CURRENT THERAPEUTIC RESEARCH
VOL. 62, NO. 9, SEPTEMBER 2001

# How the US Food and Drug Administration Defines and Detects Adverse Drug Events

Anne E. Trontell, MD, MPH

*Office of Post-Marketing Drug Risk Assessment, Division of Drug Risk Evaluation 1, US Food and Drug Administration, Rockville, Maryland*

## ABSTRACT

***Background:*** Examination of pediatric adverse drug events (ADEs) requires an understanding of the US Food and Drug Administration's (FDA's) regulatory definitions of ADEs and methods for their assessment.

***Objective:*** The aim of this paper was to characterize the tools used by the FDA to define ADEs.

***Methods:*** FDA regulations and ADE reporting databases and resources were examined, including the Adverse Event Reporting System (AERS), drug-use profiles, population databases, and active surveillance systems.

***Results:*** The US Code of Federal Regulations defines ADEs and degrees of seriousness of ADEs for regulatory reporting purposes. Drug manufacturers must report certain ADEs to the FDA, whereas health care professionals and consumers may report such events voluntarily using the MedWatch program. All reported ADEs constitute the FDA's AERS, which is used along with other postmarketing surveillance components to determine drug safety signals. AERS detects rare ADEs well and inexpensively, but underreporting and the variable quality of reports can limit its usefulness. AERS is best used in conjunction with other data resources, such as active surveillance systems, information on the volume and patterns of medication use, disease-specific background incidence rates, and population databases that can link outcomes with drug exposures.

***Conclusions:*** The FDA uses a network of data resources to supplement detection of ADEs via AERS. These data resources can be used to amplify, validate, and quantify ADE signals and then compare them to their expected background occurrence in the population. Use of additional databases and perspectives will improve the ability to detect ADEs in all settings, including the pediatric population, and to monitor risk management efforts to curtail the occurrence of known ADEs.

***Key words:*** US Food and Drug Administration, adverse drug events, pediatrics. (*Curr Ther Res Clin Exp.* 2001;62:641–649)

Presented at the Workshop on Adverse Drug Events in Pediatrics, Rockville, Maryland, April 9–10, 2001.

*Accepted for publication July 19, 2001.*
 0011-393X/01/$19.00

## INTRODUCTION

An analysis of adverse drug events (ADEs) in the pediatric population should begin with basic definitions and resources for ADEs in both adults and children. Tools used by the US Food and Drug Administration (FDA) to define and characterize ADEs are the same for both populations. The descriptions of these tools given in this paper provide a background to the proceedings of a jointly sponsored Workshop on Adverse Drug Events in Pediatrics held in Rockville, Maryland, April 9–10, 2001.*

## METHODS

The definitions of ADEs used by the FDA influence not only the nature but also the speed of ADE reporting by drug manufacturers. According to the US Code of Federal Regulations (CFR), drug companies must report to the FDA all ADEs that are known to them for all drugs that they market under a new or abbreviated drug application (NDA or ANDA). In contrast, drug companies are not required to report ADEs for products without an NDA or ANDA (eg, many over-the-counter products).

ADEs that are defined as *serious and unexpected* must be reported in an expedited fashion—that is, 15 days from the time that the drug company first becomes aware of the event. Events that are other than serious and unexpected (ie, *serious and expected, nonserious and unexpected,* and *nonserious and expected*) need only be reported to the FDA on a periodic basis. Definitions of all terms follow.

## RESULTS

The CFR[1] defines an ADE as any adverse event associated with the use of a drug marketed under an NDA or ANDA, whether or not that event is considered drug related. ADEs include accidental or intentional overdoses, events resulting from drug abuse or drug withdrawal, and failures of expected pharmacologic action.

A *serious* ADE is defined as the occurrence of any of a set of specific outcomes, regardless of dose, including death, life-threatening ADEs, hospitalization or the prolongation of hospitalization, persistent or significant disability or incapacity, congenital anomaly or birth defect, or other situations in which intervention is required to prevent the occurrence of one of the preceding events.[1] All other ADEs are defined as *nonserious*.

An *unexpected* ADE is defined as any event not listed in the current labeling for the drug product, including events that may be symptomatically and pathophysiologically related to a labeled event but differ because of greater severity or specificity. An example of an unexpected ADE would be hepatic necrosis associated with a drug where only hepatitis was labeled as an ADE. In those

*Sponsors of the workshop are listed in the Acknowledgments.

instances in which ADEs are listed in the current labeling for the drug product, they are defined as *expected.*

Pharmacists, physicians, other health care professionals, and consumers may report ADEs voluntarily, either directly to the FDA or to the drug manufacturers. Individuals reporting directly to the FDA can use MedWatch (the FDA's Safety Information and Adverse Event Reporting Program) to report ADEs by mail (c/o FDA, 5600 Fishers Lane, Rockville, MD 20852–9787), phone (1-800-FDA-1088), fax (1-800-FDA-1078), or the Internet (http://www.fda.gov/medwatch/how.htm). The MedWatch reporting form is shown in Figure 1. These reports are combined with reports from drug companies in the FDA's Adverse Event Reporting System (AERS).

AERS is the principal resource used by the FDA's Center for Drug Evaluation and Research to detect and characterize safety signals—that is, problems potentially associated with marketed drug products. The system originated in 1969 as the Spontaneous Reporting System and underwent substantial modifications and improvements in 1997, when it was renamed AERS. To date, AERS has received >2 million reports of adverse events for drug and therapeutic biologics. Vaccine safety data are not included but rather are reported to the Vaccine Adverse Event Reporting System (VAERS).

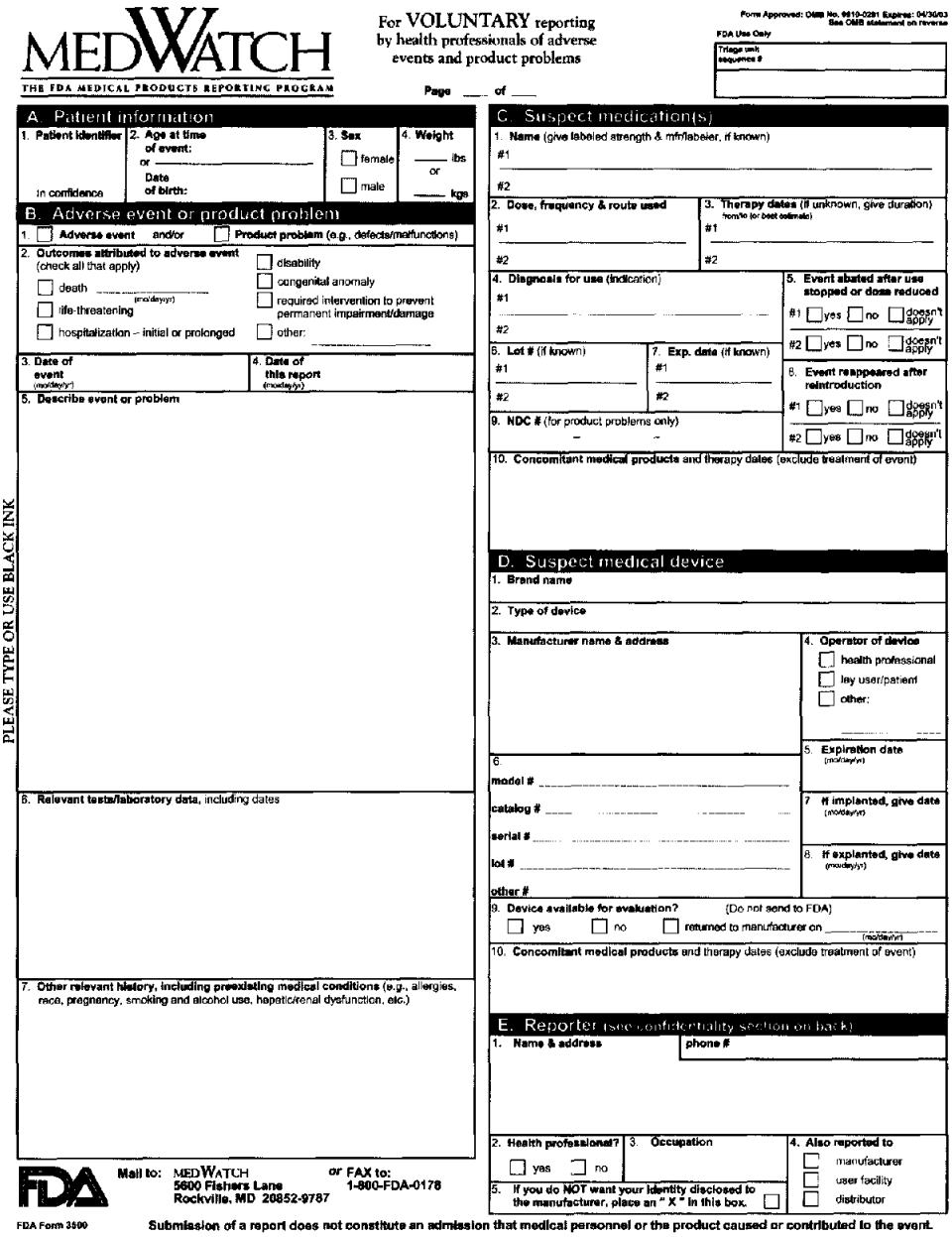
As seen in Figure 2, reporting of ADEs to the FDA has increased steadily over time, with ~300,000 ADEs now being reported annually. The vast majority (94%) of these reports come to the FDA from drug manufacturers. Contributions from the MedWatch program constitute the balance. About 35% of reports are expedited by manufacturers as serious and unexpected ADEs; the remaining 65% are submitted in quarterly or annual reports, depending on the duration of drug marketing.

## DISCUSSION

It is critical to understand the strengths and limitations of AERS for gathering and monitoring ADEs in both adult and pediatric patients (table). Strengths of AERS include its comprehensive coverage of all drug products marketed in the United States, its simplicity, and its low cost relative to active surveillance systems. AERS is particularly well configured to detect rare events (eg, liver failure and aplastic anemia), where the expected background incidence is in the range of a few cases per million people annually. In such instances, the occurrence of even a small number of cases raises safety concerns.

Limitations of AERS are typical of those seen with a passive or voluntary reporting system. The information submitted in reports is frequently incomplete or of poor quality. Underreporting of ADEs is extensive and has been estimated to range from 62% to 99%.[2–4] Reporting is also subject to secular influences, including the length of time a drug has been on the market[5] and the amount of publicity and media attention that has been given to a drug.

Detecting safety signals among the nearly 300,000 reports submitted annually to the FDA is a challenging task. Data mining approaches have been devel-



MEDWATCH
THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For VOLUNTARY reporting by health professionals of adverse events and product problems

Page ___ of ___

Form Approved: OMB No. 9910-0291 Expires: 04/30/03
See OMB statement on reverse

FDA Use Only
Triage unit sequence #

A. Patient information
1. Patient identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex: ☐ female ☐ male
4. Weight: ___ lbs or ___ kgs

B. Adverse event or product problem
1. ☐ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)
2. Outcomes attributed to adverse event (check all that apply)
☐ death (mo/day/yr)
☐ life-threatening
☐ hospitalization – initial or prolonged
☐ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☐ other:
3. Date of event (mo/day/yr)
4. Date of this report (mo/day/yr)
5. Describe event or problem
6. Relevant tests/laboratory data, including dates
7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. Suspect medication(s)
1. Name (give labeled strength & mfr/labeler, if known)
#1
#2
2. Dose, frequency & route used
#1
#2
3. Therapy dates (if unknown, give duration) (mo/da/yr (or best estimate))
#1
#2
4. Diagnosis for use (indication)
#1
#2
5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply
6. Lot # (if known)
#1
#2
7. Exp. date (if known)
#1
#2
8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply
9. NDC # (for product problems only)
– –
10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device
1. Brand name
2. Type of device
3. Manufacturer name & address
4. Operator of device
☐ health professional
☐ lay user/patient
☐ other:
5. Expiration date (mo/day/yr)
6.
model #
catalog #
serial #
lot #
other #
7. If implanted, give date (mo/day/yr)
8. If explanted, give date (mo/day/yr)
9. Device available for evaluation? (Do not send to FDA)
☐ yes ☐ no ☐ returned to manufacturer on (mo/day/yr)
10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)
1. Name & address
phone #
2. Health professional? ☐ yes ☐ no
3. Occupation
4. Also reported to
☐ manufacturer
☐ user facility
☐ distributor
5. If you do NOT want your identity disclosed to the manufacturer, place an " X " in this box. ☐

PLEASE TYPE OR USE BLACK INK

FDA
Mail to: MEDWATCH 5600 Fishers Lane Rockville, MD 20852-9787
or FAX to: 1-800-FDA-0178

FDA Form 3500

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

**Figure 1.** The US Food and Drug Administration's MedWatch reporting form.

**Table.** Strengths and limitations of the US Food and Drug Administration's Adverse Event Reporting System.

| Strengths | Limitations |
|---|---|
| Comprehensive | Underreporting |
| Simple | Variable quality of reports |
| Inexpensive | Influenced by secular factors |
| Good for rare outcomes | Cannot be used for incidence rates |

oped to systematically compare the ADEs associated with individual drugs with those of all products in the AERS system. In one method used by the FDA, Bayesian statistics are applied to generate relative signal scores of observed-to-expected values.[6,7] Graphic interfaces can be used to indicate the relative intensity of potential signals in comparison to the overall background observed for all drug products.

Vagaries in AERS reporting complicate determination of the actual number of ADEs related to a particular drug, thus influencing any attempts to determine the rate at which these events occur. The denominator of users or person-time

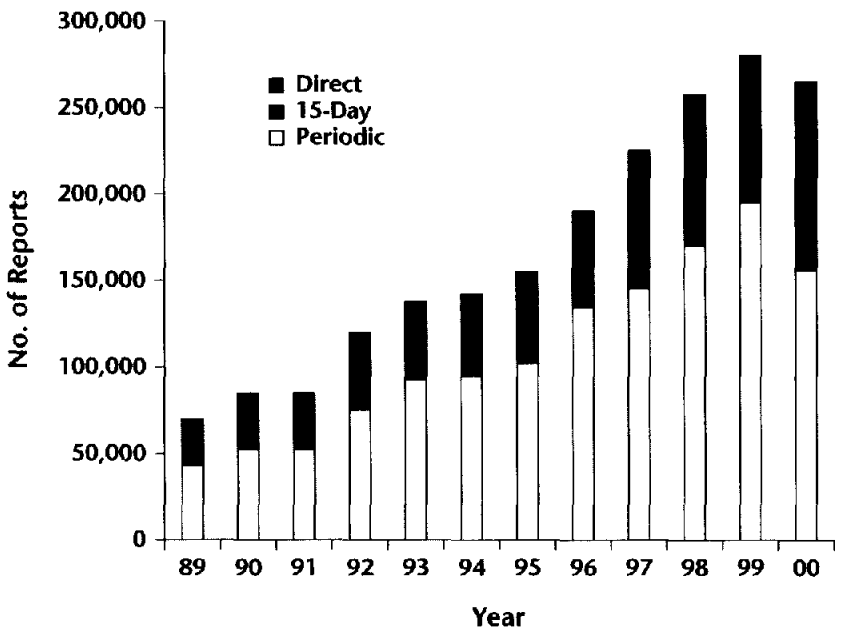



**Figure 2.** Adverse events reported to the US Food and Drug Administration's Adverse Event Reporting System from 1989 through 2000. Direct = MedWatch reports from individuals; 15-day = reports of serious unlabeled events from manufacturers; periodic = all reports (except serious unlabeled reports) from manufacturers.

exposure must be inferred from estimates of prescriptions dispensed and patterns of drug use. Obtaining this information is particularly complex for over-the-counter drug products and drugs used in inpatient settings. ADE rates based on spontaneous reports are referred to as reporting rates. They should be distinguished from incidence rates, which have sufficiently well characterized numerators of events and denominators of exposure time to allow meaningful (and statistical) estimation.

AERS is best viewed as the central component of a comprehensive postmarketing surveillance program, with 4 complementary data resources providing an integrated assessment of a drug's safety profile (Figure 3). Drug use data can be used to determine reporting rates and patterns of use, external health care databases can be used to validate and quantify signals of potential drug safety problems, active surveillance systems can supplement signal detection, and disease-specific background incidence rates can be used for comparative purposes.

Drug use data are available from a variety of commercial vendors for outpatient settings. Inpatient drug use data have historically been difficult to obtain, but these data may become available commercially in the near future. Outpatient drug use data may reveal the number of prescriptions dispensed; the average number of tablets per prescription; patient age, sex, and illnesses; and the types of physician specialists writing the prescriptions. Cross-sectional and longitudinal analyses of these types of data permit inferences about population exposure, survival analyses of the occurrence of ADEs for varying durations of exposure, and assessment of interventions designed to increase safety by modifying use patterns. Using information about the number of prescriptions written and the approximate duration of use enables estimates of person-years of

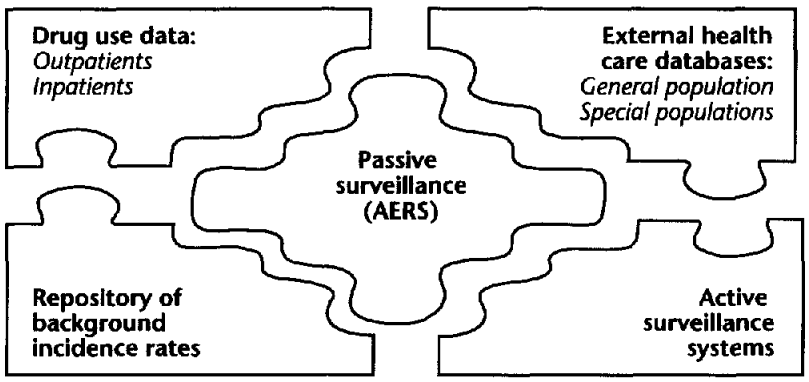



**Figure 3.** Components of a comprehensive postmarketing surveillance program. AERS = Adverse Event Reporting System.

exposure, especially for chronically administered drugs. These exposure estimates are the basis for the ADE reporting rates described previously.

External health care databases are population-based databases of inpatient and/or outpatient services linked to pharmacy claims. Such databases are available without personal identifiers through managed care and federal programs such as Medicare and Medicaid. The FDA has a network of such databases through its cooperative agreement program. Linked pharmacy and outcome claims can be used to validate and quantify safety signals from spontaneous reporting systems (eg, AERS) if the covered population exposed to the drug product is sufficiently large.

In instances in which an ADE is suspected but inconclusively associated with a drug product, active surveillance systems that solicit drug safety information may be helpful. Active surveillance systems may be useful in detecting or amplifying ADE signals by making specific queries or analyses of data systems. An example is the National Electronic Injury Surveillance System (NEISS), an emergency room surveillance system funded by the Consumer Product Safety Commission. The NEISS has recently expanded its data collection to include drug-associated injuries, and the FDA is exploring its potential usefulness in ADE surveillance. Similarly, the FDA is piloting an active surveillance system, the Medical Product Surveillance Network (MedSuN). This hospital-based program for device safety problems will eventually be expanded to include drug products.

When ADE reporting rates are calculated from spontaneous reports or when incidences are estimated from population databases, background rates of adverse outcomes provide an important context for comparison. Drug-associated occurrence rates that meet or exceed the background rate are worrisome, because ADEs are typically underreported. In instances in which the underlying disease carries some elevated risk of the event occurring (eg, sudden death among patients with epilepsy, liver failure among patients with diabetes), use of a background incidence rate in the specific subpopulation is desirable but rarely achieved. Background rates are often defined from literature sources that capture the disease experience of a particular geographic area.[8–10] In some instances, the background rate of a common drug-associated event has been estimated from public use databases (eg, the National Hospital Discharge Survey) that offer nationally representative samples of the US population.[11]

Once an ADE has been convincingly associated with a drug product using the FDA's AERS or other data resources, management or mitigation of risk begins. Risk management options often focus on drug relabeling, either to highlight the ADEs or to recommend modifications in use to improve the risk/benefit profile. For example, concomitant administration of certain drugs or the presence of comorbid illnesses may be contraindications, or a drug may be recommended for use only in severely ill patients or when first-line alternatives have failed. Patients can be enlisted to help detect and control the occurrence of safety

problems through education by means of patient package inserts and medication guides. Other risk management options include various restrictions on marketing and distribution to limit unsafe exposures (eg, black box warnings, informed consent, restricted distribution, mandatory patient registries).

When a drug product has been relabeled to modify its use, FDA data resources may help to determine whether recommendations are being followed. For example, drug use data can be used to track whether the appropriate populations are receiving the drug. Population databases can be examined to determine whether contraindicated medications or conditions are being avoided and patients are being monitored as recommended. One of the population-based resources available to the FDA through its network of cooperative agreements was used to determine whether pemoline was being reserved for second-line use in the treatment of attention-deficit hyperactivity disorder and whether the children receiving the drug were having their liver function monitored at an appropriate frequency (Mary Willy, FDA, personal communication, August 2001).

## CONCLUSIONS

The FDA uses a combination of data resources to support its detection of ADEs through AERS. These population and drug use resources enable the FDA to amplify, validate, and quantify the safety signals detected through AERS and to assess whether efforts to reduce safety problems are succeeding. Continued expansion and refinement of FDA data resources to include active surveillance and longitudinal and inpatient drug use are important priorities.

## ACKNOWLEDGMENTS

The Workshop on Adverse Drug Events in Pediatrics was sponsored by the National Institute of Child Health and Human Development, the US Food and Drug Administration, the Agency for Healthcare Research and Quality, and the United States Pharmacopeia.

The views expressed are those of the author. No official support or endorsement by the US Food and Drug Administration is provided or should be inferred. No commercial interest or other conflict of interest exists between the author and the manufacturers of the products.

## REFERENCES

1. *Federal Register* (codified at 21 CFR 314.80). US Government Printing Office, Washington, DC.
2. Scott HD, Rosenbaum SE, Walters WJ, et al. Rhode Island physicians' recognition and reporting of adverse drug reactions. *R I Med J.* 1987;70:311–316.
3. Bortnichak EA, Dai WS. Epidemiologists and adverse event data—a challenge to the field. *Pharmacoepidemiol Drug Saf.* 1999;8:457–461.

4. Martin RM, Kapoor KV, Wilton LV, Mann RD. Underreporting of suspected adverse drug reactions to newly marketed ("black triangle") drugs in general practice: Observational study. *Br Med J.* 1998;317:119–120.
5. Weber JCP. Epidemiology of adverse reactions to nonsteroidal anti-inflammatory drugs. In: Rainford KD, Velo GP, eds. *Advances in Information Research.* Vol 6. New York: Raven Press; 1984:1–7.
6. DuMouchel W. Bayesian data mining in large frequency tables, with an application to the FDA spontaneous reporting system. *Am Statistician.* 1999;53:177–190.
7. O'Neill RT, Szarfman A. Discussion: Bayesian data mining in large frequency tables, with an application to the FDA spontaneous reporting system, by William DuMouchel. *Am Statistician.* 1999;53:190–196.
8. Erie JC, Hodge DO, Gray DT. The incidence of primary angle-closure glaucoma in Olmsted County, Minnesota. *Arch Ophthalmol.* 1997;115:177–181.
9. Kannel WB. Need and prospects for prevention of cardiac failure. *Eur J Clin Pharmacol.* 1996;49(Suppl 1):S3–S9.
10. Boggild H, Tuchsen F, Orhede E. Occupation, employment status and chronic inflammatory bowel disease in Denmark. *Int J Epidemiol.* 1996;25:630–637.
11. La Grenade LA, Kornegay C, Graham DJ. Using publicly available data to derive background rates when evaluating adverse drug reaction reports. *Pharmacoepidemiol Drug Saf.* 2000;9:S70–S71.

**Address correspondence to:**
Anne E. Trontell, MD, MPH
Office of Post-Marketing Drug Risk Assessment
Division of Drug Risk Evaluation 1
HFD-430, Parklawn Room 15B-08
US Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
E-mail: trontella@cder.fda.gov