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Delivering Personalized Medicine and Helping Mitigate Drug Shortages: The 503B Outsourcing Story

Presented by:

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Senior GMP Quality Expert at Govzilla

General Overview

Jason:

- 503B Background
- Current Regulatory Framework
- Quality Challenges within the 503B industry
- Quality Metrics – KPIs – small case study
- 503B and FDA collaboration during COVID-19 pandemic – drug shortages
- 503B future

Jerry

- The 503B Inspection / Compliance Landscape
- Leveraging machine learning technology for regulatory compliance actions
- How an AI tool can analyze an FDA warning letter and provide additional insight

New Industry Framework - DQSA

Section 503A (enacted 1997)	Section 503B (enacted 2013)
<p>Conditions under which drug products compounded by a licensed pharmacist in a State-licensed pharmacy or Federal facility, or by a licensed physician, can qualify for exemptions from certain requirements of the FD&C Act:</p> <ol style="list-style-type: none">(1) New drug approval requirements (section 505),(2) Labeling with adequate directions for use (section 502(f)(1)), and(3) Current good manufacturing practice (CGMP) requirements (section 501(a)(2)(B))	<p>Conditions under which drug products compounded by or under the direct supervision of a licensed pharmacist in an outsourcing facility can qualify for exemptions from certain requirements of the FD&C Act:</p> <ol style="list-style-type: none">(1) New drug approval requirements (section 505),(2) Labeling with adequate directions for use (section 502(f)(1)), and(3) Drug supply chain security requirements (section 582). <p>Outsourcing facilities remain subject to CGMP requirements.</p>

Regulatory Update – FDA Priority Plan

2018 – published June 2018

- Risk-Based Approach to Manufacturing Standards for Outsourcing Facilities
- Restricting Compounding of Drugs that are Essentially Copies (of Registered Drugs)
- Regulating Compounding from Bulk Drug Substances
- Solidifying FDA’s Partnership with State Regulatory Authorities
- Finalize Biological Products Guidance Compliance

2019 – published Apr 2019

- Maintaining Quality Manufacturing and Compliance
- Regulating Compounding from Bulk Drug Substances
- Finalizing Memorandum of Understanding with the States
- Compounding by Hospital and Health Systems
- Improve the Quality of Compounded Drugs for Patients for which there is a Clinical need

2020 – nothing published

- FDA listening session June for industry stakeholders

Regulatory Update – FDA Priority Plan

2020 – nothing published

- **FDA listening session June for industry stakeholders**
 - Temporary guidance for compounders during COVID-19 Public Health Emergency
 - Compounding using bulk drug substances under section 503B
 - Compounded drugs that are “essentially copies” under 503B
 - Memorandum of understanding (MOU) addressing certain distributions of compounded human drug products between states and FDA
 - Product Reporting
 - Compounding Quality Center of Excellence

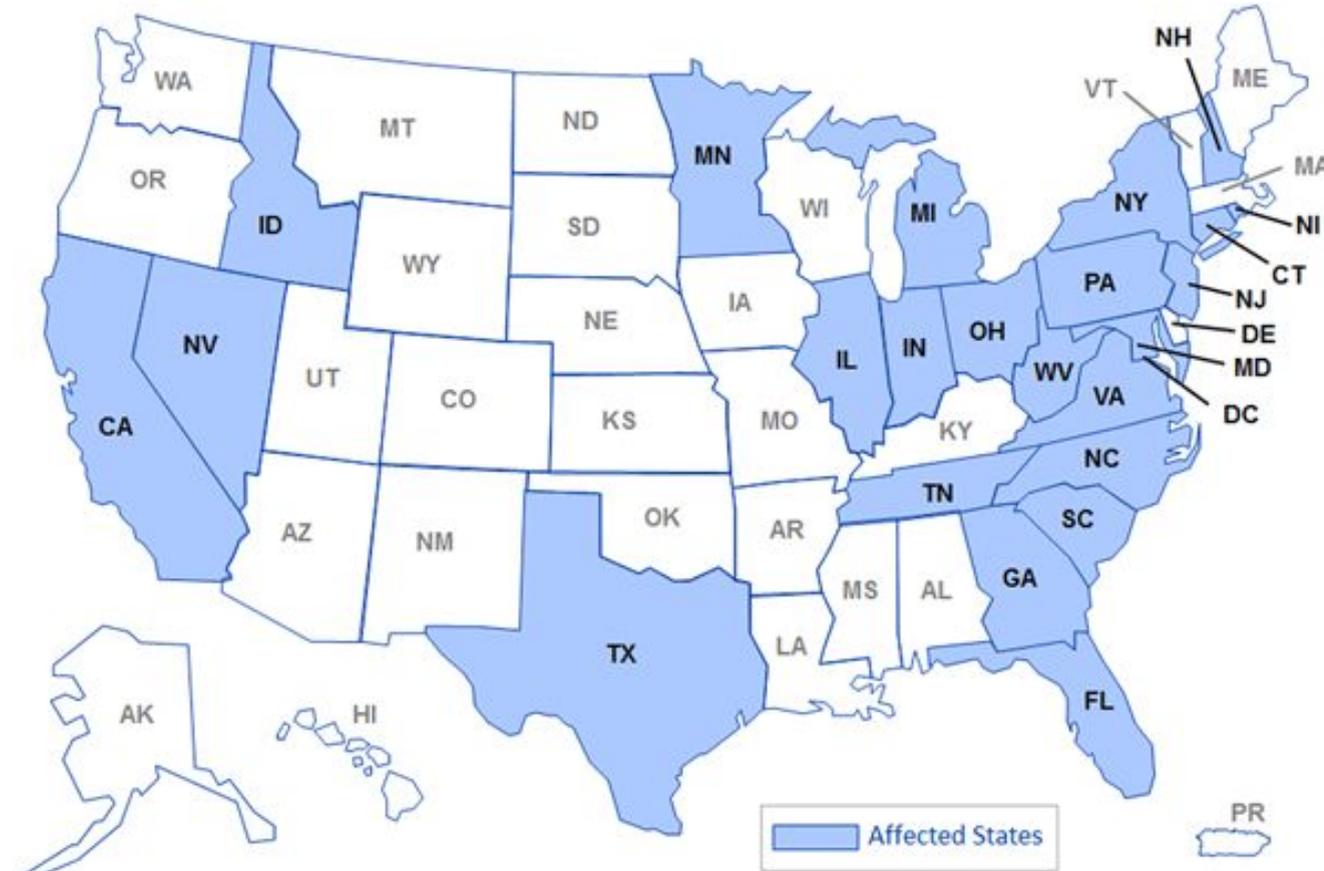
Agency & Compounding Relationship

Historically tenuous

- Private Practice vs Big Government
- Lawyer vs Inspector
- Pharma vs Pharmacy
- Dialogue vs Diatribe

Industry practices had to Change

- **Tragedy – 2012**
 - Outbreak of fungal meningitis traced back to NECC
 - 793 confirmed cases and 64 deaths



Frequent FDA Actions Taken

Voluntary Recalls Informal recommendations for voluntary recalls Formal FDA requests for voluntary recalls	Advisory Actions Warning Letters Untitled Letters Regulatory Meetings
Enforcement Actions Civil Injunctions Criminal actions Seizures	State Referrals For 503A facilities Inspectional findings Complaints

FDA Current and Future Policies

Current Impact Policies

- Compounding drugs that are essentially copies
- Compounding from bulk drug substances
- 5 Temporary, final, or in effect COVID-19 GFI documents
- 59 total GFI released since March

Future Policies

- CFR 213???

Current Good Manufacturing Practice—Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act
Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

New GMP Guidance for Outsourcers

Provides more specificity to the Agency's expectations for the industry (31 more pages)

- Heavy focus on Quality Control
- Adds significant color to stability testing requirements
- Detailed expectations re: Quality Agreements
- Provides more science-based rationale
 - (high vs med risk)

296

297 In general, processes and procedures at an outsourcing facility should minimize contamination
298 risks posed by, for example, the number and complexity of manipulations, number of
299 simultaneous operations and workstations, and staging of materials used in the process.

300

Quality Reality Check and Reset

Change in mindset

- Quality, Quality, Quality
- Lack of expertise

Its more than just testing

- Wholistic approach to Quality Management



Culture Change

- Leadership must exemplify
 - Quality culture essential to maintain long term success
- Right Strategy
 - Investment into staff and facilities
 - Education and training
 - Continuous improvement



QM Program Maturity

Leading vs lagging indicators

Develop useful product and site-specific metrics

Senior management engagement

Quality culture commitment

Evolution of quality metrics program over time

FDA Quality Metric Program

2015 FDA created a voluntary reporting program/GFI designed to increase transparency of key metrics for the industry

Goals:

Establish objective measures

- Quality of drug product
- Quality of a site
- Effectiveness of systems utilized with the manufacture of pharmaceutical products

Conduct continuous monitoring, assessment, and reporting on the state of quality across the inventory of drug products and facilities regulated by the FDA

Current State

Quality Metrics are Good Business Practice

FDA performed collaborative research with St Gallen Univ.

- Sites with Low (Process) Stability have the highest risk profile for:
 - Rejected batches
 - Customer Complaint Rate
- Quality Maturity attributes have positive correlation with Quality Behavior attributes
- The measurable KPIs in the draft guidance are reasonable and make sense for a regulator
- Cultural excellence should be incorporated into a regulatory program

■ ***Increases the profitability of the business***

Foundational elements



APQR



MANAGEMENT
REVIEWS



SUPPLY
SURVEILLANCE



INTERNAL
AUDITS

Quality Culture Change - Tactically

KPIs

- Objective measures to evaluate health of the facility

What?

- Right First Time (RFT)
- Cost of Non-Conformance

Why?

- Identify adverse trends
- Proactive event identification and resolution management

Quality Metric Drivers

Promotes responsible practices and quality driven corporate culture

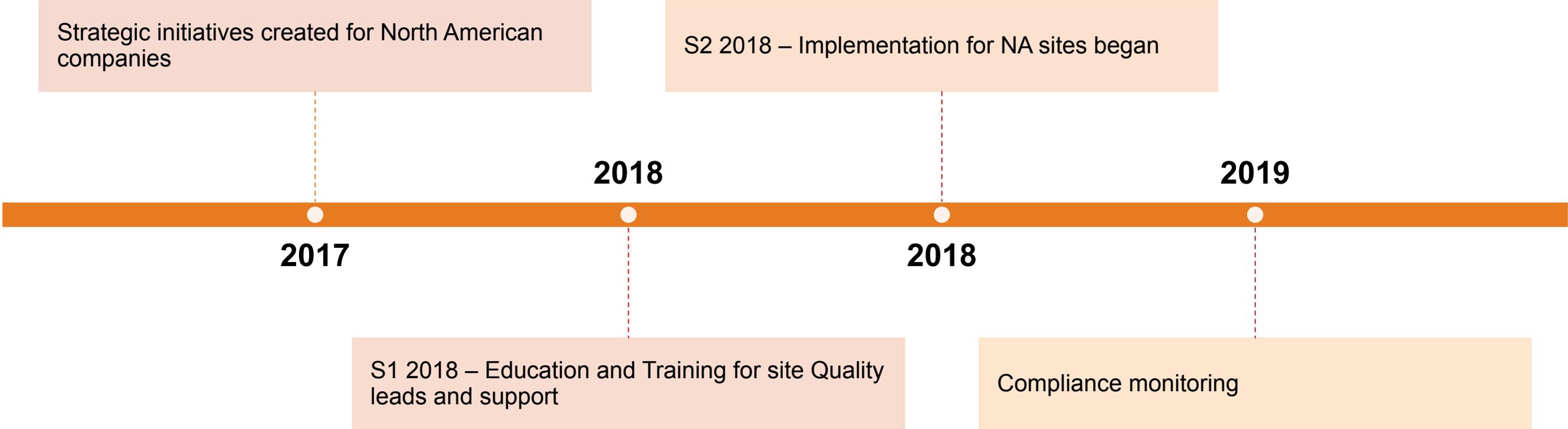
Identify situations in which there may be a risk for drug shortages

Improve Agency's evaluation of drug manufacturing and control operations

Improve efficiency and effectiveness of establishment inspections

Enhance the FDA's risk based inspection scheduling

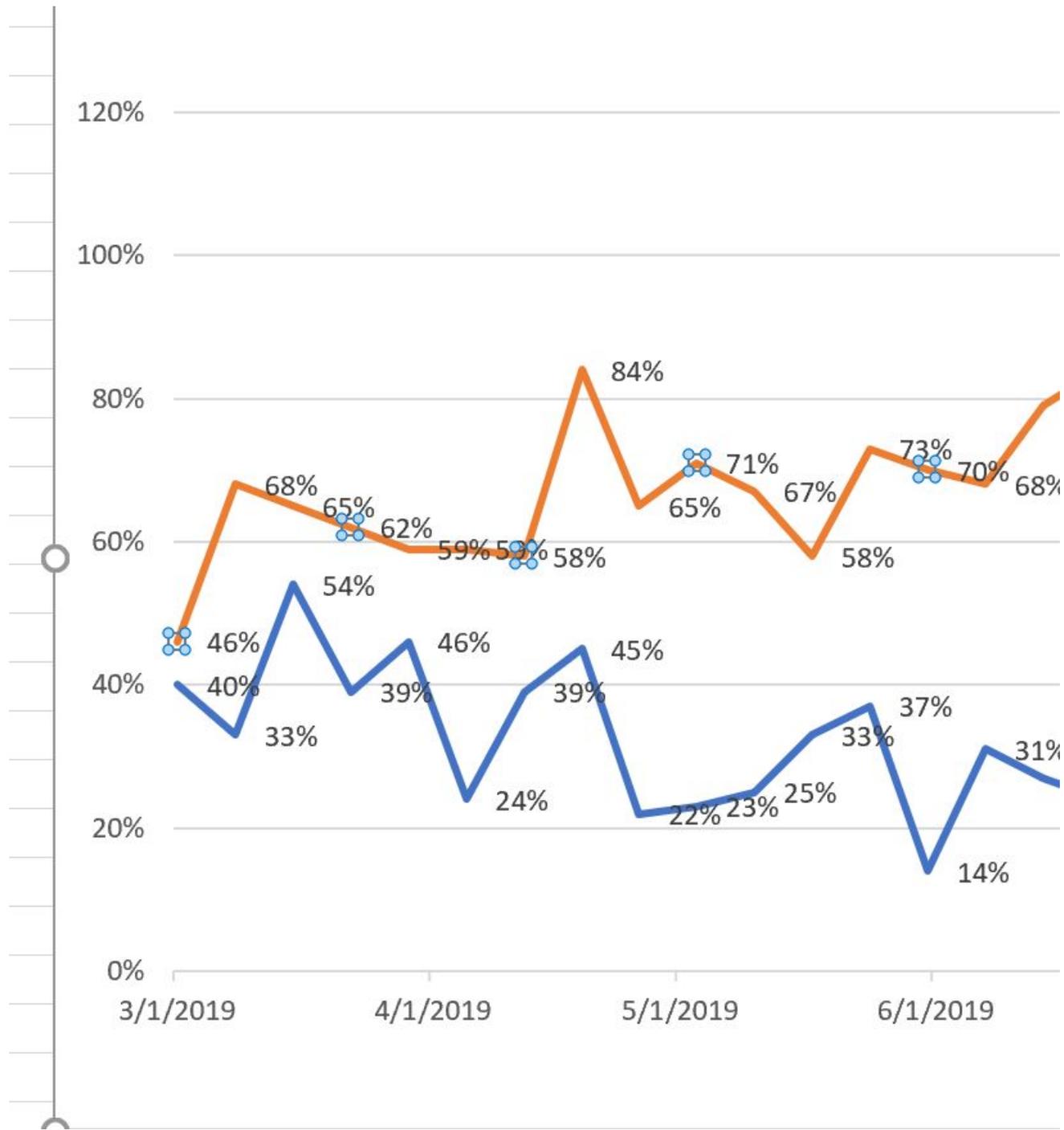
Case Study – KPI Implementation



Case Study KPIs

Early lessons learned

- Engagement with all stakeholders was not properly managed
- Communication between quality and operations on the KPI strategy needed to be better
- Structurally and Organizationally each site was different and thus metric reporting was a mixed bag
- Leadership transition and reorganization likely to cause disruption in data collection
- Necessary to have strong data analysts

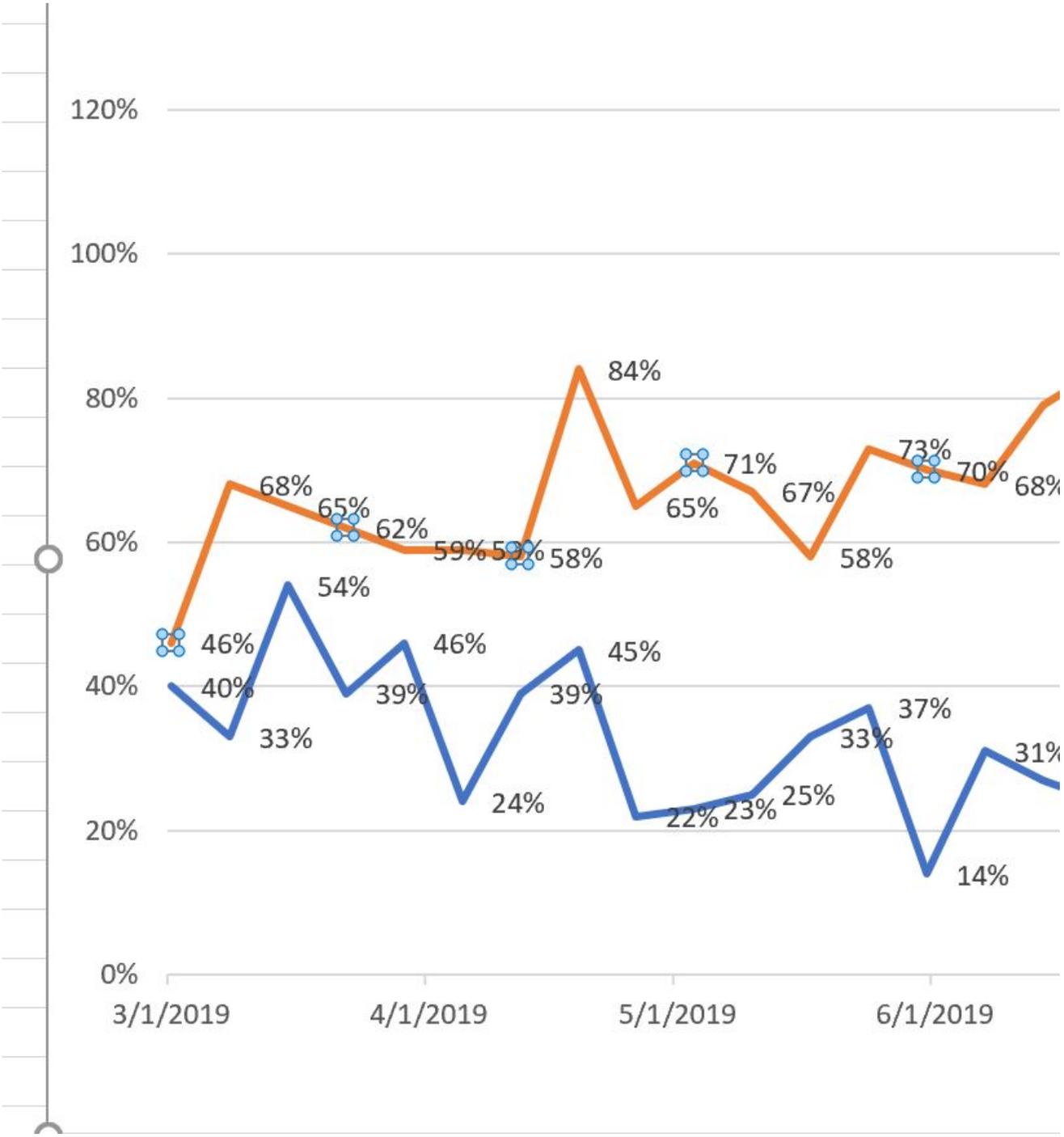


Case Study – KPI RFT

Houston...

Case Study – KPI RFT

Why?
What's the real issue?



Case Study – KPI RFT

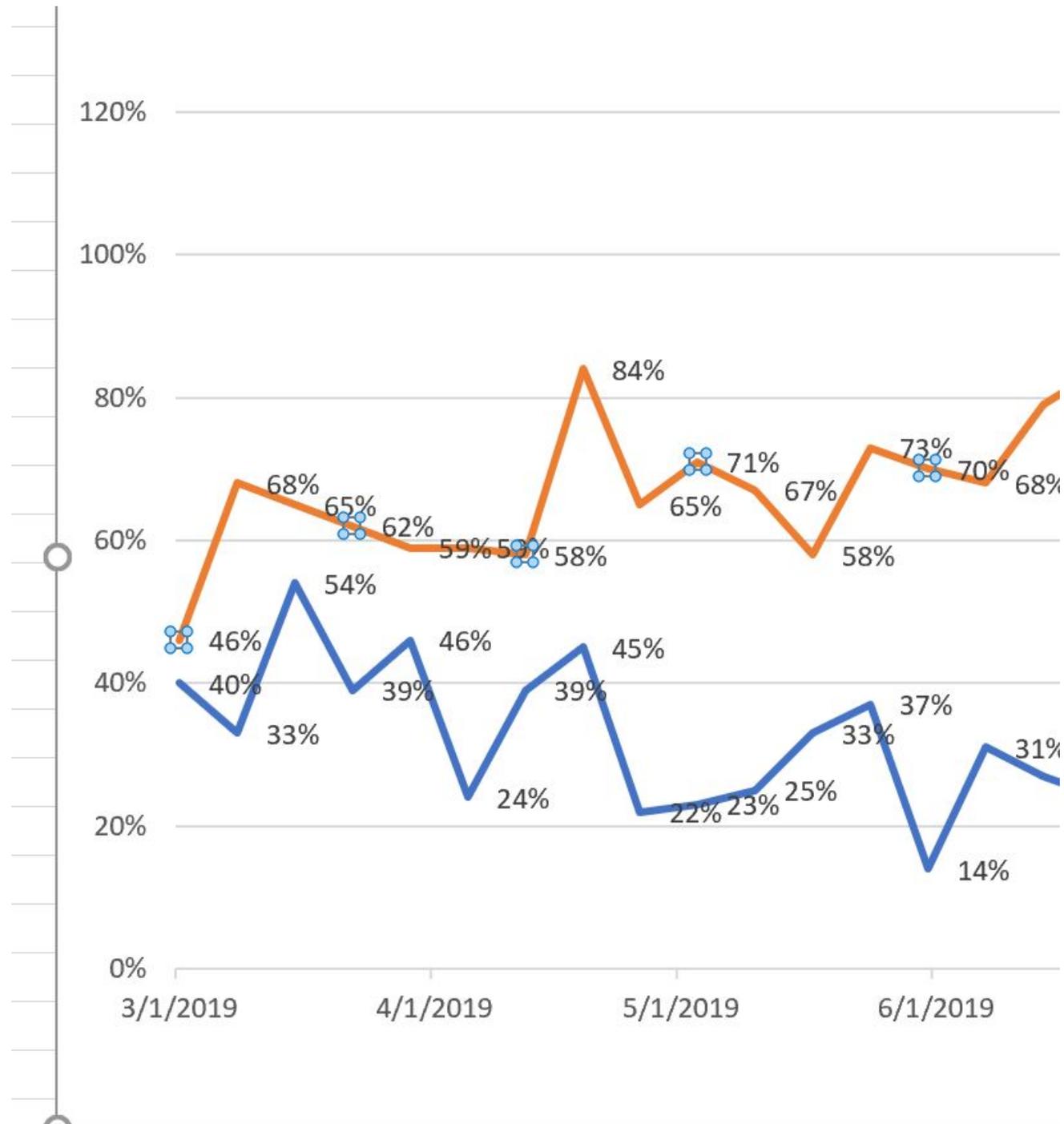
Why? What's the real issue?

Boiled down to:

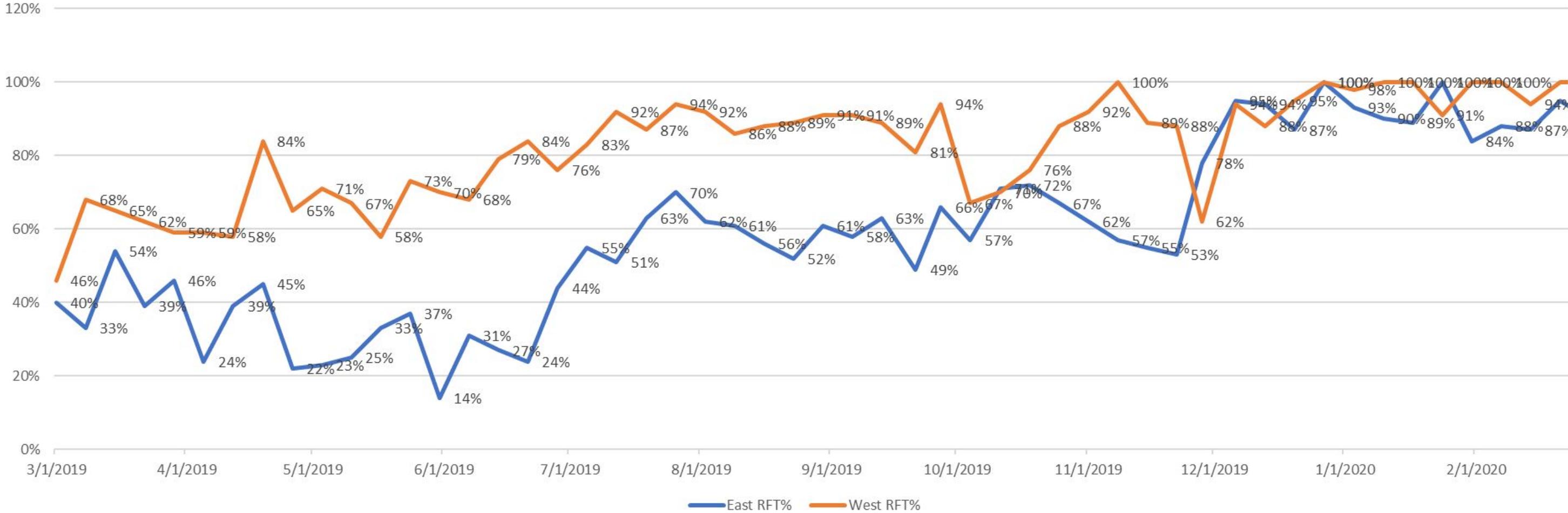
Lack of Quality Culture

Lack of alignment btwn Ops and QA

Restart



Weekly RFT



FDA and 503B Collaboration during COVID

- Good Manufacturing Practice Considerations for Responding to COVID-19 Infection in Employees in Drug and Biological Products Manufacturing
- Policy for Temporary Compounding of Certain Alcohol-Based Hand Sanitizer Products During the Public Health Emergency
- Temporary Policy for Compounding of Certain Drugs for Hospitalized Patients by Outsourcing Facilities During the COVID-19 Public Health Emergency (Revised)
- Temporary Policy for Compounding of Certain Drugs for Hospitalized Patients by Pharmacy Compounders not Registered as Outsourcing Facilities During the COVID-19 Public Health Emergency (Revised)
- Temporary Policy Regarding Non-Standard PPE Practices for Sterile Compounding by Pharmacy Compounders not Registered as Outsourcing Facilities During the COVID-19 Public Health Emergency

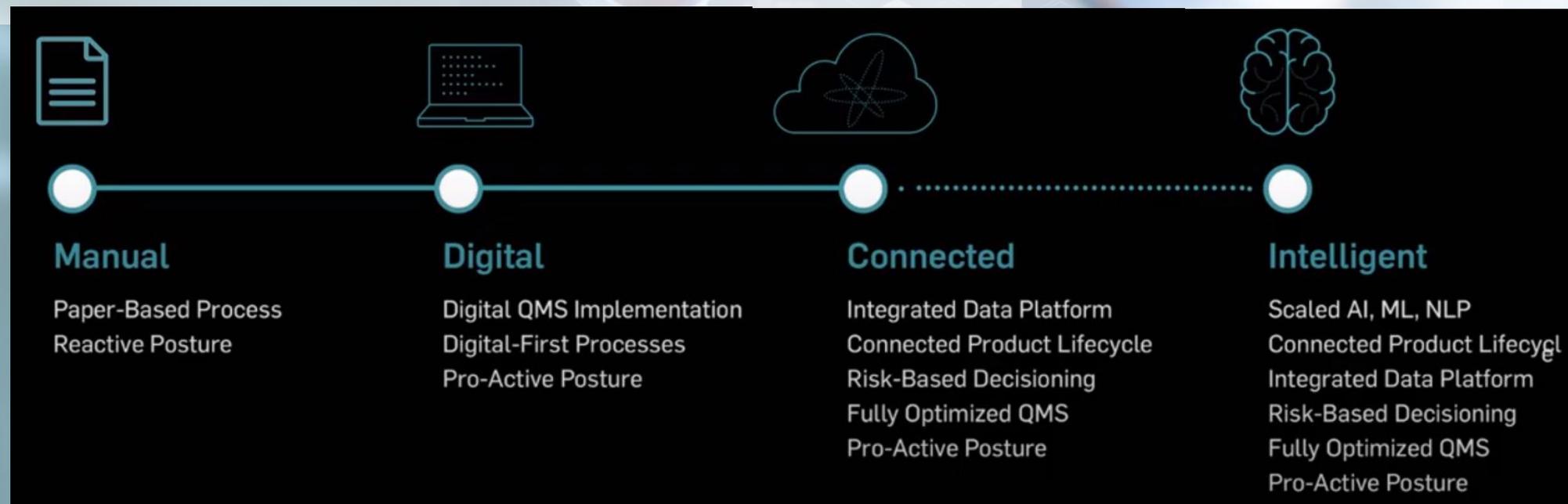
FDA and 503B Collaboration during COVID

- Guidance created to rapidly produce with a risk based strategy
- Drug shortages (~150 currently)
 - Finished product and API
 - Limited BUD/expiry to provide healthcare systems
- Discussions with HHS and FDA
 - Support the Stockpile
- Hand sanitizers
 - Rapid development and deployment in high quality environments

Demonstrative regulatory framework in place for the last several years has proven 503B can provide high quality medicines in times of crisis.

The Future is ~~Digitized~~ **Digitized**

- Data-Centric, Not Document-Centric
- Ahead of the Regulatory Curve
- Quality Across the Product Lifecycle
- Risk-Based Action
- Artificial Intelligence & Machine Learning



Current Climate – 503B Outsourcing Facilities

Partnership w/ Agency

- Embracing the regulations
- More compliance driven and focused on patient safety
- Receptive to audits and feedback



Future of Outsourcing Facilities - Embracing the Challenge

- Continue to play a role with drug shortages and other emergent healthcare needs
- Increased quality, safety, and compliance with regulations
- Consolidation will continue due to compliance and quality issues
- Partnerships w/ industry to provide higher quality clinical trial materials
- Role in providing some stability to increasing healthcare costs

The 503B Inspection/Compliance Landscape: Using AI Tools to Dive Deeper into 503B Warning Letters

Jerry Chapman

Senior GMP Quality Expert

Govzilla



A Promise and a Suggestion

A Promise:

You will learn something new

A Suggestion:

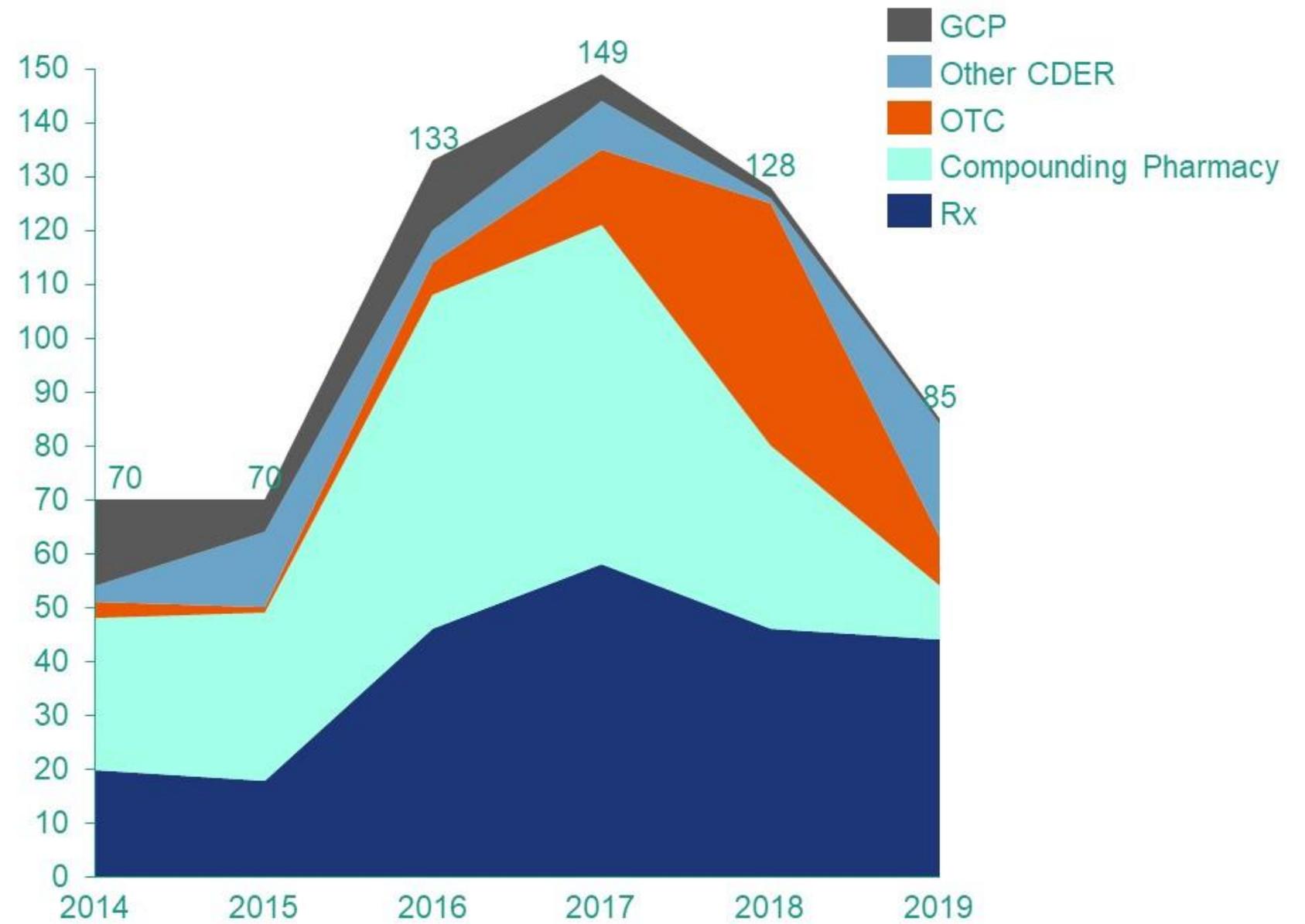
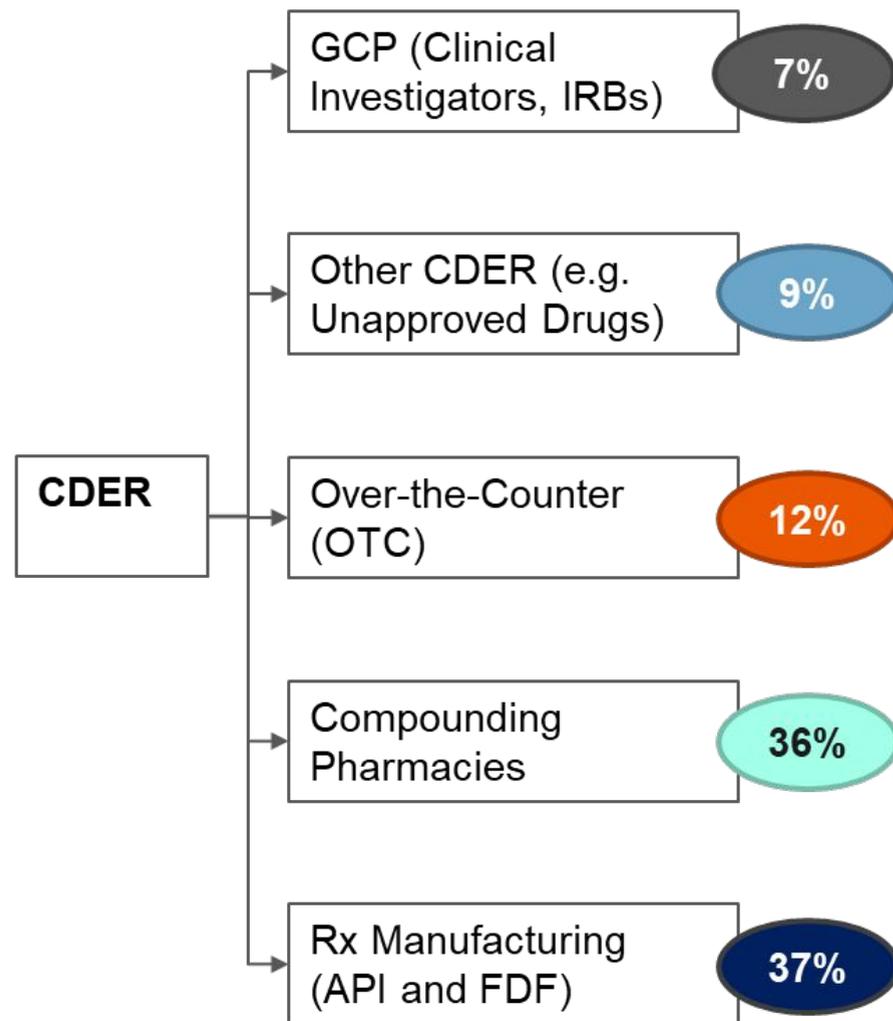
Buckle up, there's a lot to cover

Another exciting talk on FDA inspections? No. This will be very different from what you are used to seeing.



FDA Warning Letters by Facility Type

Warning Letters issued by facility type, FY (1)
Percent

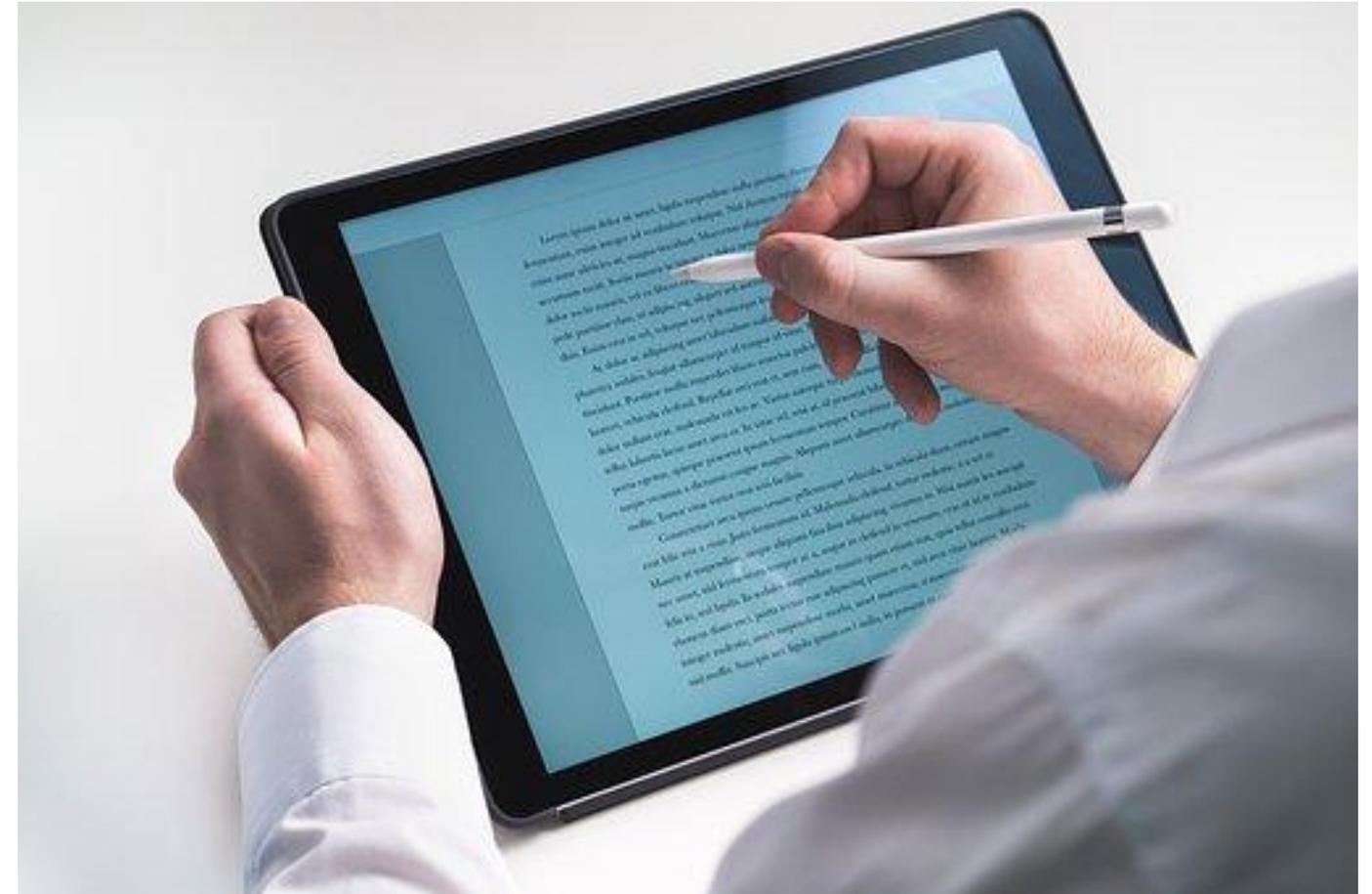


Notes:

1. Dates: FDA Fiscal Year used (October – September), data through Aug 18, 2019

Moving from 503A to 503B

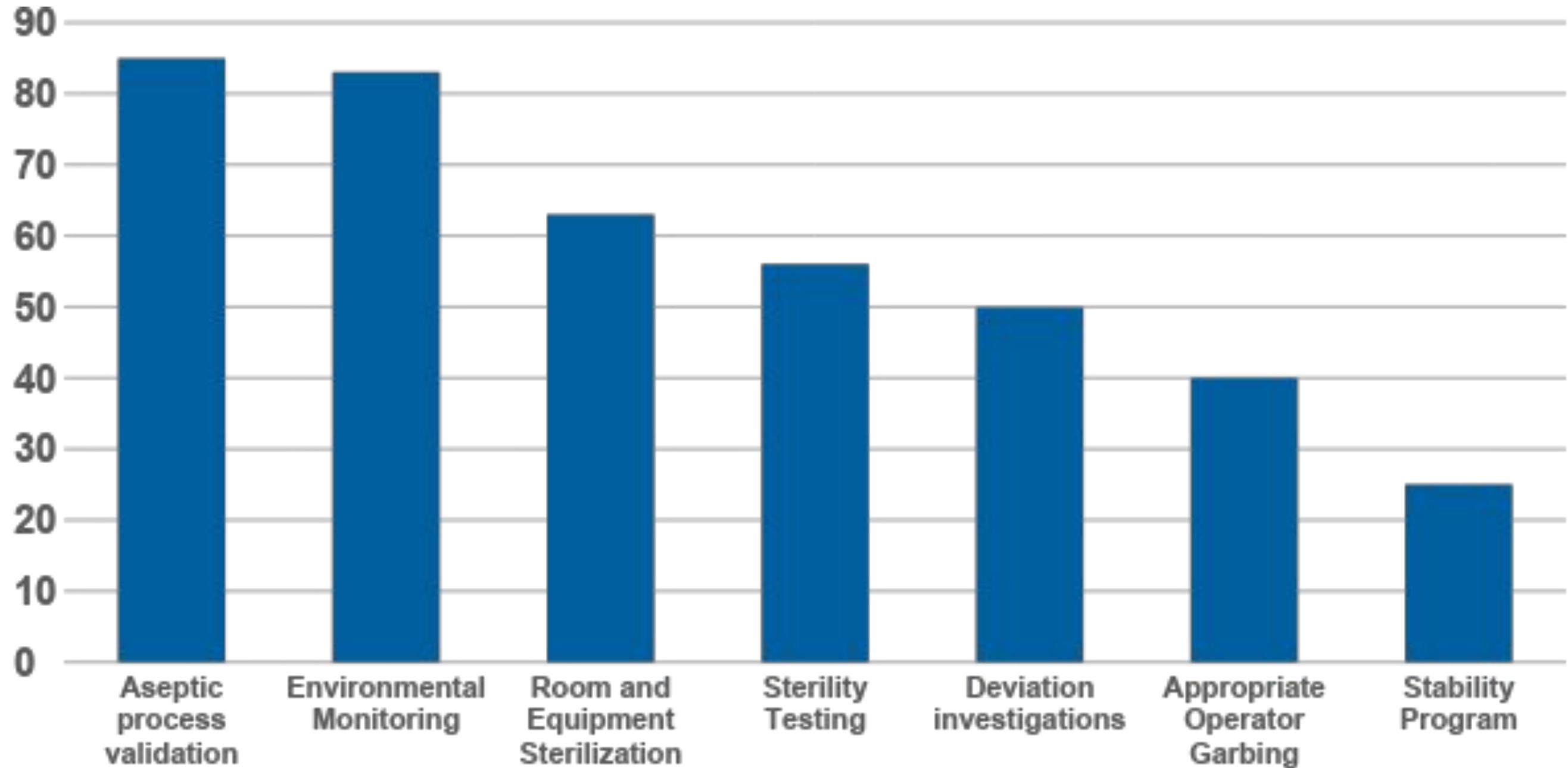
- Discussed earlier all the new systems that need to be developed and managed
- Developing and managing these systems requires a different type of expertise and mindset
- How does the FDA inspection data reflect the 503B industry's success at meeting these challenges?



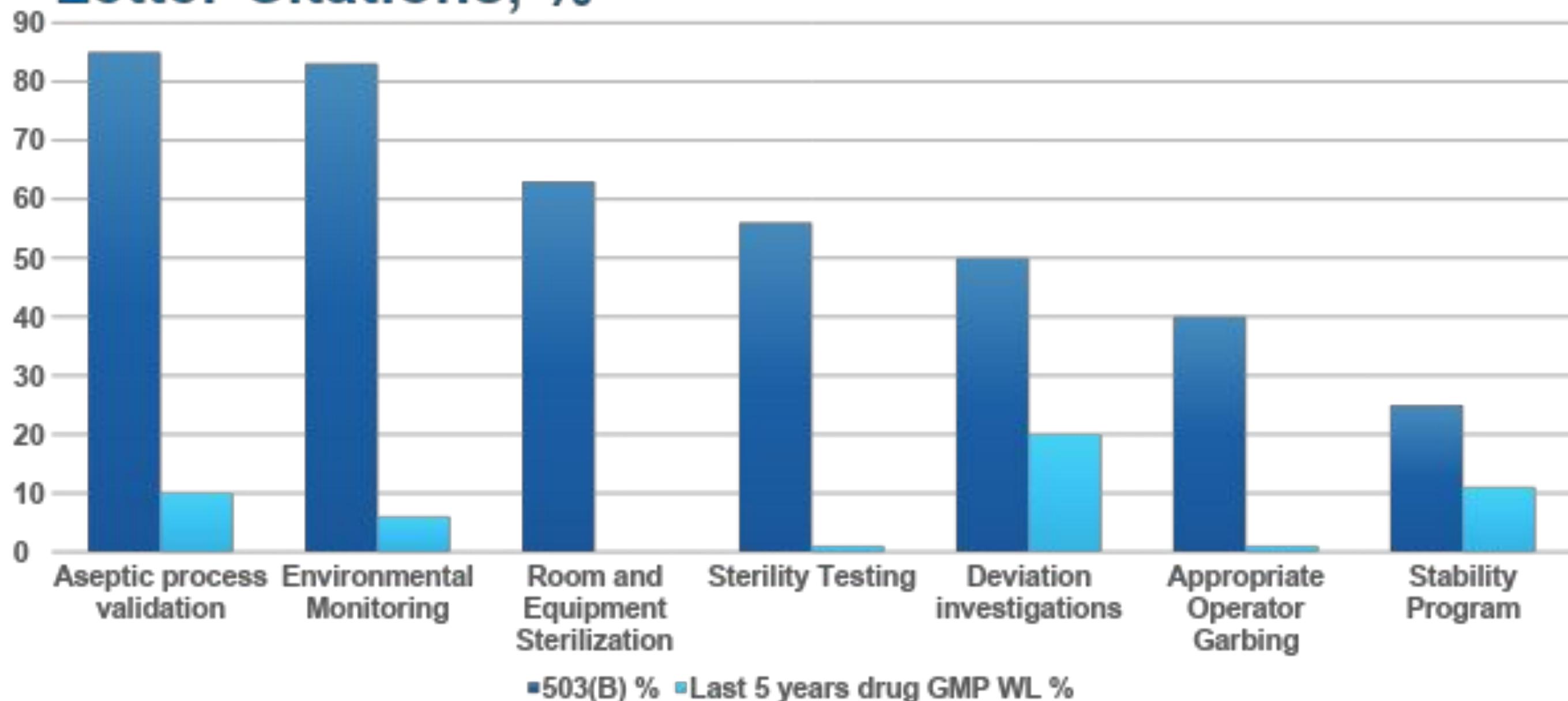
Warning Letter Populations for Analysis

503(B) FDA warning letters to date since 2014*	59
Number with CFR citations (mostly after 2014)	52
Last 5 years of ALL FDA Drug GMP Warning Letters*	205
Searched and analyzed by CFR citation	All

Citation areas in warning letters to 503B Sites, %



Comparing 503B to Drug GMP Warning Letter Citations, %

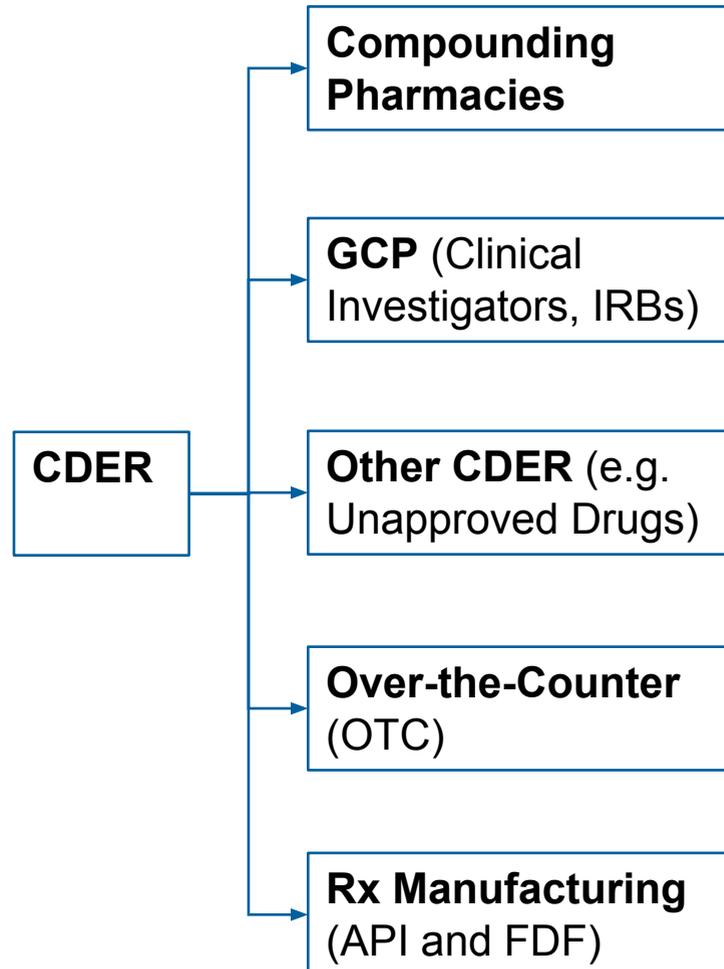


Deep Dive into 503B Warning Letters: AI Tools

Data Sources

- **All data are from PUBLIC sources**
- FDA Inspections databases (CLIL and FACTS) – Dec 8, 2018
- FDA CFR Citations database
- Warning Letters from FDA.gov – Feb 4, 2019
- 35,000+ 483s, responses and EIRs obtained via FOIA and FDA.gov
- FDA registration databases (e.g. GDUFA)
- FDA 21 CFR 211 catalogue (Cornell University)
- Experts - Jerry Chapman (GMP), Barbara Unger (GMP), Jane Wastl (GMP), and Jamie Colgin (GCP)

Site Tags



Other Footnotes

- Inspections linked to Warning Letters via the reference text in the document
- 483 text obtained via OCR (optical character recognition) and re-typing
- Investigator(s), FDA Center, and address information obtained via the Inspections Database
- FDA inspections are not “complete” until 4-5 months after the inspection date due to the “check-in” time (YOY) absolute comparisons cutoff at August 31)
- FDA fiscal year is from October 1 to September 31

Compliance Analysis Algorithm

- Govzilla has created an AI tool that allows deep and rapid analysis of compliance data sets.
- An initial part of the project is creating an algorithm using machine learning and other AI tools and associated data sets to analyze FDA warning letters and 483s.
- To begin to train the AI algorithm and prepare the documents for examination, there are initial, important steps that must be taken first.

NLP - Text Parsing

Warning Letter 320-19-39

August 22, 2019

Dear Dr. Feoli:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Polimeros y Servicios S.A. at Parque Industrial Condal, Calle Pantano, Tibas, San Jose, from February 4 to 8, 2019.

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See 21 CFR, parts 210 and 211.

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

We reviewed your March 1, 2019, response in detail.

During our inspection, our investigator observed specific violations including, but not limited to, the following.

1. Your firm failed to have, 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 (21 CFR 211.165(a)).

Your firm manufactures and distributes topical analgesic, antifungal, acne, and skin protectant creams and (b) (4) for the U.S. market. Our inspection found that you did not test your over-the-counter (OTC) finished drug products to determine whether each batch meets identity and strength of active ingredient specifications before releasing those drug products to the U.S. market.

Complete testing of each batch before release is essential to determine if the drug products you manufacture meet appropriate specifications.

In your response, you stated that you will use a third-party testing laboratory to test for identity of the active

Drug GMP Warning Letter “parts”

- name
- recipient
- introduction
- **deficiency title 1**
- deficiency description 1
- deficiency action 1
- deficiency feedback 1
- **deficiency title 2**
- deficiency description 2
- deficiency action 2
- deficiency feedback 2
- **deficiency title n**
- deficiency description n
- deficiency action n
- deficiency feedback n
- cgmp consultant recommended
- format_type
- conclusion
- reply_to
- identification number
- footer

NLP - Text Parsing: 503B Warning Letters

- Introduction
 - You registered with the U.S. Food and Drug Administration (FDA) as an outsourcing facility...
 - During the inspection, the investigators observed serious deficiencies...
- A. Compounded Drugs under the FDCA
 - The Drug Quality and Security Act (DQSA) was enacted on November 27, 2013...
- B. Violations of the FDCA (the legal basis for issuing the letter)
 - The investigators noted that drug products that were intended or expected to be sterile were prepared, packed, or held under insanitary conditions...
 - In addition, the FDA investigators observed that your facility failed to meet the conditions of section 503B, which applied to your facility at the time of the inspection...
 - Adulterated Drug Products ([CFR citations are listed here, with other observations](#))
 - Misbranded Drug Products
- C. Corrective Actions (actions promised in response to the 483, sometimes other observations from the inspection)
- D. Conclusion
 - The violations cited in this letter are not intended to be an all-inclusive statement of violations at your facility...
 - Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps you have taken to correct violations...
- FDA Signature

NLP - Text Parsing: 503B Warning Letters

- Introduction
 - You registered with the U.S. Food and Drug Administration (FDA) as an outsourcing facility...
 - **During the inspection, the investigators observed serious deficiencies...**
- A. Compounded Drugs under the FDCA
 - The Drug Quality and Security Act (DQSA) was enacted on November 27, 2013...
- B. Violations of the FDCA
 - **The investigators noted that drug products that were intended or expected to be sterile were prepared, packed, or held under insanitary conditions...**
 - **In addition, the FDA investigators observed that your facility failed to meet the conditions of section 503B, which applied to your facility at the time of the inspection...**
 - **Adulterated Drug Products (CFR citations are listed here, with other observations)**
 - Misbranded Drug Products
- C. **Corrective Actions (actions promised in response to the 483, sometimes other observations from the inspection)**
- D. Conclusion
 - The violations cited in this letter are not intended to be an all-inclusive statement of violations at your facility...
 - Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps you have taken to correct violations...
- FDA Signature

503B Warning Letters parsed differently

- Some CFR citations can return false positives:
- *CFR citation: “Your firm failed to clean, maintain, and, as appropriate for the nature of the drug, sanitize and/or sterilize equipment and utensils at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements. (21 CFR 211.67(a))”*
- We do not question the CFR citations FDA gives, but take them as given, and look for additional possible issues “hiding in plain sight” – **how?**
- Begin by putting the letters through a series of Natural Language Processing (NLP) tools.

NLP - Text Cleaning

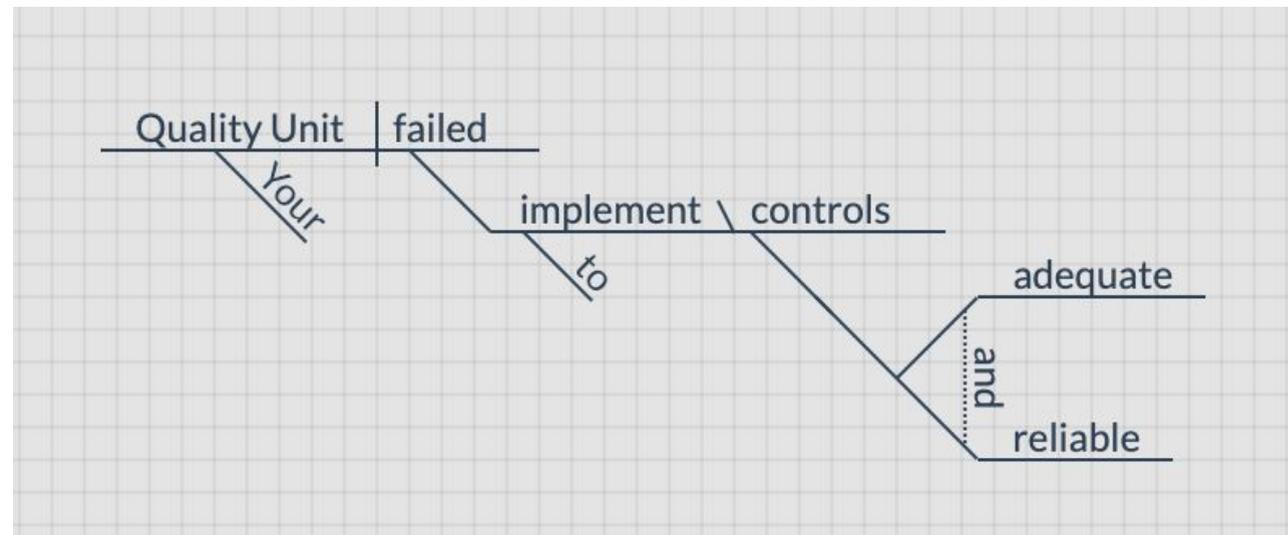
- Text Cleaning is the process of clearing out the “junk” from a sentence.
- Examples:
 - Remove extra spaces
 - Make all words lowercase
 - Remove typos & misspelling

NLP - Tokenization

- Splitting up a sentence into tokens. The most basic of which is just to split a sentence into individual words.
- “Your Quality Unit failed to implement adequate and reliable controls for ensuring that distributed drug products always comply with the efficacy and quality they represent to possess.”
- ['Your', 'Quality', 'Unit', 'failed', 'to', 'implement', 'adequate', 'and', 'reliable', 'controls', 'for', 'ensuring', 'that', 'distributed', 'drug', 'products', 'always', 'comply', 'with', 'the', 'efficacy', 'and', 'quality', 'they', 'represent', 'to', 'possess', '.']

NLP - Tokens & Parts of Speech (POS) tagging

“Your Quality Unit failed to implement adequate and reliable controls for ensuring that distributed drug products always comply with the efficacy and quality they represent to possess.”

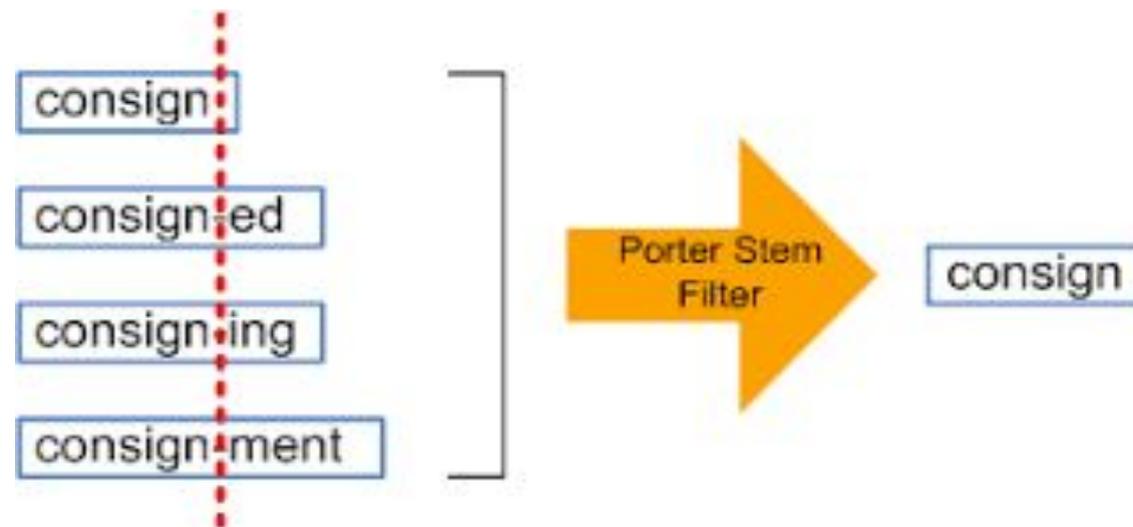


[('Your', 'PRP\$'), ('Quality', 'NNP'), ('Unit', 'NNP'), ('failed', 'VBD'), ('to', 'TO'), ('implement', 'VB'), ('adequate', 'JJ'), ('and', 'CC'), ('reliable', 'JJ'), ('controls', 'NNS'), ('for', 'IN'), ('ensuring', 'VBG'), ('that', 'IN'), ('distributed', 'VBN'), ('drug', 'NN'), ('products', 'NNS'), ('always', 'RB'), ('comply', 'VBP'), ('with', 'IN'), ('the', 'DT'), ('efficacy', 'NN'), ('and', 'CC'), ('quality', 'NN'), ('they', 'PRP'), ('represent', 'VBP'), ('to', 'TO'), ('possess', 'VB'), ('.', '.')]]

NLP - Stemming

Stemming is the process of reducing each word in a written document into its word stem, base or root form. This will not necessarily become a proper word but all permutations of a word will stem to the same root.

“Your Quality Unit failed to implement adequate and reliable controls for ensuring that distributed drug products always comply with the efficacy and quality they represent to possess.”



your qualiti unit fail to implement adequ and reliabl control for ensur that distribut drug product
always compli with the efficaciaci and qualiti they repres to possess.

NLP – n-grams

An n-gram is a contiguous sequence of n items from a given sample of text or speech

“Your Quality Unit failed to implement adequate and reliable controls for ensuring that distributed drug products always comply with the efficacy and quality they represent to possess.”

Bi-gram

('Your', 'Quality')

('Quality', 'Unit')

('Unit', 'failed')

('failed', 'to')

Tri-gram

('Your', 'Quality', 'Unit')

('Quality', 'Unit', 'failed')

('Unit', 'failed', 'to')

('failed', 'to', 'implement')

('to', 'implement', 'adequate').....and longer ones

GMP Classification Categories (Human Drugs)

Quality System	Packaging & Labeling	Facilities & Equipment	Materials	Laboratory	Production		Data Integrity
<ul style="list-style-type: none"> •Agency Notification (4 subs) •Audit (2 subs) •CAPA •Change Control •Complaint Management •Records and Reports (13 subs) •Deviations / Investigations (8 subs) •Qualified Personnel (3 subs) •Quality Unit Inadequate (1 sub) •Risk Mgmt. 	<ul style="list-style-type: none"> •Drug product containers and closures (3 subs) •Label and Packaging Controls •Line Clearance •Serialization 	<ul style="list-style-type: none"> •Cleaning (3 subs) •Design (9 subs) •Maintenance (3 subs) •Alarm Management •HVAC •Pest Control •Records and Reports 	<ul style="list-style-type: none"> •Distribution •Material Receipt and Handling (3 subs) •Material Sampling and Testing (3 subs) •Material Storage and Control •Retain Samples 	<ul style="list-style-type: none"> •Method Validation •OOS/ OOT •Stability (2 subs) •Systems Controls •Testing (4 subs) •Reagents and Standards •Records and Reports •Sample Management 	<ul style="list-style-type: none"> •API •Batch Records •Clean Utilities •Cleaning validation or verification •Contamination Control •High Potency/ Allergenic •Nonsterile products (2 subs) •Penicillin and Cephalosporin •Personnel Responsibilities •Process control (5 subs) 	<ul style="list-style-type: none"> •Process Monitoring / Continued Process Verification •Process Validation (2 subs) •Product Contamination •Records and Reports •Retain Samples •Sterile Products (8 subs) 	<ul style="list-style-type: none"> •Accurate •Attributable (3 subs) •Backup and Archival •Contemporaneous •Data Destruction •Data Manipulation •Legible •Original Data •Paper Record Controls •System Controls •Testing into Compliance

Note: The algorithm has been put through numerous iterations with human experts grading and adjusting.

Running the Algorithm

Experts create n-grams for each subcategory;
also Turbo EIR text

Process a group FDA warning letters

Run the algorithm against them

Training the model: Experts grade parsing and tagging, iterative, “machine learning” – why is it not right?

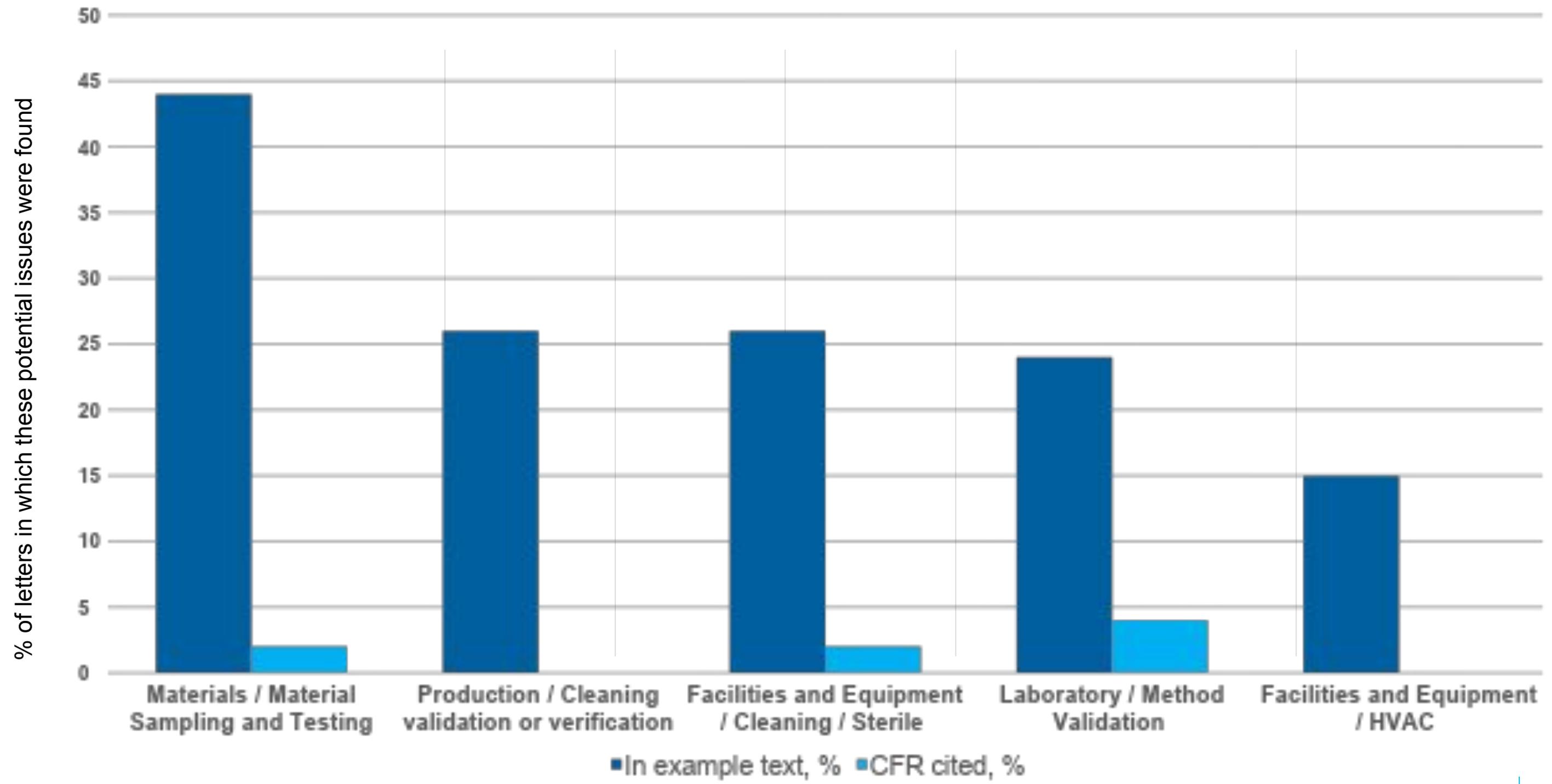
Changes to n-grams, algorithm, fuzzy matching

Find secondary potential areas of concern not cited by CFR, but contained in the narrative

“Hiding in plain sight”



Probable 503B Issues Not Cited: Hiding in Plain Sight



Future of Outsourcing Facilities - Embracing the Challenge

- Continue to play a role with drug shortages and other emergent healthcare needs
- Increased quality, safety, and compliance with regulations
- Consolidation will continue due to compliance and quality issues
- Partnerships w/ industry to provide higher quality clinical trial materials
- Role in providing some stability to increasing healthcare costs

Resources – Links to Referenced and Helpful Info Regarding Compounding

<u>FDA Compounding Laws and Policies</u>	<u>FDA: Compounding Inspections, Recalls, and other Actions</u>
<u>Current Good Manufacturing Practice—Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act Guidance for Industry (December 2018 draft)</u>	<u>CDER Outsourcing Facility Information</u>
<u>FDA Compounding Center of Excellence at CDER</u>	<u>An In-Depth Look at the History of Compounding Issues in the US that began in 2012</u>

Thank You!



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