Annual Adverse Drug Experience Report: 1995

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INTRODUCTION

This report presents a descriptive overview of the 130,950 evaluable[1], postmarket adverse drug experience (ADE) cases received by the US Food and Drug Administration (FDA) during calendar year 1995[2]. A case consists of the original report of an ADE on a patient plus any followup information.

FDA has long conducted a program to monitor ADEs for marketed drugs. As part of this program, a computerized ADE database was begun in 1969 and has accumulated about 1.2 million cases. The primary purpose for maintaining the database is to serve as an early warning or signalling system for ADEs not detected during premarket testing. The ADE system depends upon detection of an adverse clinical event by a health professional or consumer, attribution of the clinical event to prior administration of a particular drug ("suspect" drug), and reporting of the ADE to the manufacturer of the suspected drug or directly to FDA. Data from these ADE cases are coded and entered into the computerized ADE database. Copies of the ADE cases are stored on microfilm or an imaging system. Up to five drugs per case may be entered into the computerized ADE database; the five can be a combination of "suspect" and "concomitant" drugs. Up to four adverse events per case and their associated body systems can be coded into the database, using FDA's "Coding Symbols for Thesaurus of Adverse Reaction Terms" (COSTART).

Reporting of postmarket ADEs by health professionals and consumers is voluntary. They may send their reports directly to FDA ("Direct" reports), to the drug manufacturer ("Manufacturer" reports), or both. Drug manufacturers are required by law and regulation to submit to FDA any postmarket ADE reports received by any means from health professionals or consumers.

It is important to remember certain caveats when using data from FDA's postmarket ADE database:

1. For any given ADE case, there is no certainty that the suspected drug caused the ADE. This is because physicians and consumers are encouraged to report all suspected ADEs, not just those that are already known to be caused by the drug. The adverse event may have been related to an underlying disease for which the drug was given, to other concomitant drugs, or may have occurred by chance at the same time the suspect drug was administered.

2. Accumulated ADE cases may not be used to calculate incidences or estimates of drug risk. Numbers from these data should be carefully interpreted as reporting rates and not occurrence or incidence rates.

Over the next pages, various kinds of data and information are presented on the postmarket ADE cases computerized into the FDA ADE database during calendar year 1995. Due to rounding,

[1]Excludes “React Uneval” cases.

[2]The 1995 postmarket ADE computerized data file used for this report was created June 1996.

the percentages in tables and graphs may not total to 100%. Figures 1 and 2 present copies of the postmarket ADE forms used by manufacturers and health professionals or consumers, respectively.

TYPES OF REPORTS

There are three types of reports in the FDA computerized postmarket ADE database:

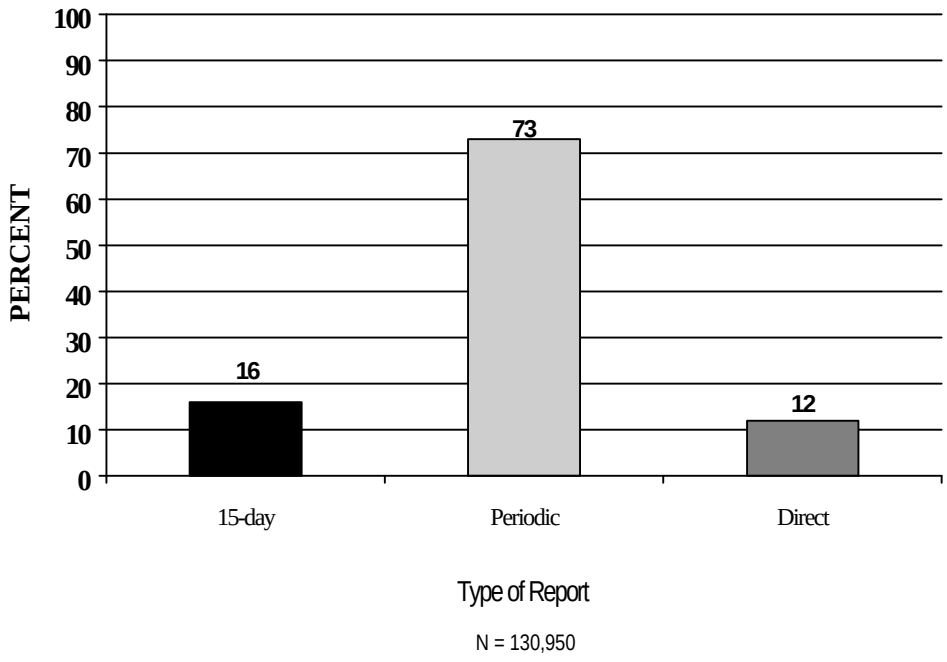
1. Manufacturer-reported cases concerning ADEs not in present official FDA labeling with serious outcomes (ie, death, life-threatening, hospitalization, permanent disability, congenital anomaly, cancer, or overdose). These cases are known in regulatory language as "**15-day Alert Reports**" because the manufacturer has 15 working days to submit this type of report to FDA.

2. All other manufacturer-reported cases. These cases are known in regulatory language as "**Periodic Reports**" because the manufacturer is required to submit them to FDA on a cyclical basis.

3. Cases sent directly to FDA by health professionals or consumers ("**Direct Reports**").

As shown in Figure 3, reports submitted to FDA via manufacturers accounted for 88% (115,663) of the 130,950 postmarket ADE cases. Only 12% (15,287) were submitted directly to FDA. 15-day reports were 16% (20,434) of the total.

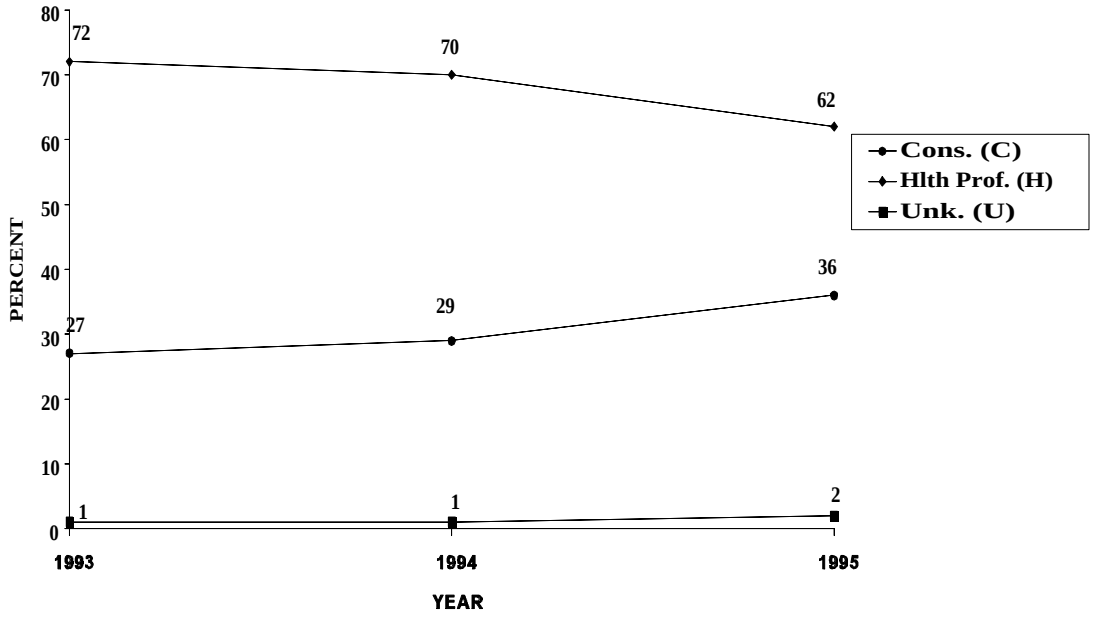
Figure 3. Postmarket ADE Reports By Type of Report: 1995



REPORTING BY HEALTH PROFESSIONALS AND CONSUMERS

As shown in Figure 4, in 1995, for a little over one-third of the 130,950 postmarket ADE cases, consumers were the initial reporters. Figure 4 also shows that, over a three-year trend (1993-5), reports from consumers have increased both in absolute numbers and proportionally, whereas those from health professionals have done the opposite.

Figure 4. ADE Reports By Health Professionals and Consumers, 1993-5



N (000s)	
C	32
H	86
U	1

N (000s)	
C	35
H	84
U	1

N (000s)	
C	48
H	81
U	2

GEOGRAPHIC LOCATION OF INITIAL REPORTER

As shown in Table 1, the initial reporter for 83% (108,735) of the 130,950 postmarket ADE cases was located within the US or its territories. Nine percent (11,843) of the cases were missing location source. For the 108,735 US cases, the top-two ranked regions, Middle and South Atlantic, accounted for two-fifths of the cases.

There were eight percent (10,372) of the postmarket ADE cases where the initial report source was foreign. There were four countries which each accounted for ≥10% of the foreign cases: France (22%, 2,288), Japan (14%, 1,490), Germany (13%, 1,310), and United Kingdom (12%, 1,289).

Table 1. Postmarket ADE Reports by Geographic Location of Initial Reporter: 1995

	N	*%*
All Locations	*130,950*	*100*
US CENSUS REGION:	108,735	83
[a]Middle Atlantic	21,507	20
South Atlantic	21,264	20
East North Central	16,748	15
Pacific	14,498	13
West South Central	9,003	8
West North Central	7,246	7
New England	6,664	6
Mountain	6,204	6
East South Central	5,475	5
Trust Territories	126	<1
FOREIGN:	10,372	8
[b]France	2,288	22
Japan	1,490	14
Germany	1,310	13
United Kingdom	1,289	12
UNKNOWN	11,843	9

[a]US Census Regions are percentaged to 108,735.
[b]Foreign countries are percentaged to 10,372.

SEX AND AGE OF PATIENTS

As shown in Table 2, the ratio of female-to-male postmarket ADE cases was 1.6:1. For females, the 20-39 year age group accounted for the greatest number of known sex-age cases, whereas for males, it was the ≥60 year age group.

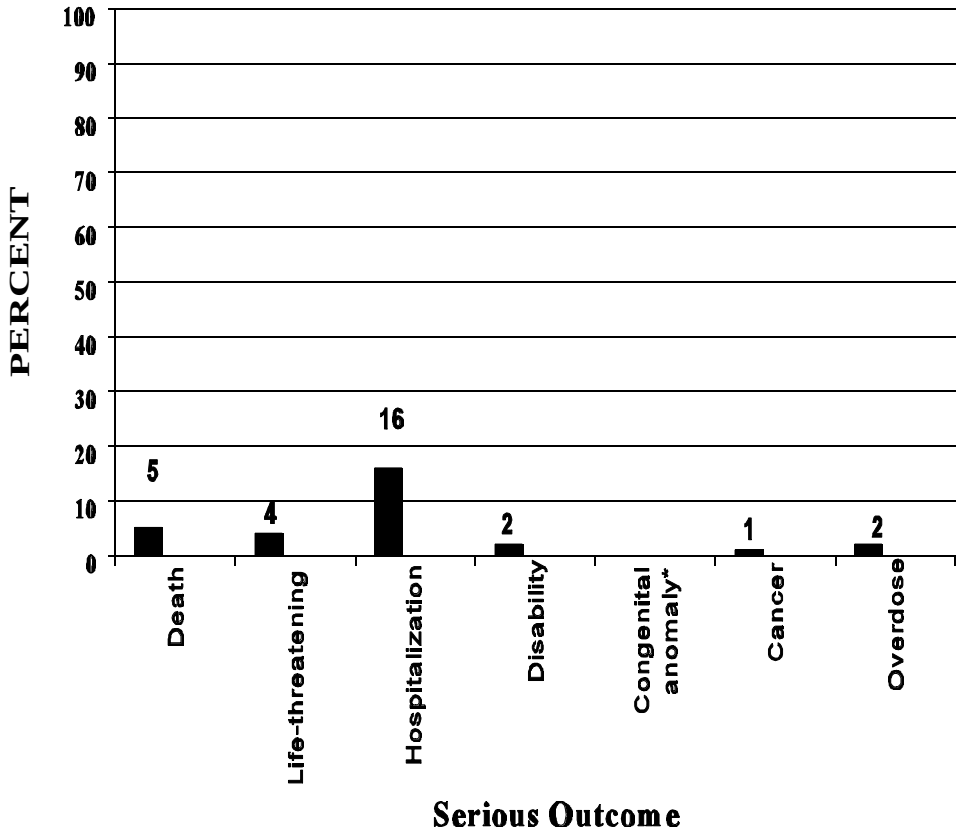
Table 2. Postmarket ADE Reports by Sex & Age of Patient: 1995

	N	*%*
All Sexes & Ages	*130,950*	*100*
ALL FEMALES:	73,341	56
≤19 yrs	5,202	4
20-39 yrs	18,311	14
40-59 yrs	15,092	12
≥60 yrs	15,651	12
Unknown age	19,085	14
ALL MALES:	44,473	34
≤19 yrs	3,886	3
20-39 yrs	6,485	5
40-59 yrs	9,779	7
≥60 yrs	14,298	11
Unknown age	10,025	8
UNKNOWN SEX:	13,136	10
≤19 yrs	284	<1
20-39 yrs	120	<1
40-59 yrs	174	<1
≥60 yrs	241	<1
Unknown age	12,317	9

SERIOUS OUTCOMES

As shown in Figure 5, hospitalization was the most recorded serious outcome; congenital anomaly, the least.

Figure 5. Postmarket ADE Reports by Type of Serious Report: 1995



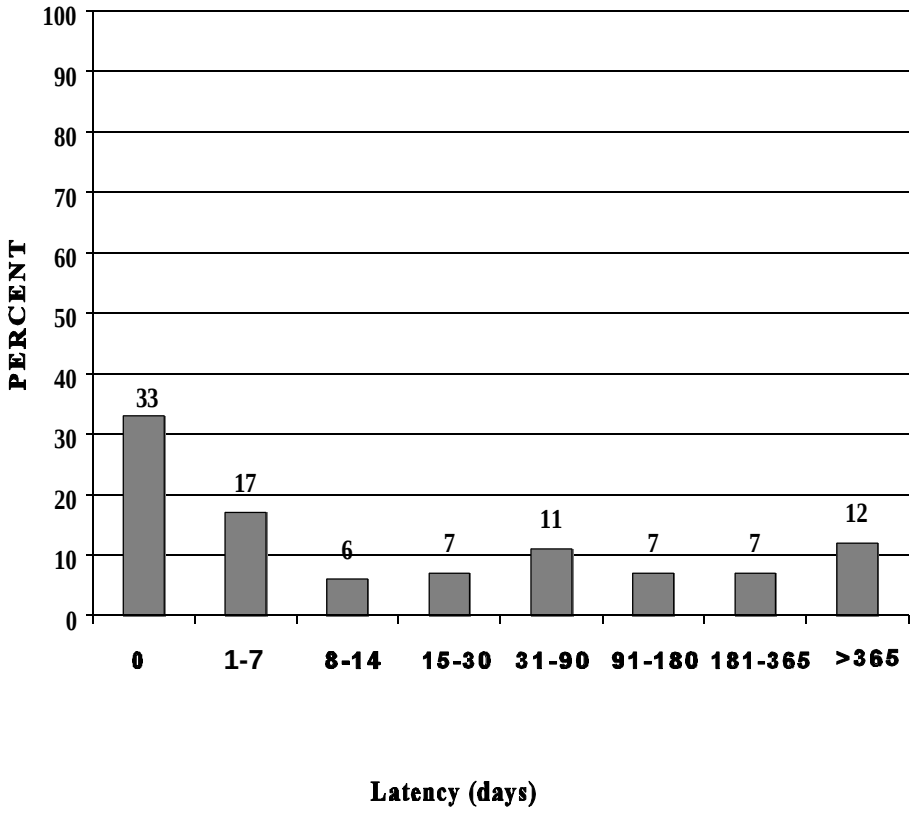
N = 130,950

*Less than 1%.

LATENCY BETWEEN SUSPECT DRUG ADMINISTRATION AND ADE ONSET

As shown in Figure 6, of the 130,950 postmarket ADE cases, 47% (61,412) had both a drug start date and an adverse experience onset date for the first-listed suspect drug and first-listed adverse experience, respectively, and where the drug date was computerized as occurring before the adverse experience date. About half of these cases noted that the adverse event occurred within one week of drug initiation.

Figure 6. Postmarket ADE Reports by Latency Period: 1995



N = 61,412

CLASSES OF SUSPECT DRUGS

Table 3 presents the top-10 ranked drug classes associated with the 153,842 suspect drugs computerized from the 130,950 postmarket ADE cases. The top-ranked drug class, central nervous system agents, accounted for approximately one-quarter of the drug class mentions.[3] Together with the second and third ranked drug classes, hormones and synthetic substitutes and cardiovascular drugs, these top three ranked drug classes comprised about half of the total drug class mentions.

Table 3. Postmarket ADE Reports by Top-10 Ranked Classes of Suspect Drugs: 1995

	N	*%*
All Suspect Drug Mentions	*153,842*	*100*
Central nervous system agents	42,254	28
Hormones & synthetic substitutes	21,173	14
Cardiovascular drugs	15,711	10
Anti-infective agents	14,117	9
Antineoplastic agents	10,191	7
Skin & mucous membrane agents	9,115	6
Autonomic drugs	6,658	4
Gastrointestinal drugs	5,589	4
Unclassified	5,436	4
Blood formation & coagulation	3,812	2

[3]The drug classification used was the American Hospital Formulary Service Pharmacologic - Therapeutic Classification (American Society of Health-System Pharmacists, Bethesda, Maryland, 1996).

SUSPECT DRUGS BY ENTRY NAME AND NEW MOLECULAR ENTITY STATUS

Table 4 shows the top-10 ranked suspect drugs as entered on the 130,950 postmarket ADE reporting forms. Three are nonprescription drugs, Aleve™, Today™, and Humulin™ insulin. Three are used by females (Norplant™, Depo-Provera™, and Today™) and one primarily by males (Rogaine™).

New Molecular Entities (NMEs) are defined as new drugs approved within the past three years. For this 1995 report, NMEs are new drugs approved during 1992-5. Of the 153,842 suspect drugs computerized from the 130,950 postmarket ADE cases, 15% (23,275) involved NMEs.

Table 4. Postmarket ADE Reports by Top-10 Ranked Suspect Drugs: 1995

	N	*%*
All Postmarket ADE Reports	*130,950*	*100*
Aleve™	6,642	5
Norplant™	5,712	4
Prozac™	3,253	2
Depo-Provera™	2,647	2
Risperdal™	2,540	2
Today™	2,319	2
Rogaine™	2,244	2
Humulin™ insulin	1,988	2
Mevacor™	1,940	1
Biaxin™	1,661	1

DRUG CLASSES STRATIFIED BY HEALTH PROFESSIONALS OR CONSUMERS, TYPE OF REPORT, AND YEAR

Table 5 shows the top-five ranked drug classes[3] associated with suspect drugs, stratified by whether the initial reporter was a health professional or consumer, the type of report, and year the case was computerized into the FDA postmarket ADE database.

1995 Data. In 1995, there were 141,578 drug class mentions where type of initial reporter and type of report were known. For consumers, only two of the top-five ranked drug classes were common to all report types: central nervous system agents and hormones and synthetic substitutes. For health professionals, there were four drug classes of the top-five ranked drug classes common to all report types: central nervous system agents, antineoplastic agents, anti-infective agents, and cardiovascular drugs. The only drug class in the top-five ranked drug classes common to both consumers and health professionals across report types was central nervous system agents.

Trend Data. Trend data from 1993 to 1995 show that only one drug class in the top five-ranked drug classes was common to both consumers and health professionals as well as all report types for all years: central nervous system agents.

[3]See previous.

ROUTES OF SUSPECT DRUGS

Table 6 presents the top-10 ranked routes of administration associated with the suspect drugs. There were 125,726 routes mentioned in conjunction with the 130,950 postmarket ADE cases. About three-fifths of the route mentions noted the oral route of administration.

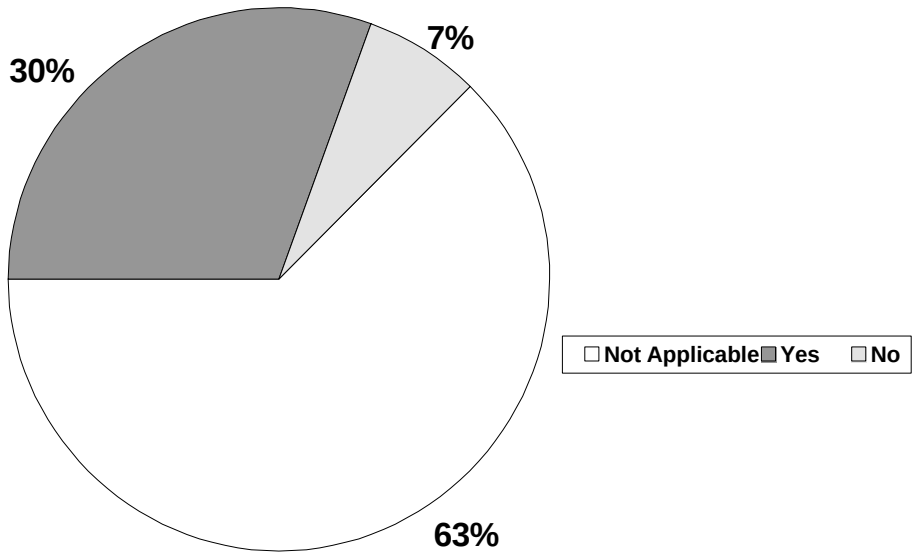
Table 6. Postmarket ADE Reports by Top-10 Ranked Routes of Administration of Suspect Drugs: 1995

	N	*%*
All Routes	*125,726*	*100*
Oral	77,320	62
Intravenous	13,648	11
Subcutaneous	9,534	8
Topical	6,101	5
Intramuscular	4,444	4
Vaginal	3,426	3
Transdermal	2,568	2
Inhalation	2,266	2
Ophthalmic	1,721	1
Nasal	1,014	1

ABATEMENT OF ADVERSE EVENT

For the 153,842 suspect drug mentions, 74% (113,921) had an answer to the question of whether the adverse event abated after the suspect drug was stopped or the dose was reduced. Figure 7 shows the distribution of responses. Thirty percent (34,433) of these 113,921 abate mentions indicated a positive dechallenge ("Yes" response).

Figure 7. Postmarket ADE Reports by Abate Response: 1995

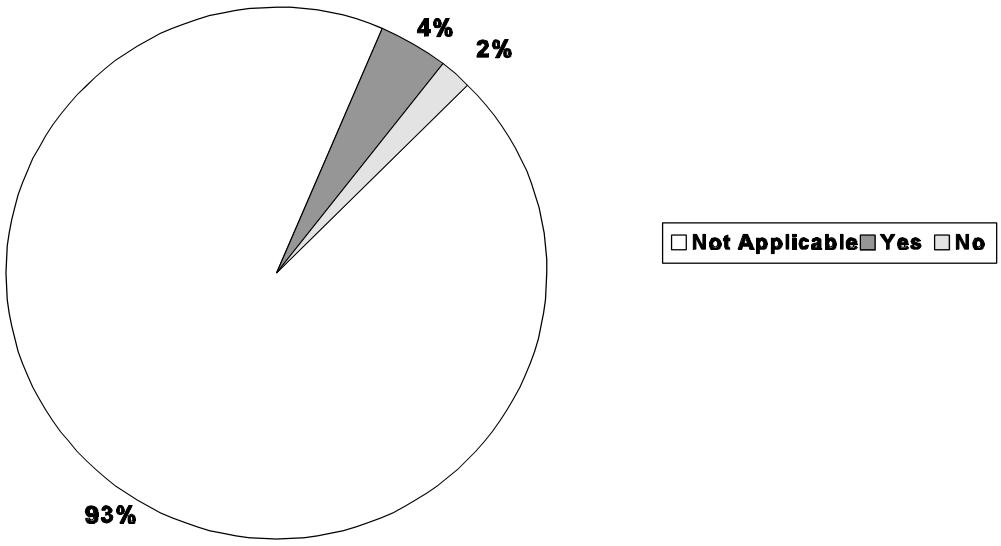


N = 113, 921

REOCCURRENCE OF ADVERSE EVENT

For the 153,842 suspect drug mentions, 70% (107,439) had an answer to the question of whether the adverse event reappeared after reintroduction of the suspect drug. Figure 8 shows the distribution of responses. Four percent (4,635) of these 107,439 reoccur mentions indicated a positive rechallenge ("Yes" response).

Figure 8. Postmarket ADE Reports by Reintroduction Response: 1995

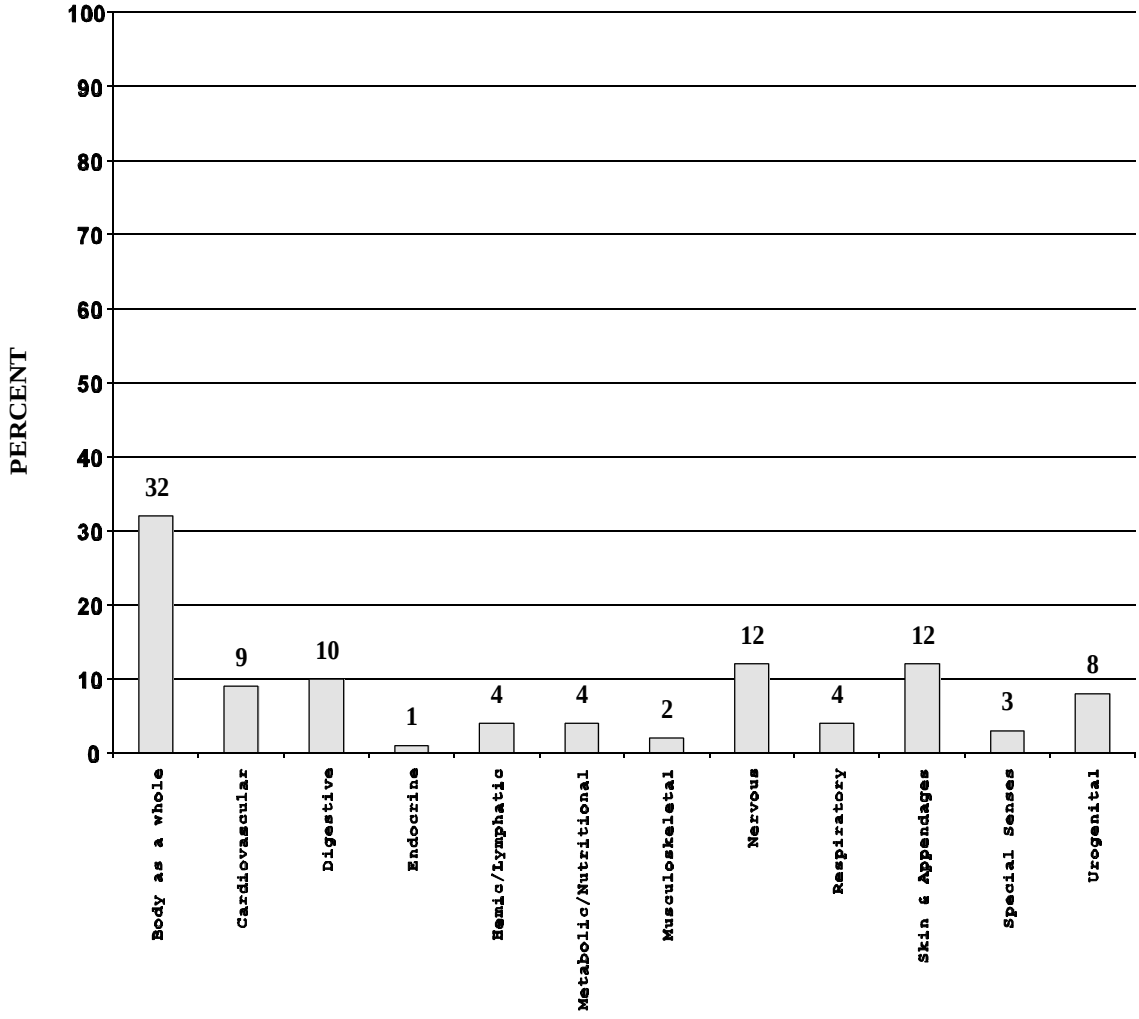


N = 107,439

BODY SYSTEMS

There were 140,182 body system mentions associated with the adverse events of the 130,950 postmarket ADE cases. The distribution of these mentions across the 12 body systems is presented in Figure 9. Four body systems each had ≥10% of the 140,182 body system mentions: body as a whole (systemic adverse events) - 32%, nervous and skin and appendages systems - each with 12%, and digestive system - 10%.

Figure 9. Postmarket ADE Reports by Body System: 1995
(N = 140, 182)



ADVERSE EVENTS

Table 7 shows the top-10 ranked adverse events reported with the 130,950 postmarket ADE cases. The top ranked ADE was "no drug effect"; 10% of the ADE cases reported this event. Metrorrhagia (2% of ADE cases), of course, would be female associated.

Table 7. Top-10 Ranked Adverse Events: 1995

Adverse Event	*N*	*%*
All Postmarket ADE Reports	*130,950*	*100*
No drug effect	13,416	10
Rash	3,036	2
Application site reaction	2,978	2
Aggravation of existing reaction	2,757	2
Headache	2,525	2
Metrorrhagia	2,354	2
Urticaria	2,291	2
Alopecia	2,021	2
Allergic reaction	1,924	1
Device migration	1,498	1

DRUG CLASSES ASSOCIATED WITH BODY SYSTEM ADVERSE EVENTS

Table 8 presents the four body systems comprising the most adverse events, each of which has been crosstabulated by its top-five ranked suspect associated drug classes.[3] Central nervous system agents and hormones and synthetic substitutes held the top-two ranks, respectively, for all four body systems. Two other drug classes were in the top-five ranks for all four body systems, cardiovascular drugs and anti-infective agents.

Table 8. Top-4 Ranked Body Systems with Their Respective Top-5 Ranked Suspect Drug Classes: 1995

Body System	*Suspect Drug Class*	*N*	*%*
Body as a whole	*All*	*44,257*	*100*
	Central nervous system agents	12,499	28
	Hormones & synthetic substitutes	5,074	11
	Cardiovascular drugs	4,478	10
	Anti-infective agents	4,074	9
	Antineoplastic agents	2,689	6
Skin & appendages	*All*	*17,284*	*100*
	Central nervous system agents	4,148	24
	Hormones & synthetic substitutes	2,294	13
	Anti-infective agents	1,907	11
	Skin & mucous membrane agents	1,816	10
	Cardiovascular drugs	1,654	10
Nervous	*All*	*16,930*	*100*
	Central nervous system agents	4,421	26
	Hormones & synthetic substitutes	3,202	19
	Cardiovascular drugs	1,966	12
	Anti-infective agents	1,578	9
	Antineoplastic agents	1,242	7
Digestive	*All*	*13,333*	*100*
	Central nervous system agents	4,131	31
	Hormones & synthetic substitutes	2,234	17
	Cardiovascular drugs	1,199	9
	Anti-infective agents	1,144	8
	Antineoplastic agents	838	6

[3] See Previous