Serious cutaneous adverse reaction related labeling changes: An evaluation of supporting evidence and labeling features

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Introduction

- Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are serious, rare, and life-threatening dermatologic adverse reactions.
- Clinical management of SJS/TEN relies on identification and cessation of the causative agent; inclusion of SJS/TEN into labeling is critical for prescriber awareness of this serious adverse reaction.
- SJS and TEN are rarely detected in premarket drug development programs and are typically identified in the postmarket period when the causative agent is used more broadly.
- An in-depth understanding of the current practice trends for SJS/TEN signal identification is critical for determining areas of improvement.

Purpose

To characterize the evidence supporting SJS/TEN Safety-related Labeling Changes (SrLC) and language used to convey the risk in the Prescribing Information (PI).

Materials and Methods

- FDALabel was used to identify New Drug Applications (NDA) and Biologic License Applications (BLA) that contained the terms “Johnson syndrome,” “SJS,” and “toxic epidermal” in any section of the PI. [1]
- The FDA SrLC database was used to identify NDA/BLAs with a labeling change related to SJS/TEN in the Boxed Warnings (BW), Contraindications (CI), Warnings and Precautions (WP), and Adverse Reactions (AR) sections of the PI from January 1, 2016 to December 31, 2020. [2]
- Pharmacologic class of the NDA/BLA product was identified using the World Health Organization Anatomical Therapeutic Chemical (ATC) Classification System.
- Two reviewers retrospectively reviewed FDA’s internal document repositories to identify the initiator of the SrLC (i.e., Applicant or FDA) and the safety trigger source.
- Trigger source was defined as the source that initially prompted the evaluation of a new safety signal. The granular trigger source was defined as the data source that served as the initial evidence for SJS/TEN inclusion onto the PI.
- Data sources for granular trigger sources that were spontaneous reports were identified from FAERS, the Applicant global safety database, or medical literature.
- WP headings were collected from the most recent PI and grouped by similar features.
- Labeling information was obtained from Drugs@FDA, DailyMed, and Physicians’ Desk Reference.

Results

Overall Characteristics

- We identified 63 SrLCs meeting our inclusion criteria, of which 90% (n=57) were NDAs.
- The most frequent pharmacological class with an SJS/TEN SrLC was *antineoplastic and immunomodulating agents* (n=24, 38%), followed by *antiinfectives for systemic use* (n=15, 24%).
- Of the *antineoplastic and immunomodulating agents* with an SJS/TEN SrLC, 79% occurred within the first 10 years after approval

Labeling Characteristics

- 12 PIs described SJS alone, 1 described TEN alone, and 50 described both SJS and TEN.
- 53 NDA/BLAs did not have SJS/TEN in the PI at approval. Of these, 38 added SJS/TEN for the first time within the study period. The other 15 added SJS/TEN after approval and before the study period.
- SJS/TEN was described in 4 CI, 46 WP, and 51 AR sections of identified PIs. SJS/TEN was not described in any identified PI BW.
- Of 46 PIs with SJS/TEN in WP, 25 different WP subsection titles were used.
- 8 WP subsection title groups were created. The most common WP subsection title group was “Severe Cutaneous Adverse Reactions” n=27, followed by “Immune-Mediated Dermatologic Adverse Reactions” n=4.
- In 38 PIs, the inclusion of SJS/TEN generated a new WP subsection.

Results (Continued)

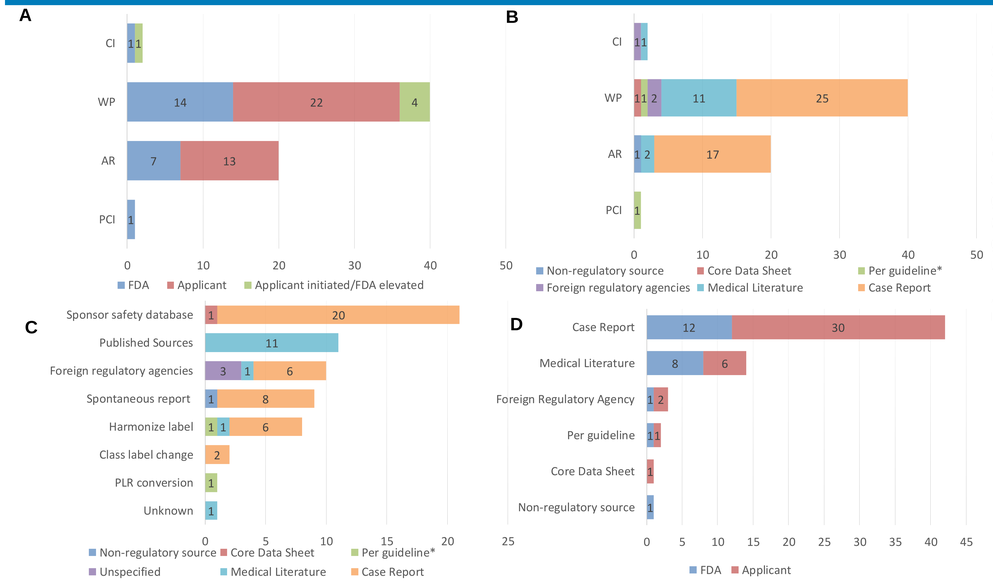

Figure 1 (Top). Counts of (A) Initiators with highest section of PI affected by SrLC; (B) Granular trigger sources with highest section of PI affected by SrLC; (C) Source that initiated FDA signal investigation versus granular trigger source; and (D) Initiators with the granular trigger source used.

*Per guideline refers to PLR conversion or harmonizing the PI within the product.

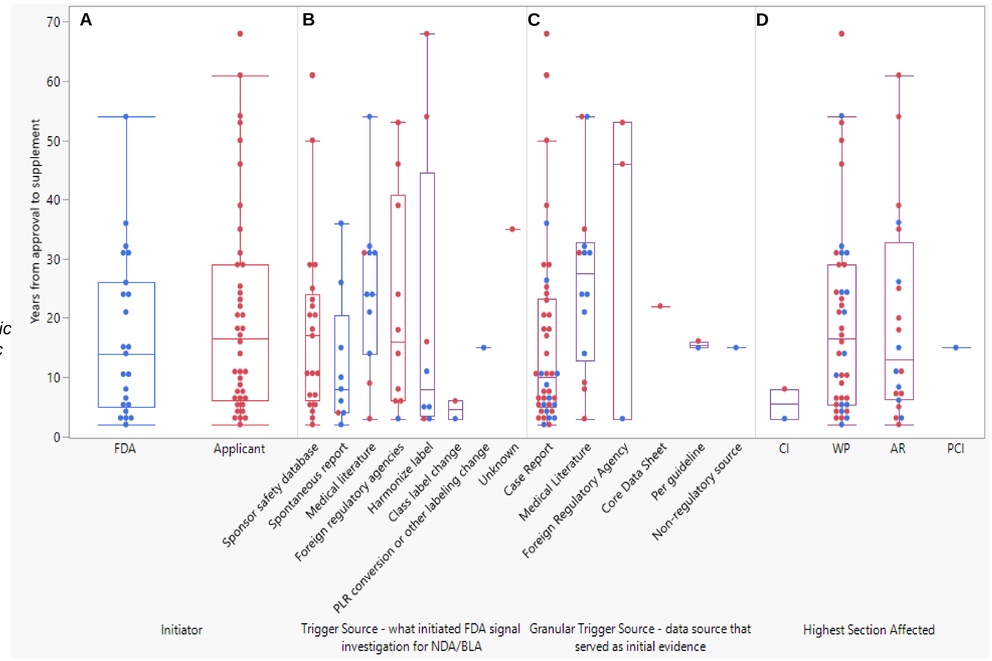

Figure 2 (Bottom). Time in years from the approval of the NDA/BLA until the SJS/TEN SrLC, analyzed by subdividing the data in four ways: (A) by the initiator; (B) the trigger source; (C) the granular trigger source; and (D) the highest section of the PI affected by the SrLC.

Additional Abbreviations: CTE = Clinical Trials Experience, PME = Post Marketing Experience, PCI = Patient Counseling Information, FAERS = FDA Adverse Event Reporting System PLR = Physician Labeling Requirement

Results (Continued)

SrLC and Granular Trigger Source Characteristics

- SJS/TEN SrLCs commonly involved an addition to WP. This includes an addition to WP and AR simultaneously (n=14), an elevation from AR to WP (n=16), or an addition to WP without an addition to AR (n=10) (Fig. 1A).
- Case reports were responsible for triggering most SrLCs involving WP and/or AR (Fig. 1B).
- For SJS/TEN SrLCs triggered by data from sponsor safety databases, most safety reviews were triggered by case reports (Fig. 1C). Published sources were typically case reports or case series reports. A single published trigger source was an observational study.
- 63% (n=40) of SrLCs were Applicant initiated. Of those, 5 were elevated by the FDA after Applicant initiation (Fig. 1D).
- 75% of both Applicant and FDA-initiated SrLCs were made within the first three decades [median 14 years (IQR 5, 26) and 17 years (IQR 6, 29) from the FDA and Applicant, respectively] (Fig. 2A). The other 25% of SrLCs occurred from 31 to 68 years after approval and were triggered by a variety of sources (Fig. 2B).
- Most case reports triggered an SrLC within the first two decades after approval [median 11 years (IQR 5, 25)] (Fig. 2C).
- The postapproval time to SJS/TEN SrLC to AR does not appear to be different from WP (median 13 years (IQR 6, 33) and 17 years (IQR 5, 29), respectively) (Fig. 2D).

Discussion

Trigger Sources

- Identification of the granular trigger sources that were spontaneous reports was limited to what was specified in the documentation.
- Medical literature was the second highest reported SrLC trigger source. Six of these SrLCs were part of a class investigation of radiographic contrast agents that were triggered by the same article and initiated by the FDA.
- None of the SrLCs were triggered by new postmarket clinical studies. One SrLC was triggered by an observational study.
- Notably, many *antineoplastic and immunomodulating agents* had an SrLC within the first 10 years of approval. The greater number of SrLCs observed in this medication class is consistent with oncology products representing a disproportionately dominant therapeutic area of approvals. [3]

Labeling Features

- Most of the WP subsections titles were generated upon the addition of SJS/TEN to WP, and most of the SJS/TEN additions to WP were made within the study time period.
- Although there are many WP subsection titles, many of PIs have overlapping content that is described in the WP.

Conclusion

- Case reports serve as the primary data source for postmarket SJS/TEN SrLCs. Although case reports are traditionally viewed as low in the evidence hierarchy, they serve as an important tool for identification of safety signals. Well documented case reports may provide enough evidence for regulatory action for rare events, such as SJS/TEN, and is consistent with FDA guidance.[4]
- The FDA and Applicant utilized similar trigger sources, which primarily consisted of spontaneous reporting.
- Labeling language utilized to describe SJS/TEN varied across applications; further evaluation is planned for characteristics related to SJS/TEN language included in the PI.

Disclaimer

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