OVER-THE-COUNTER DRUGS AND PRESCRIPTION DRUGS: DEVELOPMENT OF A REGULATORY DATABASE AND DATA ANALYSIS OF WARNING LETTERS BETWEEN FISCAL YEARS 2015-2019

by

HELEN KIJUNG BAI

(Under the Direction of Michael Bartlett)

ABSTRACT

According to 21 Code of Federal Regulation (CFR) Part 211, OTC manufacturers must establish and follow current good manufacturing practices (cGMP) to produce quality products while meeting regulatory standards. The warning letters issued by the U.S. Food and Drug Administration (FDA) reveals quality inadequacies that may impact the safety and effectiveness of these products. This study provides an analysis of warning letters and cited violations from FY2015 to FY2019 to identify the most common areas of quality issues and to understand the FDA's current thinking on regulatory expectations. Violations relating to product and process controls significantly increased, while violations relating to labeling decreased over the years. Despite these changes in violation numbers, the number of violations increased in most categories, thus projecting the continual increase of quality inadequacies in the OTC industry.

INDEX WORDS: US Food and Drug Administration, Good Manufacturing Practices, Inspections, Warning Letters, Over-the-counter Drugs, Rx

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DEDICATION

All praise, honor, and glory to my Lord Jesus Christ for His grace and mercy.

Thank you, Jesus.

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CHAPTER 1

INTRODUCTION

1.1 Purpose of Research

With recent years' increasing attention in the safety and efficacy of Over-the-Counter (OTC) drugs, the U.S. Food and Drug Administration (FDA) began to reform the regulatory system overseeing OTC drugs. The purpose of this research study was to examine the current status of quality inadequacies of OTC drugs and to compare these with prescription (Rx) drugs in the United States. This was achieved by developing a regulatory database of warning letters from fiscal years 2015 – 2019 and by performing data analysis on the Code of Federal Regulations (CFR) violations extrapolated from the obtained warning letters.

1.2 Problem Statement

In recent years, the reformation to modernize OTC regulations was initiated to assess emerging safety issues and to accommodate drug innovation.[10]. Due to the expansion of scientific innovation, current OTC drugs have become more challenging to review and regulate with the initial OTC drug regulation system.[10] This regulatory gap between the OTC drug regulation and currently marketed products is seen through the violations captured in issued warning letters. Many violations related to current good manufacturing practices (cGMP), labeling, and quality controls are reported in the warning letter. Understanding these violations and assessing quality inadequacies from the OTC drug manufacturers are critical because they can highlight safety and effectiveness issues that may negatively impact OTC drug consumers.

1.3 Outcomes of Research

This research evaluates warning letters and inspections issued to OTC drug manufacturers by the US FDA. Specifically, this study provides information on the frequency of CFR violations in cGMP, labeling, laboratory controls, process and product controls, and the general quality control unit. The study also provides information on the differences and similarities between OTC and Rx drugs in their violations with current drug regulations. Overall, the identification and analysis of violations gives critical insight on the FDA's current thinking in the implementation of drug regulations and provide suggestions to OTC manufacturers for strengthening their quality systems to produce more safe and effective OTC drugs.

CHAPTER 2

BACKGROUND

2.1 Overview of the Over-the-Counter Drugs

Over-the-Counter (OTC) drugs, also known as nonprescription drugs, are drugs that are found to be safe and effective for direct consumer usage. OTC drugs are available without a prescription and there are more than 300,000 OTC products marketed in the United States.[11] An average of 60,000 products in volume are sold each year which consists of more than 80 therapeutic categories including acne, analgesics, heartburn, sleeping aids, and allergy.

According to the FDA's Office of Non-Prescription Drugs (ONPD), the benefits of OTC drugs include low potential for misuse and abuse, greater weight of benefits versus risks, ease of self-diagnosis, adequacy in labeling, and availability of safe and effective drug products without a health professional.[5] The availability of OTC drugs also leads to savings of $146 billion each year for the U.S. Healthcare system.[12] The price difference between the OTC drugs and prescription (Rx) drugs and unrequired clinical visits to buy OTC drugs are the primary reasons for this saving.[12] These characteristics reflect how OTC drugs play a vital role in today's health care system.

The U.S. FDA's Center for Drug Evaluation and Research (CDER) is responsible for regulating OTC, as well as Prescription (Rx) drugs. More specifically, the Office of Compliance (OC) under CDER currently oversees the quality, safety, and efficacy of OTC drugs. According to the U.S. FDA, the duties of the OC include, but are not limited to:

- Providing responses to inquiries from industry, agencies, and consumer groups regarding the regulatory status of OTC drugs

- Developing policies based on emerging regulatory, political, and social issues
- Evaluating product ingredients and labeling for meeting scientific and legal standards
- Requiring knowledge of technological and marketing innovations and trends in the OTC drug industry
- Identifying and evaluating problems related to the OTC drug industry and initiate solutions
- Assure safety and efficacy of OTC drugs by taking actions such as Warning letters, untitled letters, regulator meetings, inspection requests, recommendations for recalls, seizures, injunctions, and/or criminal sanctions.[1]

The OC consists of several offices, including the Office of Unapproved Drugs and Labeling Compliance (OUDLC) and the Office of Manufacturing and Product Quality (OMQ).[2] Regulatory compliance related to approval and labeling requirements for OTC drugs are issues for which these offices hold responsibility. These offices strive to mitigate the risk of poor-quality OTC drugs reaching the consumers by carrying out the duties mentioned above.

2.2 History of OTC Review

The implementation of drug regulation began with the original Federal Food and Drug Act (FD&C) of 1906. The revision of this FD&C Act took place in 1938 with a new provision of prohibiting distribution of any new drug without the filing of a New Drug Application (NDA) and approval by the U.S. FDA to ensure the safety of the drug.[3] The legal distinction between Rx and OTC drugs began with the enactment of the Durham-Humphrey Amendment in 1951 by separating drugs that cannot be used without medical supervision. This led to restricting sales

only on prescriptions provided by health professionals. In 1962, the Kefauver-Harris Amendment passed to ensure not only the safety but also the efficacy of drugs produced in the market.[3] Drug manufacturers were required to provide evidence including scientific data and clinical data to support the efficacy of the new drugs marketed. These additional Amendments to the FD&C Act initiated the Drug Efficacy Study Implementation (DESI) Review to perform a retrospective evaluation of efficacy on the OTC drugs already on the market without FDA review.[4] By 1972, the OTC Drug Review was established to further evaluate the safety and efficacy of OTC products marketed before May 11, 1972. Since then, the OTC Drug Review has become the process of creating OTC Drug Monographs (today's current OTC regulatory system) to ensure the quality of OTC drugs.

The process of OTC Drug Review consists of three phases: a review of active ingredients by an advisory panel, a review of active ingredients by the FDA, and the publication of a final monograph.[5,6] The ingredients are classified in three different groups (Category I, II, III) during the review to identify the safety and efficacy level of each ingredient. Category I are ingredients regarded as Generally Recognized As Safe and Effective (GRASE) and not misbranded, Category II includes ingredients regarded as not GRASE and misbranded, and Category III includes ingredients requiring additional data for classification.[7] Extensive scientific and clinical data is reviewed for the classification of ingredients and only those ingredients determined to have sufficient evidence are included in the final monograph.

2.2 OTC to Market

2.2.1 OTC drug monograph

The OTC drug monograph is the regulatory standard published in the Federal Register for OTC drugs[7]. It is a "recipe book" that covers categories of acceptable active ingredients, formulations, indications of use, doses, and labeling of OTC products. The drug is considered GRASE and not misbranded once it is manufactured in compliance with the final monograph. Any marketed drug not manufactured in accordance with the requirements of the OTC drug monograph is considered as a "new drug".[9] All "new drugs" require U.S. FDA approval and must to go through the New Drug Application (NDA) process before it can be marketed.[4]

The OTC drug monograph and the general GRASE requirements for OTC drugs can be found in 21 Code of Federal Regulation (CFR) Part 330.[13] Each therapeutic class-specific monograph is listed in the following 21 CFR parts and more detailed information is shown in Table 1.[14]

Table 1 OTC Monograph Specific Regulations

Therapeutic Class	Regulations
Antacids	21 CFR Part 331
Antiflatulents	21 CFR Part 332
Topical Antimicrobial drugs	21 CFR Part 333
Antidiarrheal drugs	21 CFR Part 335
Antiemetic drugs	21 CFR Part 336
Nighttime sleep-aids	21 CFR Part 338
Stimulant drugs	21 CFR Part 340
Cold, cough, allergy, bronchodilator, and antiasthmatic drugs	21 CFR Part 341
Internal analgesic, antipyretic, and antirheumatic drugs	21 CFR Part 343
Topical otic drugs	21 CFR Part 344
Anorectal drugs	21 CFR Part 346
Skin protectant drugs	21 CFR Part 347
External analgesic drugs	21 CFR Part 348
Ophthalmic drugs	21 CFR Part 349
Antiperspirant drugs	21 CFR Part 350

Sunscreen drugs	21 CFR Part 352
Anticaries drugs	21 CFR Part 355
Miscellaneous internal drugs	21 CFR Part 357
Miscellaneous external drugs	21 CFR Part 358

For each monograph, the GRASE active ingredients including dosage strength and form are listed. Specific labeling requirements such as indications, warnings, and directions for use are also listed within the monograph. An example of an Antiflatuelent drug monograph (21 CFR Part 332) is shown below:

- §332.10 Antiflatulent active ingredients.
    - Simethicone; maximum daily dose 500 mg. There is no dosage limitation at this time for professional labeling.
- §332.30 Labeling of antiflatulent drug products.
    - *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as an "antiflatulent," "antigas," or "antiflatulent (antigas)."
    - *Indications.* The labeling of the product states, under the heading "Indications," one or more of the phrases listed in this paragraph (b), as appropriate. Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in this paragraph (b), may also be used, as provided in §330.1(c)(2) of this chapter, subject to the provisions of section 502 of the Federal Food, Drug, and Cosmetic Act (the act) relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery

for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.[15]

2.2.2 Other OTC Drug-Related Regulations

According to 21 CFR 211.1(a), all finished pharmaceutical drugs administered to humans or animals must meet the minimum current good manufacturing practices (cGMP) for the preparation of drug products.[24] The FDA ensures the quality of the drug by monitoring the drug maker's manufacturing practices including methods, facilities, and controls. This regulation also applies to OTC drugs to make sure that the drug product has the ingredients and strength it claims to have as well as its safety for use.[24] The overview of cGMP (21 CFR 211) is provided in Table 2.

Table 2 Current Good Manufacturing Practice (cGMP) Regulations

Active Ingredients	Regulations
A - General	211.1, 211.3
B - Organization and Personnel	211.22, 211.25, 211.28, 211.34
C - Building and Facilities	211.42, 211.44, 211.46, 211.48, 211.50, 211.52, 211.56, 211.58
D - Equipment	211.63, 211.65, 211.67, 211.68, 211.72
E - Control of Components, Container and Closures	211.80, 211.82, 211.84, 211.86, 211.87, 211.89, 211.94
F - Production and Process Controls	211.100, 211.191, 211.103, 211.105, 211.110, 211.111, 211.113, 211,115
G - Packaging and Labeling Controls	211.122, 211.125, 211.130, 211.132, 211.134, 211.137
H - Holding and Distribution	211.142, 211.150
I - Laboratory Controls	211.160, 211.165, 211.166, 211.167, 211.170, 211.173, 211.176
J - Records and Reports	211.180, 211.183, 211.184, 211.186, 211.188, 211.192, 211.194, 211.196, 211.198
K - Returned and Salvaged Drug Products	211.204, 211.208

Labeling requirements for OTC drugs also must be met for GRASE. The general labeling requirements for all OTC drugs are covered in 21 CFR 201.60 (Subpart C).[36] The specific labeling requirements for each therapeutic class is stated within the OTC drug monograph (Table 1). Labeling requirements for certain OTC products pertaining to specific active ingredients are listed in 21 CFR 310.[26] Active ingredients listed in this regulation are considered as "new drugs" due to the lack of data to support the safety and effectiveness of the drug (Not GRASE).[26] Therefore, any labeling claims of these active ingredients for OTC use is considered false, misleading, or unsupported by scientific data under the FD&C Act.[26] An anticholinergic in cough-cold OTC drug (21 CFR 310.533) is provided below as an example:

- §310.533 Drug products containing active ingredients offered over-the-counter (OTC) for human use as an anticholinergic in cough-cold drug products.
    - (a) Atropine sulfate, belladonna alkaloids, and belladonna alkaloids as contained in Atropa belladonna and Datura stramonium have been present as ingredients in cough-cold drug products for use as an anticholinergic. Anticholinergic drugs have been marketed OTC in cough-cold drug products to relieve excessive secretions of the nose and eyes, symptoms that are commonly associated with hay fever, allergy, rhinitis, and the common cold. Atropine sulfate for oral use as an anticholinergic is probably safe at dosages that have been used in marketed cough-cold products (0.2 to 0.3 milligram); however, there are inadequate data to establish general recognition of the effectiveness of this ingredient. The belladonna alkaloids, which contain atropine (*d, dl* hyoscyamine) and scopolamine (*l*- hyoscine), are probably safe for oral use at dosages that have been used in marketed cough-cold products

(0.2 milligram) but there are inadequate data to establish general recognition of the effectiveness of these ingredients as an anticholinergic for cough-cold use.

2.2.3 New Drug Applications

Any OTC drug that does not meet monograph requirements is considered a new drug and requires a New Drug Application (NDA) to be marketed.[4,16] As previously mentioned, the NDA was created by the FD&C Act in 1938 to ensure the safety and effectiveness of OTC drugs. The extensive amount of data such as pre-clinical and clinical results, identification of active ingredients and materials, studies on drugs impacting the body, and plans of manufacturing, processing, and packaging are required in an NDA.[16] Once submitted, this supporting evidence is reviewed and approved by the FDA. The approval of the NDA allows the drug to be marketed as a prescription (Rx) drug. The Rx drug can be switched to OTC drug by the Rx-to-OTC Switch process.[17] However, additional studies and applicable labeling requirements must be met due to the differences in regulation of NDA and OTC drug monographs. Table 3 provides the major differences between the NDA and OTC drug monographs.

Table 3 Differences between NDA and OTC Monographs [17]

NDA	OTC Monograph
Pre-market approval – FDA reviews and approves formulation and labeling prior to marketplace	No pre-market approval – FDA sets forth specific conditions for GRASE, or in the case of a developing monograph, sets forth conditions that allow for continued marketing pending a final monograph. Oversight occurs on a post-marketing basis
Confidential filing	Public process

Drug-product specific	Active ingredient (API) specific and evaluated by OTC drug category
May require a user fee	No user fee
Potential for marketing exclusivity	No Marketing exclusivity
FDA review timelines	Manufacturers responsible for ensuring a compliant product with no FDA-mandated review
Approved labeling is unique to the drug	Labeling is defined by the monograph. Once marketed, the FDA can review the complete labeling at any time to determine whether it is truthful or misleading
May require clinical studies, including studies on label comprehension and actual use	Generally, does not require clinical studies. Label comprehension and actual use studies are not required for ingredients already covered by a final or tentative final monograph
Approved NDA is your license to market	Final monograph is open to anyone
Trade name reviewed prior to marketing	No review of trade name prior to marketing. Once marketed, FDA can review the trade name at any time

One of the significant differences between the NDA process and an OTC monograph is the requirement for pre-market approval. Because the ingredients listed in the final monograph have been previously reviewed and considered GRASE, any additional review for the drugs within an OTC monograph is unnecessary. With this, the general process timeline (from the development of the OTC drug to its availability to the market) of an OTC monograph is significantly shorter than an Rx-to-OTC Switch, thus giving incentives to OTC drug manufacturers to follow the OTC drug monograph for production.[17]

OTC drugs also differ from Rx drugs in their post-marketing surveillance requirements. For Rx drugs, the Office of Surveillance and Epidemiology (OSE) maintains a post-marketing surveillance system to identify adverse events for already marketed products and the requirements on post-marketing reporting of adverse drug experience is defined in 21 CFR 214.80.[39] For OTC drugs, however, the regulation relating to post-marketing requirement is not clearly defined in the CFR and adverse event reporting is not required for OTC drugs subject to monographs. This indicates the difference in the pharmacovigilance expectations between the OTC and Rx drugs.

As previously mentioned, labeling requirements for GRASE OTC drugs are included within the OTC monograph. The general formats and contents requirements such as drug facts, uses, warnings, and directions are included in 21 CFR 201.60.[36] Unlike OTC drugs, the labeling for Rx drugs are reviewed and approved during the NDA process. The labeling requirements for Rx drugs, covered in 21 CFR 201.50 (Subpart B), include but not limited to prescribing information, use in a specific population, risk summary, and pre-clinical and clinical studies, [37] More extensive information is needed for Rx drugs due to the uncertainty of safety and effectiveness of the new drug.

2.3 Warning Letters

Warning Letters are issued by the U.S. FDA to notify of significant regulatory violations of the FD&C Act made by the manufacturers.[18] The warning letter is important because it identifies the need for prompt corrective action and gives the opportunity for drug manufacturers to take voluntary actions before the enforcement action is initiated.[18] The enforcement action includes recalls, seizure, injunctions, administrative detention, and civil monetary penalties.[19]

Before the issuance of the warning letter, an inspection is conducted by the FDA investigator. Any observations made during the inspection is recorded in the FDA Form 483.[20] Specific inspections and enforcement actions can also be found in the FDA's Data Dashboard.[22] Once the manufacturers receive the Form 483, they are encouraged to respond to the FDA with the appropriate corrective action plan within 15 working days.[21] If this requirement is unmet due to unresponsiveness or an insufficient response, a warning letter is issued as an escalation from the 483.[20] The warning letter is far more serious than a Form 483 and the manufacturer's implementation of corrective actions is required by law.

As previously mentioned, OTC drug products are regulated under the CDER. Therefore, the OTC drug warning letters are directly issued by CDER Office of Compliance.[18] Violations involving labeling, cGMP, unapproved new drug, misbranding, adulteration, advertising, etc. are summarized in the warning letter.[18] Specifically, the CFR associated with each violation is listed in the warning letter with observation descriptions corresponding to the CFR.[21] The violation examples of OTC drug warning letters is provided below:

- Your firm failed to perform, for each batch of drug product, appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release, and conduct appropriate laboratory testing for each batch of drug product required to be free of objectionable microorganisms (21 CFR 211.165(a)).[21]
    - Your firm manufactures over-the-counter (OTC) **(b)(4)** drug products, including those specifically marketed to children. You released certain drug products without conducting identity and strength testing. For example, you

released your **(b)(4)** without testing for identity and strength of its labeled active ingredients: **(b)(4)**.[21]

- Your response is inadequate. You failed to test all your reserve samples of drug products containing **(b)(4)** as active ingredients within expiry to determine whether they meet established specifications for identity and strength. You did not commit to perform the assay test for **(b)(4)** in your finished drug products.[21]
- Your response is also inadequate because you did not include information about your testing procedures, methods, timeline for implementation, or a detailed description of the tests you will conduct (e.g., identity, strength, and purity).[21]

- Your firm failed to test samples of each component for identity and conformity with all appropriate written specifications for purity, strength, and quality (21 CFR 211.84(d)(1)).[21]
  - Your firm failed to test incoming components used to manufacture your drug products to determine their identity. For example, your firm did not ensure that at least (b)(4) specific identity test was conducted for (b)(4) lot of components, including active ingredient identity testing for (b)(4) received from another site in your network.[21]
  - It is your responsibility to ensure that you perform at least (b)(4) test to verify the identity of all of the components used in drug product manufacturing, including your active ingredient (b)(4).[21]

CHAPTER 3

METHODOLOGY, RESULTS, AND DISCUSSION

3.1 Methods

Regulatory database and analysis

To identify and evaluate quality inadequacies in OTC drugs, this study incorporated the following steps: extraction of CFR violations, categorization of violations, statistical analysis of data, and interpretation of results. To carry out these steps, a regulatory database was created by obtaining OTC drug specific warning letters issued by CDER from fiscal years 2015 to 2019. All warning letters were obtained from the U.S. FDA warning letter site.[23] A total of 116 OTC drug warning letters were issued by the FDA during these years.[23] Cited CFR regulations, observations from the inspections, and general product information was extracted from these warning letters.

Violations with similar themes were categorized into four major categories (Quality unit, Labeling, Drug product and process controls, and Laboratory controls) by the specific CFR associated with each category. Each category was further dissected into violation groups by the frequency of violations made each year. Due to the small sample size, the statistical analysis was done using the Fisher's exact test with the alpha value of 0.05 (5%) for significance level. IBM SPSS was used as the statistical tool to calculate the p-value.

Rx drug warning letters were also collected and violations were extracted to compare the quality inadequacies between OTC to Rx drugs.[23] Three out of four of the same violation categories were used for Rx drugs to make the appropriate comparison between the two groups.

Due to the difference in labeling requirements for Rx drugs, the evaluation of Rx drug labeling violations was omitted from this study.

3.2 Explanation of Violation Categories

Category 1: General quality violations

All 21 CFR violations cited within the warning letters were categorized into four major categories: general quality, labeling, drug product and process controls, and laboratory controls. The general quality violations were sorted into seven violation groups by their subject. Specific regulations covered in Category 1 are shown in Table 4.

Table 4 General Quality Violations

VG#	Violation Group	Regulation cited
1	Quality control unit	21 CFR 211.22(a)
2	General written procedures, records and reports	21 CFR 211.22(d), 21 CFR 211.56(b), 21 CFR 211.180(a)
3	Approve and reject procedures or specifications	21 CFR 211.22(c)
4	Lab facilities	21 CFR 211.22(b)
5	Cleaning, sanitizing, and maintenance	21 CFR 211.52, 21 CFR 211.56(a), 21 CFR 211.67(a), 21 CFR 211.42, 21 CFR 211.113
6	Electronic Records	21 CFR 11.10

- *Violation Group 1 - Quality control unit:*

  This violation group contains violations relating to the establishment of the quality control unit. Per 21 CFR 211.22(a), "The quality control unit is required and they shall have the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and

drug products, and the authority to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated. The quality control unit is also responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company." Most violations involved in this group were the absence of a quality control unit.

- *Violation Group 2 - General written procedures, records, and reports:*

  This violation group contains violations relating to the establishment of general written procedures, records, and reports. Sections in these regulations state the requirement of written procedures for responsibilities and procedures applicable to organizations, buildings, and the quality control unit.[24] Most violations included a lack of written procedures and procedures not followed.

- *Violation Group 3 - Approve and reject procedures or specifications:*

  This violation group contains violations relating to the quality of the drug product. Per 21 CFR 211.22 (c), "The quality control unit shall have the responsibility for approving or rejecting all procedures or specifications impacting on the identity, strength, quality, and purity of the drug product." Most violations in this group involved the lack of the quality control unit's responsibility for approving and rejecting procedures.

- *Violation Group 4 - Lab facilities*

  This violation group contains violations relating to quality inadequacies in lab facilities. Per 21 CFR 211.22(b), "Adequate laboratory facilities for the testing and approval (or rejection) of components, drug product containers, closures, packaging materials, in-process materials, and drug products shall be available to the quality

control unit." Most violations in this group included the unavailability of adequate lab facilities for testing and the lack of lab facilities to approve or reject drug products.

- *Violation Group 5 - Cleaning, sanitizing, and maintenance:*

  This violation group contains any issues relating to contamination. Sections in these regulations state the requirement for cleaning, sanitizing, and maintenance of building, facilities, and equipment.[24] Most violations included not properly maintaining equipment and buildings not constructed to facilitate cleaning, maintenance, and proper operations. A lack of procedures to prevent microorganisms from being introduced into drug products were also common.

- *Violation Group 6 - Electronic Records*

  Although this regulation is not part of cGMP, this regulation was cited within the OTC warning letters since most OTC drug manufacturers transitioned to using electronic records from paper records. Per 21 CFR 11.10, "Persons who use closed systems to create, modify, maintain, or transmit electronic records shall employ procedures and controls designed to ensure the authenticity, integrity, and, when appropriate, the confidentiality of electronic records, and to ensure that the signer cannot readily repudiate the signed record as not genuine." Violations relating to data integrity in electronic records are covered in this group. Most violations included not meeting the retention and audit trail requirements to ensure the electronic records used are trustworthy and reliable.

Category 2: Labeling violations

The labeling violations were sorted into five violation groups. Regulations cited in these warning letters were based on the review of labels and advertisements of the OTC drugs in the market. Specific regulations covered in this group are shown in Table 5.

Table 5 Labeling Violations

VG#	Violation Group	Regulations Cited
1	Unapproved new drug	21 CFR 310, 21 CFR 310.3(h)(5), 21 CFR 201.115, 21 CFR 330.11
2	Inadequate required information	21 CFR 201.66, 21 CFR 201.300-328, 21 CFR 329.100(a)
3	Misbranding	21 CFR 201.128, 21 CFR 330.1, 21 CFR 201.15, 21 CFR 201.61, 21 CFR 201.327(c)
4	Expiration date issues	21 CFR 211.137(a), 21 CFR 201.17, 21 CFR 201.166
5	Drug/monograph specific issues	21 CFR 331-358

- *Violation Group 1 - Unapproved New Drug:*

  Sections in these regulations are related to labeling requirements for drugs containing non-GRASE ingredients.[26] Any new labeling claims for ingredient usages makes the product an unapproved new drug. Therefore, most violations included in this group are marketing of a new drug as an OTC drug without the U.S. FDA's approval.

- *Violation Group 2 - Inadequate required information*

  This violation group contains labels missing the required content. Specific labeling requirements for specific drug products are listed in 21 CFR 201.300 to 21 CFR 201.328. These requirements provide information such as warning statements to

provide additional guidance to the consumer. Most violations in this group included inadequate warning statements or directions.

- *Violation Group 3 - Misbranding*

  This violation group contains false labeling and statements related to misleading labeling. According to 21 CFR 201.61, the statement of identity must include the accurate general pharmacological category of the drug or the principal intended action of the drug. The prominent and conspicuous statement of the general pharmacological actions or principle intended actions are required for OTC mixture products. Most violations in this group included an inaccurate statement of identity and failure to state the principle intended use of the drug.

- *Violation Group 4 - Expiration Date Issues*

  This violation group contains violations relating to labeling of expiration dating. Per 21 CFR 211.137, (b) Expiration dates shall be related to any storage conditions stated on the labeling, as determined by stability studies described in §211.166; (d) Expiration dates shall appear on labeling in accordance with the requirements of §201.17 of this chapter." Most violations in this group included inaccurate expiration dates and labeling expiration dates without any supporting stability studies. These labeling violations were often related to stability program violations.

- *Violation Group 5 - Drug/monograph specific issues*

  As previously mentioned, the requirements for each therapeutic class are stated within the OTC monograph. This violation group contains violations relating to these OTC monographs. Most violations in this group included active ingredients not listed as described in the monograph and not used in consistency with the conditions proposed

in the monograph. These inadequacies also led to the marketing of unapproved new drugs, thus violating associated regulations.

Category 3: Drug product and process control violations

All drug product and process control related violations were sorted into six violation groups. Regulations cited in this group mainly addressed the drug product itself and its process controls for producing quality products. Specific regulations covered in this violation group are shown in Table 6.

Table 6 Drug Product and Process Control Violations

VG#	Violation Group	Regulations Cited
1	Representative sample	21 CFR 211.84 (b)
2	Component verification (active ingredients, excipients, raw materials)	21 CFR 211.84 (a)
3	Production and control records	21 CFR 211.186(a), 21 CFR 211.186(b), 21 CFR 211.188, 21 CFR 211.192
4	Control procedures and validation	21 CFR 211.110(a)
5	Procedures for deviations	21 CFR 211.100(b)
6	Written procedures	21 CFR 211.100(a), 21 CFR 211.113(b)

- *Violation Group 1 - Representative sample*

  This violation group contains violations relating to representative samples for testing and approval or rejection of components, drug product containers, and closures. According to 21 CFR 211.84(b), representative samples of each shipment of each lot are required to be collected for testing or examination. The number of containers to be sampled, and the amount of material to be taken from each container, should be

based upon appropriate criteria such as statistical criteria for component variability, confidence levels, and degree of precision desired, the past quality history of the supplier, and the quantity needed for analysis. Most violations in this group included representative samples not taken of each shipment and the sampled amount taken from each container was not based upon appropriate criteria.

- *Violation Group 2 - Component verification*

  This violation group contains violations relating to the verification of components such as active ingredients, excipients and raw materials. Per 21 CFR 211.84(a), "Each lot of components, drug product containers, and closures shall be withheld from use until the lot has been sampled, tested, or examined, as appropriate, and released for use by the quality control unit." Most violations in this group included not withholding each component from use until the lot has been sampled, tested, or examined. Quality control violations for releasing these components from the unit were also included.

- *Violation Group 3 - Production and control records*

  This violation group contains violations relating to inadequacy in production and control records. Sections in these cited regulations (21 CFR 211.186, 21 CFR 211.188, 21 CFR 211.192) state the requirements for maintaining records for master production, batch production, and production record review in compliance. Some requirements listed in these records are:

  - The name and weight or measure of each active ingredient per dosage unit or per unit of weight or measure of the drug product, and a statement of the total weight or measure of any dosage unit;

- A complete list of components designated by names or codes sufficiently specific to indicate any special quality characteristic;
- An accurate statement of the weight or measure of each component, using the same weight system (metric, avoirdupois, or apothecary) for each component. Reasonable variations may be permitted, however, in the number of components necessary for the preparation in the dosage form, provided they are justified in the master production and control records;
- Identity of individual major equipment and lines used;
- Specific identification of each batch of component or in-process material used;
- Weights and measures of components used in the course of processing;
- A statement of the actual yield and a statement of the percentage of theoretical yield at appropriate phases of processing;[24]

Most violations in this group included:

- Procedures for the preparation of master production and controls are not described in a written procedure [21 CFR 211.186(a)]
- Master production and control records lack statement of theoretical yield [21 CFR 211.86(b)]
- Batch production and control records do not include complete information relating to the production and control of each batch [21 CFR 211.188]
- Failure to thoroughly review any unexplained discrepancy [21 CFR 211.192]
- Failure of a batch or any of its components to meet its specifications whether or not the batch has been already distributed [21 CFR 211.192]

- *Violation Group 4 - Control Procedure and Validation*

  This violation group contains violations relating to control procedures of manufacturing processes. Per 21 CFR 211.110(a), "To assure batch uniformity and integrity of drug products, written procedures shall be established and followed that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch. Such control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product." Most violations in this group included not establishing control procedures to monitor the output and not validating the performance of manufacturing processes that are responsible for causing variability in the in-process material and the drug product. Several violations also included not following written procedures for examinations for appropriate samples of in-process materials of each batch.

- *Violation Group 5 - Procedure for deviations*

  This violation group contains violations relating to the recording of deviations during production. Per 21 CFR 211.100(b), "Written production and process control procedures shall be followed in the execution of the various production and process control functions and shall be documented at the time of performance. Any deviation from the written procedures shall be recorded and justified." Most violations in this group included not documenting and following SOPs for deviation and not justifying deviations from written production and process control procedures.

- *Violation Group 6 - Written procedures*

This violation group contains violations relating to any inadequacy in written procedures in overall drug product and process controls. According to 21 CFR 211.100(a), written procedures for production and process controls are required to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. Any changes in procedures must be written, drafted, reviewed and approved by the appropriate organizational unit and also reviewed and approved by the quality control unit. Most violations in this group included the absence of written procedures for general production and process controls and not reviewing changes to written procedures. Several violations also included the absence of written procedures designed to prevent microbiological contamination during drug production.

Category 4: Laboratory controls violations

All laboratory control violations were sorted into seven violation groups. Regulations cited in this group cover requirements for the establishment of laboratory controls such as specifications, standards, sampling plans, and other laboratory control mechanisms to ensure the quality of laboratory performance and dependability. Specific regulations covered in this violation group are shown in Table 7.

Table 7 Laboratory Control Violations

VG#	Violation Group	Regulations Cited
1	Testing and releasing for distribution	21 CFR 211.165(a), 211.165(b), 21 CFR 167
2	Stability program	21 CFR 211.166
3	Packaging and labeling operation	21 CFR 211.130, 21 CFR 211.122, 211 CFR 132

4	Out of specification	21 CFR 160
5	Equipment design, size, and location	21 CFR 211.63, 21 CFR 211.65, 21 CFR 211.67
6	Investigation of failures	21 CFR 211.198, 21. CFR.211.192
7	Laboratory records	21 CFR 211.194(a), 21 CFR 211.194(a)(1), 21 CFR 211.194(a)(2), 21 CFR 211.165(e), 21 CFR 211.165(f)

- *Violation Group 1 - Testing and releasing for distribution*

  This violation group contains violations relating to laboratory testing and releasing for distribution. According to 21 CFR 211.165 and 21 CFR 211.167, appropriate laboratory testing is required for the conformance of final specifications for the drug product including the identity and strength of each active ingredient prior to release. Any sterility or pyrogen testing is also required so the batch of the drug product is free of objectionable microorganisms. Most violations in this group included not establishing appropriate laboratory testing for the identification of active ingredients and not testing each batch for the identification of microorganisms.

- *Violation Group 2 - Stability Program*

  This violation group contains violations relating to the stability programs for drug products. Sections in these regulations (21 CFR 211.166) state the requirements for a written program designed to assess stability characteristics. Most violations in this group included a lack of written stability program and not following the written stability testing program.

- *Violation Group 3 - Packaging and labeling operations*

This violation group is different from previous labeling violations as this group covers violations relating to the operations of packaging and labeling. Per 211.122(a), "There shall be written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, examination, and/or testing of labeling and packaging materials; such written procedures shall be followed. Labeling and packaging materials shall be representatively sampled, and examined or tested upon receipt and before use in packaging or labeling of a drug product" Most violations in this group included not establishing written procedures describing laboratory controls for examining and testing labeling and packaging materials.

- *Violation Group 4 - Out of specification*

  This violation group contains violations relating to laboratory controls for establishing specifications. Per 21 CFR 211.160(b), laboratory controls shall include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity." Most violations in this group included not having scientifically sound laboratory controls and not following established laboratory control mechanisms.

- *Violation Group 5 - Equipment design, size, and location*

  This violation group contains violations relating to equipment used in the laboratory, manufacturing, processing, packing, and holding of a drug product. Per 21 CFR 211.63, equipment used for laboratory testing must be appropriate in design, size, and suitably located to facilitate operations for its intended use and for its cleaning and

maintenance. Most violations in this group included equipment contact leading to alteration of safety, identity, strength, quality or purity of the drug product and written procedures with insufficient details of methods and equipment used.

- *Violation 6 - Investigation of failures*

  This violation group contains violations related to investigations of failures and complaint files. Per 21 CFR 211.198(b)(2), "Where an investigation under §211.192 is conducted, the written record shall include the findings of the investigation and follow-up. The record or copy of the record of the investigation shall be maintained at the establishment where the investigation occurred in accordance with §211.180(c)." Most violations in this group included not having written records of the investigation of a drug and not following-up the investigation. Several violations for not conducting investigations for unexplained discrepancies were also included.

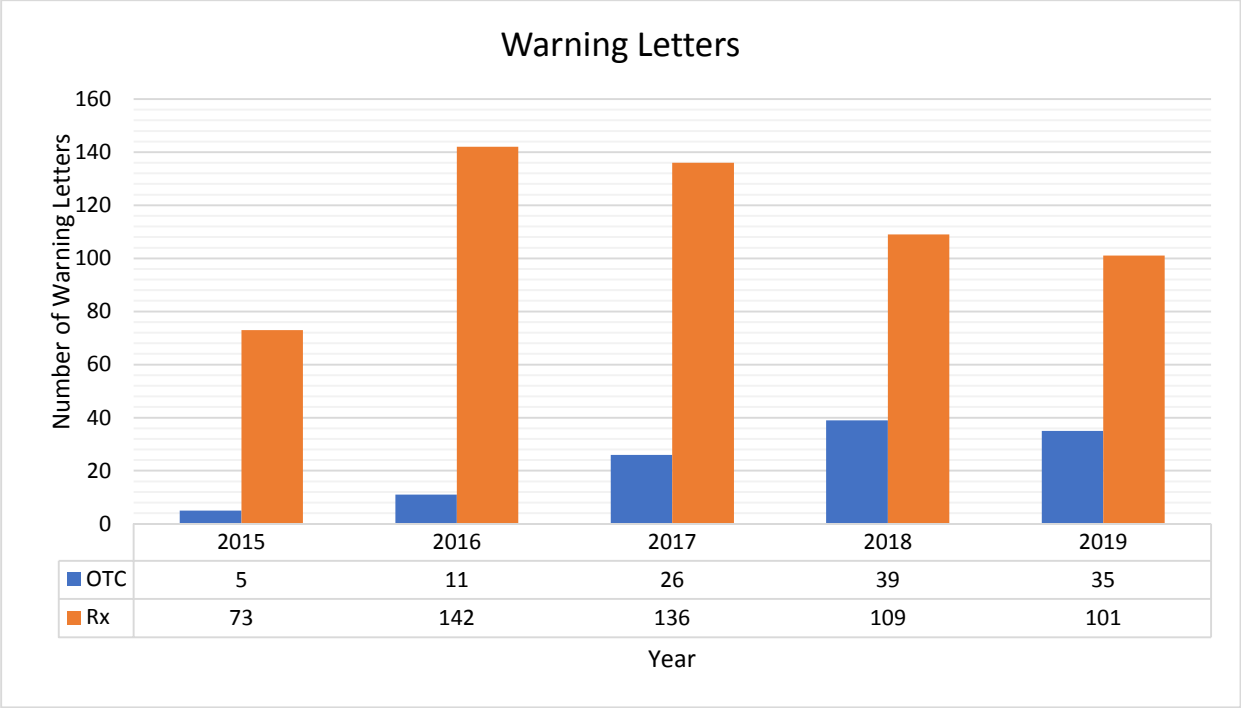
- *Violation 7 - Laboratory records*

  This violation group contains violations relating to laboratory records containing test data for compliance with specifications and standards. Sections in these regulations state the requirement for complete test data and statements of each method used in the testing of the sample. Complete records including any modifications of methods, laboratory reference standards, reagents, and solutions, and calibration of laboratory instruments are required. Most violations in this group included laboratory records not including complete records to verify the produced results that are accurate and reliable. Several violations such as not including testing data of stability and standardization of laboratory reference standards were also included.

3.3 Warning Letter Results

A total of 116 OTC warning letters were analyzed in this study. Starting from FY 2015 to 2019, the number of warning letters were 5, 11, 26, 39, and 35, respectively. A total of 561 Rx warning letters were collected to make a comparison to the number of OTC warning letters. The number of Rx warning letters from FY 2015 to 2019 was 73, 142, 136, 109, and 101, respectively. The overall comparison is shown in Figure 1 below.

Figure 1 Number of Warning Letters FY2015-FY2019



The largest number of OTC warning letters were issued in FY 2018 with 39 warning letters while the largest number of Rx warning letters were issued in FY 2016 with 142 warning letters. The least number of warning letters were issued in FY 2015 for both OTC drugs and Rx dugs (5 and 73 respectively). It is evident that the FDA issued a significantly greater number of Rx warning letters than OTC warning letters in the past five years. However, a gradual increase

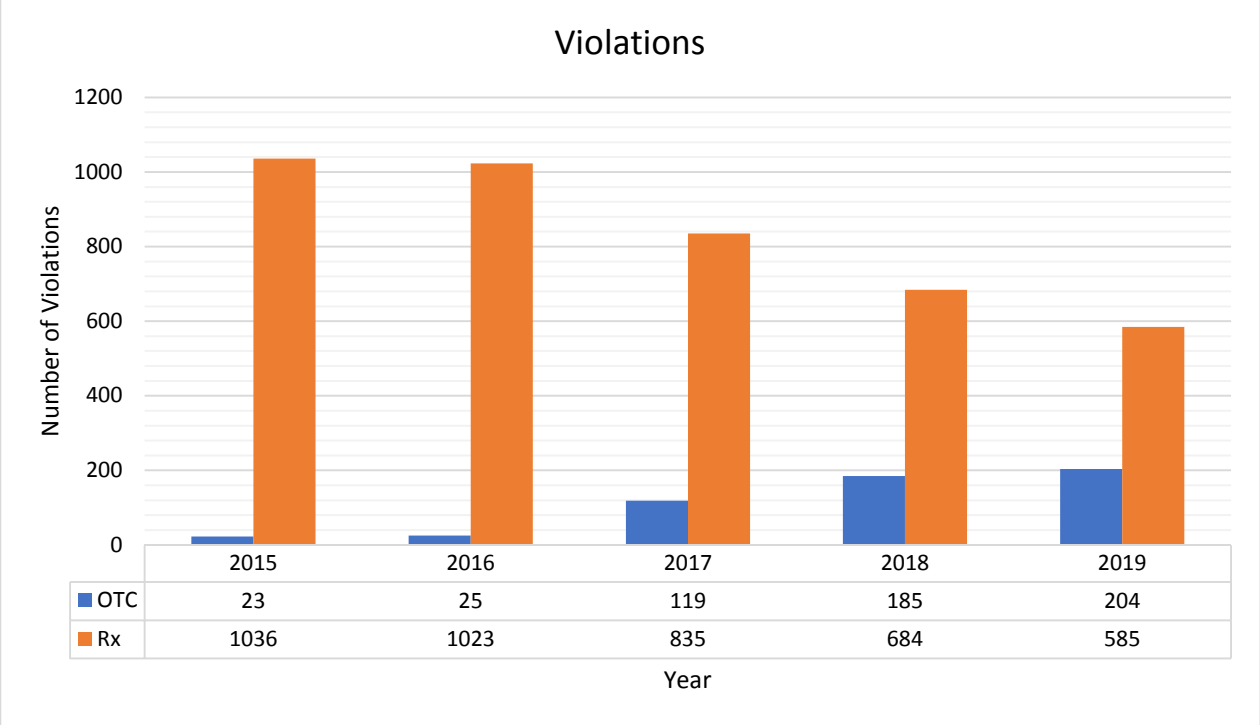
in the issuance of OTC warning letters is seen while a gradual decrease starting from FY 2016 is seen in Rx warning letters.

3.4 Violation Results

Number of overall violations

A total number of 556 violations were cited within the 116 OTC warning letters collected for this study. From FY 2015 to 2019, the number of violations was 23, 25, 119, 185, and 204, respectively. A total number of 4,163 violations were counted within the 561 Rx warning letters. From FY 2015 to 2019, the number of Rx drug violations was 1,036, 1,023, 835, 684, and 585, respectively. The overall comparison is shown in Figure 2.

Figure 2 Number of Violations FY2015-FY2019



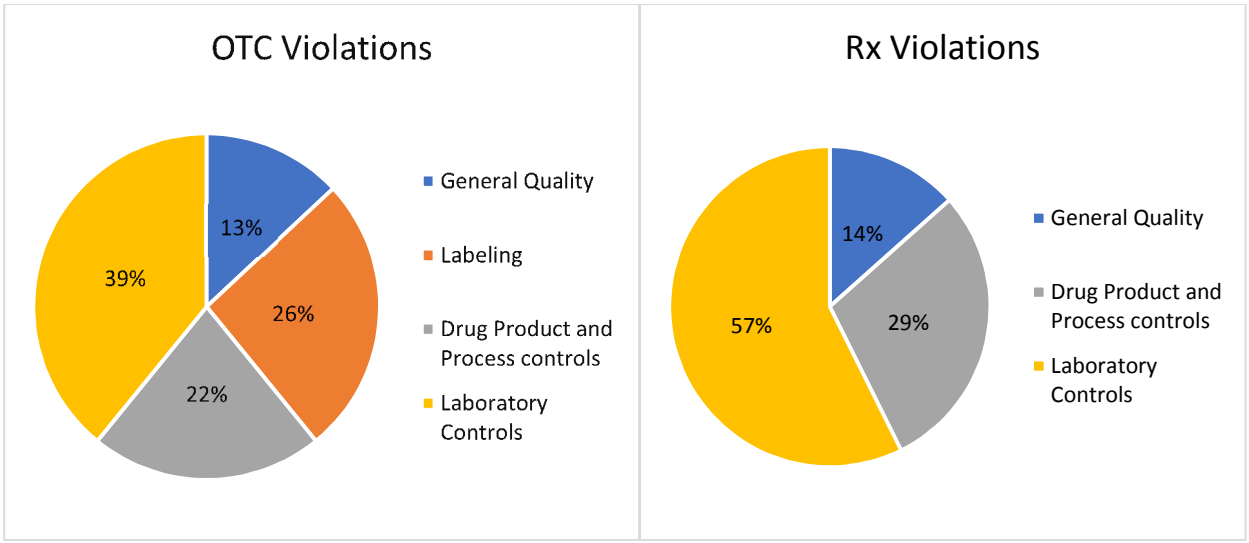
For OTC drugs, most violations were cited in 2019 with 204 violations. This number of violations was cited within 35 warning letters indicating that each warning letter contained an

average of 6 violations. For Rx drugs, most violations were counted in the year of 2015 with 1,036 violations. This number of violations was included within 73 warning letters indicating that an average of 14 violations were cited in each warning letter. Similarly, warning letter results showed a gradual increase in OTC violations over the past five years while a gradual decrease was seen in Rx violations. Even though there was a significant decrease in the number of Rx violations, these numbers still exceed the number of OTC violations.

Violations by category

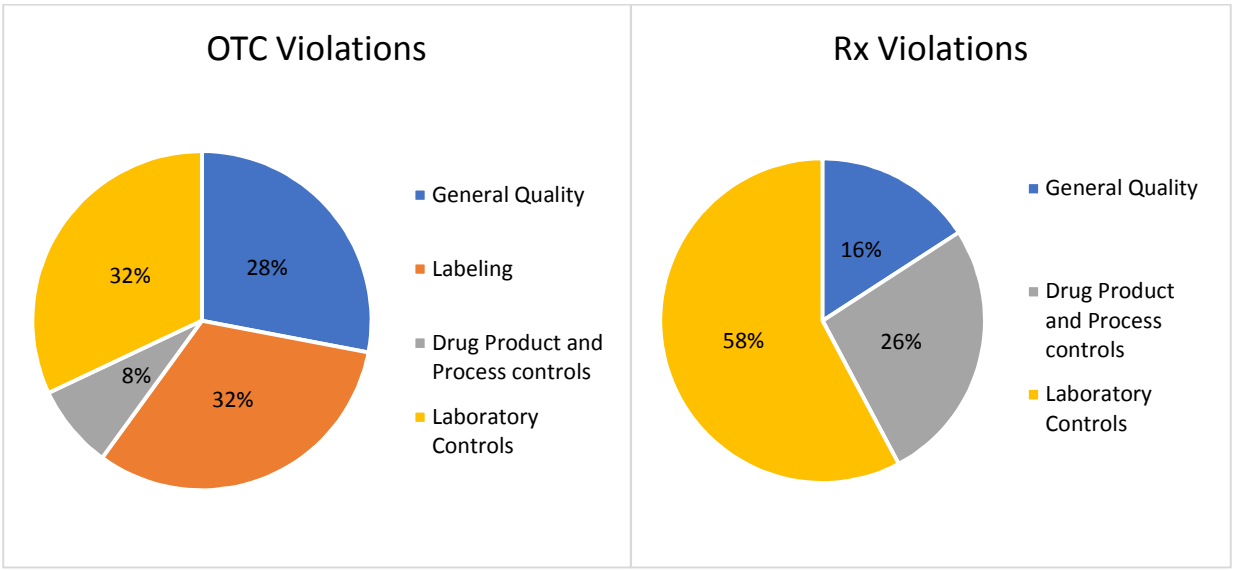
Violations pertaining to each category were evaluated to make a further comparison between OTC and Rx drugs. Violation categories from each year were calculated into a percentage to display the relative proportions to the total number of violations. For Rx drugs, the labeling category was excluded from this analysis due to the difference in labeling requirements from OTC drugs. The categorical analysis is shown in Figures 3, 4, 5, 6, and 7. The table including violation count is provided in Appendix I.

Figure 3 FY2015 Violations by Category



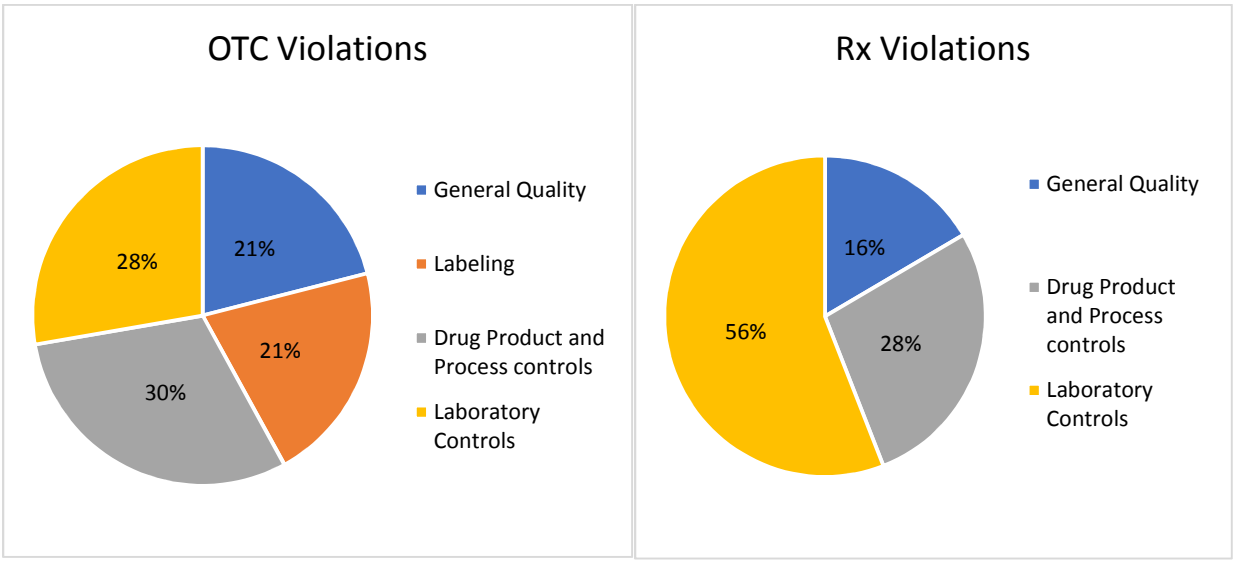
For OTC drugs, the following categories contained the most violations to least violations in FY 2015: laboratory controls (39%), labeling (26%), drug product and process controls (22%), and general quality (13%). For Rx drugs, the following categories contained the most violations to least violations in the same year: laboratory controls (57%), drug product and process controls (29%), and general quality (14%).

Figure 4 FY2016 Violations by Category



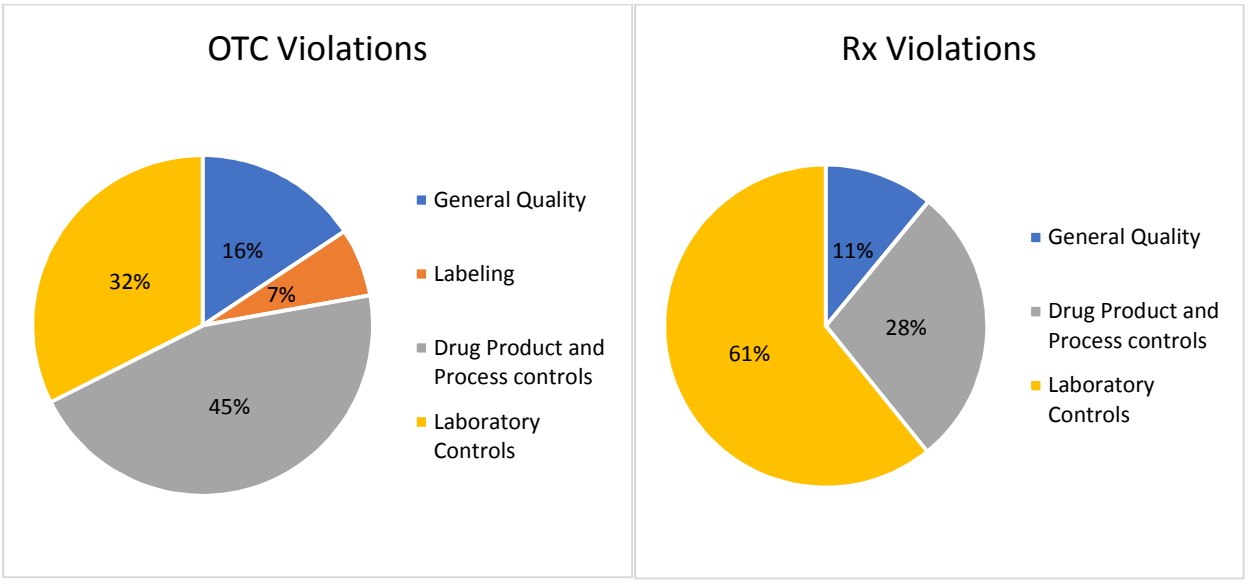
For OTC drugs, the following categories contained the most violations to least violations in FY 2016: laboratory controls (32%), labeling (32%), general quality (28%), and drug product and process controls (8%). For Rx drugs, the following categories contained the most violations to least violations in the same year: laboratory controls (58%), drug product and process controls (26%), and general quality (16%).

Figure 5 FY 2017 Violations by Category



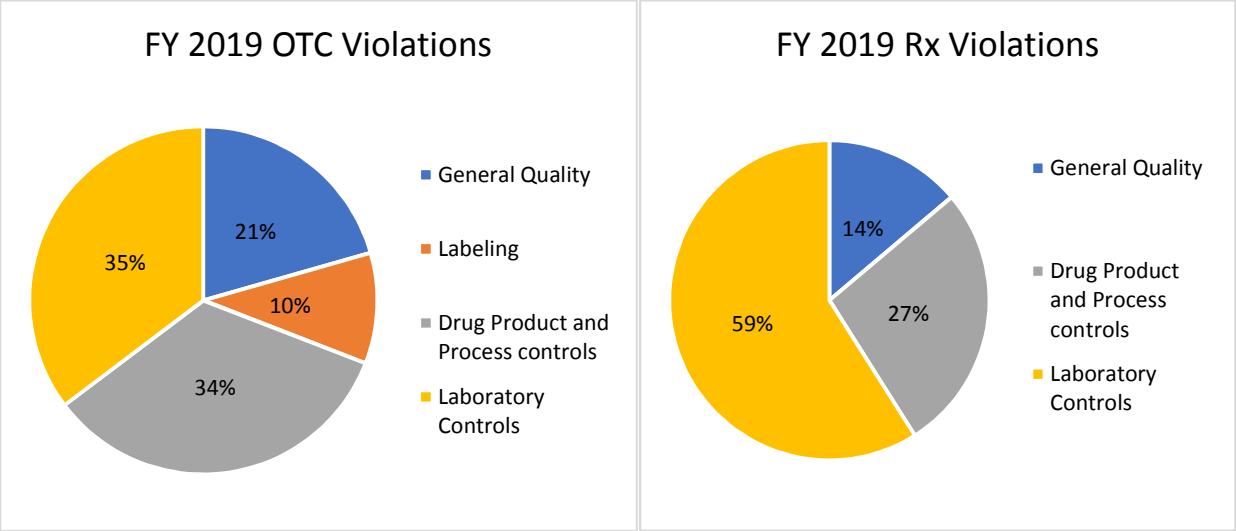
For OTC drugs, the following categories contained the most violations to least violations in FY 2017: drug product and process controls (30%), laboratory controls (28%), labeling (21%), and general quality (21%). For Rx drugs, the following categories contained the most violations to least violations in the same year: laboratory controls (56%), drug product and process controls (28%), and general quality (16%).

Figure 6 FY 2018 Violations by Category



For OTC drugs, the following categories contained the most violations to least violations in FY 2018: drug product and process controls (45%), laboratory controls (32%), general quality (16%), and labeling (7%). For Rx drugs, the following categories contained the most violations to least violations in the same year: laboratory controls (61%), drug product and process controls (28%), and general quality (11%).

Figure 7 FY 2019 Violations by Category



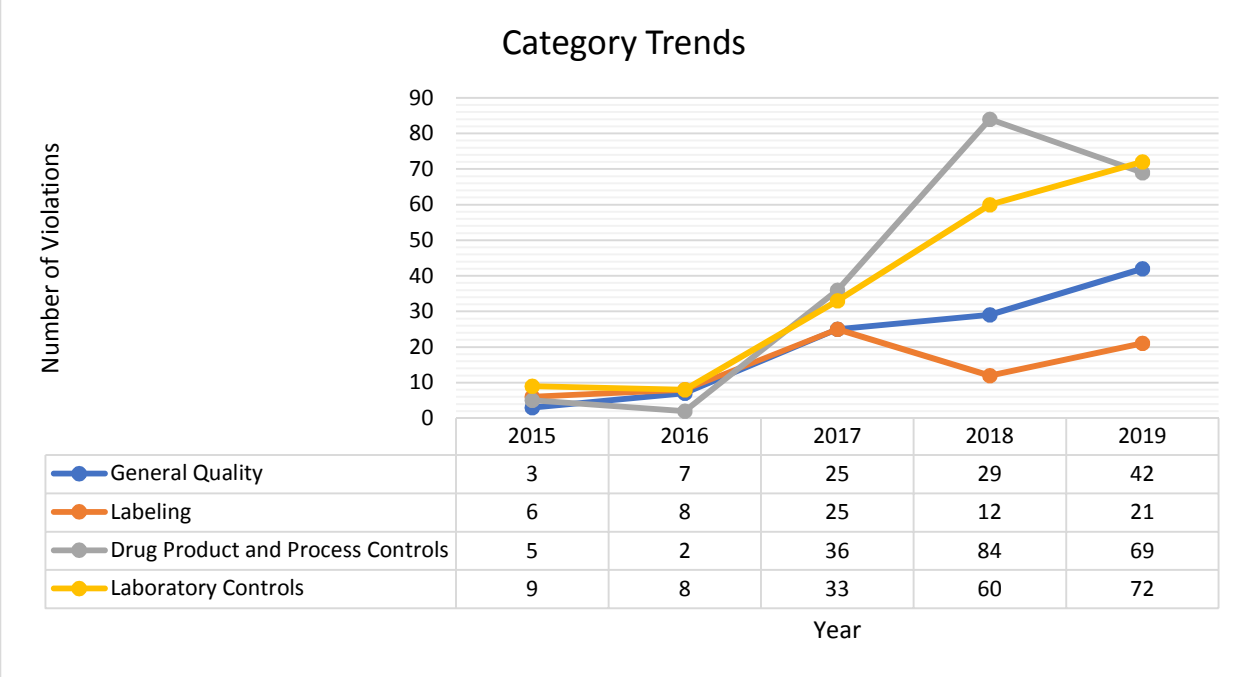
For OTC drugs, the following categories contained the most violations to least violations in FY 2019: laboratory controls (35%), drug product and process controls (34%), general quality (21%), and labeling (10%). For Rx drugs, the following categories contained the most violations to least violations in the same year: laboratory controls (59%), drug product and process controls (27%), and general quality (14%).

Overall, the OTC drug violations from each category greatly varied each year while Rx drug violations generally stayed consistent. Out of 4 categories, the labeling category and drug product and process controls category showed the greatest proportional change with 25% decrease and 37% increase, respectively.

OTC violation category trend analysis

A trend analysis of OTC drug violations was done to examine the past performance of the OTC manufacturers and to identify patterns to predict FDA's regulatory expectations. The overall trend analysis is shown in Figure 8.

Figure 8 OTC Trend Analysis



As previously mentioned in the overall warning letter results section, the overall number of violations in OTC drugs gradually increased from FY2015 to FY2019. While the greatest increase in violation categories (drug and product and process controls and laboratory controls) occurred between FY2016 and FY2017, the greatest decrease (labeling) also occurred during those years. The separation of points (FY2018) also indicated that the number of violations in each category significantly differed from previous years. Based on trending points in FY2019, it can be predicted that violations in 2 out of 4 violation categories (laboratory controls and general quality violations) may continue to increase in FY2020.

OTC violation group statistical analysis

More extensive analysis was done by using a statistical tool to further identify specific violations relating to each category. These specific violations were sorted into violation groups and the determination of significant differences between the fiscal years were calculated using the Fisher's exact test. The results for each violation group is shown in Table 8, 9, 10, and 11.

Table 8 OTC General Quality

VG#	Violation Group	2015 n=3	2016 n=7	2017 n=25	2018 n=29	2019 n=42	Total n=106	P-value
1	Quality control unit	0	1(14%)	9(36%)	7(24%)	9(21%)	26(24%)	0.5
2	General written procedures, records and reports	2(67%)	1(14%)	8(32%)	5(17%)	6(14%)	22(21%)	0.12
3	Approve and reject procedures or specifications	0	1(14%)	0	0	0	1(1%)	<0.01*
4	Lab facilities	0	1(14%)	1(4%)	0	4(10%)	6(6%)	0.38
5	Cleaning, sanitizing, and maintenance	0	2(30%)	5(20%)	8(28%)	9(21%)	24(23%)	0.82
6	Electronic Records	1 (33%)	1 (14%)	2 (8%)	9 (31%)	14 (34%)	27 (25%)	0.17

*Significance level $p<0.05$ ($\alpha = 0.05$) used

A total of 106 general quality violations were cited in OTC warning letters from FY2015 to FY2019. Out of 106 violations, most cited violations were related to electronic record (VG6; 27 violations; 25%) and the least cited violations were related to approving and rejecting procedures or specifications (VG3; 1 violation; 1%). However, the least cited group (VG3) showed the most significant difference based on Fischer's exact test due to the frequency of one violation in 2016. This category showed the least number of violation changes between the five years by having only one violation group being significantly different.

Table 9 OTC Labeling

VG#	Violation Group	2015 n=6	2016 n=8	2017 n=25	2018 n=12	2019 n=21	Total n=72	P-value
1	Unapproved New Drug	0	4(50%)	6(24%)	4(33%)	0	14(19%)	0.01*
2	Inadequate required information	2 (33%)	1 (12.5%)	5 (20%)	3 (25%)	5 (24%)	16(22%)	0.91
3	Misbranding	1 (17%)	0	4 (16%)	4 (33%)	12 (57%)	21(29%)	<0.01*
4	Expiration Date issues	2 (33%)	1 (12.5%)	3 (12%)	0	2 (9.5%)	8(11%)	0.33
5	Drug/monograph specific issues	1 (17%)	2 (25%)	7 (28%)	1 (9%)	2 (9.5%)	13(18%)	0.44

*Significance level $p<0.05$ ($\alpha = 0.05$) used

A total of 72 labeling violations were cited within the warning letters and most violations were related to misbranding of the OTC drugs (VG3; 21 violations; 29%). The least amount of violations was related to expiration date issues (VG4; 8 violations; 11%) with no violations cited in FY 2018. Two violation groups (VG1 and VG3) showed significant differences between the past five years. These significant differences were observed in unapproved new drugs marketed as OTC drugs and in misbranding of OTC drugs.

Table 10 OTC Drug Product and Process Controls

VG#	Violation Group	2015 n=5	2016 n=2	2017 n=36	2018 n=84	2019 n=69	Total n=196	P-value
1	Representative sample	2(40%)	0	6(17%)	14(17%)	24(35%)	46(24%)	<0.01*
2	Component verification (active ingredients, excipients, raw materials)	1(20%)	0	7(19%)	29(35%)	25(36%)	62(32%)	<0.01*
3	Production and control records	0	0	5(14%)	4(5%)	5(7%)	14(7%)	0.53
4	Control procedures and validation	1(20%)	0	1(3%)	18(21%)	0	20(10%)	<0.01*
5	Procedures for deviations	1(20%)	1(50%)	8(22%)	0	0	10(5%)	<0.01*
6	Written procedures	0	1(50%)	9(25%)	19(22%)	15(22%)	44(22%)	0.06

*Significance level $p<0.05$ ($\alpha = 0.05$) used

A total of 196 drug product and process control violations were cited within the warning letters and most violations were related to failure of component verifications (VG2; 62 violations; 32%). The least cited violations for this category were failure to make an appropriate report for deviation procedures (VG5; 10 violations; 5%). Five out of six violation groups (VG1, VG2, VG4, and VG5) in this category showed significant differences in the number of violations during the past five years. This category also contained the largest number of violations (n=196) compared to other categories. These result indicated that most changes in violations occurred in drug product and process controls.

Table 11 OTC Laboratory Controls

VG#	Violation Group	2015 n=8	2016 n=7	2017 n=32	2018 n=60	2019 n=72	Total n=179	P-value
1	Testing and releasing for distribution	2(25%)	3(43%)	10(31%)	10(17%)	19(27%)	44(25%)	0.39
2	Stability program	3(38%)	0	11(35%)	26(42%)	29(40%)	69(39%)	0.23
3	Packaging and labeling operation	1(12%)	0	1(3%)	0	0	2(1%)	0.03*
4	Out of specification	0	1(14%)	2(6%)	4(7%)	3(4%)	10(6%)	0.21
5	Equipment design, size, and location	0	0	4(13%)	6(10%)	15(21%)	25(13%)	0.16
6	Investigation of failures	0	0	1(3%)	4(7%)	3(4%)	8(4%)	0.81
7	Laboratory records	2(25%)	3(43%)	3(9%)	10(17%)	3(4%)	21(12%)	<0.01*

*Significance level $p<0.05$ ($\alpha = 0.05$) used

A total of 179 laboratory control violations were cited within the OTC warning letters and most-cited violations were related to lack of a stability program (VG2; 69 violations; 39%). The least number of cited violations were related to laboratory controls involved in packaging and labeling operations (VG3; 2 violations; 1%). Statistical significant differences were seen in

packaging and labeling operation violations (VG3) and failures related to laboratory records (VG7). The change in frequency of packaging and labeling operations related violations were seen FY2015 and FY2017 and the change in frequency of laboratory records related violations were seen in FY2017 to FY 2019.

3.5 Discussion

Comparison of OTC and Rx drugs

Examining the differences in quality issues involved in both drug types is critical to understand the regulatory expectations of ensuring the safety and effectiveness of these drugs. Due to the difference in the market approval process for OTC and Rx drugs, the violations seen within the warning letters also varied greatly. Each violation category for Rx drugs generally stayed consistent during the FY 2015-2019. More than 50% of these violations were related to laboratory controls while more than 20% of violations were related to drug product and process controls each year. The rest of the violations (average of 14%) were related to general quality issues. According to the FDA, the quality control laboratory serves as one of the most important functions in pharmaceutical production and control.[27] It is important for manufacturers to set appropriate laboratory controls as any out-of-specification results from laboratory errors can lead to product failures, which can impact the quality of the drug product.[27] Therefore, this higher number of laboratory control violations indicates that the FDA's expectations of manufacturers meeting laboratory control requirements are critical.

Unlike Rx drugs, each violation category showed notable differences in OTC drugs. Over the years, the number of drug product and process control violations increased significantly reaching 45% (from 8%) in FY 2018. While laboratory control violations and general quality

violations stayed consistent (average of 20% to 30%), the labeling violations decreased significantly from 32% to 7%. These results are interesting because the increasing violations reflect the need for fundamental cGMP compliance for OTC manufacturers. Setting the appropriate production and process controls during the manufacturing process is important because it helps manufacturers to increase their ability to produce products repeatedly and reproducibly while meeting the quality standards.[28] It is evident that there is an increasing emphasis on the regulation of production and process controls for OTC drugs.

According to the FDA, the Office of Pharmaceutical Quality (OPQ) initiated a program with CDER in FY2017 to provide "One Quality Voice" regarding facility evaluation and inspections.[38] This program improved the inspection coverage to ensure quality of manufacturing processes of OTC drugs and aimed to inspect all previously uninspected sites by the end of FY2019.[38] It can be predicted that this shift in the FDA's thinking on quality expectations and execution of inspection focus program is the reason for the increase in OTC drug violations.

General quality violations

General quality violations were issued to OTC manufacturers for violations that are not specifically related to the manufacturing operations. Out of all violations, 19% (n=106) of these violations were related to general quality issues. Among the six violation groups, violations relating to electronic records had the greatest increase.

With the advancement of technology in recent years, the FDA's intent on a narrow interpretation of 21 CFR Part 11 was announced through the Guidance Document for Electronic Records. While this regulation clarified previous confusion regarding the usage of the electronic record, the FDA's exercise of enforcement on record regulations increased.[29] This may have been

the reason for the increasing number of violations in the electronic records group. As OTC manufacturers adopt this new technology, it is the manufacturer's responsibility to set critical controls that meet the FDA's quality standards guidelines.

Other violation groups such as the quality control unit, general written procedures, records, and reports, and cleaning, sanitizing and maintenance showed consistency in violations with 24%, 21%, and 23%, respectively. Only one violation group (approve and reject procedures or specifications) showed significant difference between the past five years. These results showed that there is a lack of fundamental cGMP understanding in OTC manufacturers and this recognition is critical as cGMP is the main regulatory standard for ensuring pharmaceutical quality.[30] The strict adherence to cGMPs is important not only during the production of the drug but also during the building of quality systems to assure the safety and effectiveness of drug products.

Labeling violations

For OTC drug manufacturers, following the standardized format for OTC labeling is critical due to its direct availability to the consumers. Since OTC labeling is intended for safe and effective usage of OTC drugs, it must contain accurate information following the labeling requirements.[31] In our study, misbranding of the product was most common (29%) compared to other violation groups and showed the significant change difference between the years. Often, these misbranding violations included OTC labels making therapeutic claims without any scientific support. The OTC monograph specific violations were cited along with the unapproved new drug violations. As previously mentioned in chapter 2, the monograph contains GRASE ingredients and any deviations from the monograph classify the OTC drug as an unapproved new

drug. This correlation was supported by a similar number of violations cited for both violation group (14 unapproved new drug violations; 13 monograph specific violations).

Drug product and process control violations

The violation category related to drug product and process controls contained the most violations when compared to other categories (35% n=196). Within this category, most of the violations were specifically related to material component verification. According to 21 CFR 211.84, the OTC manufacturers are required to conduct a test to verify the identity of each component of the drug product. This is required to ensure the material components' conformity with specifications for purity, strength, and quality. Based on the results of this study, there is an increase in observations of materials used by OTC manufacturers that do not meet quality standards. Even though it is difficult to accurately determine the overall quality level of currently marketed OTC drug products, the increased number of observations of lack of quality systems regarding material verifications is concerning.

Our study results also indicated a lack of representative sampling (24%) of OTC drug products. Determining a representative sample is critical since it is intended to portray the overall quality of the batch produced. It is also important for OTC manufacturers to test appropriate representative samples for approval and rejection of the products.[33]

Four out of six groups showed a statistically significant difference in this category. The number of violations varied greatly in the representative sample, component verification, control procedures and validation, and procedures for deviations. The significant decrease was seen in procedures for deviations and control procedures and validation groups while a significant increase was seen in representative sample and component verification. This result indicated that

out of four categories, most quality inadequacies are present in drug product and process controls.

Laboratory control violations

Thirty-two percent (n=176) of all OTC violations were related to the laboratory control category and most of these violations were due to the lack of a stability program. The stability program is an essential requirement of cGMP because it determines the expiration date and storage conditions for the drug product.[35] The shelf-life duration and expiration dates must be supported by the stability testing results and it is the OTC manufacturer's responsibility to establish the appropriate stability program for the product. However, our study results indicate that a significant number of current OTC manufacturers do not have appropriate stability programs in place.

Compared to other violation groups, VG1 (testing and releasing for distribution) contained the second most violations (25%). Inspections found that some OTC manufacturers released lots before proper testing for distribution. This final testing before release is critical to identify any deviations and to make an investigation on those deviations. The gradual increase in number of violations indicated that a number of current OTC manufacturers also do not meet laboratory controls for this group.

3.6 Conclusion

This study provides insight into the quality inadequacies relating to current marketed OTC drugs through the evaluations of warning letters issued by the FDA. The comparison analysis between the OTC and Rx drugs and the trend analysis from FY2015 to FY2019

provides an assessment of the current status of these quality inadequacies pertaining to certain violation categories. The statistical analysis of violations further provides greater awareness of the specific quality issues that may negatively impact the safety and effectiveness of OTC drugs and identifies violations with significant changes between the FY 2015 to 2019.

The results from this study indicate that significant quality inadequacy have been observed in OTC drugs. The quality issues are mostly seen in cGMP violations specifically in the drug product, process, and laboratory controls. Most significant violation changes are also seen in drug product and process controls. The overall number of violations in OTC drugs has been increasing in the past five years and the analysis results provide a projection for continued increases in violations unless OTC manufacturers move to address these issues.

Different regulatory and pharmacovigilance expectations in quality systems are seen through regulation differences between OTC and Rx drugs. More specifically, the changes in quality expectations of OTC drugs are seen through the increased number of inspections by the FDA. Even though this study provides an overall quality analysis of OTC warning letters and cited violations, more studies should be conducted to understand the risk to consumers using OTC drug products due to the trends associated with these observations.

CHAPTER 4

FUTURE WORK

On October 30, 2019, new OTC monograph reformation legislation was introduced for the modernization of the current OTC monograph. The key provisions from this reformation include but are not limited to the addition of user fees, setting limited exclusivity for certain OTC drug products, and changing the monograph process to be issued by order.[34]

Based on the findings from this research, it is determined that the observation of quality inadequacies within the OTC industry are growing each year. And with the enactment of this new reformation, it would be interesting to see if there are changes in observations of quality inadequacies among OTC drugs. Further studies should be conducted using the recently issued warning letters to determine which violation categories are impacted. The changes made due to the reformation can help to further identify and understand where the improvements in the quality system were made in OTC drugs.

It would be interesting to conduct further clinical studies targeting individuals who generally consume OTC drug products. Even though this study assesses the quality issues within the OTC industry, it does not provide insight into the actual impact of these inadequacies to current OTC consumers. Therefore, additional clinical studies would provide a deeper understanding of how quality issues translate direct to consumers and help address the risk to patients from OTC quality system issues

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APPENDIX I

(Figure 1) Number of Warning Letters FY 2015 - FY 2019

Year	2015	2016	2017	2018	2019
OTC	5	11	26	39	35
Rx	73	142	136	109	101
Total	78	152	162	148	136

(Figure 2) Number of Violations FY 2015 - FY 2019

Year	2015	2016	2017	2018	2019
OTC	23	25	119	185	204
Rx	1036	1023	835	684	585
Total	1059	1048	954	869	787

(Figure 3) FY 2015 Number of Violations

Category	OTC	Rx
General Quality	3	139
Labeling	6	N/A
Drug Product and Process controls	5	303
Laboratory Controls	9	594
Total	23	1036

(Figure 4) FY 2016 Number of Violations

Category	OTC	Rx
General Quality	7	162
Labeling	8	N/A
Drug Product and Process controls	2	270
Laboratory Controls	8	591
Total	25	1023

(Figure 5) FY 2017 Number of Violations

Category	OTC	Rx
General Quality	25	138
Labeling	25	N/A
Drug Product and Process controls	36	230
Laboratory Controls	33	467
Total	119	835

(Figure 6) FY 2018 Number of Violations

Category	OTC	Rx
General Quality	29	75
Labeling	12	N/A
Drug Product and Process controls	84	193
Laboratory Controls	60	416
Total	185	684

(Figure 7) FY 2019 Number of Violations

Category	OTC	Rx
General Quality	42	81
Labeling	21	N/A
Drug Product and Process controls	69	159
Laboratory Controls	72	345
Total	204	585