Postmarket Assessment for Drugs and Biologics Used in Dermatology and Cutaneous Adverse Drug Reactions

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KEYWORDS

• Postmarket surveillance • Cutaneous adverse drug reactions • Severe cutaneous adverse reactions • Stevens–Johnson syndrome • Toxic epidermal necrolysis • Adverse event reporting

KEY POINTS

- The US Food and Drug Administration maintains a system of postmarketing surveillance programs to identify and evaluate new safety concerns after a drug's approval.
- Dermatologists play a critical role in identifying, managing, and reporting adverse events associated with dermatologic treatments and cutaneous adverse events.
- Postmarketing adverse event reports have been particularly vital in the detection and evaluation of serious cutaneous adverse reactions and resulting risk mitigation actions, such as labeling changes.

INTRODUCTION

The US Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) ensures that safe and effective drugs are available to improve the health of individuals in the United States.[1] To fulfill this mission, the CDER balances the promotion of drug development, the availability of high-quality drugs for patients, and the maintenance of a favorable benefit/risk profile for approved drugs[2] through risk management, a combination of risk assessment and risk minimization.[3] Pharmacovigilance, "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems,"[4] informs the CDER's risk management of drugs using a variety of postmarketing safety data sources to identify new safety signals and conduct risk assessments to continually assess the benefit-to-risk profile of a regulated drug.[4]

Cutaneous adverse drug reactions (CADR) are reported to be one of the most frequently reported adverse events occurring in patients undergoing drug therapy, ranging between 1% and 3% in hospitalized patients and from 10 to 38% of all reported adverse drug reactions (ADR).[5,6] Morbilliform eruptions account for approximately 95% of all CADR.[7] Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are the concerning CADRs, with significant morbidity and mortality. In the general population, events of SJS/TEN are uncommon, estimated between 1 and 2 cases per million people for TEN and between 1 and 7 cases per million people for SJS, although SJS may occur at higher rates in the United States (≤9.2 cases per million people).[8] Uncommon adverse events such as SJS/TEN are

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unlikely to occur during the preapproval studies given the size of the study population; thus, the potential risk of for SJS/TEN is usually unknown at the time of drug approval. The identification of an uncommon adverse event may occur once the drug is broadly used in a larger population.[9]

The identification of new safety issues using spontaneous adverse event reporting is based on the clinical observations made at the patient–health care provider level.[10] In dermatology, spontaneous adverse event reports have resulted in regulatory actions for drugs prescribed by dermatologists for cutaneous disorders, such as efalizumab for psoriasis,[11] and CADR, such as chemical leukoderma with the use of the methylphenidate transdermal system.[12]

The involvement of dermatologists in pharmacovigilance is of increasing importance as the number of drugs being investigated for dermatologic conditions is increasing[13] and a variety of life-threatening and non–life-threatening CADRs have been reported.[14–16] In the American Academy of Dermatology's 1996 Guidelines of Care for Cutaneous Adverse Reactions, under the heading *Recommendations–Miscellaneous,* the authors' advise that adverse drug reactions "may be voluntarily reported to the manufacturer or to" the FDA.[17] Dermatologists, as the prescriber of several newly approved drugs or in consultation with patients with suspected serious, uncommon CADR such as SJS/TEN, play a valuable and critical role in identifying important, new drug safety information in the postmarketing period.

The goal of this article is to describe the FDA's postmarket surveillance of drugs and highlight the important role of dermatologists in pharmacovigilance.

DEFINITIONS

Approval: For ease of reference, this article uses the term approval to refer to both drug approval and biologic licensure.

Applicant: The company that submits an application to the FDA for approval to market a drug product in the United States.[18]

Drug: For ease of reference, this article uses the term drug to refer to all human drug and therapeutic biological products regulated by the CDER.

Label: Any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing on a package containing any consumer commodity.[19]

Labeling: Includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.[19]

Pharmacovigilance: "The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems."[20]

Risk evaluation and mitigation strategy: "A Risk Evaluation and Mitigation Strategy, or REMS, is a safety plan to manage a known or potential serious risk associated with a medicine and to enable patients to have continued access to such medicines by managing their safe use."[18]

Safety signal: Information from 1 or more sources that suggests a new potential causal association, or a new aspect of a known association, between a drug and an adverse event that warrants further action to verify.[21,22]

Serious adverse drug experience: "Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition."[23]

DISCUSSION

US Food and Drug Administration Postmarketing Surveillance of Drugs

Pharmacovigilance began in the mid-19th century and has evolved into a global effort as the manufacture and distribution of drugs has changed. A brief timeline highlighting the history of drug safety regulation in the United States is provided in **Table 1**.[24-26]

The US Code of Federal Regulations defines the Applicant's responsibilities to conduct postmarketing surveillance for medical products (21 CFR §314.80 and §600.80 for approved drugs and biological products, respectively), and the Food, Drug & Cosmetics Act outlines the FDA's duty[27]; postmarketing surveillance is a shared responsibility, and the focus of this discussion is on the FDA's surveillance practices.

The CDER regulates drugs, which includes over-the-counter and prescription drugs, as well as biological therapeutics and generic drugs. Drugs, as defined by regulation, also includes antiperspirants, dandruff shampoos, and sunscreen.[28]

Table 1
Milestones in the US FDA's regulation of drug safety

1938	The Federal Food, Drug, and Cosmetic (FDC) Act creates a new public health system requiring new drugs to be shown safe prior to marketing.
1951	The Durham–Humphrey Amendment defines drugs that cannot be used safely without medical supervision and restricts the sale of these drugs by requiring prescription by a licensed practitioner.
1966	The Fair Packaging and Labeling Act requires consumer products to be honestly and informatively labeled, with the FDA enforcing requirements on drugs among other products.
1970	In Upjohn v Finch, the Court of Appeals rules that commercial success alone does not constitute substantial evidence of drug safety and efficacy, upholding the enforcement of the 1962 Kefauver–Harris Drug Amendments.
1993	The FDA introduces MedWatch to facilitate the voluntary reporting by health care professionals to the FDA of adverse events that may be due to FDA regulated drugs and devices.
1998	The Adverse Event Reporting System (AERS), a computerized information database to support postmarketing surveillance is introduced.
2005	The FDA publishes 3 guidances describing the processes for the risk management of regulated drugs.
2006	The FDA approves the final rule "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products" to improve the usability of FDA-approved labeling by health care professionals.
2007	Title IX, section 915 of The FDA Amendments Act (FDAAA) grants the FDA the authority to require Applicants to conduct postmarketing studies to enhance understanding of drug safety, require Applicants to comply with Risk Evaluation and Mitigation Strategies (REMS), and enforce safety-related label changes. FDAAA also requires the FDA to prepare summary analysis of adverse drug reaction reports received by 18 mo post-approval or after use of the drug by 10,000 individuals, whichever is later of any new risks not previously identified, potential new risks, or unknown risks reported in unusual number. In addition, FDAAA requires regular, biweekly screening of AERS and quarterly posting of any new safety information or potential signal of a serious risk identified by AERS within the last quarter.
2016	21st Century Cures Act (Cures Act) eliminates the requirement for the FDA summary analyses for drugs and adds a requirement for the FDA to make publicly available guidelines describing best practice for drug safety surveillance using the FAERS and criteria for public posting of adverse event signals. In addition, the Cures Act removes the requirement for biweekly screening and summary analysis of the FAERS as required by FDAAA.

Within the CDER, the Office of Surveillance and Epidemiology monitors and evaluates the safety of drugs using a variety of safety experts and surveillance tools throughout the life cycle of the drugs[29] along with the divisions that regulate premarket, drug development programs and drug approvals. The Office of Surveillance and Epidemiology includes the Divisions of Pharmacovigilance, the Divisions of Epidemiology, and the Office of Medication Error Prevention and Risk Management. The Divisions of Pharmacovigilance's safety teams are composed of medical officers and safety evaluators with each team assigned a portfolio of therapeutic drug classes, collectively covering all approved drugs.[30] The procedures for how the Office of Surveillance and Epidemiology conducts postmarketing surveillance are outlined in a variety of internal and external documents[3,4,26] and describes the processes for the monitoring of *adverse events*, defined as:

> *any untoward medical occurrence associated with the use of a drug product in humans, whether or not it is considered related to the drug product. An adverse event can occur in the course of the use of a drug product; from overdose of a drug product, whether accidental or intentional; from abuse of a drug product; from discontinuation of the drug product (eg, physiologic withdrawal); and it includes any failure of expected pharmacologic action.*[31]

Data Sources for Postmarketing Surveillance

During postmarketing surveillance, safety signals can arise from various data sources. The source of a signal typically includes spontaneous reports to the FDA and medical literature but can also come from a variety of other sources, including postmarket studies.[21,22,26] Upon identification of a safety signal, a comprehensive, in-depth assessment of the drug–adverse event combination is initiated.

US Food and Drug Administration Adverse Event Reporting System

The FDA's Adverse Event Reporting System (FAERS) contains information on adverse event and medication error reports submitted to the FDA in the format of individual case safety reports. Since its inception in 1968, as of December 31, 2021, the FAERS contained 23,663,780 total reports.[32] Individual case safety reports are submitted to the FDA voluntarily from the public; the FAERS relies on health care professionals, patients, caregivers, and others to report adverse events voluntarily either to the product's manufacturer, which will subsequently report them to the FDA according to regulations, or to the FDA directly. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation[33] and are compliant with the Health Insurance Portability and Accountability Act Privacy Rule.[34] The advantage of the FAERS is the ability to detect rare and serious adverse events, such as SJS; although, as a passive form of surveillance, there are limitations to the FAERS, which include underreporting, duplicate reports, an inability to calculate the incidence of an adverse event, and variable data quality. Notwithstanding these limitations, the FAERS remains a primary and vital source of new safety information in postmarketing surveillance.[35]

Reported adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The MedDRA provides a clinically validated, multilingual resource that provides standard terminology for adverse event reporting that can be used throughout the drug's life cycle to report adverse events and allow the retrieval of reports at varying levels of granularity.[36] The MedDRA is routinely updated to keep the MedDRA terms current. Although the MedDRA allows for standardization, increased specificity by including nonadverse event terms (eg, medical history, social history, surgical procedures, diagnostic testing), and flexibility in report retrieval, the use of the MedDRA may also contribute to signal dilution due to the number of terms available.[37] To address some limitations, Standardized MedDRA Queries were created to facilitate the retrieval of cases using grouped search terms that may not be related in its hierarchical structure. For example, Standardized MedDRA Queries were developed for drug reaction and eosinophilia and systemic symptoms as well as severe cutaneous adverse reactions.[38] Despite its limitations, the MedDRA is widely used across regulatory agencies and industry to conduct pharmacovigilance.

Medical literature

The body of published medical literature also serves as an important source for postmarketing safety signals. In contrast with FAERS, published cases are fewer in number, but are often higher in quality given the peer review process. Published case reports tend to include more clinical details to support the confirmation of a particular adverse event and allow a more thorough causality assessment. For example, in a case of SJS associated with a drug, published case reports tend to include details such as skin biopsy results, allergy testing, treatment management, and drug exposure history, according to expert diagnostic and management guidelines.[39,40] The Divisions of Pharmacovigilance staff use automated alerts available in the major biomedical literature databases (eg, PubMed, Embase) to monitor for adverse event reports for a given drug.

FAERS data mining and reporting rates

In addition to monitoring the FAERS and the medical literature for safety signals, the FDA also conducts data mining of the FAERS data.[35] Given the exponentially increasing size of the FAERS database, data mining supports the detection of safety signals in a systematic manner through disproportionality analysis. In this case, an increased proportion of a specific adverse event–drug combination compared with the adverse event reported with all other drugs may indicate a potential safety signal. To generate this safety signal hypotheses for a potential adverse event–drug combination, the FDA can search the FAERS database for a specific adverse event, such as SJS, and generate a test statistical of the adverse event for a particular drug. For example, the proportional reporting ratio (PRR) for SJS and drug X can be calculated by taking the proportion of SJS reports for drug X and dividing it by the proportion of SJS reports for all other drugs in the FAERS database. Using the example data in **Table 2**, the PRR for SJS and drug X can be calculated, where PRR = [(A/A + B)/(C/C + D)]. In this example,

the PRR is 5.9 and, because the PRR is greater than 1, would be interpreted as FAERS reporting for SJS and drug X is 5.9 times more frequent than what is observed for SJS and all other drugs in the FAERS. This outcome suggests but does not confirm a possible safety signal; the SJS–drug X combination would need to be further evaluated as a potential safety signal.

Although the incidence of an adverse event with a drug cannot be calculated using the FAERS data, reporting rates (sometimes referred to as reporting ratios) of an adverse event with a drug may provide context for a specific adverse event–drug combination, such as the potential population at risk. The reporting rate can be calculated by dividing the number of US cases reported for the adverse event by an estimate of the drug's use in a period of time (eg, number of US prescriptions dispensed). Like data mining results, reporting rates may suggest a potential safety signal and is not confirmation of a signal. As an example, if the reporting rate for SJS and drug X exceeds the expected background rate of SJS in the general population (ie, 1–7 cases per million people), then drug X may be a potential cause of the excess cases reported.

Of note, the underlying limitations of the data used to calculate disproportionality measures and reporting rates must be considered in interpreting these analyses.

Sentinel

Sentinel is the FDA CDER's drug safety surveillance system using national electronic health care data. The FDA Sentinel Initiative was launched in response to the FDA Amendments Act of 2007 and started with the Mini-Sentinel Pilot before transitioning to the full Sentinel System in September 2014.[41] In 2016, the FDA established the Active Postmarket Risk Identification and Analysis System, integrating the Sentinel System into the FDA's regulatory programs.[42] Analyses from the Active Postmarket Risk Identification and Analysis system have provided significant contributions to the evaluations of safety issues including for CADRs. For example, the system has been used to evaluate occurrence of nonmelanoma skin cancer after hydrochlorothiazide use[43] and resulted in updating the drug label to include the following language.

Nonmelanoma skin cancer Hydrochlorothiazide is associated with an increased risk of nonmelanoma skin cancer. In a study conducted in the Sentinel System, increased risk was predominantly for squamous cell carcinoma and in white patients taking large cumulative doses. The increased risk for squamous cell carcinoma in the overall population was approximately 1 additional case per 16,000 patients per year, and for white patients taking a cumulative dose of >50,000 mgthe risk increase was approximately 1 additional SCC case for every 6,700 patients per year.[44]

Safety Signal Evaluation

Once a signal is identified, a multidisciplinary safety team conducts a comprehensive review of the available evidence related to the adverse event–drug combination. Available data sources include preclinical data, literature, other safety databases, clinical trials and studies from preapproval development programs, epidemiologic studies, product use data, and reporting rates (or ratios); all available data are considered in the formulation of conclusions regarding the causal association between a suspect drug and an adverse event.[21,22,26] The safety team includes safety evaluators, medical officers, and epidemiologists, as well as any other subject matter experts that can provide additional expertise relevant to the specific adverse event–drug combination, such as pharmacogenetic aspects.

For CADRs, given the rarity of serious cutaneous reactions like SJS/TEN, case data often are critical to signal evaluation. To develop case-level data, the safety team develops a case series using selection criteria to query the FAERS database broadly and identify potential individual cases. The selection criteria includes "specific combinations of signs, symptoms, and test results" based on "the medical literature and current expert clinical guidelines."[26] Each FAERS report is individually screened to determine if the report includes the adverse event of interest and sufficient information to allow for an assessment of drug

Table 2
Disproportionality analysis example[a]: FAERS SJS reporting with drug X and all other drugs in the FAERS database

	SJS	All other events in the FAERS
Reports for drug X	10 (A)	500 (B)
Reports for all other drugs	50 (C)	15,000 (D)

[a] Not real data from the FAERS; values chosen to illustrate potential case.

causality. If the FAERS report lacks information, the safety evaluator may contact the reporter to obtain the additional information needed. The identified FAERS reports are reviewed against the selection criteria for inclusion in the case series and duplicate reports are screened out. This process is repeated for published case reports in the medical literature. The selected, deduplicated case reports comprise the case series that then undergoes assessment for causal association.

The focus of causal association is the evaluation of relatedness between the adverse event and the reported drug exposure of the individual. Aspects considered by the safety evaluator include:[26]

(1) Chronologic data (eg, plausible temporal sequence, dechallenge, rechallenge)
(2) Precedents (eg, similar adverse events with the same product or related products)
(3) Biological or pharmacologic plausibility (eg, toxic drug concentration in body fluid, occurrence of a recognized pharmacodynamic phenomenon)
(4) Information quality, and
(5) Alternative etiologies (eg, concurrent diseases or conditions, concomitant medications).

In general, the information from the FAERS and published case reports cannot provide definitive evidence of causal association between an adverse event and drug. "However, a well-documented case of a rare adverse event, that is usually drug-related, or a well-documented report of positive rechallenge can be sufficient to strongly suggest or even establish a causal association."[26] Of note to dermatologists, the determination for a causal association between a drug and the adverse event of SJS/TEN can be made based on a single, well-documented case report; thus, it is important for dermatologists to report these clinical observations, either to the FDA or via publication.

The safety signal evaluation also evaluates the case series cumulatively, reviewing the summary of clinical characteristics (eg, age, sex, dosage) for patterns or trends and causal assessments at the drug–adverse event level (eg, precedents, biological or pharmacologic plausibility).[26] In addition, if possible and depending on the risk prioritization of the adverse event–drug combination, drug use, reporting rates (or ratios), and review of epidemiologic studies (ie, the Sentinel System, review of published epidemiologic studies) are integrated into the safety signal evaluation. At the conclusion of the evaluation, a determination is made regarding the adverse event–drug association based on the strength of evidence reviewed from all available information.

Regulatory Action Based on the Safety Signal Evaluation

After completion of the evaluation, a multidisciplinary team within the CDER determines if regulatory actions are needed to ensure continued safe use of the drug.[45] Depending on the potential impact to the public health, the actions can include modifying the drug labeling to reflect the new information, issuing a drug safety communication to the public, requiring the applicant conduct a postmarketing study to better characterize the risk, and requiring or updating an approved risk evaluation and mitigation strategy to minimize the identified risk.

Communication of a Newly Identified Safety Risk

Drug labeling

A drug's FDA-approved labeling is the primary information source of a drug's safety and efficacy. The labeling summarizes for the prescriber the evidenced-based information that is essential for the safe and effective use of the drug. The FDA can require applicants to modify the currently approved labeling to include new safety-related information.[46] The structure and content of the labeling is defined in regulation; the FDA has published several guidances describing the process of safety-related labeling changes and how to communicate risks according to the degree of potential impact.[47–50] **Table 3** includes examples of labeling language used to inform health care providers of the risk of SJS/TEN.

Communications

The FDA also uses other forms of communication to disseminate newly identified safety risks to the public. The Drug Safety Communication is one tool used to communicate emerging safety issues that may potentially lead to serious or life-threatening events; Drug Safety Communications generally convey a summary of the data reviewed by the FDA along with recommended actions for health care providers and patients, if appropriate to the risk.[50,26] In addition, the FDA can require the applicant to issue "Dear Healthcare Provider" letters describing significant hazards to safety, announce important changes to drug labeling, or emphasize corrections in prescription drug advertising and drug labeling.[50,26] In certain cases, the FDA can also create and include on its web site Consumer Updates describing safety information for consumers. The FDA-identified safety risks are also published in the biomedical literature. **Table 4** highlights examples of these types of communications relevant to the practice of dermatology.[11,12,51–55]

Table 3
Examples[a] of labeling language that describes the risk of serious skin reactions with the approved drug's use

Labeling Section	Language
Boxed Warning	*WARNING: SERIOUS SKIN RASHES* LAMICTAL XR can cause serious rashes requiring hospitalization and discontinuation of treatment. The incidence of these rashes, which have included Stevens–Johnson syndrome, is approximately 0.8% (8 per 1000) in pediatric patients (aged 2–16 years) receiving immediate-release lamotrigine as adjunctive therapy for epilepsy and 0.3% (3 per 1000) in adults on adjunctive therapy for epilepsy. In a prospectively followed cohort of 1983 pediatric patients (aged 2–16 years) with epilepsy taking adjunctive immediate-release lamotrigine, there was 1 rash-related death. LAMICTAL XR is not approved for patients younger than 13 years. In worldwide postmarketing experience, rare cases of toxic epidermal necrolysis and/or rash-related death have been reported in adult and pediatric patients, but their numbers are too few to permit a precise estimate of the rate. The risk of serious rash caused by treatment with LAMICTAL XR is not expected to differ from that with immediate-release lamotrigine. However, the relatively limited treatment experience with LAMICTAL XR makes it difficult to characterize the frequency and risk of serious rashes caused by treatment with LAMICTAL XR. Other than age, there are as yet no factors identified that are known to predict the risk of occurrence or the severity of rash caused by LAMICTAL XR. There are suggestions, yet to be proven, that the risk of rash may also be increased by (1) coadministration of LAMICTAL XR with valproate (includes valproic acid and divalproex sodium), (2) exceeding the recommended initial dose of LAMICTAL XR, or (3) exceeding the recommended dose escalation for LAMICTAL XR. However, cases have occurred in the absence of these factors. Nearly all cases of life-threatening rashes caused by immediate-release lamotrigine have occurred within 2–8 weeks of treatment initiation. However, isolated cases have occurred after prolonged treatment (e.g., 6 months). Accordingly, duration of therapy cannot be relied upon as means to predict the potential risk heralded by the first appearance of a rash. Although benign rashes are also caused by LAMICTAL XR, it is not possible to predict reliably which rashes will prove to be serious or life threatening. Accordingly, LAMICTAL XR should ordinarily be discontinued at the first sign of rash, unless the rash is clearly not drug related. Discontinuation of treatment may not prevent a rash from becoming life threatening or permanently disabling or disfiguring *[see Warnings and Precautions (5.1)]*.
Section 4: Contraindications	REYATAZ is contraindicated:• in patients with previously demonstrated clinically significant hypersensitivity (eg, Stevens–Johnson syndrome, erythema multiforme, or toxic skin eruptions) to any of the components of REYATAZ capsules or REYATAZ oral powder [*see Warnings and Precautions* (5.2)].

(*continued on next page*)

Table 3
(*continued*)

Labeling Section	Language
Section 5: Warnings and Precautions	**Serious Skin Reactions** Serious skin reactions have occurred following treatment with Celebrex, including erythema multiforme, exfoliative dermatitis, Stevens–Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP). These serious events may occur without warning and can be fatal. Inform patients about the signs and symptoms of serious skin reactions, and to discontinue the use of CELEBREX at the first appearance of skin rash or any other sign of hypersensitivity. CELEBREX is contraindicated in patients with previous serious skin reactions to NSAIDs [*see Contraindications (4)*].
Section 6: Adverse Reactions	6.2 Postmarketing experience The following additional adverse reactions have been identified during post-approval use of ERLEADA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure. . . Skin and subcutaneous tissue disorders: Stevens–Johnson syndrome/toxic epidermal necrolysis

[a] Language obtained from labels of different applications available on https://www.accessdata.fda.gov/scripts/cder/daf/.

The Role of Dermatologists in Postmarketing Surveillance

The American Medical Association (AMA) Code of Medical Ethics (Code) describes the values physicians embody as members of the medical profession and is based on the Hippocratic oath to "relieve suffering and promote well-being in a relationship of fidelity with the patient."[56] The AMA code includes Opinions of the AMA Council on Ethical and Judicial Affairs to provide guidance to the medical profession, of any specialty, on the essentials of ethical behavior.[57] Opinion 8.8 (Required Reporting of Adverse Events) was updated in 2016 by the AMA House of Delegates and states:[58]

Physicians' professional commitment to advance scientific knowledge and make relevant information available to patients, colleagues, and the public carries with it the responsibility to report suspected adverse events resulting from the use of a drug or medical device. As professionals who prescribe and monitor the use of drugs and medical devices, physicians are best positioned to observe and communicate about adverse events. A physician who suspects that an adverse reaction to a drug or medical device has occurred has an ethical responsibility to:

(a) Communicate that information to the professional community through established reporting mechanisms.
(b) Promptly report serious adverse events requiring hospitalization, death, or medical or surgical intervention to the appropriate regulatory agency.

More recently, in the *British Journal of Dermatology*, an editorial by Garcia-Doval and colleagues[59] called on article authors whose submissions describe adverse events to report the case to the available pharmacovigilance systems. In addition, the authors conclude stating that the *British Journal of Dermatology* will work to ensure that published case reports include the relevant details to enhance its usefulness in postmarketing surveillance as a part of the journal's commitment to drug safety.[59]

Spontaneous reporting is inherently subject to reporting bias given its voluntary nature.[10,66] Physicians have been found to be the least likely of the health care professionals evaluated to report ADRs.[64] In one study, the attitudes of physicians toward adverse reaction reporting were summarized as:[60,61]

"I am unsure how to report an ADR."

Table 4
Examples of FDA communications relevant to dermatologists

Type of Communication	Title of Communication
Drug Safety C ommunication	FDA Drug Safety Communication: FDA warns about rare but serious skin reactions with mental health drug olanzapine (Zyprexa, Zyprexa Zydis, Zyprexa Relprevv, and Symbyax). FDA Drug Safety Communication for Tumor Necrosis Factors (TNF) Blockers, Azathioprine & Mercaptopurine.
Dear Healthcare Provider Letter	"Dear Doctor" letter from Hoffmann–LaRoche (February 26, 1998) on the inclusion of "psychiatric disorders" into the warning section of labeling.
Consumer update	Do not use: black salve is dangerous and called by many names.
Publication	Thambi L, Konkel K, Diak I-L, Reyes M, McCulley L. Cosmetic disfigurement from black salve. Drugs & Therapy Perspectives. 2020;36(11):526–528. Cheng C, La Grenade L, Diak IL, Brinker A, Levin RL. Chemical Leukoderma Associated with Methylphenidate Transdermal System: Data From the US FDA Adverse Event Reporting System. J Pediatr. 2017;180:241–246. Kothary N, Diak IL, Brinker A, Bezabeh S, Avigan M, Dal Pan G. Progressive multifocal leukoencephalopathy associated with efalizumab use in psoriasis patients. J Am Acad Dermatol. 2011;65(3):546–551.

"I may appear foolish if I report a suspected ADR."
"I may expose myself to legal liability by reporting an ADR."
"I am too busy to report ADRs."
"I am reluctant to admit that I caused harm."
"I would rather collect cases and publish them."
"Only safe drugs are marketed."

The AMA Code Opinion on Required Reporting of Adverse Events addresses physician reluctance to report stating physicians "need not be certain that there is such an event or even that there is a reasonable likelihood of a causal relationship, to suspect that an adverse event has occurred."[57] MedWatch, as described by the FDA Commissioner at the time, was designed to encourage "health care professionals to regard reporting as a fundamental professional and public health responsibility."[25] To facilitate reporting, MedWatch allows submission of cases through an online form, but also provides a downloadable form for submission; the online form supports submission of images, which can be helpful for cutaneous adverse reaction cases. **Box 1** summarizes the options for submitting cases to MedWatch. Although the minimum information required to complete a report include 4 data points (ie, the patient, adverse event, suspect drug, and reporter name), a thorough report takes approximately 15 to 20 minutes to complete.[62] Because it is not practical to submit every case, several authors have recommended reporting suspected ADRs that are serious or unexpected, from newly approved drugs (within 3 years of approval), and are considered high risk by regulatory agencies.[63–65] During a busy clinic or hospital day, finding the time to report may pose a challenge to timely, complete submissions. To address this, some health organizations allow for an operationalized approach leveraging pharmacists and nurses, or a drug safety officer, to support the routine submission of ADR reports.[62,63]

The FAERS is limited by the variability and lack of information included in reports. Improving the usefulness of spontaneous reporting systems

Box 1
Options for submitting cases to FDA's MedWatch program

Online: MedWatch Website	www.fda.gov/medwatch/report.htm
Phone (toll-free)	1–800-FDA (332)-1088
Fax (toll-free)	1–800-FDA(332)-0178

includes increasing reporting of suspected ADRs as well as improving the quality of the reports submitted. Notably, capturing a small proportion of ADRs through reporting may still have a large impact if those reports contain the necessary information to make an adequate assessment of causal association.[65,66] In the case of rare adverse events, such as SJS/TEN, the infrequent occurrence of the adverse event compounds the limitations of underreporting and lack of details in poor quality reports. Several guidelines exist to ensure that case reports include the necessary information to make an assessment of the adverse event-drug association.[67] Specific to dermatology, the National Institutes of Health Working Group developed a validated case report form for SJS/TEN through a consensus process identifying the elements to include in a standardized case report form; the form does not include a specific causality assessment tool, but serves to provide the necessary information to aid in the diagnosis for a condition where no diagnostic criteria exist.[68]

As articulated by Raschi and colleagues,[69,70] dermatology is experiencing an increase in documented drug-induced skin toxicities, as well as an increase in the use of biologics to treat skin disease, which may have serious noncutaneous adverse reactions. Dermatologists, at the front line of making these clinical observations, are poised to identify new drug safety information that is relevant for improving the public's health. The submission of high-quality case reports, either through postmarketing surveillance systems or published in the literature, can provide valuable clinical data to drug safety regulators. Timely and informative case reports are particularly helpful in informing a drug's safety profile and may lead to updates in the drug's labeling, ultimately improving patient safety and health care provider awareness of safety risks.

SUMMARY

Dermatologists should become more familiar with the regulatory reporting processes for ensuring the continued safe use of approved drugs because of the increase in new drugs approved for dermatologic conditions, approvals for novel drugs with unique mechanisms indicated for nondermatologic conditions where a dermatologist may be consulted for drug-induced adverse events, the common occurrence of CADR, and the rarity of Severe Cutaneous Adverse Reactions. Because dermatologists play a key role in differentiating different types of CADR and in identifying the likely culprit drug in the clinical setting, dermatologists can have a large impact on patient safety through spontaneous reporting of suspected adverse event-drug combinations to the FDA.

CLINICS CARE POINTS

- The drug labeling is a current and comprehensive summary of the safety and efficacy information reviewed by the FDA for approved drugs marketed in the United States.
- The voluntary reporting of observed adverse events with use of drugs enhances the postmarketing surveillance by the FDA, particularly if necessary details are included according to reporting guidelines.
- Dermatologists are positioned to identify the association between a drug and a cutaneous adverse reaction, particularly for uncommon reactions like SJS/TEN, and can aid in signal detection by submitting reports to the FAERS using MedWatch.

DISCLOSURE

This publication reflects the views of the authors and do not necessarily represent the FDA's views or policies.

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