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Pediatric Postmarketing Pharmacovigilance Review

Date:	June 30, 2025
Reviewers:	Debra Ryan, PharmD, MBA, Safety Evaluator Division of Pharmacovigilance I (DPV-I) Ivone Kim, MD, Medical Officer DPV-I
Team Leader:	Carmen Cheng, PharmD DPV-I
Division Director:	Monica Muñoz, PharmD, PhD, BCPS DPV-I
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TABLE OF CONTENTS

Executive Summary 1
1 Introduction 2
  1.1 Pediatric Regulatory History 2
  1.2 Relevant Labeled Safety Information 3
2 Methods and Materials 6
  2.1 FAERS Search Strategy 6
3 Results 6
  3.1 FAERS 6
    3.1.1 Selection of U.S. Serious Pediatric Cases in FAERS 6
    3.1.2 Summary of U.S. Fatal Pediatric Cases (N=0) 7
    3.1.3 Summary of U.S. Serious Non-Fatal Pediatric Cases (N=0) 7
4 Discussion 8
5 Conclusion 8
6 References 8
7 Appendices 9
  7.1 Appendix A. FDA Adverse Event Reporting System (FAERS) 9

EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Dupixent (dupilumab) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with dupilumab in pediatric patients.

Dupixent (dupilumab) is an interleukin-4 receptor alpha antagonist and was initially approved in the U.S. on March 28, 2017. Dupilumab is currently indicated for:

- Treatment of atopic dermatitis in adult and pediatric patients aged 6 months and older with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Dupilumab can be used with or without topical corticosteroids.
- Add-on maintenance treatment of asthma in adult and pediatric patients aged 6 years and older with moderate-to-severe asthma characterized by an eosinophilic phenotype or with oral corticosteroid dependent asthma. Limitations of use: not for the relief of acute bronchospasm or status asthmaticus.
- Add-on maintenance treatment of chronic rhinosinusitis with nasal polyps in adult and pediatric patients aged 12 years and older with inadequately controlled chronic rhinosinusitis with nasal polyps.
- Treatment of eosinophilic esophagitis in adult and pediatric patients aged 1 year and older, weighing at least 15 kg.
- Treatment of prurigo nodularis in adult patients.
- Add-on maintenance treatment for chronic obstructive pulmonary disease in adult patients with inadequately controlled chronic obstructive pulmonary disease and an eosinophilic phenotype.
- Treatment of chronic spontaneous urticaria in adult and pediatric patients 12 years and older with chronic spontaneous urticaria who remain symptomatic despite H1 antihistamine treatment. Limitations of use: not indicated for other forms of urticaria.

This pediatric postmarketing safety review for dupilumab was stimulated by the following pediatric labeling:

- October 19, 2018: FDA approved use of dupilumab for the add-on maintenance treatment in patients aged 12 years and older with moderate to severe asthma with an eosinophilic phenotype or with oral corticosteroid dependent asthma.
- March 11, 2019: Expanded the use of dupilumab to a new patient population: patients aged 12 to <18 years with moderate-to-severe atopic dermatitis.
- May 26, 2020: Expanded the use of dupilumab to a new patient population: patients aged 6 to <12 years with moderate-to-severe atopic dermatitis.
- October 20, 2021: Expanded the use of dupilumab to a new patient population: add-on maintenance treatment of patients aged 6 to <12 years with moderate-to-severe asthma.
- June 7, 2022: Expanded the use of dupilumab to a new population: patients aged 6 months to <6 years with moderate-to-severe atopic dermatitis.

DPV reviewed all U.S. serious FAERS reports with dupilumab in pediatric patients less than 18 years of age from March 28, 2017, through February 3, 2025, and identified 1,363 reports; however, all reports were excluded from further discussion.

There were no new safety signals identified, no increased severity of any labeled adverse events, and no deaths directly associated with dupilumab in pediatric patients less than 18 years of age.

DPV did not identify any new pediatric safety concerns for dupilumab at this time and will continue routine pharmacovigilance monitoring for dupilumab.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Dupixent (dupilumab) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with dupilumab in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Dupixent (dupilumab) is an interleukin-4 receptor alpha antagonist and was initially approved in the U.S. on March 28, 2017. Dupilumab is currently indicated for:[1]

- Treatment of atopic dermatitis in adult and pediatric patients aged 6 months and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Dupilumab can be used with or without topical corticosteroids.
- Add-on maintenance treatment of asthma in adult and pediatric patients aged 6 years and older with moderate-to-severe asthma characterized by an eosinophilic phenotype or with oral corticosteroid dependent asthma. Limitations of use: not for the relief of acute bronchospasm or status asthmaticus.
- Add-on maintenance treatment of chronic rhinosinusitis with nasal polyps in adult and pediatric patients aged 12 years and older with inadequately controlled chronic rhinosinusitis with nasal polyps.
- Treatment of eosinophilic esophagitis in adult and pediatric patients aged 1 year and older, weighing at least 15 kg.
- Treatment of prurigo nodularis in adult patients.
- Add-on maintenance treatment for chronic obstructive pulmonary disease in adult patients with inadequately controlled chronic obstructive pulmonary disease and an eosinophilic phenotype.
- Treatment of chronic spontaneous urticaria in adult and pediatric patients 12 years and older with chronic spontaneous urticaria who remain symptomatic despite H1 antihistamine treatment. Limitations of use: not indicated for other forms of urticaria.

This pediatric postmarketing safety review for dupilumab was stimulated by the following pediatric labeling summarized in Table 1.

Table 1. Pediatric Labeling Changes for Dupilumab	
Date	**Labeling Change**
October 19, 2018	FDA approved use of dupilumab for the add-on maintenance treatment in patients aged 12 years and older with moderate to severe asthma with an eosinophilic phenotype or with oral corticosteroid dependent asthma.[2]
March 11, 2019	Expanded the use of dupilumab to a new patient population: patients aged 12 to <18 years with moderate-to-severe atopic dermatitis.[3]
May 26, 2020	Expanded the use of dupilumab to a new patient population: patients aged 6 to <12 years with moderate-to-severe atopic dermatitis.[4]
October 20, 2021	Expanded the use of dupilumab to a new patient population: add-on maintenance treatment of patients aged 6 to <12 years with moderate-to-severe asthma.[5]
June 7, 2022	Expanded the use of dupilumab to a new patient population: patients aged 6 months to <6 years with moderate-to-severe atopic dermatitis.[6]

A pediatric safety review for dupilumab has not previously been presented to the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION

The Dupixent labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For additional Dupixent labeling information, please refer to the full prescribing information.

---------------------------------**CONTRAINDICATIONS**---------------------------------

- Known hypersensitivity to dupilumab or any excipients in DUPIXENT.

-------------------------WARNINGS AND PRECAUTIONS-------------------------

- Hypersensitivity: Hypersensitivity reactions including anaphylaxis, serum sickness, angioedema, urticaria, rash, erythema nodosum, and erythema multiforme have occurred. Discontinue DUPIXENT in the event of a hypersensitivity reaction.
- Conjunctivitis and Keratitis: Advise patients to report new onset or worsening eye symptoms to their healthcare provider. Consider ophthalmological examination, as appropriate.
- Eosinophilic Conditions: Be alert to vasculitic rash, worsening pulmonary symptoms, and/or neuropathy, especially upon reduction of oral corticosteroids.
- Reduction of Corticosteroid Dosage: Do not discontinue systemic, topical, or inhaled corticosteroids abruptly upon initiation of DUPIXENT. Decrease steroids gradually, if appropriate.
- Psoriasis: Advise patients to report new-onset psoriasis symptoms to their healthcare provider. If symptoms persist or worsen, consider dermatologic evaluation and/or discontinuation of DUPIXENT.
- Arthralgia and Psoriatic Arthritis: Advise patients to report new onset joint symptoms to their healthcare provider. If symptoms persist or worsen, consider rheumatological evaluation and/or discontinuation of DUPIXENT.
- Parasitic (Helminth) Infections: Treat pre-existing helminth infections before initiating DUPIXENT. If patients become infected while receiving DUPIXENT and do not respond to anti-helminth treatment, discontinue DUPIXENT until the infection resolves.
- Vaccinations: Avoid use of live vaccines.

-----------------------------ADVERSE REACTIONS-----------------------------

Most common adverse reactions are:

- Atopic Dermatitis (incidence >1%): injection site reactions, conjunctivitis, blepharitis, oral herpes, keratitis, eye pruritus, other herpes simplex virus infection, dry eye, and eosinophilia.
- Asthma (incidence >1%): injection site reactions, oropharyngeal pain, and eosinophilia.
- Chronic Rhinosinusitis with Nasal Polyps (incidence >1%): injection site reactions, eosinophilia, insomnia, toothache, gastritis, arthralgia, and conjunctivitis.
- Eosinophilic Esophagitis (incidence >2%): injection site reactions, upper respiratory tract infections, arthralgia, and herpes viral infections.
- Prurigo Nodularis (incidence >2%): nasopharyngitis, conjunctivitis, herpes infection, dizziness, myalgia, and diarrhea.
- Chronic Obstructive Pulmonary Disease (incidence >2%): viral infection, headache, nasopharyngitis, back pain, diarrhea, arthralgia, urinary tract infection, local administration reactions, rhinitis, eosinophilia, toothache, and gastritis.
- Chronic Spontaneous Urticaria (incidence ≥2%): injection site reactions.

-----------------------------USE IN SPECIFIC POPULATIONS-----------------------------

8.4 Pediatric Use

Atopic Dermatitis
The safety and effectiveness of DUPIXENT have been established in pediatric patients 6 months of age and older with moderate-to-severe AD, whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

Use of DUPIXENT in this age group is supported by data from the following clinical trials:

- AD-1526 which included 251 pediatric subjects 12 to 17 years of age with moderate-to-severe AD. Of the 251 subjects, 82 were treated with DUPIXENT 200 mg Q2W (<60 kg) or 300 mg Q2W (≥60 kg) and 85 were treated with matching placebo.
- AD-1652 which included 367 pediatric subjects 6 to 11 years of age with severe AD. Of the 367 subjects, 120 were treated with DUPIXENT 300 mg Q4W + TCS (15 to <30 kg) or 200 mg Q2W + TCS ≥30kg and 123 were treated with matching placebo.
- AD-1539 which included 162 pediatric subjects 6 months to 5 years of age with moderate-to-severe AD. Of the 162 subjects, 83 were treated with DUPIXENT 200 mg Q4W + TCS (5 to <15 kg) or 300 mg Q4W + TCS (15 to <30 kg) and 79 subjects were assigned to be treated with matching placebo + TCS.
- AD-1434, an open-label extension study that enrolled 275 pediatric subjects 12 to 17 years of age treated with DUPIXENT ± TCS, 368 pediatric subjects 6 to 11 years of age treated with DUPIXENT ± TCS, and 180 pediatric subjects 6 months to 5 years of age treated with DUPIXENT ± TCS.
- Liberty-AD-HAFT which included 27 pediatric subjects 12 to 17 years of age with atopic dermatitis with moderate-to-severe hand and/or foot involvement treated with DUPIXENT (N=14) or matching placebo (N=13).

The safety and effectiveness were generally consistent between pediatric and adult patients. In addition, hand-foot-and-mouth disease was reported in 9 (5%) pediatric patients and skin papilloma were reported in 4 (2%) pediatric subjects 6 months to 5 years of age treated with DUPIXENT ± TCS in AD-1434. These cases did not lead to study drug discontinuation.

Safety and effectiveness in pediatric patients younger than 6 months of age with AD have not been established.

Asthma
The safety and effectiveness of DUPIXENT for an add-on maintenance treatment in patients with moderate-to-severe asthma characterized by an eosinophilic phenotype or with oral corticosteroid dependent asthma have been established in pediatric patients 6 years of age and older. Use of DUPIXENT for this indication is supported by evidence from adequate and well controlled studies in adult and pediatric patients 6 years and older.

Pediatric Subjects 12 to 17 Years of Age:
A total of 107 pediatric subjects 12 to 17 years of age with moderate-to-severe asthma were enrolled in QUEST and received either 200 mg (N=21) or 300 mg (N=18) DUPIXENT (or matching placebo either 200 mg [N=34] or 300 mg [N=34]) Q2W. Asthma exacerbations and lung function were assessed in both pediatric subjects 12 to 17 years of age and adults. For both the 200 mg and 300 mg Q2W doses, improvements in FEV_1 (LS mean change from baseline at Week 12) were observed (0.36 L and 0.27 L, respectively). For the 200 mg Q2W dose, subjects had a reduction in the rate of severe exacerbations that was consistent with adults. Dupilumab exposure was higher in pediatric subjects 12 to 17 years of age than that in adults at the respective dose level which was mainly accounted for by difference in body weight.

The adverse event profile in pediatric subjects 12 to 17 years of age was generally similar to the adults.

Pediatric Subjects 6 to 11 Years of Age:
A total of 408 pediatric subjects 6 to 11 years of age with moderate-to-severe asthma were enrolled in VOYAGE, which evaluated doses of 100 mg Q2W or 200 mg Q2W. Improvement in asthma exacerbations and lung function were demonstrated. The effectiveness of DUPIXENT 300 mg Q4W in subjects 6 to 11 years of age with body weight 15 to <30 kg was extrapolated from efficacy of 100 mg Q2W in VOYAGE with support from population pharmacokinetic analyses showing higher drug exposure levels with 300 mg Q4W. Subjects who completed the treatment period of the VOYAGE study could participate in the open-label extension study (LTS14424). Eighteen subjects (≥15 to <30 kg) out of 365 subjects were exposed to 300 mg Q4W in this study, and the safety profile in these eighteen subjects was consistent with that seen in VOYAGE. Additional safety for DUPIXENT 300 mg Q4W is based upon available safety information from the pediatric AD indication.

Safety and effectiveness in pediatric patients younger than 6 years of age with asthma have not been established.

CRSwNP
The safety and effectiveness of DUPIXENT for add-on maintenance treatment in patients with inadequately controlled chronic rhinosinusitis with nasal polyps (CRSwNP) have been established in pediatric patients aged 12 years and older. Use of DUPIXENT for this indication is supported by evidence from adequate and well-controlled studies of DUPIXENT as add-on maintenance treatment in adults with inadequately controlled CRSwNP (SINUS-24 and SINUS-52) with the following additional data:
- Pharmacokinetic (PK) data from adult and pediatric patients aged 12 years and older with moderate-to-severe asthma and adult patients with inadequately controlled CRSwNP.
- Safety data in pediatric patients aged 12 years and older with moderate-to-severe asthma

Safety and effectiveness in pediatric patients younger than 12 years of age with CRSwNP have not been established.

EoE
The safety and effectiveness of DUPIXENT for the treatment of EoE have been established in pediatric subjects 1 year of age and older, weighing at least 15 kg. Use of DUPIXENT in this population is supported by an adequate well-controlled study in adults and 72 pediatric subjects 12 to 17 years of age (Study EoE-1), a clinical study in 61 pediatric subjects 1 to 11 years of age (Study EoE-2), and pharmacokinetic data in adult and pediatric subjects 1 to 17 years of age. The safety of DUPIXENT in pediatric subjects 1 to 17 years of age was similar to adults.

Safety and effectiveness in pediatric patients younger than 1 year of age, or weighing less than 15 kg, with EoE have not been established.

Prurigo Nodularis
Safety and effectiveness in pediatric patients younger than 18 years of age with PN have not been established.

Chronic Obstructive Pulmonary Disease
The safety and effectiveness in pediatric patients less than 18 years of age with COPD have not been established. COPD is largely a disease of adult patients.

Chronic Spontaneous Urticaria
The safety and effectiveness of DUPIXENT for the treatment of CSU in patients who remain symptomatic despite H1 antihistamine treatment have been established in pediatric patients 12 years of age and older. The use of DUPIXENT in this indication is supported by evidence from two adequate and well-controlled studies in adults with additional pharmacokinetic data in 6 pediatric patients 12 years of age and older, and safety data in pediatric patients in other indications.

Safety and effectiveness in pediatric patients younger than 12 years of age, and/or weighing less than 30 kg, with CSU have not been established.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 2.

Table 2. FAERS Search Strategy*	
Date of search	February 4, 2025
Time period of search	March 28, 2017† - February 3, 2025
Search type	RxLogix Pediatric Focused Review
Product term	Product Active Ingredient: Dupilumab
MedDRA search terms (Version 27.1)	All Preferred Terms
Other criteria‡	Case Seriousness: Serious Country Derived: USA
* See Appendix A for a description of the FAERS database. † Dupixent (dupilumab) U.S. approval date. ‡ For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events. Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; USA=United States of America	

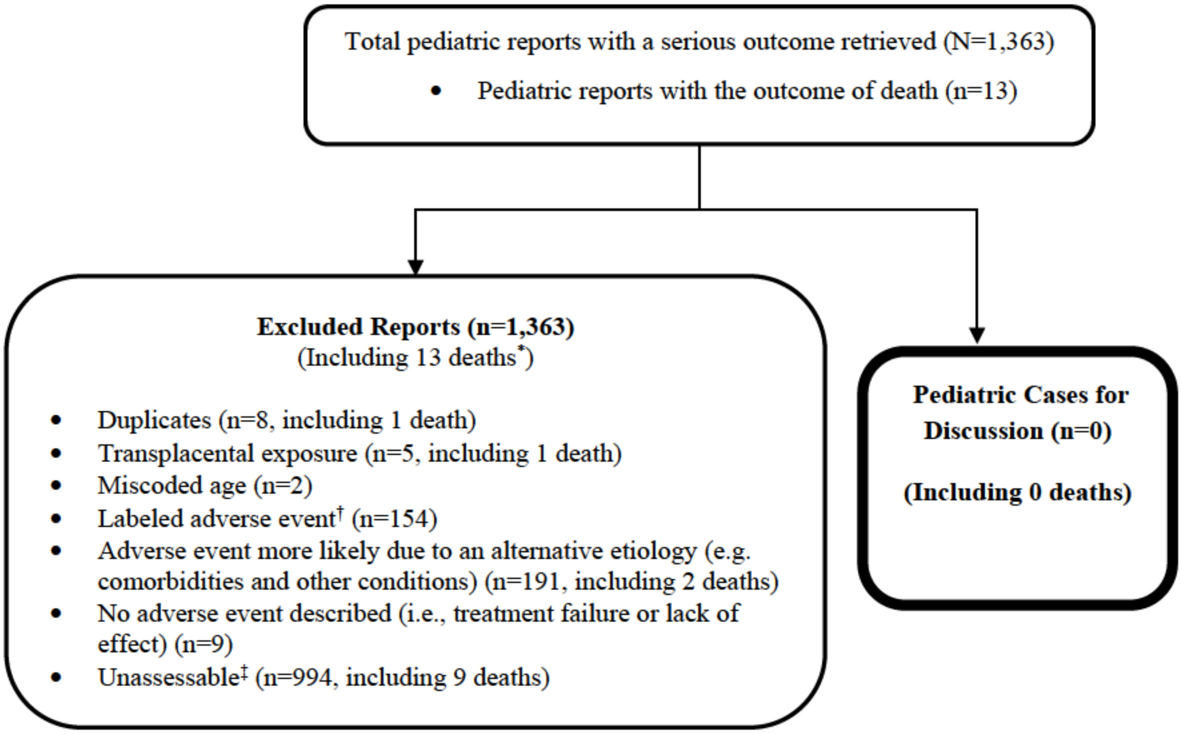
3 RESULTS

3.1 FAERS

3.1.1 Selection of U.S. Serious Pediatric Cases in FAERS

Our FAERS search retrieved 1,363 U.S. serious pediatric reports for patients less than 18 years old from March 28, 2017 - February 3, 2025. We excluded all 1,363 reports from the case series for the reasons listed in Figure 1.

Figure 1. Selection of U.S. Serious Pediatric Cases with Dupilumab



* We identified 13 reports describing a fatal outcome. After accounting for duplicate reporting (n=1) we identified 12 unique cases describing a fatal outcome. One case described death of a fetus due to multiple congenital anomalies (congenital high airway obstruction syndrome, Tetralogy of Fallot, and ascites). Two cases described fatal events due to other causes: one case reported the patient was “a victim of [redacted] and the other case described a patient who died from pneumonia complicated by hypoxic ischemic brain injury. The remaining cases (n=9) had insufficient information to determine if dupilumab contributed to the fatal event.

† Labeled adverse event does not represent increased severity.

‡ Unassessable: The report cannot be assessed for causality because there is insufficient information reported (i.e., unknown time to event, concomitant medications and comorbidities, clinical course and outcome), the information is contradictory, or information provided in the report cannot be supplemented or verified.

3.1.2 Summary of U.S. Fatal Pediatric Cases (N=0)

There are no fatal pediatric adverse event cases for discussion.

3.1.3 Summary of U.S. Serious Non-Fatal Pediatric Cases (N=0)

There are no non-fatal pediatric adverse event cases for discussion.

4 DISCUSSION

DPV reviewed all U.S. serious FAERS reports with dupilumab in pediatric patients less than 18 years of age from March 28, 2017, through February 3, 2025, and identified 1,363 reports; however, all reports were excluded from further discussion.

There were no new safety signals identified, no increased severity of any labeled adverse events, and no deaths directly associated with dupilumab in pediatric patients less than 18 years of age.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for dupilumab at this time and will continue routine pharmacovigilance monitoring for dupilumab.

6 REFERENCES

1. Dupixent (dupilumab) [package insert]. Tarrytown, NY. Regeneron Pharmaceuticals, Inc. Revised April 2025.

2. BLA 761055 Supplement Approval Letter. Available at Drugs@FDA: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2018/761055Orig1s007ltr.pdf. Accessed: May 27, 2025.

3. BLA 761055 Supplement Approval Letter. Available at Drugs@FDA: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2019/761055Orig1s012ltr.pdf Accessed: May 27, 2025.

4. BLA 761055 Supplement Approval Letter. Available at Drugs@FDA: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2020/761055Orig1s020ltr.pdf Accessed: May 27, 2025.

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6. BLA 761055 Supplement Approval Letter. Available at Drugs@FDA: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2022/761055Orig1s042ltr.pdf Accessed: May 27, 2025.

7 APPENDICES

7.1 Appendix A. FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.