

REPORT OF THE COUNCIL ON SCIENTIFIC AFFAIRS

CSA Report 6-A-05

Subject: Enhanced Physician Access to Food and Drug Administration (FDA) Data

Presented by: Melvyn L. Sterling, MD, Chair

Referred to: Reference Committee E
(Daniel W. van Heeckeren, MD, Chair)

1 Resolution 529 (A-04), submitted by the American Academy of Child and Adolescent Psychiatry
2 and the American Psychiatric Association and adopted by the House of Delegates, asked that the
3 Council on Scientific Affairs (CSA) study the issue of enhancing physician access to Food and
4 Drug Administration (FDA) data on the safety and efficacy of medications and develop
5 recommendations designed to improve access to clinically relevant research collected by the
6 FDA. CSA Report 10 (A-04) previously addressed one approach to this issue; the need for a
7 comprehensive clinical trial registry to establish the universe of clinical trials conducted on
8 therapeutic interventions, with the added requirement that trials contained in the registry be linked
9 to results, either found in standard publication vehicles (print and electronic scientific journals) or
10 electronic databases.

11
12 Attention has been refocused on the issue of drug safety by recent high-profile developments
13 including the withdrawal of certain drugs from the market, controversy about the risks and
14 benefits of antidepressant use in children and adolescents, and emergent concerns about the
15 cardiovascular safety of nonsteroidal anti-inflammatory agents (NSAIDs) that selectively inhibit
16 the cyclo-oxygenase type 2 enzyme (COX-2 inhibitors). Accordingly, questions have been raised
17 about timely access to scientifically credible, but sometimes proprietary data related to drug
18 safety and efficacy, especially for drugs that are already marketed and in widespread clinical use.

19
20 This report briefly reviews the system for drug approval and postmarketing surveillance in the
21 United States, its legal requirements, the type of information available to the FDA, and its public
22 availability. The report focuses on prescription drugs and biologics (which generally have similar
23 requirements) and does not discuss generic drugs, over-the-counter drugs, or devices. In addition
24 to explaining the drug approval and drug safety processes in the United States, this report
25 illustrates some recent examples of drug safety problems and briefly notes some potential
26 approaches to improving risk communication on prescription drugs. Finally, the report offers
27 some recommendations for enhancing the transparency of the drug approval and postmarketing
28 surveillance process, particularly as they relate to the availability of clinically relevant
29 information that affects risk/benefit decisions involving the use of prescription drugs.

30
31 Methods

32
33 The primary sources of information for this report are the laws, regulatory requirements, and
34 federal agency interpretations governing the drug approval process; namely, the federal Food,
35 Drug, and Cosmetic (FD&C) Act and amendments; the corresponding FDA portion of the Code
36 of Federal Regulations (Title 21), which interprets the FD&C Act and related statutes; and other
37 relevant guidance documents generated by the FDA. Additionally, literature searches were

1 conducted in the MEDLINE database for English-language articles published between 1995 and
2 March 2005 using the search term “drug” in combination with “approval,” “regulation,” “safety,”
3 and “post-marketing surveillance” to compile relevant opinions and ideas that have been
4 suggested by others on how to improve the process of drug approval and safety assessment,
5 particularly after drugs have been approved for marketing. Additional references were identified
6 from the bibliographies of articles obtained via the above literature searches.

7 8 Evolution of the U.S. Drug Approval Process

9
10 Establishing Standards of Drug Purity, Labeling, Safety, and Efficacy. The U.S. drug approval
11 process has gradually evolved as a result of: (1) business entrepreneurs developing products in a
12 free-market economy; (2) a strong commitment of the U.S. government as a guarantor of patents,
13 generator of research funds, and guardian of drug safety; (3) a societal commitment to research;
14 and (4) laws enacted due to human tragedy resulting from inadequate drug regulation. The FDA
15 attempts to ensure that beneficial medical products are available and labeled with adequate
16 information on their risks and benefits while protecting the public from unsafe products or false
17 claims.

18
19 The original Pure Food and Drugs Act passed by Congress in 1906 prohibited interstate
20 commerce in misbranded and adulterated foods, drinks, and drugs, setting the initial standard for
21 drug purity, strength, and quality. The 1912 Sherley Amendment prohibited labeling medicines
22 with false therapeutic claims intended to defraud the purchaser. In 1937, elixir of sulfanilamide,
23 which contained the poisonous solvent diethylene glycol, led to the death of 107 persons,
24 including many children. Subsequently, the FD&C Act of 1938 established the requirement that
25 new drugs must be shown to be safe before marketing.¹ In 1951, the Durham-Humphrey
26 Amendment established the prescription drug class, noting that certain drugs could not be safely
27 used without medical supervision and restricting their sale to prescription by a licensed
28 practitioner, as well as prohibiting refills without the express consent of the prescriber.²

29
30 In 1962, thalidomide, a new sleeping pill, caused birth defects in thousands of babies born in
31 western Europe. An FDA medical officer, Frances Kelsey, MD, played a key role in delaying
32 approval of the drug for the U.S. market. Subsequently, the Kefauver-Harris Drug Amendments
33 to the FD&C Act were passed to strengthen control over prescription drugs by establishing the
34 requirement that new drugs demonstrate “substantial evidence” of both efficacy and safety
35 through “adequate and well-controlled investigations.”³ Interestingly, around the same time,
36 President John F. Kennedy proclaimed a “Consumer Bill of Rights” in a message to Congress,
37 including the “right to be heard, the right to be informed, the right to choose, and the right to
38 safety.” To “catch up,” the FDA contracted with the National Academy of Sciences/National
39 Research Council to evaluate the effectiveness of drugs that had been approved on the basis of
40 safety assessments alone between 1938 and 1962. This review process, termed the Drug Efficacy
41 Study Implementation (DESI), has been completed.

42
43 Measures to Expand Access. In 1983, the Orphan Drug Act was passed, enabling the FDA to
44 promote research and marketing of drugs and biologics needed for treating rare diseases with a
45 population prevalence of less than 200,000.⁴ The 1984 Drug Price Competition and Patent Term
46 Restoration Act (Hatch-Waxman) expedited the availability of less costly generic drugs by
47 permitting the FDA to approve applications to market generic versions of brand-name drugs
48 without repeating the research done to prove them safe and effective.⁵ In 1987, the
49 investigational drug regulations were revised to expand access to experimental drugs for patients
50 with serious diseases with no alternative therapies.⁶

1 In 1992, the FDA published new regulations, later incorporated into the Food and Drug
2 Modernization Act (FDAMA), to establish a process for the FDA to grant marketing approval
3 under an accelerated review process for products that treat serious and life-threatening illnesses
4 and that provide meaningful therapeutic benefit over existing therapies.⁷

5
6 Thus, over the last century, the drug approval process in this country evolved from establishing
7 drug labeling standards, to drug safety and efficacy, to expanding access to needed therapies for
8 patients with certain diseases and disorders.

9
10 Enhancing and Speeding the Drug Approval Process. Because of a perceived “drug lag” in the
11 United States in the late 1980s and early 1990s, attention shifted to improving FDA drug review
12 timelines. In 1992, Congress passed the Prescription Drug User Fee Act (PDUFA). This was
13 reauthorized by FDAMA in 1997 (PDUFA II) and again by the Public Health Security and
14 Bioterrorism Preparedness and Response Act of 2002 (PDUFA III). These acts challenged the
15 FDA to: (1) speed agency review of new drug applications (NDAs) and biologics licensing
16 applications (BLAs) without compromising safety; (2) improve the efficiency of drug
17 development before submission of new drug or biologic applications; and (3) further improve the
18 quality and efficiency of drug development, review, and risk management for newly approved
19 products.⁸

20
21 PDUFA authorized the FDA to collect fees from companies that produce drug and biological
22 products. Under PDUFA, the pharmaceutical industry provides funding in exchange for FDA
23 agreement to meet drug review performance goals, which emphasize timeliness. Before PDUFA,
24 the FDA approved about 40% of the new molecular entities introduced on the world market either
25 first or within 1 year of their introduction in another country. After PDUFA and through 2002,
26 this percentage nearly doubled.⁹ Additionally, the median total review time for new drugs and
27 biologics decreased from approximately 23 months to 12 months, with even shorter median
28 approval times for drugs designated for priority review. Concern has been expressed about the
29 number of drugs approved under PDUFA that have been withdrawn for safety reasons. However,
30 an analysis of the rate of withdrawal for safety reasons of new molecular entities approved prior
31 to PDUFA (2.7%) compared to those approved under the PDUFA program (2.5%) showed no
32 significant difference.

33 34 General Overview of the Current New Drug Approval Process

35
36 The FDA regulates the market approval for drugs, biologics, and medical devices for human use
37 through three of its centers: Center for Drug Evaluation and Research (CDER); Center for
38 Biologics Evaluation and Research (CBER); and Center for Devices and Radiological Health.
39 Pharmaceutical companies or other sponsors apply the scientific method to the conduct of research
40 trials in human subjects to establish safety and efficacy for a new drug or biologic in order to develop
41 information (labeling) to guide use of the drug in human subjects, and obtain FDA approval for
42 marketing in the United States. Clinical testing is conducted under the aegis of two formal
43 applications; a Notice of Claimed Investigational Exemption for a New Drug (more commonly
44 referred to as an Investigational New Drug Application [IND]), and a New Drug Application (see
45 below). INDs can be commercial (ie, submitted by a pharmaceutical manufacturer) or non-
46 commercial (ie, submitted by a clinical investigator). A graphic display of the drug approval
47 process is shown in the Appendix.

48
49 Investigational New Drug Applications. Before an investigational new drug can be tested in
50 humans the applicant must file an IND.¹⁰ If an investigator wants to study an already approved
51 drug for a new indication, the filing is a Supplemental New Drug Application (SNDA). The IND

1 must contain information in three broad areas: (1) chemistry, manufacturing, and control
2 information; (2) pre-clinical safety (animal pharmacology and toxicology) information; and (3) a
3 description of the general investigational plan and protocols for specific human studies, and prior
4 human experience, if any. After filing the IND, the sponsor can begin clinical testing 30 days
5 after the FDA receives the IND unless the FDA notifies the applicant that a clinical “hold” has
6 been placed. Testing can begin earlier than 30 days if the FDA notifies the applicant that clinical
7 investigations can commence. Investigational Review Board (IRB) approval of an informed
8 consent document to be signed by the patient is necessary for all INDs.

9
10 Clinical testing during the IND phase comprises three distinct phases, each with a different
11 objective. *Phase 1* studies are usually conducted in no more than 20 to 100 (usually disease-free)
12 volunteers to establish safety at escalating doses and to derive pharmacokinetic data that will
13 assist in establishing dosing parameters. *Phase 2* studies are randomized controlled trials
14 principally designed to determine therapeutic efficacy, generally in 100 to 300 individuals with
15 the disease or disorder. Initial data on dose-response relationships, drug metabolism, common
16 short-term side effects, and potentially serious adverse drug reactions also are determined. *Phase*
17 *3* represents larger adequate and well-controlled clinical trials designed to verify that an
18 acceptable benefit-to-risk ratio for drug effectiveness is shown under conditions of anticipated
19 usage. Additional information on common side effects and (common) serious adverse drug
20 reactions is obtained. Applicants are required to submit periodic IND safety reports and annual
21 IND progress reports during this process.^{11,12}

22
23 New Drug Applications (NDA). It has been the FDA’s position that Congress generally intended
24 to require at least two adequate and well controlled clinical trials, each convincing on its own, to
25 establish effectiveness for a new drug. The general requirements for these types of studies have
26 been described.¹³ Because of technological advances and improvements in clinical trial design,
27 the FDA has sometimes relied on only a single adequate and well controlled efficacy study to
28 support approval.¹⁴ The flexibility to use this approach was codified in FDAMA when Congress
29 amended the FD&C Act to clarify that the agency may consider “data from one adequate and
30 well-controlled clinical investigation and confirmatory evidence” to constitute substantial
31 evidence.¹⁴ This type of trial is usually a well designed, robust, multicenter trial. Under the
32 accelerated approval process, the FDA may approve products based on a surrogate marker or
33 other clinical effect that is reasonably likely to predict clinical benefit, provided that the applicant
34 conducts postmarketing studies to verify and describe the clinical benefit when there is
35 uncertainty about the relation between the data submitted and clinical benefit or ultimate
36 outcome. Biological products are held to the same standard.

37
38 An NDA is filed with the FDA when all data from Phase 3 are collected and evaluated, and a
39 decision is made by the applicant to seek approval to market the product. The NDA is an
40 assembly of information that has been obtained during the IND phase. Technical sections
41 include: (1) chemistry, manufacturing, and controls; (2) preclinical pharmacology and
42 toxicology; (3) human pharmacokinetics and bioavailability; (4) clinical data; and (5) statistical
43 analysis.¹⁵ The actual review time for any given drug varies depending on the priority rating
44 given to the NDA by the FDA, based on the potential benefit of the drug and the quality of the
45 data submitted. Within 60 days after receipt of an NDA, the agency will determine whether the
46 application may be officially filed, which starts the 180-day filing clock. Within 180 days of
47 receipt of an NDA, the FDA will review it and send the applicant an approval letter, an
48 approvable letter, or a not approvable letter. This 180-day period is called the review clock.

1 The NDA is required to contain a summary that may be used by the FDA or applicant to prepare
2 the Summary Basis of Approval document for public disclosure when the application is
3 approved.¹⁶

4
5 Other routes to approval include the SNDA for additional indications; an Abbreviated New Drug
6 Application (ANDA) for generic equivalents; and Orphan Drug and Accelerated/Fast Track
7 Approvals as noted above.

8 9 Postmarketing Studies

10
11 Postmarketing Study Commitments. These are studies, required of or agreed to by a sponsor, that
12 are conducted after the FDA has approved a product for marketing. They are not part of an IND
13 or NDA. Mandatory postmarketing studies have been incorporated into the regulation of fast-
14 track products, approved on an accelerated basis, and products for which safe use in children
15 needs to be determined or more clearly defined. The FDA uses these studies to gather additional
16 information about a product's safety, efficacy, or optimal use. An annual progress report is
17 required for each postmarketing study required by the FDA, and for studies that applicants
18 committed to at the time of (or after) NDA or SNDA approval.¹⁷ In addition, the FDA is required
19 to report annually in the *Federal Register* on the performance of postmarketing commitment
20 studies.

21
22 Annual Reports. Sponsors must submit an annual report on marketed products that details
23 information obtained during the annual reporting interval.¹⁸ The report must contain, among
24 other elements, a brief summary of significant new information from the previous year that might
25 affect the safety, effectiveness, or labeling of the drug product. Also, the report must contain new
26 clinical data, including: (1) published clinical trials on the drug (or abstracts of them), such as
27 clinical trials on safety and effectiveness; clinical trials on new uses; biopharmaceutic,
28 pharmacokinetic, and clinical pharmacology studies; and reports of clinical experience pertinent
29 to safety (for example, epidemiological studies or analyses of experience in a monitored series of
30 patients) conducted by, or otherwise obtained by, the applicant; (2) summaries of completed
31 unpublished trials, or prepublication manuscripts if available, conducted by, or otherwise
32 obtained by, the applicant (a study is considered completed 1 year after it is concluded); and (3)
33 analysis of available safety and efficacy data in the pediatric population and changes proposed in
34 the labeling based on this information.

35
36 Data from ongoing clinical trials conducted in support of an SNDA or ANDA (see below) are
37 contained within the status reports pertaining to those applications, and public disclosure
38 requirements are similar to those for NDAs.

39 40 Postmarketing Surveillance (Pharmacovigilance)

41
42 In the absence of formal postmarketing studies, (spontaneous) observational data are the
43 cornerstone for evaluating and characterizing a drug's risk profile in actual clinical use. The FDA
44 uses the term "pharmacovigilance" to apply to all "observational (nonrandomized) postapproval
45 scientific and data gathering activities relating to the detection, assessment, and understanding of
46 adverse events."

47
48 MedWatch. Currently, the FDA maintains an adverse event reporting system termed MedWatch
49 (Medical Products Reporting Program). Our AMA has been a partner and strong supporter of
50 MedWatch and shares a common goal with the FDA to optimize the benefit/risk balance of drug
51 therapy and to minimize the risks of drug and biological products. MedWatch incorporates both a

1 mandatory adverse event reporting system for IND reporters, manufacturers, distributors, and
2 importers subject to the agency's postmarketing safety reporting regulations, and a voluntary
3 adverse event reporting system for health care professionals, consumers, and patients.^{11,19,20}
4 Adverse drug events include those occurring: (1) in the course of use of a drug product in
5 professional practice; (2) from drug overdose whether accidental or intentional; (3) from drug
6 abuse; (4) from drug withdrawal; and (5) from any "failure of expected pharmacological action."
7 Good reporting practices (ie, characteristics, developing case series, assessing causality) were
8 recently addressed in a proposed FDA regulation, as well as other industry guidances.²¹
9

10 MedWatch is especially interested in receiving reports of serious adverse event reports that are
11 not currently included in the drug's labeling; all serious events associated with new drugs during
12 their first 3 years on the market; and previously reported reactions if they are serious and occur in
13 clusters. A serious adverse drug reaction is defined as one that results in or prolongs
14 hospitalization, is life-threatening, contributes to significant disability, or results in the death of
15 the patient. Manufacturers are required to report serious or unexpected adverse events within 15
16 days. Otherwise, periodic reports are required quarterly for the first 3 years of marketing, and
17 annually thereafter. Applicants with an approved ANDA operate under the same general
18 requirements for these and other postmarketing reports.
19

20 The MedWatch program is limited by its reliance on voluntary reporting, which inevitably leads
21 to underreporting. This, combined with uncertainty about the actual extent of exposure, makes it
22 difficult to estimate true rates of occurrence. Because of their observational nature, spontaneous
23 reports also are limited in their ability to establish causality. Nevertheless, spontaneous reporting
24 systems like MedWatch can be effective in revealing unusual or rare adverse events that occur
25 with the use of a medication, and such reports may often be sufficient to assign causality.
26 However, spontaneous reports do not reliably detect adverse drug events that occur widely
27 separated in time from the original use of the drug or that represent a common occurrence in
28 populations not exposed to the drug such as increased blood pressure, heart attack or stroke.
29

30 Adverse Event Reporting System. The adverse event reports received via MedWatch are
31 compiled within a computerized database termed the Adverse Event Reporting System (AERS).
32 The FDA codes all reported adverse events using a standardized international terminology,
33 MedDRA (the Medical Dictionary for Regulatory Activities). FDA staff use reports from the
34 AERS in conducting postmarketing drug surveillance, compliance monitoring activities, and in
35 responding to outside requests for information. These reports are evaluated by clinical reviewers
36 in CDER and CBER to detect safety signals, and to monitor drug safety. They form the basis for
37 hypothesis generation and further epidemiological studies to confirm or disprove potential signals
38 arising from spontaneous reports. As a result of information in the AERS, the FDA may take
39 regulatory actions to improve product safety and protect the public health, such as updating a
40 product's labeling information, requiring sponsors to send out a "Dear Health Care Professional"
41 letter, or re-evaluating an approval decision.
42

43 Physician Access to FDA Information

44

45 The FDA's general policy is that it will make the "fullest possible disclosure of records to the
46 public, consistent with the rights of individuals to privacy, the property rights of persons in trade
47 secrets and confidential commercial or financial information, and the need for the agency to
48 promote frank internal policy deliberations and to pursue its regulatory activities without
49 disruption."²² Data and information submitted or divulged to the FDA that fall within the
50 definitions of a trade secret or confidential commercial or financial information are not available
51 for public disclosure.²³

1 Public Disclosure of INDs and IND Information. The *existence* of an IND application will not be
2 disclosed by the FDA unless it has previously been publicly disclosed or acknowledged. The
3 applicant is required to submit annual reports to the FDA on the progress of clinical
4 investigations, as well as IND safety reports on serious or unexpected reactions, or information
5 pointing to potential teratogenic/carcinogenic activity.^{11,12} The availability for public disclosure
6 of all data and information in an IND application for a new drug is handled in accordance with
7 the provisions for the confidentiality of data and information in NDAs and biologics (see
8 below).²⁵ Persons who were subjects in an IND-based clinical trial can request copies of IND
9 safety reports, and information that is required to be publicly disclosed for investigations
10 involving an exception from informed consent (ie, life-threatening situations) can be obtained
11 under the Freedom of Information Act.²⁴

12
13 Public Disclosure of NDAs and NDA Information. The FDA will not publicly disclose the
14 *existence* of an NDA, SNDA, or ANDA before an approvable letter is sent, unless the existence
15 of the application has been previously publicly disclosed or acknowledged.²⁵ Even then, the FDA
16 will not disclose data or information before the agency sends an approval letter except for a
17 summary of selected portions that are appropriate for public consideration of a specific pending
18 issue (eg, advisory committee deliberation).²⁴

19
20 If the FDA approves an NDA and sends an approval letter, the Summary Basis of Approval is
21 immediately available for public disclosure.²⁴ As part of the final approval process, the applicant
22 and the FDA agree on the materials and language comprising the product labeling. The package
23 insert is that portion of the approved labeling directed to physicians, and for most drugs is the
24 primary risk management tool (see below). The agency also maintains a Web-based catalogue of
25 FDA-approved drug and biological therapeutic products.²⁵ This site contains the approval history
26 and related documents, including the NDA for most new drugs approved since 1999, and has
27 links to label information, as well as copies of correspondence related to approval, labeling, and
28 safety issues.

29
30 Public Disclosure of Formal Postmarketing Studies. The FDA is required under FDAMA to
31 report annually in the *Federal Register* on the status of postmarketing study commitments made
32 by sponsors of approved drug and biological products. However, this report is nothing more than
33 a general scorecard. More specific information on postmarketing study commitments can be
34 found in the approval letters sent by the FDA to the applicant. As previously stated, the approval
35 letters for most new drugs marketed since 1999 are available on the drugs@FDA Web site.

36
37 Applicants are required to submit annual reports on the status of required postmarketing studies.¹⁷
38 Technically, the FDA can publicly disclose information on postmarketing status reports except
39 for trade secrets, or where disclosure of information would constitute an unwarranted invasion of
40 personal privacy.^{23,26} Information in these reports is considered to be public information to the
41 extent that it is necessary to: (1) identify the sponsor; and (2) establish the status of a study
42 described, and the reasons, if any, for failure to carry out the study. In practice, clinically relevant
43 data from most formal postmarketing studies are unavailable until they are published or released
44 by the manufacturer. However, the FDA does maintain a searchable database of basic
45 information on postmarketing studies for drugs and biological products.²⁷

46
47 Public Disclosure of Annual Report Information. Annual reports are considered proprietary and
48 are not available for public disclosure. These reports represent a rich source of information on
49 marketed drug products, much of which is not in the public domain.

1 Public Disclosure of Adverse Event Information. The FDA posts two main classes of safety-
2 related information on the MedWatch home page, safety labeling changes and safety alerts.²⁸ The
3 former includes drug products with safety labeling changes (since 1996) to the *Contraindications*,
4 *Boxed Warnings*, *Precautions*, or *Adverse Reactions* sections. The modified sections are noted,
5 along with a description of new or modified safety information in the *Contraindications* or
6 *Warnings* sections, and a link is provided to the revised prescribing information. Safety alerts
7 represent a broader array of safety issues, including manufacturing-related problems; newly
8 recognized drug interactions, name confusion, problems in special patient populations, labeling
9 changes, etc. Physicians can register to receive safety alerts automatically via email. According
10 to the FDA, approximately 46,000 individuals currently subscribe to this system. Additionally,
11 approximately 160 MedWatch partners, including our AMA, assist in disseminating safety alert
12 information. Important FDA safety alerts are also disseminated through Medscape to its
13 subscribers. Finally, several drug information services (eg, Micromedex; Epocrates) disseminate
14 new drug information or alerts supplied by the FDA to their subscribers.

15 16 Examples of Recent Drug Safety Problems

17
18 Several recent developments have focused attention on: (1) the knowledge gap that exists
19 between what is known by the FDA and that which is generally available to prescribers; (2)
20 inadequacies of the current postmarketing surveillance program; and (3) problems with risk
21 communication. The following discussion is not intended to provide an exhaustive review or case
22 analyses, but to briefly cite examples that illustrate the types of problems that have occurred,
23 which might be remedied by enhancing physician access to clinical research data and
24 information.

25
26 Lack of Physician Knowledge Regarding Drug Efficacy. In 2004, attention was focused on
27 reports of suicidality (both suicidal ideation and suicide attempts) in conjunction with the use of
28 antidepressants in pediatric patients with major depressive and other psychiatric disorders. These
29 reports prompted the Subcommittee on Oversight and Investigations (Committee on Energy and
30 Commerce, U.S. House of Representatives) to hold a hearing on “Publication and Disclosure
31 Issues in Anti-Depressant Pediatric Clinical Trials” on September 9, 2004.²⁹ Shortly thereafter, a
32 joint meeting of the Psychopharmacologic Drugs Advisory Committee and Pediatric Advisory
33 Committee was held on September 13-14, 2004, to discuss reports of the occurrence of
34 suicidality.³⁰ These hearings were preceded by two FDA Public Health Advisories. One
35 concerned reports of suicidality in pediatric patients being treated with antidepressant
36 medications, and the other related to the FDA’s request for a labeling change for antidepressant
37 drugs to include a Warning statement related to the potential for worsening depression and
38 suicidality in both adults and pediatric patients treated with these agents.

39
40 Accordingly, the focus of these hearings was on the potential for an increased risk of suicidal
41 ideation during the early phases of treatment with antidepressants; the Subcommittee also was
42 interested in why the public was not generally aware of this *potential* risk. Of perhaps even
43 greater interest was the fact that information presented at both hearings noted that as many as 15
44 clinical trials had been conducted using selective serotonin reuptake inhibitors (SSRIs) and other
45 antidepressants for the treatment of depression in children and adolescents, and with one
46 exception,³¹ only trials conducted using fluoxetine had been judged by the FDA to demonstrate
47 efficacy.^{32,33} These studies were done largely in response to FDAMA (and later the Best
48 Pharmaceuticals for Children Act) which authorized the FDA to grant additional marketing
49 exclusivity (referred to as pediatric exclusivity) to pharmaceutical manufacturers who conducted
50 studies of their drugs in pediatric populations. Accordingly, fluoxetine remains the only
51 antidepressant labeled for the treatment of depression in children and adolescents.

1 Despite the fact that several trials had been conducted with negative results, physicians prescribed
2 certain other SSRIs off-label at higher rates than fluoxetine in pediatric patients over this period, a
3 pattern mirroring prescribing trends for adults. With few exceptions the individual negative trials
4 were not published. One published trial involving paroxetine was positive on certain outcomes
5 and another represented a pooled analysis of two separate but identical trials involving sertraline,
6 neither of which demonstrated efficacy on its own.^{34,35} Information about trials that had failed to
7 meet the FDA's efficacy standard was not incorporated into the product labeling because it was
8 proprietary and clinical trial data in the package insert generally is limited to information
9 pertaining to labeled uses. However, in its October 23, 2003, Public Health Advisory the FDA
10 noted:

11 [The] FDA emphasizes that, for the 7 drugs evaluated in pediatric major depressive
12 disorder (MDD), data reviewed by FDA were adequate to establish effectiveness in MDD
13 for only one of these drugs, (fluoxetine). Failure to show effectiveness in any particular
14 study in pediatric MDD, however, is not definitive evidence that the drug is not effective
15 since trials may fail for many reasons. FDA recognizes that pediatric MDD is a serious
16 condition for which there are few established treatment options, and that clinicians often
17 must make choices among treatment available for adult MDD.
18

19
20 The most appropriate solution to a general lack of knowledge about negative clinical trial results
21 is a comprehensive clinical trial registry that is linked to results. Additionally, new clinical trial
22 information on marketed drug products is contained in the annual reports that manufacturers are
23 required to file. It may be useful to explore ways in which at least a portion of the clinical trial
24 information and results contained in the annual report can be made publicly available.
25

26 Lack of Physician Knowledge About Serious Adverse Events. The recent controversy about the
27 potential cardiovascular toxicity of COX-2 selective NSAIDs is another example of a knowledge
28 gap that existed between the FDA and physicians. This issue was the focus of a 3-day joint
29 meeting of the FDA's Arthritis and Drug Safety and Risk Management Advisory Committees
30 held February 14-16, 2005.³⁶ Much has been written on this issue since the first of these drugs
31 (celecoxib) was approved in 1998. Evidence of potential cardiovascular risks of rofecoxib was
32 noted in the medical review of the NDA.³⁷ Peer-reviewed publication of this evidence appeared
33 18 months later, but was incomplete.³⁸
34

35 Biological plausibility for the cardiovascular toxicity of COX-2 inhibitors was slow to be
36 acknowledged even though evidence that both rofecoxib and celecoxib suppressed formation of
37 prostaglandin I₂ (prostacyclin) was reported in 1999.³⁹ This cardioprotective metabolite, which is
38 elaborated by the vascular endothelium, inhibits platelet aggregation, causes vasodilation, and
39 opposes vascular smooth muscle cell proliferation. Interpretation of the potential cardiovascular
40 risks of COX-2 inhibitors was confounded by the design of the osteoarthritis efficacy trials
41 conducted to support the NDAs. These trials were relatively short term and lacked placebo
42 groups; some allowed aspirin use; and the relative cardioprotective effect of comparators such as
43 naproxen was uncertain.⁴⁰ Some, but not all, epidemiologic studies showed evidence of
44 cardiovascular risk, but these studies were also subject to confounding.⁴¹⁻⁴³
45

46 Nevertheless, there was a call in 2001 for a mandatory "trial, specifically assessing [the]
47 cardiovascular risk and benefit of COX-2 inhibitors."⁴⁴ At least two other industry-sponsored
48 trials demonstrating cardiovascular risk were never published. Eventually, the product labeling
49 for rofecoxib was modified in April 2002 to advise caution for use in patients with ischemic heart
50 disease. The new label provided additional information to the *Clinical Studies, Precautions,*
51 *Drug Interactions,* and *Dosage and Administration* sections. The labeling change accomplished

1 in the *Precautions* section noted that “prospective studies specifically designed to compare the
2 incidence of serious cardiovascular events in patients taking rofecoxib versus NSAID
3 comparators or placebo have not been performed.”
4

5 Nearly 6 years passed before definitive evidence of the cardiovascular toxicity of COX-2
6 inhibitors was obtained. This evidence was obtained as part of the safety monitoring of COX-2
7 inhibitors for cardiovascular events in efficacy trials conducted for postoperative pain relief and
8 prophylaxis versus colonic polyps.⁴⁵⁻⁴⁷ A cumulative meta-analysis of randomized controlled
9 trials comparing rofecoxib with other NSAIDs or placebo, and cohort and case-control studies of
10 cardiovascular risk and naproxen use, concluded that the cardiovascular risk of rofecoxib could
11 have been established much earlier.⁴⁸ All of these developments occurred against a backdrop of
12 direct-to-consumer and physician advertising emphasizing primarily the benefits of these drugs.
13 In retrospect, as noted by Drazen,⁴⁹ the “same zeal that had driven the clinical investigations [for
14 the COX-2 inhibitors] to show their gastrointestinal safety was not evidenced by studies designed
15 to show their cardiovascular safety.”
16

17 This example illustrates the need for a more direct approach in confronting *potential* safety
18 problems when they are identified. This specific issue could have been addressed by requiring a
19 prospective clinical trial to examine and quantify the cardiovascular risks of COX-2 inhibitors in
20 patients more representative of the actual use population; however, the FDA lacks the authority to
21 mandate such a postmarketing study. To a certain extent, this example also highlights the
22 limitation of the package insert (see below) as an efficient risk communication document.
23 Whether uncertainty about a specific drug safety issue is best served by establishing an
24 independent external drug safety board (as some have suggested), or is best served by extending
25 the authority of the FDA to mandate postmarketing studies where needed, is subject to debate.
26 The FDA has announced its own proposal to establish an independent drug safety board within
27 the Agency (see below).
28

29 Effective Postmarketing Surveillance. Concerns have been raised about the FDA’s ability to
30 detect serious adverse events occurring during the postmarketing phase given the limitations of
31 spontaneous reporting systems and the inherent conflict of interest in asking the pharmaceutical
32 industry to monitor its own drugs. Although the process can be effective, reliance on
33 spontaneous observational reports delays the recognition of safety signals and is limited in its
34 ability to assign causality. The premarketing adverse event database is also limited in
35 anticipating serious adverse events because the clinical trials that were conducted in support of an
36 NDA are conducted on a small, fairly homogenous group of subjects. These subjects are
37 generally not representative of the population that will be exposed once the drug is marketed. For
38 example, in actual clinical use, patients may have comorbid conditions, be at the extremes of age,
39 take the drug for long periods, or be using other drugs or dietary supplements.
40

41 This problem is magnified in the current marketing climate, which is characterized by intense
42 direct-to-consumer advertising and promotional efforts directed toward physicians, particularly
43 during the initial product launch phase. This may lead to rapid uptake and the exposure of a large
44 number of patients to a drug that has only previously been tested in a few thousand individuals.
45 Suggested approaches to improve postmarketing surveillance and drug safety during the first few
46 years of marketing include requiring applicants to conduct formal postmarket exposure studies
47 and to use active postmarket surveillance strategies (eg, data mining of drug utilization
48 databases).
49

50 Effective Risk Communication. While the examples cited above focus on a knowledge gap, or
51 slowness to gather relevant data and directly investigate potential drug safety issues, difficulties

1 can arise even when the FDA identifies a problem, answers the question, and communicates new
2 risk information to physicians in the form of labeling changes, including the use of Black Box
3 Warnings and/or directed communications (ie, "Dear Doctor" letters). There are several
4 examples of drugs that were withdrawn from the market (eg, terfenadine; bromfenac; cisapride,
5 troglitazone; cerivastatin) in part due to poor or ineffective management by physicians and/or
6 pharmacists of known risks related to contraindications, drug interactions, or monitoring
7 recommendations that were highlighted in the product labeling.

8
9 In part, this is attributable to the fact that the current package insert for prescription drugs is a
10 barrier to effective risk communication because it has become a legal document rather than a
11 source of useful information for busy practicing physicians. In December 2000, the FDA issued a
12 proposed rule (not yet finalized) to modify the format and content of the package insert with the
13 goal of making the information more useful and user-friendly to physicians, including a proposed
14 "Highlights of Prescribing Information." Our AMA (and the FDA) believes that the package
15 insert, combined with effective postmarketing surveillance, should constitute the risk
16 management plan for the vast majority of drug and biological products.

17
18 However, many other more restrictive approaches exist that can be used, such as patient
19 agreements or registries; the use of specialized systems or records; enrollment of physicians in
20 special education or certification programs; and linking product availability to laboratory testing
21 results or other documentation. A number of these would directly manage or restrict physician
22 prescribing and may have unintended consequences including preventing some patients (who
23 might benefit) from having access to higher risk drugs, or contributing to inappropriate
24 prescribing patterns if, for example, other less effective drugs are simply much easier to use.

25
26 The CSA believes that the FDA, the pharmaceutical industry, and physician organizations must
27 collaborate and identify innovative ways to communicate new risk information about a drug or
28 biological product to physicians so they will be aware of it, remember it, accept it, and act on it
29 when prescribing a drug. Previously, our AMA presented a number of potential ways for the
30 FDA to accomplish this goal in collaboration with physician organizations including: (1)
31 undertaking a major continuing medical education initiative on risk communication; (2) working
32 with major medical journals and medical society Web site editors to identify standard places for
33 the dissemination of important new risk information about drugs and biological products; (3)
34 changing the format of "Dear Doctor" letters to emphasize the need for action by the prescribing
35 physician and disseminating them by electronic means in addition to direct mailings; and (4)
36 encouraging pharmaceutical companies to train and provide incentives for their sales forces to
37 educate physicians on important new risk information about company products.

38 39 Recent FDA Proposals to Strengthen Safety Assessment

40
41 In an effort to strengthen safety assessments, the FDA announced on November 5, 2004, its
42 commitment to sponsoring an Institute of Medicine study on drug safety systems with an
43 emphasis on the postmarket phase; appointing a Director for the Office of Drug Safety;
44 implementing a program for adjudicating differences of professional opinions by FDA review
45 staff and outside experts; and publishing risk management guidelines for industry.⁵⁰ The latter
46 has been accomplished.

47
48 Following through on its pledge to conduct drug safety/risk management assessments in
49 consultation with other stakeholders, the FDA announced on February 16, 2005, a series of new
50 initiatives intended to improve the way the FDA manages drug safety information, including the
51 creation of an independent Drug Safety Oversight Board comprised of FDA staff and medical

1 experts from other Department of Health and Human Services agencies and government
 2 departments.⁵¹ This board is charged with overseeing the management of important drug safety
 3 issues within CDER in consultation with other medical experts and representatives of patient and
 4 consumer groups.

5
 6 The FDA also pledged to expand existing communication channels and create new ones to ensure
 7 that established and emerging drug safety data are quickly available to the public (and physicians)
 8 in an easily accessible form with the intent of enabling “patients and their health care
 9 professionals to make better-informed decisions about individual treatment options.” In addition,
 10 the agency proposed a new "Drug Watch" Web page for emerging data and risk information and
 11 increased use of consumer-friendly information sheets written especially for health care
 12 professionals and patients. A primary concern associated with this approach is the dissemination
 13 of emerging, and perhaps preliminary, information prior to regulatory action and in the absence of
 14 clear advice.

15
 16 These proposals, if effectively implemented, respond to some of the concerns noted above.

17
 18 Unlabeled Uses

19
 20 As previously noted, as part of its regulatory function in approving drug products for marketing in
 21 the United States, the FDA also approves each drug product's labeling; ie, container label,
 22 package insert, and certain advertising. Unlabeled uses are defined as the use of a drug product
 23 for indications or in patient populations, doses, or routes of administration that are not included in
 24 FDA-approved labeling. Under the federal FD&C Act, a drug approved by the FDA for
 25 marketing may be labeled, promoted, and advertised by a manufacturer only for those uses for
 26 which the drug's safety and efficacy have been established. This requires submission of data by
 27 the manufacturer to the FDA demonstrating substantial evidence of efficacy and safety for each
 28 labeled indication. Even though PDUFA has reduced the review time for efficacy supplements,
 29 manufacturers may not prepare supplemental NDAs to have new uses added to the label because
 30 of the cost involved.

31
 32 The FD&C Act does not limit the manner in which a physician may use an FDA-approved drug.
 33 A physician may choose to prescribe a drug for uses or in treatment regimens or patient
 34 populations that are not in approved labeling. This decision is made by the physician in light of
 35 all information available and in the best interests of the individual patient. Prescribing for an
 36 unlabeled use only requires the physician to use the same judgment and prudence as exercised in
 37 medical practice in general for it to conform to accepted professional standards. Unlabeled uses
 38 are especially common in oncology, rare diseases, and pediatrics.

39
 40 Given the prevalence of unlabeled uses and the fact that in many clinical situations such use may
 41 represent the most appropriate treatment, the prescribing of FDA-approved drugs for unlabeled
 42 uses is often necessary for optimal patient care. Therefore, our AMA's policy is:

43
 44 ...that a physician may lawfully use an FDA approved drug product for an
 45 unlabeled indication when such use is based upon sound scientific evidence
 46 and sound medical opinion... (Policy H-120.988, AMA Policy Database)

47
 48 The need for physicians to prescribe drugs for unlabeled uses is unchallenged. The position of
 49 the FDA on physician prescribing of unlabeled uses essentially supports that of our AMA. The
 50 FDA's published statement that addresses the appropriateness and legality of prescribing FDA-
 51 approved drugs for unlabeled uses includes the following:

1 The Food, Drug and Cosmetic Act does not limit the manner in which a
2 physician may use an approved drug. Once a product has been approved for
3 marketing, a physician may prescribe it for uses or in treatment regimens or
4 patient populations that are not included in approved labeling. Such
5 “unapproved” or, more precisely, “unlabeled” uses may be appropriate and
6 rational in certain circumstances, and may, in fact, reflect approaches to drug
7 therapy that have been extensively reported in medical literature.

8
9 Therefore, given the disparity between actual submission for SNDAs and the
10 evolution of medical practice, as steps are taken to improve drug safety, physician
11 prescribing for unlabeled uses must not be impeded.

12 Discussion

13
14 An elaborate system of laws, regulations, and guidances governs the drug approval process in the
15 United States. This system has evolved over the last century, and has previously shown an ability
16 to respond to significant issues affecting the risks and benefits of prescription drug use.
17 Pharmaceutical manufacturers, the FDA, and the end users (physicians and patients) all play
18 essential roles in minimizing the risks and enhancing the benefits of prescription drug products.
19 Currently, the FDA is prohibited from disclosing information about INDs and NDAs unless that
20 information has already been publicized. In any event, most physicians have little interest in the
21 content and information comprising IND and NDA applications. Nevertheless, a considerable
22 amount of clinical data and documentation related to premarket assessments and the FDA review
23 and approval of new drugs is publicly available. Although the FDA has improved the efficiency
24 of the drug review process, similar improvements in postmarketing surveillance have not
25 occurred. Recently, a series of high-profile developments (drug withdrawals; use of
26 antidepressants in children; concerns about the cardiovascular toxicity COX-2 inhibitors) have
27 directed attention to a knowledge gap between important clinical research data available to the
28 FDA and what is generally available to physicians and the public. This has occurred against a
29 backdrop of increased direct-to-consumer advertising and targeted promotional efforts, especially
30 during the early phase of new product availability, that contributes to a surge of patient exposure
31 in the absence of comprehensive safety information.

32
33 Several steps can be taken immediately to improve drug safety and reduce the knowledge gap
34 between the FDA and physicians about the risks and benefits of certain drug products. Chief
35 among these are steps to establish a more transparent process with respect to clinical research
36 data obtained by the FDA. This process can be enhanced by the development of a comprehensive
37 clinical trial registry, creation of an independent drug safety board within the FDA, better risk
38 communication for marketed products, the use of more active and directed postmarketing
39 surveillance activities, and conducting mandatory postmarketing studies where needed.

40 RECOMMENDATIONS

41
42
43 In light of the above discussion, the Council on Scientific Affairs recommends that the following
44 recommendations be adopted and the remainder of this report be filed. That out AMA:

- 45
46
47 1. Urge the Food and Drug Administration (FDA) to issue a final rule, as soon as possible,
48 implementing modifications to the format and content of the prescription drug package
49 insert with the goal of making the information more useful and user-friendly to
50 physicians. **(Directive to Take Action)**

- 1 2. Urge the FDA to collaborate with physician organizations to develop better risk
2 communication vehicles and approaches. **(Directive to Take Action)**
3
- 4 3. Urge the FDA to apply new tools to gather data after drugs are approved for marketing,
5 including a broader use of targeted post-approval studies, institution of active and
6 sentinel event surveillance, and data mining of available drug utilization databases.
7 **(Directive to Take Action)**
8
- 9 4. Monitor the design and implementation of any independent drug safety board that may be
10 instituted within the FDA, or external to the agency, and respond as appropriate.
11 **(Directive to Take Action)**
12
- 13 5. That our AMA support adequate funding to implement an improved FDA postmarketing
14 prescription drug surveillance process. **(Directive to Take Action)**

Fiscal Note: No Significant Fiscal Impact

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Appendix

