Benzoyl peroxide, salicylic acid, sulfur and resorcinol/sulfur are marketed, active ingredients for over-the-counter (OTC) topical acne monograph products for the treatment of acne vulgaris. Both single-ingredient and combination OTC topical acne products are regulated by the OTC monograph in 21 CFR 333 and are considered GRAS (Generally Recognized as Safe and Effective). In 2006, the Federal Food, Drug and Cosmetic Act was amended by Public Law 109-662, to require that all serious adverse events be reported for dietary supplements and nonprescription OTC drugs marketed without an approved application when used in the US. This analysis was initiated due to the identification of an increasing number of hypersensitivity-related reports associated with the use of OTC topical acne monograph products.

We assessed data from the FDA Adverse Event Reporting System (FAERS) to evaluate the postmarket adverse event experience for topical OTC acne monograph products in association with serious hypersensitivity reactions, with benzoyl peroxide, salicylic acid, sulfur or resorcinol/sulfur as active ingredients.

We searched the FAERS database for reports of OTC topical acne products associated with hypersensitivity reactions submitted from the database inception (1969) to January 28, 2013. To provide context for the adverse event reports submitted to the FAERS database, the retail sales of these products were assessed using the OTC International Market Tracking database.

Because of the clinical significance of anaphylaxis, each hypersensitivity case-report was further evaluated to identify cases of anaphylaxis. Each case of anaphylaxis met the following criteria: 1) Reporting of one of the following adverse events: anaphylaxis, anaphylactoid reaction, systemic shock, anaphylactoid shock, angioedema, or shock; 2) Involvement of skin or mucosal tissue, and 3) Assessment of at least one of the following organ systems: respiratory or cardiovascular. The remaining cases were considered non-anaphylaxis in nature and classified as a non-anaphylaxis hypersensitivity reaction.

Limitations of FAERS data include: underreporting, stimulated reporting, biased reporting, variable quality and content, and no certainty that the reported event is due to the product.

We identified 131 cases associated with OTC topical acne products (benzoyl peroxide, n=110; salicylic acid, n=21). Reported adverse events ranged from application site reactions to anaphylaxis. Of the 131 cases, 50 met our case definition for anaphylaxis. No fatalities were identified; however, hospitalization was required in 44% of these cases. Four patients reported a reoccurrence of their hypersensitivity reaction once the suspected product was reintroduced (positive rechallenge). The OTC topical acne products cited in these cases were marketed under 21 brand names such as Proactiv, Neutrogena, MaxClarity, Oxy, Ambi, Aveno, Clean & Clear, and store brands. These products are available as gels, lotions, face washes, solutions, cleansing pads, toners, and face scrubs.

In 2012, approximately 15.7 million bottles/packages of OTC topical acne products were sold from retail store outlets. Of these, the majority of OTC topical acne products contained salicylic acid at approximately 61% (9.6 million bottles/packages). OTC topical acne products containing benzoyl peroxide followed at 35% (5.4 million bottles/packages).

**DISCUSSION AND CONCLUSION**

FDA postmarket data demonstrate that there may be an association of serious hypersensitivity reactions, including anaphylaxis, with use of OTC topical acne monograph products containing benzoyl peroxide and salicylic acid. While multiple active ingredients are allowable for marketing, we only observed hypersensitivity adverse events with benzoyl peroxide and salicylic acid. The reason for this observation is not known; however high use associated with products containing these two active ingredients may contribute to this observation (see Figure 2). In addition, based on the information reported to FDA, we cannot determine if the hypersensitivity reactions were triggered by the acne products’ active ingredients, benzoyl peroxide and salicylic acid, the inactive ingredients, or by a combination of both.

Based on these findings, the FDA issued a drug safety communication in June 2014 to alert the public regarding rare but serious hypersensitivity reactions with certain OTC topical acne products. This warning alerts consumers to the following:

- To test the product upon first use, by applying a small amount topically to affected area for three days; if no discomfort is experienced, then continued product use is recommended per directions.
- To stop use with topical acne products and immediately seek medical attention if they experience hypersensitivity reactions such as throat tightness, difficulty breathing, feeling faint, swelling of the eyes, face, lips or tongue; develop hives or itching.
- To avoid using an OTC topical acne product again if they have previously experienced a hypersensitivity reaction with its use.

**TABLE 1. Hypersensitivity-Specific Case Selection**

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>Number of Cases</th>
<th>Number of Reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzoyl Peroxide</td>
<td>11</td>
<td>48</td>
</tr>
<tr>
<td>Salicylic Acid</td>
<td>43</td>
<td>7</td>
</tr>
</tbody>
</table>

**FIGURE 1. Hyperosensitivity-Specific Case Selection**

**FIGURE 2. Nationally estimated number of bottles/packages of OTC topical acne products sold from U.S. retail store outlets, years 2007-2012: Data extracted April 2013.**