7.4.3.: ADVERSE EVENT SUMMARY

TABLE OF CONTENTS

7.4.3. OVERVIEW 2
7.4.3.1. AE Data on the Candidate Product 3
7.4.3.2. ALCS AE Data on Similar Products to the Candidate Product 3
7.4.3.2.1. ALCS Consumer Call Center Data Collection System 3
7.4.3.2.2. Summary of ALCS AE Data from Consumer Call Center 4
7.4.3.3. Conclusion 8
7.4.3.4. Literature Cited 8

LIST OF TABLES

Table 7.4.3-1: Adverse Events (AEs) Categorized by MedDRA PT (Top Five) as a Percent of Total AEs 6
Table 7.4.3-2: Adverse Events (AEs) Categorized by MedDRA SOC (Top Five) as a Percent of Total AEs 7
Table 7.4.3-3: Severity Levels of AE Cases 7
Table 7.4.3-4: SAE Cases with AE PTs and Outcome 8

LIST OF FIGURES

Figure 7.4.3-1: Total Calls (1,353) with AEs by Month 5
Figure 7.4.3-2: Total AEs (2,546) Reported By Month 6

7.4.3. OVERVIEW

The FDA, in Section V(B) of the Modified Risk Tobacco Product Application (MRTPA) Draft Guidance (2012), states:

> "FDA may request other information FDA finds it needs to determine whether a 911(g) order is appropriate. For example, FDA may request:
>
> …For products that have been on the market prior to the MRTPA submission, a summary of information that the manufacturer possesses regarding the product, including, but not limited to, adverse events from use of the product, levels of product use in the market, and consumer feedback regarding the product."

This section provides a summary of information ALCS possesses on adverse events (AEs) related to the candidate product.

The candidate product is a grandfathered product (FDA Grandfather Status # GF1200194) (Appendix 2.3-1), commercially marketed in the U.S. as of February 15, 2007. As such, it is not a new tobacco product as defined by FDCA Section 910(a) (1) and does not require premarket review and authorization.[1]

The AE information presented in this section is from two sources:

- AE data collected during a clinical study (Study #ALCS-RA-17-02-MST, Appendix 7.3.1-1) on the candidate product, and
- AE data collected by ALCS on similar products to the candidate product

We summarize the AEs as follows:

1. The AEs observed in the clinical study demonstrate that the candidate product is well tolerated and no deaths or serious AEs were reported. Furthermore, the Principal Investigator of the study considered the AEs reported during the use of the candidate product as "unlikely related or "not related" to the product. The AEs resolved quickly after candidate product use and are similar to the AEs reported with the use of nicotine polacrilex gum in the clinical study (Appendix 7.3.1-1).
2. The AE data collected on similar products from the Consumer Call Center shows that relative to the billions of U.S. Smokeless Tobacco Company (USSTC) cans of moist smokeless tobacco (MST) sold, the numbers of AEs reported by consumers are very few and are mostly mild in severity.

[1] Copenhagen® Fine Cut and variants thereof have been on the market since 1822. Since 2007, USSTC made minor modifications to Copenhagen® Snuff Fine Cut, which are the subject of a separate pending Substantial Equivalence review. The candidate product subject to the MRTPA is the product for which FDA granted grandfathered status (Grandfather Number – GF1200194) on November 1, 2012.

7.4.3.1. AE Data on the Candidate Product

ALCS conducted a single Clinical Study[2] using a crossover study design (Appendix 7.3.1-1) on the candidate product to measure nicotine pharmacokinetics and subjective effects from use of the candidate product compared to nicotine polacrilex gum and the subject's own brand cigarettes.

Overall, 14 (58%) subjects experienced a total of 22 AEs in this study during stages 1 and 2 (combined). Most AEs occurred following use of the Subject's Own Brand Cigarette and Nicotine gum. Mild headache was the most frequently reported AE, experienced by a total of eight (33%) subjects. The majority of AEs were mild in severity and two were moderate. The Principal Investigator (PI) considered all AEs unlikely related or not related to the study product. Additionally, no deaths or SAEs were reported and no subjects were discontinued due to AEs.

The AEs reported by the study participants for the candidate product were similar in nature to those reported for nicotine polacrilex gum. There were relatively few number of subjects reporting AEs for the candidate product (one subject over a 4-hour *ad lib* use and two subjects with single use) as well as for nicotine gum (four subjects over a 4-hour *ad lib* use and two subjects with single use) (Appendix 7.3.1-1; Table 23). Each of the subjects had only one AE to report and none of the AEs were considered by the PI to be related to the product and all the AEs resolved quickly.

7.4.3.2. ALCS AE Data on Similar Products to the Candidate Product

7.4.3.2.1. ALCS Consumer Call Center Data Collection System

ALCS uses an established and documented AE collection system to capture and classify spontaneous calls[3] of unsolicited consumer complaints and unverified AEs temporally associated with the use of USSTC's MST products sold in the marketplace.

ALCS defines an AE as "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment." An AE can therefore be "any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure"(International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)).

[2] The clinical study (Moist Snuff Tobacco Product, Study No. ALCS-RA-17-02-MST, Appendix 7.3.1-1) was conducted in compliance with FDA regulations as described in the Code of Federal Regulations (CFR) 21 Parts 50 and 56; Department of Health and Human Services regulations as described in 45 CFR 46; guidelines resulting from the International Council for Harmonisation (ICH); and Good Clinical Practice (GCP). The clinical study involved collection and measurement in biospecimens (e.g. plasma nicotine measurements).

[3] Consumers report complaints and potential adverse events (AEs) through the ALCS Consumer Call Center by using information found on the product packaging or the "Contact Us" option found on the company and branded websites. The ALCS Consumer Call Center currently uses the term alleged physical effect (APE) rather than AE. APE is defined by ALCS as any complaint that alleges symptoms, illness or injury.

Calls to the ALCS Consumer Call Center may include cases with various issues, such as general questions about product use, complaints about product quality, and reports of potential AEs associated with the use of USSTC's MST products. Each consumer call is received by a call handler who is trained to follow a series of predefined scripts, ensuring that every consumer complaint is collected in a defined and consistent manner in order to identify any potential AEs. If the call includes a potential AE, the call handler administers the Adverse Event Survey Questionnaire (Appendix 7.4.3-1). The survey consists of questions to obtain detailed information about the nature of the reported AE, as well as the consumer's pre-existing medical conditions, medications, and exposure to MST and other tobacco products.

Each AE is captured in a tracking system and classified according to the "Medical Dictionary for Regulatory Activities" (MedDRA) (Medical Dictionary for Regulatory Activities (MedDRA) version 19.1).[4] The AEs are also rated using a 3-point severity scale as defined by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)) or as an SAE.[5] Each call can result in one or more AEs. Each call from a consumer (or case) is then assigned one overarching severity level resulting from the highest severity level AE.

7.4.3.2.2. Summary of ALCS AE Data from Consumer Call Center

Across its product portfolio, the MST products marketed by USSTC contain the same tobacco types and consistent manufacturing processes over time. The similarity of the candidate product to the other MST products marketed by USSTC allows us to draw insights regarding likely AEs that will be observed for the candidate product.

We summarize the consumer call AE data for the MST products marketed by USSTC during the period January 2012 through June 2017. ALCS does not have coded AE data for consumer calls prior to January 1, 2012.

During this period, USSTC sold over 4.4 billion cans of MST products and recorded 1,353 calls from consumers with AEs. The 1,353 calls from consumers resulted in 2,546 AEs that were MedDRA-coded and assigned a severity level as described above.

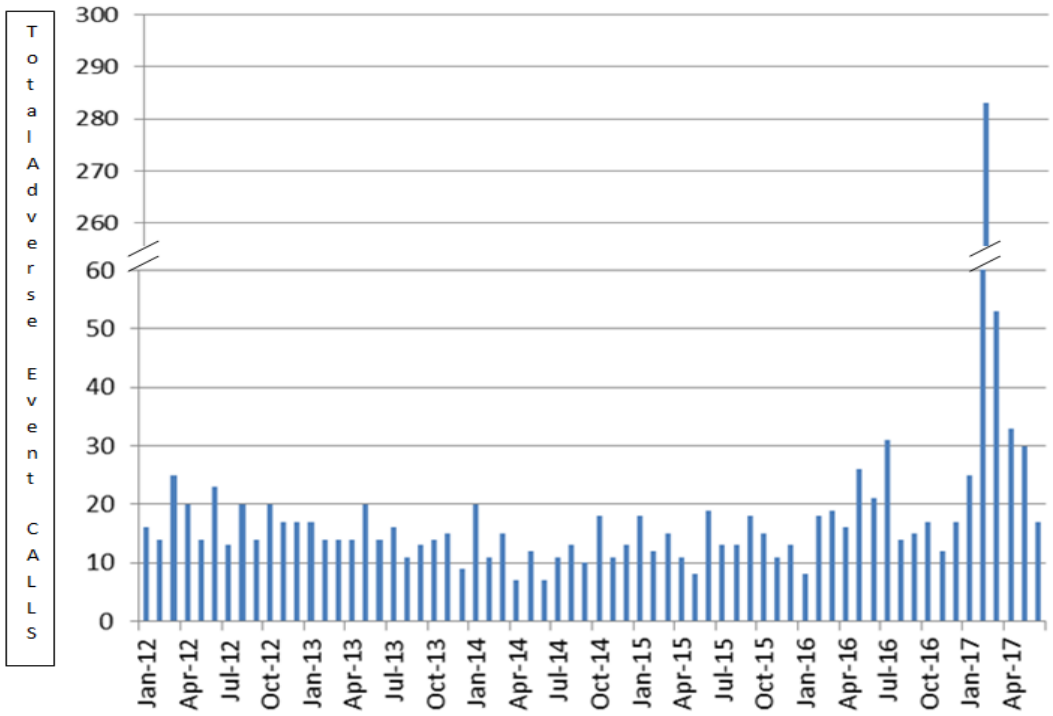
ALCS analyzes and reviews AEs monthly. Figure 7.4.3-1 depicts the number of AE cases received by month for USSTC MST products for the 1,353 calls. The number of calls per month ranged from 7 to 283. This number, 283 is an unusually high number as a result of the February 2017 announcement of a product recall (FDA Recall Tracking RES-76382) due to

[4] MedDRA v19.1 used for data from January 1, 2012 to May 12, 2016 while MedDRA v18.1 was used for data from May 13, 2016 to June 30, 2017.

[5] A serious adverse event (SAE) is defined as an outcome that is associated with any of the following: death, life-threatening, hospitalization (initial or prolonged), disability or permanent damage, or congenital anomaly/birth defect; or any other important medical events that may not result in death, be life-threatening, or require hospitalization but based upon appropriate medical judgment, may jeopardize the patient or subject or may require medical or surgical intervention to prevent one of the other outcomes listed in this definition. ICH Guideline for Clinical safety data management: Definitions and standards for expedited reporting (E2A) (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)).

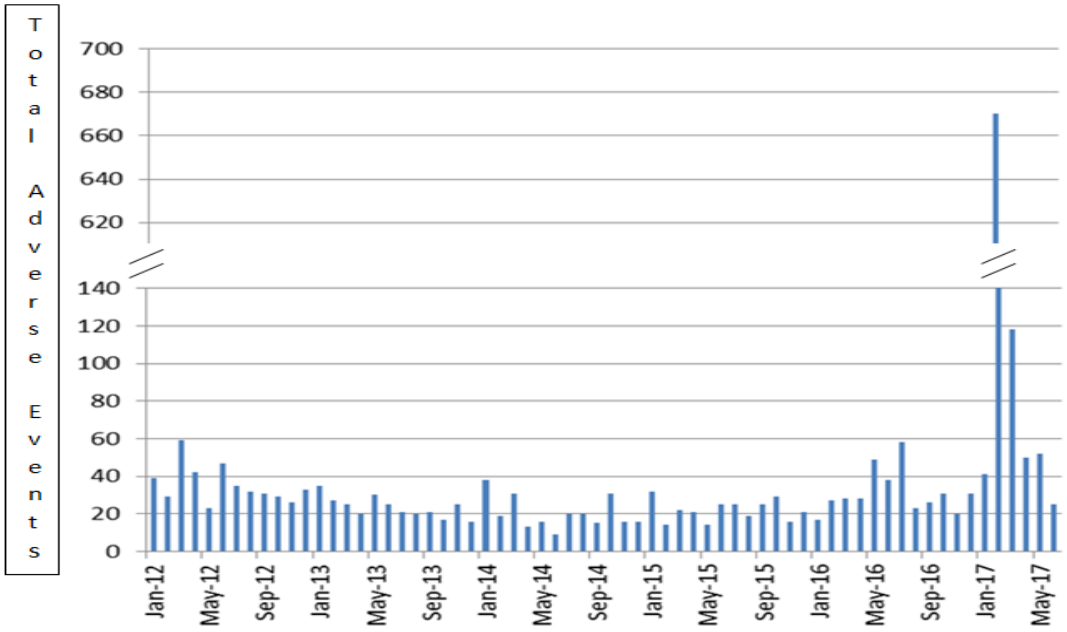
intentional tampering by someone knowledgeable of USSTC's manufacturing process. The average number of calls per month was about 20 calls if we include the outlier February 2017 data point and 16 calls if we exclude this data point.

Figure 7.4.3-1: Total Calls (1,353) with AEs by Month



The monthly total number of AEs for USSTC MST products reported during January 2012 to June 2017 is presented in Figure 7.4.3-2. The average number of AEs was about 38.5 per month. The AEs ranged from 9 to 670 per month. This number, 670, is an unusually high number as a result of the February 2017 announcement of a product recall (FDA Recall Tracking RES-76382) due to intentional tampering by someone knowledgeable of USSTC's manufacturing process. The AEs received during the recall period were mostly due to foreign material causing injuries to the lip, gingiva and mouth. AEs per month gradually declined and approached the usual frequency of AEs at 27 per month.

Figure 7.4.3-2: Total AEs (2,546) Reported By Month



The two tables below show the AEs categorized by MedDRA Preferred Term (PT) and System Organ Class (SOC) as a percent of the 2,546 total AEs received by ALCS during January 2012 to June 2017. Table 7.4.3-1 shows AEs categorized by MedDRA PT as a Percent of Total AEs. The PTs with the highest incidence of AEs are gastrointestinal disorders (Table 7.4.3-1). Table 7.4.3-2 shows AEs categorized by MedDRA SOC as a Percent of Total AEs. The SOC with the highest incidence of AEs is also gastrointestinal disorders, representing 53.1% of the 2,546 AEs.

The majority of the gastrointestinal disorders was mild (83.2%) in severity and generally reported as "upset stomach, nausea and vomiting, abdominal and oral discomfort." Additionally, 24.0% of the AEs were categorized to the SOC for Injury, Poisoning and Procedural Complications. The majority of those AEs was also Mild (82.0%) in severity and generally reported as "injuries to lips, cuts in gums and mouth." Two of those AEs were described by consumers as "tobacco poisoning" and both were moderate in severity.

Table 7.4.3-1: Adverse Events (AEs) Categorized by MedDRA PT (Top Five) as a Percent of Total AEs

Rank	PT	Total Number (%)
1	Lip injury	219 (8.6%)
2	Oral discomfort	166 (6.5%)
3	Abdominal discomfort	153 (6.0%)

Table 7.4.3-1: Adverse Events (AEs) Categorized by MedDRA PT (Top Five) as a Percent of Total AEs (Continued)

Rank	PT	Total Number (%)
4	Nausea	140 (5.5%)
5	Gingival injury	118 (4.6%)

Table 7.4.3-2: Adverse Events (AEs) Categorized by MedDRA SOC (Top Five) as a Percent of Total AEs

Rank	SOC	Total Number (%)
1	Gastrointestinal Disorders	1,352 (53.1%)
2	Injury, Poisoning and Procedural Complications	612 (24.0%)
3	Nervous System Disorders	211 (8.3%)
4	Respiratory, Thoracic & Mediastinal Disorders	118 (4.6%)
5	General Disorders & Administration Site Conditions	83 (3.3%)

Table 7.4.3-3 shows the 1,353 AE cases by severity level. The majority of cases were mild (84.3%). Seven (0.5%) cases were severe but not SAEs as defined by FDA. These seven severe cases were due to asthenia, gastric ulcer, hematochezia, abdominal pain, cough, nausea and vomiting.

Table 7.4.3-3: Severity Levels of AE Cases

Severity Levels	Total AE Cases Reported (%)
Mild	1,140 (84.3%)
Moderate	203 (14.9%)
Severe (non-serious AE)	7 (0.5%)
Serious Adverse Event	3 (0.3%)

ALCS categorized three cases as SAEs because the AE as described by the caller included an unverified hospitalization and met the SAE criteria. Table 7.4.3-4 describes the MedDRA PTs and outcomes for the three SAE cases.

Table 7.4.3-4: SAE Cases with AE PTs and Outcome

SAE Case	AE PTs and Outcome
1	Cough, Haemoptysis, Haematochezia, Vein Rupture; (Outcome: hospitalization)
2	Pyrexia, Vomiting, Hyperhidrosis, Blister, Blood Pressure Increased, Loss of Consciousness; (Outcome: hospitalization)
3	Hypersensitivity, Rhinorrhoea, Oropharyngeal Pain, Gastric Disorder (Outcome: hospitalization)

7.4.3.3. Conclusion

The AEs observed in the clinical study demonstrate that the candidate product is well tolerated and no deaths or serious AEs were reported. Furthermore, the Principal Investigator of the study considered the AEs reported during the use of the candidate product as "unlikely related or "not related" to the product. The AEs resolved quickly after candidate product use and are similar to the AEs reported with the use of nicotine polacrilex gum in the clinical study (Appendix 7.3.1-1).

The number of AEs reported by consumers of USSTC MST products is significantly low relative to the over 4.4 billion cans sold. The rate of AEs among consumers of USSTC MST products is less than one per million (0.6/1M) cans sold during a period of five and a half years. The highest incidence of AEs was Gastrointestinal Disorders (53.1%). The majority of AE cases were "Mild" (84.3%) in severity. For the period January 2012 through June 2017, less than one percent (0.8%) of the AE cases associated with the use of USSTC MST products were "Severe." And three were SAEs, which were primarily due to hospitalizations. Overall, the vast majority of the AEs reported over a five and a half year period were mostly mild and non-life threatening.

ALCS's AE data demonstrates that the candidate product will be well-tolerated. Generally, AEs associated with the candidate product and other USSTC MST products resolve quickly after product use.

7.4.3.4. Literature Cited

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) ICH Guidelines. Retrieved from http://www.ich.org/home.html

Medical Dictionary for Regulatory Activities (MedDRA) version 19.1. Retrieved from http://meddra.org