Food and Drug Administration

Center for Drug Evaluation and Research

Office of New Drugs

Office of Nonprescription Drugs

Scientific Review Supporting Proposed Administrative Order

June 14, 2024

Order ID: OTC000035

Order Title: Amending Over-the-Counter Monograph M013: Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use

OTC Monograph: M013

Active Ingredient: Acetaminophen

Safety Signal: Serious skin reactions

I. Introduction

This scientific review describes the findings and conclusions supporting Proposed Administrative Order (OTC000035), amending the requirements for internal analgesic, antipyretic, and antirheumatic (IAAA) drug products for over-the-counter (OTC) human use (OTC IAAA drug products), as currently described in Over-the-Counter Monograph M013: Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use (OTC Monograph M013). OTC Monograph M013 describes the conditions under which OTC IAAA drug products are generally recognized as safe and effective (GRASE).[1] In this evaluation, FDA considered scientific data to inform a determination under section 505G(b)(1)(A) of the Federal Food, Drug, and Cosmetic (FD&C) Act whether, in order for an OTC IAAA drug product containing acetaminophen to be GRASE, a warning on the labeling about serious skin reactions is required.

[1] OTC Monograph M013 is set forth in Final Administrative Order OTC000027 Over-the-Counter Monograph M013: Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use, available via the OTC Monographs@FDA portal at https://dps.fda.gov/omuf.

II. Background

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare, acute, severe life-threatening disorders of the skin. SJS and TEN are part of a spectrum of severe mucocutaneous reactions that are characterized by necrosis and sloughing of the epidermis, with mucous membrane (e.g., ocular, oral, genital) involvement in more than 90 percent of cases (Ellender et al. 2014; High 2020). SJS and TEN differ in the degree of blistering and skin detachment, with SJS affecting less than 10 percent of body surface area, and TEN covering more than 30 percent (Bastuji-Garin et al. 1993). A degree of blistering and detachment between 10 percent and 30 percent is classified as SJS/TEN overlap. Biopsy in established SJS/TEN shows necrotic keratinocytes and full-thickness epidermal necrosis with separation from the dermis (Kowalski et al. 2011). Early lesions of SJS/TEN may show apoptotic keratinocytes in the basal and immediate suprabasal layers of the epidermis, with early subepidermal blister formation (Klimas 2015). SJS and TEN are usually drug-induced but can be idiopathic or caused by an infection (Auquier-Dunant et al. 2002; Mockenhaupt et al. 2008; Paulmann and Mockenhaupt 2015).

Acute Generalized Exanthematous Pustulosis (AGEP) is a rare, serious skin hypersensitivity adverse reaction. It is usually not life-threatening and involves the eruption of dozens to hundreds of sterile, nonfollicular superficial pustules in the presence of diffuse edematous erythema. It can also be accompanied by fever and elevated neutrophil counts. One of the main differential diagnoses is generalized pustular psoriasis (raised bumps on the skin filled with pus), but skin biopsy usually differentiates the two (Halevy et al. 2010; Kardaun et al. 2010). AGEP is usually drug-induced (Chang et al. 2008).

As discussed below, acetaminophen is associated with a risk of these rare but serious skin reactions.

III. Scientific Review

FDA conducted a comprehensive review of data for evidence of an association between acetaminophen and SJS, TEN, and AGEP to determine whether the label of OTC IAAA drug products containing acetaminophen must include a warning about serious skin reactions. The comprehensive review included a:

1. Review of FDA Adverse Event Reporting System (FAERS)[2] data and medical literature evaluated by FDA for a Drug Safety Communication
2. Review of updated FAERS data
3. Review of current medical literature

[2] The FDA Adverse Event Reporting System (FAERS) is a database that contains adverse event reports, medication error reports and product quality complaints resulting in adverse events that were submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. For more information, see Questions and Answers on FDA's Adverse Event Reporting System (FAERS) available at https://www.fda.gov/drugs/surveillance/questions-and-answers-fdas-adverse-event-reporting-system-faers (accessed June 11, 2024).

A. FDA's Review for a Drug Safety Communication

On August 1, 2013, FDA warned the public that acetaminophen has been associated with a risk of rare but serious skin reactions in the Drug Safety Communication titled, *FDA warns of rare but serious skin reactions with the pain reliever/fever reducer acetaminophen* (2013 DSC).[3] The 2013 DSC was based on FDA's review of data, including FAERS data and the medical literature, for evidence of an association between acetaminophen and SJS, TEN, and AGEP. Three published cases in which patients were rechallenged with acetaminophen and experienced a recurrence of the skin reaction provide evidence supporting causality between acetaminophen and serious skin reaction (Leger et al. 1998; Halevi et al. 2000; Trujillo et al. 2010). In addition to the three positive rechallenge cases, the medical literature (through 2012) contains several cases of SJS, TEN, or AGEP (3, 17, and 6 cases, respectively) in which the only drug exposure prior to the serious skin reaction was acetaminophen, or acetaminophen hypersensitivity was confirmed by skin testing (e.g., patch, prick, or injection) or other means (e.g., skin biopsy and positive lymphocyte test, or diagnoses by a dermatologist) following observed serious skin reactions (De Coninck et al. 1996; Khare et al. 1997; Szepietowski 1997; Mashiah and Brenner 2003; Prins et al. 2003; Bygum et al. 2004; Takeuchi 2004; Wohl et al. 2004; Gerdts et al. 2007; Sezer et al. 2007; Pyo 2008; Yun et al. 2008; Dragojevic-Simic V 2009; Verneuil et al. 2009; Yamane et al. 2009; Bouziri et al. 2011; Reese et al. 2011). Although there were no reported deaths in the literature, the majority of cases required hospitalization. All cases resolved with discontinuation of the drug.

A search of FAERS from 1969 to 2012 identified 91 cases of SJS or TEN and 16 cases of AGEP, which resulted in 67 hospitalizations and 12 deaths. The majority of the cases involved single-ingredient acetaminophen products. A small number of cases involved injectable acetaminophen products or oral acetaminophen/opioid fixed-dose combination products. Indications for acetaminophen use varied between pyrexia and analgesia, and the majority of the reported doses were consistent with labeled dosing recommendations.

Of the 91 cases of SJS/TEN, six were categorized as probable cases associated with acetaminophen, with the rest categorized as possible cases. Of the 16 cases of AGEP, one was categorized as a probable case associated with acetaminophen, with the rest categorized as possible cases. These seven probable cases had a confirmed diagnosis of SJS/TEN or AGEP by a dermatologist and/or histological findings temporally associated with acetaminophen; confounding drugs were not administered within 2 weeks preceding the events. The time-to-event, which was measured from the initiation of acetaminophen to the onset of cutaneous signs and symptoms, ranged from fewer than 24 hours to 8 days. Among these probable cases, six people were hospitalized, and one died.

FDA's review of five SJS/TEN case-control studies and one of AGEP indicates that risks of SJS/TEN may be increased with the use of acetaminophen and were generally independent of the effects of other drugs (Roujeau et al. 1995; Sidoroff et al. 2007; Gau et al. 2008; Mockenhaupt et

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[3] See the FDA Drug Safety Communication *FDA warns of rare but serious skin reactions with the pain reliever/fever reducer acetaminophen* (August 1, 2013). Available at https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-warns-rare-serious-skin-reactions-pain-relieverfever-reducer, (accessed June 11, 2024).

al. 2008; Levi et al. 2009; Sassolas et al. 2010). However, all but two of these case control studies failed to address the possible presence of *protopathic bias*, which in this setting refers to a false increase in the risk of SJS/TEN attributable to acetaminophen, due to its use to treat fever, a prodromal symptom of SJS/TEN. In one of the two studies that controlled for the confounding effect of protopathic bias by limiting the acetaminophen exposure period to a time preceding the prodromal period, acetaminophen remained significantly associated with SJS/TEN (Levi et al. 2009).

B. Updated FAERS Review

FDA updated its review of FAERS for U.S. cases of SJS/TEN and AGEP following acetaminophen exposure reported to FDA from February 25, 2012, to June 30, 2020, using the materials and methods outlined in Appendix A: Methods and Materials and the FAERS search strategy outlined in Appendix B: FDA Adverse Event Reporting System. This analysis identified 28 U.S. FAERS cases of SJS/TEN[4] (n=25) and AGEP (n=3) following acetaminophen exposure. Of the 28 FAERS cases, 1 case was categorized as probable (SJS/TEN), and 27 cases were categorized as possible. Probable causality was assigned based on a temporal relationship, the absence of known confounders, and the exclusion of numerous infectious causes. However, the possibility of protopathic bias could not be excluded as there could have been another trigger for the serious skin reaction and acetaminophen use early in the course to treat prodromal symptoms before skin lesions became apparent.

Possible causality was assigned in 27 cases based on temporal relationship, presence of one or more confounders, possibility of alternative causes, and/or missing information. All cases had serious outcomes, including death (n=5), life-threatening events (n=21), and hospitalizations (n=8). Patients ranged in age from 21 months to 80 years. The predominant route of administration was oral, and the top reasons for use were pyrexia and pain. The time-to-event between acetaminophen exposure and the onset of serious skin reaction ranged from within 1 day to 1 month in the majority of FAERS cases, which is consistent with the known time-to-onset of drug-induced serious skin reactions. Of these cases, nearly half (n=13/28, 46 percent) occurred within 2 weeks after acetaminophen exposure. Notably, the diagnoses of serious skin reactions in the majority of cases (n=20/28, 71 percent) were confirmed by dermatologist assessment, or hospitalization with supportive clinical evidence, such as skin biopsy. Additionally, two cases (n=2) of positive dechallenge, a response observed where adverse effects improved after discontinuing acetaminophen exposure, were identified.

C. Updated Literature Review

FDA updated its review of the medical literature from February 2012 through July 2020 for evidence of a continued association between acetaminophen and SJS/TEN and AGEP using the search strategy shown in Appendix C: Literature Search (Table 2). The updated literature review identifies 19 additional publications supporting an association between serious skin reactions and acetaminophen use; this includes 18 publications describing 21 case reports (6 probable and 15 possible cases (including 14 possible SJS/TEN cases and one possible AGEP case)) and 1

[4] SJS/TEN refers to all cases on the spectrum from SJS to TEN.

publication that reviewed the European EudraVigilance Database (Khawaja et al. 2012; Umayahara et al. 2013; Biswal and Sahoo 2014; Kim et al. 2014; Harimoto et al. 2015; Rajput et al. 2015; Slim et al. 2015; Pena et al. 2016; Purkayastha 2016; Watanabe et al. 2016; Ardakani et al. 2017; Birlutiu 2018; Lebrun-Vignes et al. 2018; Milheiro Silva et al. 2018; Bruce-Hickman et al. 2019; Kara et al. 2019; Popiolek et al. 2019; Wang et al. 2019; Ishikawa 2020; Torres-Navarro et al. 2020). Of the total 21 reported literature cases supporting a drug-event association between acetaminophen and serious skin reactions, 20 involved hospitalization (all cases of SJS/TEN); for one case (an AGEP case), it was unclear from the report whether the patient was hospitalized. These 21 cases of serious skin reactions involved 7 male and 14 female patients who ranged in age from 2.5 years to 89 years. The top reasons for acetaminophen use were pyrexia and upper respiratory infection. There were no reported deaths in the medical literature. The latency for SJS/TEN ranged from 1 day to 1 month in all cases that reported a time-to-onset (time-to-onset is based on the first reported exposure to onset of hypersensitivity reactions/symptoms). One case report included a positive dechallenge (associated with concurrent corticosteroid treatment) for AGEP (Umayahara et al. 2013). Protopathic bias cannot be ruled out in cases that lacked obvious confounders.

For this literature review, case-level analysis began with categorizing the diagnosis of the event of interest as either confirmed or unconfirmed. Next, the causal relationship between the drug and the event was assigned using the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) causality criteria. Specifically, “probable” cases were categorized when there was a strong temporal relationship between exposure and onset of illness with no confounders or the existing confounders were less likely explanations for the event. Additionally, supportive clinical information, such as drug challenge testing, was considered when determining probable causality. Based on this method, the concepts of diagnostic certainty and causality were considered separately for each case. For example, a case may be categorized as both “confirmed” (i.e., a confirmed diagnosis of SJS/TEN) and “probable” (causality classification). See Appendix A: Methods and Materials for case definitions and causality classification criteria used in the literature search.

Within the 21 literature case reports described above, 6 cases were categorized as probable (Khawaja et al. 2012; Biswal and Sahoo 2014; Kim et al. 2014) (one case confirmed and probable, one case unconfirmed and probable); (Slim et al. 2015); (Purkayastha 2016). Kim et al. included one case that was unconfirmed by a dermatologist/biopsy but was considered probable based on a lack of known confounders. The remaining 5 probable cases of SJS/TEN were categorized as both confirmed and probable, and in which the only drug exposure prior to the serious skin reaction was acetaminophen, or acetaminophen hypersensitivity was confirmed by skin testing (e.g., patch, prick, or injection) or other means (e.g., skin biopsy and positive lymphocyte test, or diagnoses by a dermatologist) as the cause of the skin serious reaction (Khawaja et al. 2012); (Biswal and Sahoo 2014); (Kim et al. 2014); (Slim et al. 2015); (Purkayastha 2016). For these 5 well-documented cases of SJS/TEN categorized as both confirmed and probable, the time-to-onset of symptoms suggestive of SJS/TEN, such as rash, mucosal erosion, and/or ocular irritation, ranged from 1 to 3 days. All cases resolved after hospitalization and discontinuation of acetaminophen.

Additionally, one publication assessed serious adverse events corresponding to hypersensitivity symptoms associated with acetaminophen that were spontaneously reported to the European

EudraVigilance Database from January 1, 2007, to October 1, 2018 (Popiolek et al. 2019). While the keywords corresponding to the hypersensitivity reactions were broad (e.g., SJS/TEN, anaphylactic reactions, erythema multiforme, fixed drug eruption), they were chosen by a medical doctor who works with patients suffering from adverse drug reactions and a trained allergist who specializes in drug hypersensitivity research. Nine deaths associated with SJS or TEN were identified. Prodromes and symptoms of potentially life-threatening SJS, TEN, and AGEP were reported 129, 108, and 2 times, respectively. FDA acknowledges overlap in the assessment time periods of the European EudraVigilance Database (2007 to 2018) and the 2013 DSC FAERS cases (1969 to 2012), such that some cases may be duplicated. Also, it is unclear if protopathic bias was attempted to be limited in the analysis by Popiolek et al., or if these details were unavailable in the assessment. Nonetheless, the recent EudraVigilance Database assessment indicates that serious skin reactions associated with use of acetaminophen persist.

The updated literature review also identified one publication that does not identify an association between SJS/TEN with acetaminophen in the French population (Lebrun-Vignes et al. 2018). Lebrun-Vignes et al. reviewed cases of SJS/TEN with acetaminophen as a suspect drug registered in the French Pharmacovigilance Database from January 2002 to December 2013 and found no obvious SJS/TEN risk related to acetaminophen in the large national series (Lebrun-Vignes et al. 2018). After conducting the search in the database, cases were selected and assessed by expert reviewers (dermatologists and senior pharmacovigilance staff) who utilized the algorithm of drug causality for epidermal necrolysis (ALDEN) as a reference tool to define drug causality of SJS and TEN (Sassolas et al. 2010). Initial analysis revealed possible, probable, unlikely, and very unlikely cases caused by acetaminophen. The expert reviewers determined that the cases matched with possible or probable cause could have protopathic or confounding bias, so they recalculated the scores using an earlier day index defined as an onset of prodromes such as fever, influenza-like syndrome, ear, nose, and throat symptoms. As a result, this recalculation classified the cases originally assigned as having the highest ALDEN scores matching with a probable or possible causality, now as having a very unlikely causality. Using the modified application of the ALDEN score, this assessment concludes that no obvious SJS/TEN cases were related to acetaminophen.

Although this publication found no obvious SJS/TEN risk related to the use of acetaminophen, as defined by assessment by an expert group and utilization of ALDEN, a recent publication found that available causality assessment tools, such as ALDEN, have poor reliability and validity for drug-induced SJS/TEN, thus calling into question the conclusion of Lebrun-Vignes et al. (Goldman et al. 2019). Goldman et al. suggest that causality assessment tools, such as ALDEN could be further enhanced in usefulness and applicability if additional elements such as immunological testing, pharmacogenetic results, and pharmacokinetic data were incorporated into the assessment tool, in addition to further validating ALDEN using larger studies. Furthermore, the ALDEN score is of limited use when assessing spontaneous reports, as these reports may not include all the data necessary to calculate the score. Finally, the conclusion of Lebrun-Vignes et al. must be further questioned, given the findings of Popiolek et al.'s more extensive EudraVigilance analysis, which demonstrated an association between acetaminophen and serious skin reaction.

IV. Conclusions Based on Review

Since the publication of the 2013 DSC, which summarized evidence supporting causality between acetaminophen and serious skin reactions, FDA identified 21 case reports supporting a drug-event association between acetaminophen and serious skin reactions including SJS, TEN, SJS/TEN overlap, and AGEP. Six of these 21 cases were classified as probably related to acetaminophen and 15 of 21 cases were classified as possibly related to acetaminophen.[5] Within the 21 literature cases, there were five well-documented cases of SJS/TEN categorized as both confirmed and probable, in which the only drug exposure prior to the serious skin reaction was acetaminophen, or acetaminophen hypersensitivity was confirmed by skin testing (e.g., patch, prick, or injection) or other means (e.g., skin biopsy and positive lymphocyte test, or diagnoses by a dermatologist) as the cause of the skin serious reaction. Although a retrospective French Pharmacovigilance Database assessment found no obvious SJS/TEN risk related to acetaminophen exposure between 2002 to 2013, there is uncertainty in the reliability of the causality assessment tool (ALDEN) used. Additionally, a retrospective assessment of the European EudraVigilance Database between 2007 to 2018 identified nine deaths related to SJS or TEN; prodromes and symptoms of potentially life-threatening SJS, TEN, and AGEP were reported 129, 108, and 2 times, respectively.

Based on our comprehensive review, FDA concludes that acetaminophen continues to be associated with the risk of rare but serious skin reactions, SJS, TEN, and AGEP. We further conclude that in order for an OTC IAAA drug product containing acetaminophen to be GRASE, the labeling of such drug products must include a warning about serious skin reactions. This warning must communicate to consumers the following information, as will be required under Proposed Administrative Order (OTC000035), if finalized:

Allergy alert: Acetaminophen may cause severe skin reactions. Symptoms may include:

- skin reddening
- blisters
- rash

If a skin reaction occurs, stop use and seek medical help right away.

[5] See Appendix A: Methods and Materials (Table 1) for case definitions and causality classification criteria.

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Appendix A: Methods and Materials

Case Definition

Inclusion Criteria

Based on FDA's current pharmacovigilance practices, the concepts of diagnostic certainty and causality are considered separately. In this review, case-level analysis began with categorizing the diagnosis of the event of interest as either confirmed or unconfirmed. Next, the causal relationship between the drug and the event was assigned using the WHO-UMC causality criteria (see Table 1 below).

A case is considered **confirmed** if the following criteria are met after exposure to acetaminophen:

- Documented diagnosis of SJS, TEN, or AGEP by a dermatologist

OR

- Documented diagnosis by a nondermatologist of SJS, TEN, or AGEP with supportive clinical evidence (e.g., biopsy results, and in the case of SJS or TEN, hospitalization in a burn unit) for the diagnosis

A case is considered **unconfirmed** (less diagnostic certainty) if the following criteria are met after exposure to acetaminophen:

- Documented diagnosis of SJS, TEN, or AGEP made by a physician other than a dermatologist without supportive biopsy results

OR

- Description of a generalized bullous or pustular condition requiring hospitalization and clinical manifestations compatible with SJS, TEN, or AGEP

Exclusion Criteria

- Acetaminophen combination product is implicated in the reaction
- Cases reporting a diagnosis of any of the following: acute generalized pustular psoriasis (Von Zumbusch type), staphylococcal scalded skin syndrome (SSSS), linear IgA dermatosis, pemphigus (any type), acute graft-versus-host disease, pemphigoid, toxic shock syndrome, Kawasaki syndrome, bullous impetigo, drug reaction with eosinophilia and systemic symptoms (DRESS), localized pustular contact dermatitis, mycoplasma infection, streptococcal disease, subcorneal pustular dermatosis (Sneddon-Wilkinson disease), and Sweet's syndrome

Causality Criteria

The World Health Organization-Uppsala Monitoring Centre (WHO-UMC) causality assessment system was also applied to determine if the weight of evidence suggested a causal relationship (Table 1). Specifically, "probable" cases were categorized when there was a strong temporal relationship between exposure and onset of illness with no confounders or the existing confounders were less likely explanations for the event. Additionally, supportive clinical information, such as drug challenge testing, was considered when determining probable causality. "Possible" cases had a reasonable temporal relationship between exposure and onset of illness, had confounders present that also provided a reasonable alternative explanation for the event, and/or were missing information necessary to assign stronger causality. Cases assigned as "unlikely" or "unassessable" were excluded from further review and analysis.

Table 1. Causality Classification and Criteria Based on the WHO-UMC System

Causality Term	Assessment Criteria
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely*	• Event or laboratory test abnormality, with a time-to-drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Unassessable*	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

Source: Adapted from the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) causality assessment system at https://who-umc.org/media/164200/who-umc-causality-assessment_new-logo.pdf (accessed June 13, 2023).
*Excluded from further analysis in this case series
Abbreviations: WHO-UMC, World Health Organization-Uppsala Monitoring Centre

Appendix B: FDA Adverse Event Reporting System

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 (MedDRA) 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 or not 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.

Table 2. FAERS Search Strategies

	Search 1	Search 2
Date of search	July 17, 2020	
Time period of search	February 25, 2012 - June 30, 2020	
Search type	FAERS Business Intelligence Solution (FBIS) Quick Query	
Product terms	Product active ingredient: Acetaminophen	
MedDRA search terms (Version 23.0)	Preferred terms: Acute generalised exanthematous pustulosis, Stevens-Johnson syndrome, Toxic epidermal necrolysis	
Serious outcomes	Serious	
Country	Not applicable	United States

Abbreviations: FAERS, FDA Adverse Event Reporting System; MedDRA, Medical Dictionary for Regulatory Activities

Appendix C: Literature Search

The literature search for this proposed administrative order review was performed using the strategy described in Table 3 and Figure 1.

Table 3. Literature Search Strategy

Date of Search	**February 25, 2012, to June 30, 2020**	
Database	Embase	PubMed
Search terms	((((('acetaminophen'/exp OR acetaminophen OR 'paracetamol'/exp OR paracetamol) AND ('stevens-johnson syndrome'/exp OR 'stevens- johnson syndrome' OR (stevens- AND johnson AND ('syndrome'/exp OR syndrome))) OR 'toxic epidermal necrolysis'/exp OR 'toxic epidermal necrolysis' OR (toxic AND epidermal AND ('necrolysis'/exp OR necrolysis))) AND [2011-2020]/py) AND 'case report'/de AND [humans]/lim) AND (2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py OR 2019:py OR 2020:py) (((acetaminophen OR paracetamol) AND title AND agep OR acute) AND generalized AND exanthematous AND pustulosis) AND 'case report'/de AND (2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py OR 2019:py OR 2020:py)	acetaminophen OR paracetamol AND stevens johnson OR toxic epidermal necrolysis acetaminophen OR paracetamol AND AGEP OR acute generalized exanthematous pustulosis
Years included in search	2012–2020	
Other criteria		Case report, pharmacovigilance database

Figure 1. Literature Case Selection (Non–United States)