan areas who provided therapeutic plasmapheresis care for large numbers of individuals with TTP.

Information from individual case reports is abstracted and entered into a relational database for cross reference and integration with ADRs that are identified from review of FDA reports. Duplicate case reports are identified by cross matching information on dates of ADR occurrence, patient age, and sex. For cases identified from more than 1 data source, a hierarchical order for case inclusion has been developed: published case report, unpublished report submitted by a clinical investigator, and the FDA’s AERS or MAUDE system, in that order. After excluding duplicate case reports, data files are generated that include detailed information for each report of a specific ADR event. For each individual case report, completeness is evaluated based on important data elements including syndrome-specific findings (eg, platelet count, hemoglobin and serum creatinine level, lactate dehydrogenase levels, peripheral blood smear findings, and neurologic examination findings supportive of TTP).

Hypotheses-based sources of pathophysiologic evidence of causality for individual types of ADRs are identified by clinical pharmacologists (for class effects), immunologists (for hypersensitivity cases such as interstitial pneumonitis, hepatitis, and antibody-mediated pure red cell aplasia [PRCA]), hematologists (for TTP, thrombocytopenia, PRCA, and hemorrhage), gastroenterologists (for hepatic sinusoidal obstructive syndrome and hepatitis), and pathologists (for drug-eluting coronary stent hypersensitivity).

For some ADRs, estimated reporting rates are derived from the numbers of identified cases of the particular event (numerator data) and the total estimated numbers of users of the particular drug (denominator data). Utilization data are obtained from the individual manufacturers. In other instances, exposure-adjusted incidence rates, rather than reporting rates, are derived based on identification of all cases of a particular ADR divided by the total estimated number of users of the related product in a given geographic area over a specific time period. In these analyses, information on the numbers of exposed individuals is obtained from the manufacturer. For common serious ADRs (ie, 1 or more cases/100 drug-exposed individuals), incidence rates are derived from prospective phase 2 and phase 3 clinical trials or large single-center retrospective studies.

For each ADR investigation, progress is monitored weekly through review of the agenda, minutes, and action items from the prior week’s meeting, following summary presentations from RADAR co-investigators who are serving as principal investigators for individual ADR assessments. When an investigation is completed, comprehensive summaries of the individual cases, quality and timeliness of case reporting from various sources, and estimated reporting rates or exposure-adjusted incidence rates are submitted to peer-reviewed medical journals, presented at national medical conferences, and/or at presentations to the FDA and postmarketing surveillance programs of the relevant pharmaceutical companies. Often, the pharmaceutical companies subsequently distribute dear doctor letters and/or revise the FDA-approved warning labels on package inserts describing the related ADR information.

RESULTS
Between 1998 and 2004, RADAR investigators identified serious ADRs associated with 16 different drugs that affected 1699 patients, 169 of whom died (Table 1). The toxicities affected multiple organ systems and included TTP (thienopyridines), hypersensitivity (drug eluting cardiac stents), interstitial pneumonitis (nonsteroidal anti-inflammatory and gemcitabine), sinusoidal obstructive syndrome (gemtuzumab), immune-mediated anemia (epoetin), thrombo-
cytopenia (megakaryocyte growth and development factor [rHu-MGDF]), thrombocytoblastic anemia (thalidomide), hepatotoxicity (nevirapine), optic neuritis (amiodarone), pseudoaneurysms (enoxaparin), and lymphoproliferative disorders (rHu-MGDF).

ADRs were identified a median of 3 years after FDA approval (range, 0–17 years). The first instances of 9 types of ADRs occurred in off-label clinical settings (settings not included in the FDA-approved package label) (Table 1). Initial cases of the 16 types of ADRs were seen first-hand by 7 RADAR investigators, reported by 4 collaborating physicians, and identified following 2 attorney inquiries or by reviewing 3 published case reports.

Additional cases of the individual ADRs were identified from diverse sources (Table 2). Review of case reports in the FDA’s AERS and MAUDE databases provided information on individual reports associated with 13 types of ADRs. Other sources included 3 types of ADRs from queries of occupational health programs and medical directors of interventional cardiology laboratories, 11 from published manuscripts and clinical trials, 2 from review of medical records at a RADAR site, 3 from unpublished clinical trial reports, and 4 from reports from attorneys, family members, or patients. Completeness of the reports of individual ADR cases was variable, with published case reports and reports from clinical trial settings being the most complete and MEDWATCH reports being the least complete.

Reporting rates, derived for 4 rare ADRs (bicalutamide and flutamide-associated interstitial pneumonitis, epoetin-associated PRCA, and clopidogrel-associated TTP), ranged from 1 in 2500 to 1 in 20,000, based on the number of instances of individual ADRs reported to the FDA (numerator) divided by the estimated number of users of the particular agent (denominator). Physician queries provided incidence estimates for 1 common ADR (hepatoxicity among health care workers in Chicago who received nevirapine HIV postexposure prophylaxis, 62%)13 and 1 rare ADR (ticlopidine-associated TTP cases identified by plasmapheresis medical directors among patients who underwent cardiac stent

Table 1. Summary of Findings From the RADAR Program, 1998-2004

<table>
<thead>
<tr>
<th>Drug or Device</th>
<th>ADR</th>
<th>Source of First Case</th>
<th>Clinical Setting With ADR, Date of First Recognized ADR Occurrence</th>
<th>Findings to Clarify Pathophysiology</th>
<th>Peak No. of At-Risk Persons/Year</th>
<th>No. of Patients/Deaths</th>
<th>Rate of ADR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zolendronate</td>
<td>Jaw osteonecrosis</td>
<td>RADAR investigator</td>
<td>Cancer, 2003</td>
<td><img src="image1.png" alt="Image" /></td>
<td>50,000</td>
<td>561/0</td>
<td>1 in 100</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Optic neuritis</td>
<td>Clinical investigator</td>
<td>Arrhythmia, 2002†</td>
<td><img src="image2.png" alt="Image" /></td>
<td>50,000</td>
<td>262/0</td>
<td>1 in 9000</td>
</tr>
<tr>
<td>Epoetin</td>
<td>PRCA</td>
<td>Clinical investigator</td>
<td>Anemia, 2002</td>
<td><img src="image3.png" alt="Image" /></td>
<td>191/0</td>
<td>1 in 9000</td>
<td></td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Thrombosis</td>
<td>Clinical investigator</td>
<td>Renal cell cancer, 2001†</td>
<td><img src="image4.png" alt="Image" /></td>
<td>17,000</td>
<td>190/12</td>
<td>1 in 3-5</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>Pneumonitis</td>
<td>Published report</td>
<td>Hodgkin disease, 1996†</td>
<td><img src="image5.png" alt="Image" /></td>
<td>175/52</td>
<td>1 in 11</td>
<td></td>
</tr>
<tr>
<td>Ticlopidine</td>
<td>TTP</td>
<td>RADAR investigator</td>
<td>Atiral fibrillation, 1989†</td>
<td><img src="image6.png" alt="Image" /></td>
<td>1 Million</td>
<td>101/20</td>
<td>1 in 6200</td>
</tr>
<tr>
<td>Gemtuzumab</td>
<td>SOS</td>
<td>Clinical investigator</td>
<td>Acute myelogenous leukemia, 2003†</td>
<td><img src="image7.png" alt="Image" /></td>
<td>50,000</td>
<td>93/67</td>
<td>1 in 3-7</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>TTP</td>
<td>RADAR Investigator</td>
<td>Cardiac stent, 1996†</td>
<td><img src="image8.png" alt="Image" /></td>
<td>5 Million</td>
<td>39/5</td>
<td>1 in 20,000</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>Hepatotoxicity</td>
<td>RADAR investigator</td>
<td>HIV postexposure prophylaxis, 2001†</td>
<td><img src="image9.png" alt="Image" /></td>
<td>22/0</td>
<td>1 in 5</td>
<td></td>
</tr>
<tr>
<td>Flutamide</td>
<td>Pneumonitis</td>
<td>Published report</td>
<td>Combined androgen blockade for prostate cancer, 1999</td>
<td><img src="image10.png" alt="Image" /></td>
<td>40,500</td>
<td>16/7</td>
<td>1 in 2500</td>
</tr>
<tr>
<td>Sirolimus-eluting cardiac stent</td>
<td>Hypersensitivity</td>
<td>RADAR investigator</td>
<td>Coronary artery disease, 2003</td>
<td><img src="image11.png" alt="Image" /></td>
<td>1 Million</td>
<td>13/2</td>
<td></td>
</tr>
<tr>
<td>rHu-MGDF</td>
<td>Thrombocytopenia</td>
<td>Attorney</td>
<td>Volunteers, 1998†</td>
<td><img src="image12.png" alt="Image" /></td>
<td>13/0</td>
<td>1 in 33</td>
<td></td>
</tr>
<tr>
<td>Bicalutamide</td>
<td>Pneumonitis</td>
<td>Published report</td>
<td>Monotherapy for prostate cancer, 1999†</td>
<td><img src="image13.png" alt="Image" /></td>
<td>90,000</td>
<td>12/3</td>
<td>1 in 10,000</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>Pseudoneuromast</td>
<td>RADAR investigator</td>
<td>Cardiac catheterization, 2002†</td>
<td><img src="image14.png" alt="Image" /></td>
<td>5/0</td>
<td>1 in 20</td>
<td></td>
</tr>
<tr>
<td>rHu-MGDF</td>
<td>Lymphomas</td>
<td>Attorney</td>
<td>Volunteers, 2003</td>
<td><img src="image15.png" alt="Image" /></td>
<td>3/0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paclitaxel-eluting cardiac stent</td>
<td>Hypersensitivity</td>
<td>RADAR investigator</td>
<td>Coronary artery disease, 2004</td>
<td><img src="image16.png" alt="Image" /></td>
<td>1 million</td>
<td>3/1</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ADR, adverse drug and device reactions; HIV, human immunodeficiency virus; PRCA, pure red cell aplasia; RADAR, Research on Adverse Drug Events And Reports; rHu-MGDF, megakaryocyte growth and development factor; SOS, sinusoidal obstructive syndrome; TTP, thrombotic thrombocytopenic purpura.

*Number indicates a reporting rate; incidence rate is unavailable.
†The first recognized instance occurred in an off-label clinical setting.
‡Additional cases of the ADR were identified by reviewing phase 1, phase 2, or phase 3 clinical trial reports (Table 2).
§Class-effect considerations also support causality assessments.
**Initial cases reported by investigators at a hospital where the RADAR program is based.
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procedures in Pittsburgh, Pa; 1 in 1600 patients).\textsuperscript{11} Incidence rates for 5 common ADRs were estimated from clinical trial reports. Forty-eight phase 2 and phase 3 clinical trials with 2170 thalidomide-treated patients provided incidence data for thalidomide-associated thromboembolism: 11% with concomitant administration of chemotherapy; 13% with concomitant administration of corticosteroids; and 5% when no other therapy was administered.\textsuperscript{37} Nineteen phase 2 clinical trial reports and 2 retrospective observational study reports with 680 gemtuzumab-treated patients provided data for sinusoidal obstructive syndrome incidence rates of 3% when the drug was administered as monotherapy in FDA-approved regimens; 7% when administered in conjunction with other chemotherapies; 6% and 16% before vs after autologous stem cell transplantation, respectively; and almost 40% when allogeneic stem cell transplantation was performed within 3 months of gemtuzumab administration.\textsuperscript{38} Nine phase 2 or phase 3 clinical trials with 230 patients provided information on incidence rates of 10% or greater for gemcitabine-associated interstitial pneumonitis among persons who received bleomycin or taxanes.\textsuperscript{39} Unpublished phase 1 reports for treatments administered to healthy participants provided information for incidence estimates for 2 ADRs: megakaryocyte growth and development factor–associated immune-mediated thrombocytopenia (3% among 325 health volunteers), and nevirapine-associated hepatotoxicity among healthy non–HIV-infected participants (25% among 40 volunteers).\textsuperscript{13,40}

Obtaining laboratory or pathology data to support hypothesized causality mechanisms was facilitated through collaboration with 12 investigators with focused areas of expertise. Findings included identification of neutralizing antibodies for 3 individuals with rHu-MGDF-associated thrombocytopenia; 13 cases of epoetin-associated PRCA; 7 persons with a disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motif, 13 (ADAMTS13)-deficiency related ticlopidine-associated TTP; and 2 with clopidogrel-associated TTP.\textsuperscript{41-44} Hepatic biopsies from 5 persons with gemtuzumab-associated sinusoidal obstructive syndrome and 1 health care worker who developed nevirapine-associated severe hepatotoxicity in the setting of HIV postexposure prophylaxis, as well as 4 autopsies of patients who developed hypersensitivity following implantation of drug-eluting cardiac stents, were helpful in evaluating etiologic associations.\textsuperscript{45-47} For epoetin-associated PRCA and interstitial pneumonitis with gemcitabine and non-steroidal anti-androgens, case reports included in the MEDWATCH database of dechallenge and rechallenge experiences in diverse clinical settings supported, but did not confirm, causality assessments. For 1 ADR, lymphoproliferative disorders, there is no proposed causal linkage with the associated drug (rHu-MGDF), and hypotheses for a casual mechanism were difficult to derive. Dear doctor letters and revised package inserts are the primary media used

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**Table 2. Numbers of Case Reports Obtained From Sources**

<table>
<thead>
<tr>
<th>Name</th>
<th>ADR</th>
<th>Total No. Cases</th>
<th>FDA/CDC Published Manuscript</th>
<th>RADAR Member</th>
<th>RADAR Collaborator</th>
<th>Attorney</th>
<th>Patient/Family Physician Query</th>
<th>Unpublished Clinical Trial/Observational Data Set</th>
<th>Published Clinical Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zoledronate</td>
<td>Osteonecrosis</td>
<td>561</td>
<td>490 (98)</td>
<td>7 (1)</td>
<td></td>
<td></td>
<td>54 (9)</td>
<td>10 (2)</td>
<td></td>
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<tr>
<td>Amiodarone</td>
<td>Optic neuritis</td>
<td>262</td>
<td>21 (82)</td>
<td>48 (18)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Epoetin alfa/beta</td>
<td>PRCA</td>
<td>191</td>
<td>180 (94)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thalidomide</td>
<td>DVT/PE</td>
<td>190</td>
<td>10 (5)</td>
<td>131 (69)</td>
<td>49 (26)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Gemcitabine</td>
<td>Pneumonitis</td>
<td>175</td>
<td>89 (51)</td>
<td>31 (18)</td>
<td></td>
<td></td>
<td>55 (21)</td>
<td></td>
<td></td>
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<tr>
<td>Ticlopidine</td>
<td>TTP</td>
<td>101</td>
<td>84 (83)</td>
<td></td>
<td></td>
<td></td>
<td>13 (13)</td>
<td></td>
<td></td>
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<tr>
<td>Gemtuzumab</td>
<td>SOS</td>
<td>93</td>
<td>79 (85)</td>
<td>14 (15)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Clopidogrel</td>
<td>TTP</td>
<td>39</td>
<td>26 (67)</td>
<td>2 (5)</td>
<td>9 (23)</td>
<td></td>
<td></td>
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<tr>
<td>Nevirapine</td>
<td>Hepatic failure</td>
<td>22</td>
<td>14 (64)</td>
<td>4 (18)</td>
<td></td>
<td></td>
<td>4 (18)</td>
<td></td>
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<tr>
<td>Flutamide</td>
<td>Pneumonitis</td>
<td>16</td>
<td>15 (94)</td>
<td>1 (6)</td>
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<tr>
<td>Sirolimus-eluting</td>
<td>Hypersensitivity</td>
<td>13</td>
<td>8 (62)</td>
<td>1 (8)</td>
<td>2 (15)</td>
<td>2 (15)</td>
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<tr>
<td>rHu-MGDF</td>
<td>Thrombocytopenia</td>
<td>13</td>
<td></td>
<td>1 (8)</td>
<td></td>
<td></td>
<td>12 (92)</td>
<td></td>
<td></td>
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<tr>
<td>Bicalutamide</td>
<td>Pneumonitis</td>
<td>12</td>
<td>11 (92)</td>
<td>1 (8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Enoxaparin</td>
<td>Hemorrhage</td>
<td>5</td>
<td></td>
<td>5 (100)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>rHu-MGDF</td>
<td>Lymphoproliferative disorders</td>
<td>3</td>
<td>2 (67)</td>
<td>1 (33)</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

Abbreviations: ADR, adverse drug and device reactions; CDC, Centers for Disease Control and Prevention; DVT/PE, deep vein thrombosis/pulmonary embolus; FDA, US Food and Drug Administration; PRCA, pure red cell aplasia; RADAR, Research on Adverse Drug events And Reports; SOS, sinusoidal obstructive syndrome; TTP, thrombotic thrombocytopenic purpura.

*Values are expressed as number (percentage) unless otherwise indicated.

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by pharmaceutical suppliers for ADR information dissemination. Of 14 ADRs associated with FDA-approved indications, pharmaceutical manufacturers described 7 in package inserts disseminated between 1 and 14 years following FDA approval of the relevant drug, with a median time of 5 years (Table 3). Only 3 ADRs, clopidogrel-associated TTP, gemtuzumab-associated sinusoidal obstructive syndrome, and hypersensitivity associated with sirolimus-eluting cardiac stent were described in dear doctor letters or package insert changes within 3 years of FDA approval. Manufacturer revisions related to ADR dissemination included adding a “black box” warning for gemtuzumab and ticlopidine, a “warning” for erythropoietin, thalidomide, and clopidogrel, and 1 sentence to the post-marketing experience sections for bicalutamide and gemcitabine (Table 3). The FDA required pharmaceutical manufacturers to mail dear doctor letters for 5 ADRs occurring between 9 months and 9 years following FDA approval. Five of the 15 ADRs associated with FDA-approved drugs or devices are not described in current package inserts. In 1 instance of thalidomide-associated thromboembolism, safety material was provided by RADAR to a state attorney general in response to a written request for information.

Following identification of these ADRs, several inconsistencies in disseminating information about ADRs from the pharmaceutical manufacturers were identified. These inconsistencies included placement of ADR information for drugs in the same therapeutic class into different categories of the package insert such as inclusion of TTP as a warning with clopidogrel and as a black box warning for ticlopidine (3 ADRs); or temporal variations in placement of revisions of ADR information for class effects in package inserts such as for PRCA with darbepoetin (2001) vs epoetin (2002) (2 ADRs); and failure to include text describing specific ADRs that occur primarily in off-label settings such as nevirapine-associated hepatotoxicity when non–HIV-infected individuals receive nevirapine post-exposure prophylaxis (3 ADRs) (Table 3). Dear

**Table 3. Timing of and Inconsistencies in Dissemination of Information for Serious ADRs Identified by Pharmaceutical Manufacturers and MEDWATCH**

<table>
<thead>
<tr>
<th>Drug or Device</th>
<th>ADR</th>
<th>FDA Approval</th>
<th>RADAR Index Case</th>
<th>Black Box Warning Precaution</th>
<th>Adverse Event</th>
<th>Dear Doctor Letter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiopurines</td>
<td>TTP</td>
<td>1997</td>
<td>1998</td>
<td>2000†</td>
<td>2000†</td>
<td></td>
</tr>
<tr>
<td>Clopidogrel</td>
<td></td>
<td>1997</td>
<td>1998</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ticlopidine</td>
<td></td>
<td>1989</td>
<td>1996</td>
<td>1998†</td>
<td>1998†</td>
<td></td>
</tr>
<tr>
<td>Epoetins</td>
<td>PRCA</td>
<td>2002</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eprex (non-US)</td>
<td>None</td>
<td>2002</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Procrit/epogen</td>
<td>1988</td>
<td>2002</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Darbepoetin</td>
<td>2001</td>
<td>NA</td>
<td>2001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paclitaxel-eluting cardiac stent</td>
<td>2004</td>
<td>2004</td>
<td>2004</td>
<td>2004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flutamide</td>
<td>1994</td>
<td>1994</td>
<td>2001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bicalutamide</td>
<td>1995</td>
<td>1999</td>
<td>2001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other agents</td>
<td>Osteonecrosis</td>
<td>2001</td>
<td>2003</td>
<td>2004</td>
<td>2005</td>
<td></td>
</tr>
<tr>
<td>Enoxaparin‡</td>
<td>Hemorrhage</td>
<td>1993</td>
<td>2002</td>
<td>2001</td>
<td>2003</td>
<td></td>
</tr>
<tr>
<td>Nevirapine[]</td>
<td>Hepatic failure</td>
<td>1996</td>
<td>2000</td>
<td>2001†</td>
<td>2001†</td>
<td></td>
</tr>
<tr>
<td>Gemtuzumab[]</td>
<td>SOS</td>
<td>2000</td>
<td>2003</td>
<td>2001</td>
<td>2001†</td>
<td>2001†</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Optic neuritis</td>
<td>1985</td>
<td>2002</td>
<td>2004</td>
<td>2004</td>
<td></td>
</tr>
<tr>
<td>Hu-MGDF</td>
<td>Thrombocytopenia</td>
<td>None</td>
<td>2003</td>
<td>2003</td>
<td>2003</td>
<td></td>
</tr>
<tr>
<td>Hu-MGDF</td>
<td>Lymphoma</td>
<td>None</td>
<td>2003</td>
<td>2003</td>
<td>2003</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ADR, adverse drug reactions; DVT/PE, deep vein thrombosis and pulmonary embolism; FDA, US Food and Drug Administration; NA, not applicable; PRCA, pure red cell aplasia; RADAR, research on adverse drug events and reports; SOS, sinusoidal obstructive syndrome; TTP, thrombotic thrombocytopenic purpura.


†This information was disseminated in direct response to a RADAR report.

§A dear doctor letter (2003) initially reported 50 instances of hypersensitivity with the sirolimus-eluting cardiac stent. One month later, a second letter indicated that upon further review, these events were unlikely to be associated with the sirolimus-eluting cardiac stent.

| If-off-label setting for the identified ADR. |
doctor letters were distributed for 8 serious ADRs. One dear doctor letter initially attributed instances of hypersensitivity to a drug eluting stent, although a follow-up dear doctor letter mailed 1 month later indicated that further review suggested that the events were most likely caused by concomitant drugs.48

COMMENT

The RADAR project is composed of a diverse group of investigators located at medical research institutions in North America and is funded entirely by peer-reviewed grants from the National Institutes of Health, the VA, and the American Cancer Society. This team evaluates initial reports of previously unrecognized but serious ADRs, identifies additional reports of each ADR, develops hypotheses for mechanistic pathways, evaluates related laboratory and pathologic findings, and derives reporting and incidence rate estimates. Summary safety information is synthesized into concise reports disseminated in medical journals, revised package inserts, and dear doctor letters and is presented at medical conferences and at meetings with officials of the FDA, the relevant pharmaceutical manufacturers, and to officials in the public sector who are evaluating pharmaceutical safety issues.

There is a group with a similar acronym RAD-AR (Risk/benefit Assessment of Drugs, Analysis and Response). This group was organized in conjunction with major pharmaceutical companies in the late 1980s and continues to operate in Japan.49 In contrast to the broader range of activities of RAD-AR Japan, as indicated by its name, the RADAR project discussed in this article is focused on uncovering previously unrecognized adverse drug and device events.

In interpreting the activities of the RADAR program, several factors should be considered. First, many current approaches to drug safety have limitations.3 Because of the large number of FDA-approved pharmaceutical agents and the greater than 400 000 ADR reports submitted to the FDA annually, the 110 members of the FDA’s Office of Drug Safety are unable to prospectively evaluate individual reports of serious ADRs possibly associated with many pharmaceutical agents. The FDA’s current postmarketing system has been characterized as a “woefully underfunded, understaffed, and haphazard system whereby postmarketing information on drug safety and adverse events is gathered, despite marketed drugs causing thousands of deaths each year.”50,51 Also, much of drug use today occurs in off-label clinical settings where clinical trial information is frequently lacking and where ADRs may occur more commonly than is described in on-label settings.52 A 20% rate of hepatic sinusoidal obstructive syndrome was observed when gemtuzumab, an agent approved as monotherapy for acute myelogenous leukemia, was administered as an off-label chemotherapy treatment with thioguanine, and a 28% rate of thromboembolism was noted when thalidomide, an agent approved as monotherapy for the cutaneous manifestations of leprosy, was administered as an off-label treatment with doxorubicin to patients with multiple myeloma.14,53

Second, initial reports of potentially unrecognized but serious ADRs were obtained primarily from personal experiences of RADAR investigators or as a result of clinical query from attorneys or other physicians. Subsequently, by identifying additional reports of cases of each of the 16 types of ADRs, we were able to synthesize large comprehensive databases containing between 3 and 561 individual reports of each of the 16 types of ADRs (Table 2). The data sources of these additional case reports have strengths and weaknesses. While clinical trial reports provide comprehensive descriptions of individual cases, relatively few reports have been obtained from these settings. In contrast, the majority of the reports for 12 of the 16 ADRs were identified following review of the FDA databases for drugs (AERS) or devices (MAUDE), sources that are limited by high rates of underreporting and incomplete case descriptions.8 Physician queries were a source of comprehensive reports for 3 ADRs but were time- and labor-intensive and subject to delays of up to 4 months consequent to review by the IRB. While unpublished clinical trial and safety reports from pharmaceutical industry representatives are sources of information, as noted by Psaty et al59 as well as our group, these data are not easily obtained. RADAR investigators have started to request ADR information from other large publicly available repositories of ADR reports including the Cochrane Collaboration, the VA, and databases maintained by postmarketing surveillance programs in Canada and the United Kingdom.

Third, reporting rate and incidence estimation efforts were difficult.34 Low reporting rates to the FDA’s ADR reporting system, estimated at 1% to 10%,35 complicated our estimation of reporting rates for 4 rare ADRs.54 However, our estimate for PRCA associated with the Eprex formulation of epoetin alfa, 40 cases per 100 000 exposed individuals per year, was virtually the same as the estimate derived independently.57 Our estimate for ticlopidine-associated TTP (1 in 6000) was also similar to those reported independently by another group (1 in 5000).56 For 3 common ADRs (nevirapine-associated hepatotoxicity rates in the setting of postexposure prophylaxis, thalidomide-associated thromboembolism, and gemtuzumab-associated sinusoidal obstructive syndrome), incidence rates were derived primarily from phase 1, phase 2, and phase 3 clinical trial reports of use in off-label settings. Recent initiatives have called for public reporting of phase 3 clinical trials,57 whereas our findings suggest that publishing toxicity information from phase 1 and phase 2 clinical trials is also important.

Fourth, inconsistencies occurred with ADR dissemination by the pharmaceutical suppliers (Table 3). Temple and Himmel of the FDA have written that black box warnings are added “to drug labels with indications to which the black box would pertain.”58 A black box warning describes TTP with ticlopidine, but not clopidogrel. The discrep-
cut with a comprehensive review of the thalidomide-associated thromboembolism material in response to their expressed concern that pharmaceutical manufacturers and the FDA may not be doing enough to ensure timely and adequate dissemination of information on toxicities that occur primarily in off-label clinical settings.

Sixth, as noted in several recent reviews, refinements to postmarketing surveillance efforts are needed. ADR reports contained in the MedWatch AERS database for drugs should be provided through the Internet, similar to the access permitted for ADR reports included in the MAUDE database for devices. Of note, following the transfer of the MAUDE database from computerized reports maintained internally by the FDA to a frequently updated database on the Internet, the number of freedom of information requests for device-related ADRs decreased dramatically. Systems could be developed to prospectively identify persons with ADRs that frequently represent drug toxicities. Suggested programs could include plasmapheresis centers reporting TTP cases, oral surgeons reporting osteonecrosis, dermatologists reporting Stevens-Johnson syndrome, or hematologists reporting agranulocytosis. Similar programs exist at liver transplantation programs targeting drugs that induce hepatic failure. Prospective FDA-mandated safety registries that are currently being developed for many drugs and devices could be revised over time to improve their comprehensiveness should clinical information support a need for prospective ADR assessments. For example, while the thalidomide registry is established to prevent use in pregnancy and therefore the drug’s potential teratogenic effects, a broader scope focusing on thromboembolism would improve our understanding of risk factors and prophylactic regimens among cancer patients. Consideration should be given to specifically developing postmarketing surveillance systems for agents that receive accelerated FDA approval, of which many have serious ADRs identified shortly after approval. One such effort could build on recent collaborations between the National Cancer Institute and the FDA to include comprehensive and timely reporting of ADR information from a consortium of National Cancer Institute-designated comprehensive cancer centers. These centers provide care for large numbers of cancer patients who receive cancer agents, many of which eventually receive accelerated FDA approval, and include investigators who have training in epidemiology, statistics, clinical pharmacology, and clinical medicine. Most important, because of concerns over potential conflicts of interest, newer postmarketing safety efforts such as this RADAR project, should be financially and operationally independent of the pharmaceutical industry and the FDA.

Limitations of the RADAR approach should be acknowledged. Dissemination of ADR data by pharmaceutical suppliers and the FDA was evaluated based on reviews of package inserts and dear doctor letters. While this information is often disseminated in other media, the former are the only relevant sources of safety information from a regulatory perspective. Also, while the FDA has recently outlined new approaches to drug safety and proposed creating an independent safety advisory board, these changes are unlikely to directly affect the RADAR program. The major proposed change is to devote personnel and resources to reviewing large automated databases maintained by private and public health insurers and managed care organizations. In contrast, none of the RADAR investigations conducted to date have been based on these data sources.

In conclusion, our investigations exemplify the potential benefits of establishing clinically based, postmarketing surveillance collaboratives that focus on serious ADRs. The RADAR group has identified and evaluated 16 serious ADRs and in response, package insert revisions, dear doctor letters, and peer-reviewed medical articles describing our findings have been disseminated. It is hoped that the ef-
forts of the RADAR project will ultimately improve safety through early detection and treatment of serious ADRs.

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REFERENCES


It is the nature of a man as he grows older, a small bridge in time, to protest against change, especially change for the better.
—John Steinbeck (1902-1968)