REDICA Systems

&

SIMCO

The Insider's Guide to Audit Readiness

Presented by:

Sam Klooster
VP of Software, SIMCO

Jerry Chapman
Senior GMP Quality Expert, Redica Systems

In theory, the mission is simple: make safe, high quality great products while meeting regulatory requirements and business demands. But…

Growth in number of regulatory agencies and requirements.

Health agencies rules and regulations vs. *how they are enforced on inspection*.

What are their expectations for your plant?

Where are those changing expectations found?

Introduction

Mining enforcement data: 483 observations, warning letter citations.

Time consuming and difficult, requires expertise.

Where is enforcement data found?

Redica Systems has built the largest dataset of inspection and enforcement documents in the world – *the data sets used for the following analysis*.

Introduction

Includes all FDA inspected and registered sites since 2000. 20 times more data than has been released on FDA.gov (targeted FOIA). More than 350,000 sites and 800,000 inspections.
Once you get the inspection data, do you have the experts to analyze it?

And if so, do they still print hard copies and use highlighting markers to analyze them?

Built proprietary AI “expert models” using machine learning and honed by industry experts

Machine Learning, Natural Language Processing (NLP), AI: Data Sources

Data Sources

- ***All data are from PUBLIC sources***
- FDA Inspections databases (CLIIL and FACTS)
- FDA CFR Citations database
- Warning Letters from FDA.gov
- 50,000+ 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), Mark Agostino (Devices), Alison Sathe (Devices), Fran Lambetecchio (GVP/GCP), others

Site Tags

CDER

- Rx manufacturing (API and FDF)
- Over-the-Counter (OTC)
- Other CDER (e.g., unapproved drugs)
- GCP (Clinical Investigators, IRBs, Sponsors)
- Compounding Pharmacies

CBER

CDRH

MHRA

Health Canada

etc.

How do we use the data?

- Investigator profiles
- CMO/CRO due diligence
- Vendor selection
- **Inspection preparation**
- Keeping PQS up to date
- Tracking changes to authoritative sources
- Tracking and trending inspection observations
- Finding observations and citations “hiding in plain sight” (case studies)
- Tip of the iceberg…

Machine Learning, Natural Language Processing (NLP), AI: Expert Model Algorithm

Compliance Analysis Algorithm

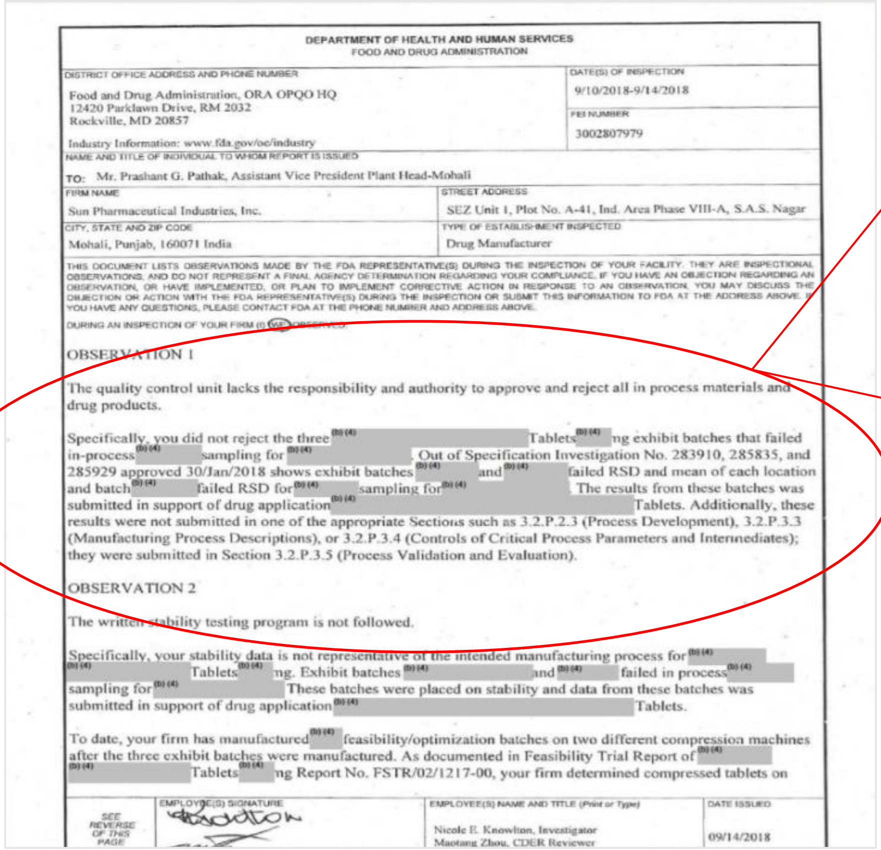
Redica Systems has created an AI tool – “expert model” – that allows deep and rapid analysis of compliance data sets.

Created an algorithm using machine learning, NLP and other AI tools and associated data sets to analyze FDA warning letters, 483s, and other documents.

To begin to train the AI algorithm and prepare the documents for examination, there are initial, important steps that must be taken first.

Natural Language Processing:
Making Scanned Documents Human and Machine Readable

Processed >50,000 483s, 483R, and EIRs



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION / FEI NUMBER
Food and Drug Administration, ORA OPQO HQ 12420 Parklawn Drive, RM 2032 Rockville, MD 20857 Industry Information: www.fda.gov/oe/industry	9/10/2018-9/14/2018 3002807979

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED
TO: Mr. Prashant G. Pathak, Assistant Vice President Plant Head-Mohali

FIRM NAME	STREET ADDRESS
Sun Pharmaceutical Industries, Inc.	SEZ Unit 1, Plot No. A-41, Ind. Area Phase VIII-A, S.A.S. Nagar
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Mohali, Punjab, 160071 India	Drug Manufacturer

THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS, AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

OBSERVATION 1

The quality control unit lacks the responsibility and authority to approve and reject all in process materials and drug products.

Specifically, you did not reject the three (b) (4) [redacted] Tablets (b) (4) [redacted] ng exhibit batches that failed in-process (b) (4) [redacted] sampling for (b) (4) [redacted]. Out of Specification Investigation No. 283910, 285835, and 285929 approved 30/Jan/2018 shows exhibit batches (b) (4) [redacted] and (b) (4) [redacted] failed RSD and mean of each location and batch (b) (4) [redacted] failed RSD for (b) (4) [redacted] sampling for (b) (4) [redacted]. The results from these batches was submitted in support of drug application (b) (4) [redacted] Tablets. Additionally, these results were not submitted in one of the appropriate Sections such as 3.2.P.2.3 (Process Development), 3.2.P.3.3 (Manufacturing Process Descriptions), or 3.2.P.3.4 (Controls of Critical Process Parameters and Internediates); they were submitted in Section 3.2.P.3.5 (Process Validation and Evaluation).

OBSERVATION 2

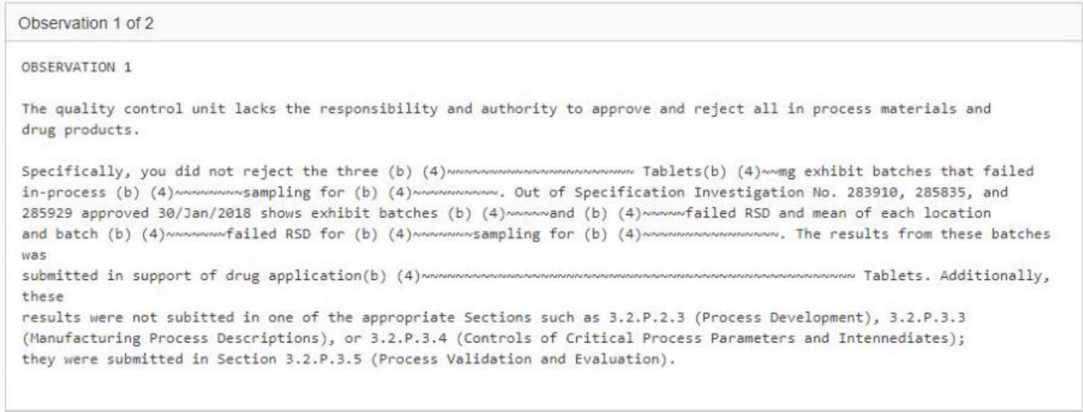
The written stability testing program is not followed.

Specifically, your stability data is not representative of the intended manufacturing process for (b) (4) [redacted] Tablets (b) (4) [redacted] ng. Exhibit batches (b) (4) [redacted] and (b) (4) [redacted] failed in process (b) (4) [redacted] sampling for (b) (4) [redacted] These batches were placed on stability and data from these batches was submitted in support of drug application (b) (4) [redacted] Tablets.

To date, your firm has manufactured (b) (4) [redacted] feasibility/optimization batches on two different compression machines after the three exhibit batches were manufactured. As documented in Feasibility Trial Report of (b) (4) [redacted] Tablets (b) (4) [redacted] ng Report No. FSTR/02/1217-00, your firm determined compressed tablets on

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
		Nicole E. Knowlton, Investigator Maotang Zhou, CDER Reviewer	09/14/2018

Clean Observation Text: OCR, Retyping



Observation 1 of 2

OBSERVATION 1

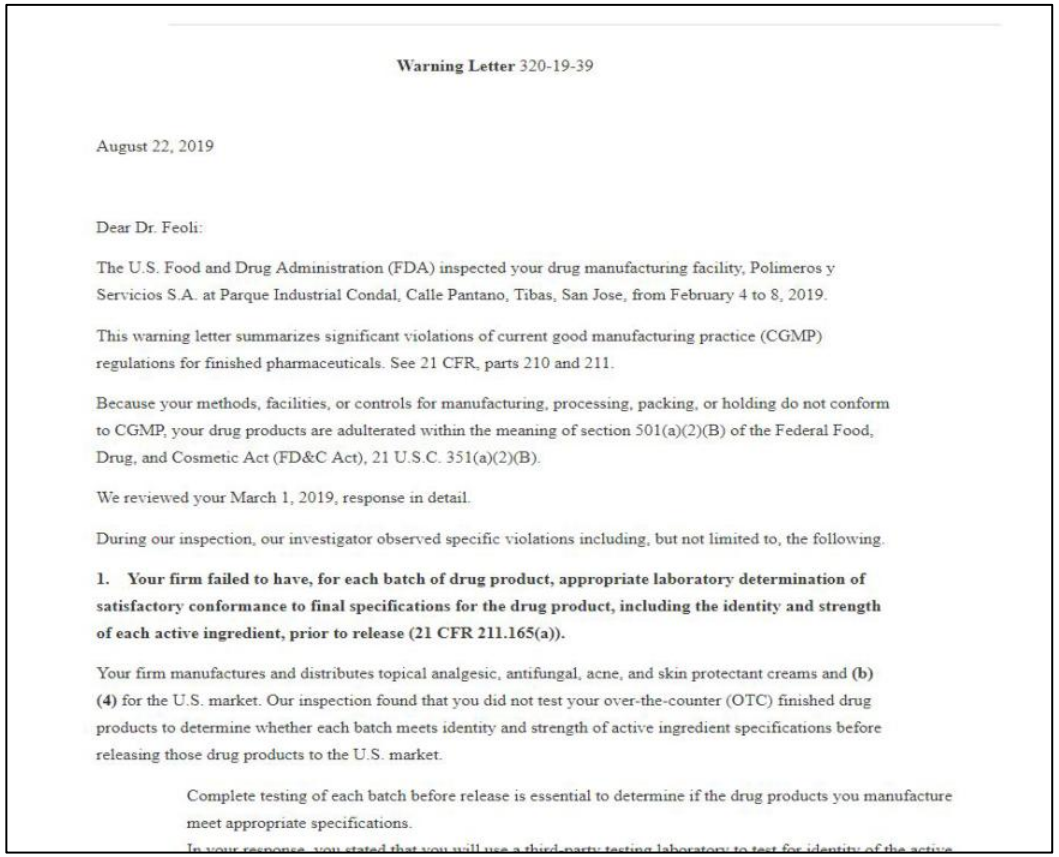
The quality control unit lacks the responsibility and authority to approve and reject all in process materials and
drug products.

Specifically, you did not reject the three (b) (4)~~~~~~~~~~~~~~~~~~~~~~ Tablets(b) (4)~~mg exhibit batches that failed
in-process (b) (4)~~~~~~~~~sampling for (b) (4)~~~~~~~~~~. Out of Specification Investigation No. 283910, 285835, and
285929 approved 30/Jan/2018 shows exhibit batches (b) (4)~~~~~~and (b) (4)~~~~~~failed RSD and mean of each location
and batch (b) (4)~~~~~~~~failed RSD for (b) (4)~~~~~~~~sampling for (b) (4)~~~~~~~~~~~~~~~~. The results from these batches
was
submitted in support of drug application(b) (4)~~~~~~ Tablets. Additionally,
these
results were not subitted in one of the appropriate Sections such as 3.2.P.2.3 (Process Development), 3.2.P.3.3
(Manufacturing Process Descriptions), or 3.2.P.3.4 (Controls of Critical Process Parameters and Intennediates);
they were submitted in Section 3.2.P.3.5 (Process Validation and Evaluation).

Parse "main topic" of Observation

```
The quality control unit lacks the
responsibility and authority to
approve and reject all in process
materials and drug products.
```

Natural Language Processing: 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

Natural Language Processing:
Text Parsing

Not all sections are searched. **Parsing is key; without it the results are worse than meaningless with an abundance of incorrect search results that will mislead and drive incorrect actions and behaviors – for example:**

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))****"*

Specifically…

It is the "specifically" or "for example" text that contains rich content

Natural Language Processing:
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

Natural Language Processing: Tokenization

Splitting up a sentence into tokens. The most basic of which is just to split a sentence into individual words.

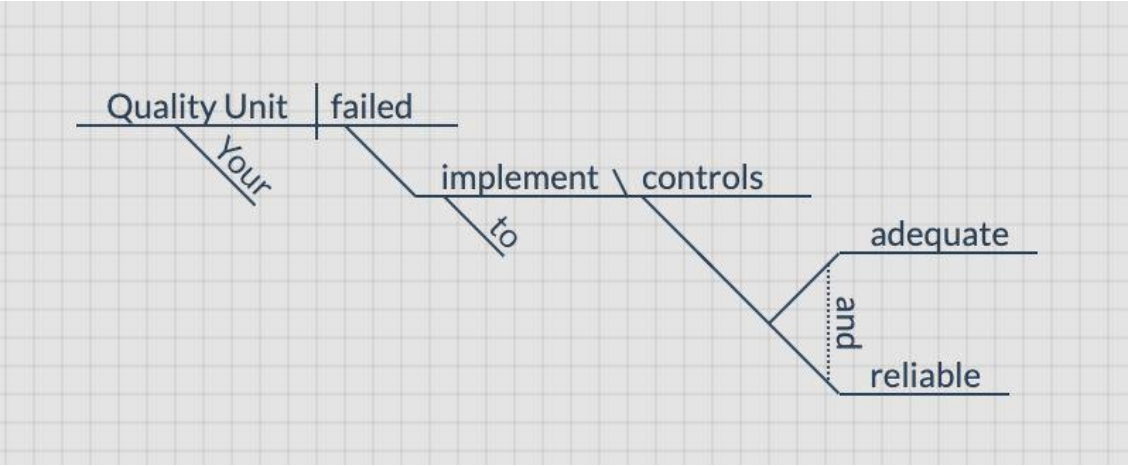
“Your Quality Unit failed to implement adequate and reliable controls for ensuring that distributed drug products always comply with the efficacy and quality they represent to possess.”

['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', '.']

Natural Language Processing:
Tokens and Parts of Speech (POS) Tagging

Tokens can be much more complex, in the example below the sentence was broken up into “Part of speech” tokens

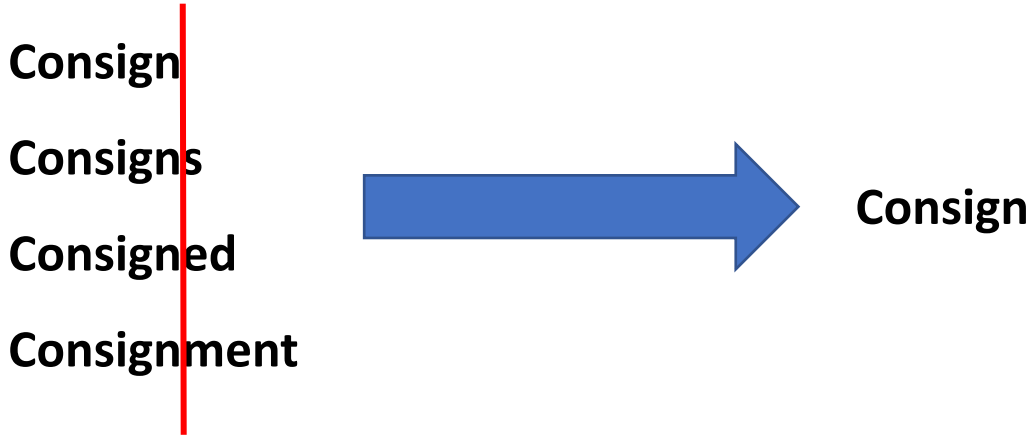
“Your Quality Unit failed to implement adequate and reliable controls for ensuring that distributed drug products always comply with the efficacy and quality they represent to possess.”



[('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'), ('.', '.')]

Natural Language Processing: Stemming/Lemmatization

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. Lemmatization is a similar process that considers the parts of speech and context in which the word is used, reducing each to a *lemma*.



"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 alway compli with the efficaci and qualiti they repres to possess

Natural Language Processing:
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')

Subject Matter Experts create n-grams from experience and compliance document language; tested over time in model iterations.

Tri-gram
(**'Your', 'Quality', 'Unit'**)
(**'Quality', 'Unit', 'failed'**)
('Unit', 'failed', 'to')
('failed', 'to', 'implement')
('to', 'implement', 'adequate’)…….and longer ones

Building and Applying the Models

Experts create n-grams for each category and subcategory; also, TurboEIR 483 text

For drugs, organized by FDA's 6 quality systems + 1 (DI)

Models for human drugs, medical devices, and clinical trial investigators are completed and deployed

Other FDA models for ● clinical trials (GCP) (institutional review boards) ● APIs ● human cell and tissue/GTP ● human drug recalls, and ● models for Health Canada inspections and other geographies – e.g., MHRA, EMA – in various testing phases

Different parsing models, n-grams, TurboEIR text, and SMEs: **contextual (contemporaneous)**

Building and Applying the Models: GMP Classification Categories (Human Drugs)

Quality System

- 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.

Packaging & Labeling

- Drug product containers and closures (3 subs)
- Label and Packaging Controls
- Line Clearance
- Serialization

Facilities & Equipment

- Cleaning (3 subs)
- Design (9 subs)
- Maintenance (3 subs)
- Alarm Management
- HVAC
- Pest Control
- Records and Reports

Materials

- Distribution
- Material Receipt and Handling (3 subs)
- Material Sampling and Testing (3 subs)
- Material Storage and Control
- Retain Samples

Laboratory

- Method Validation
- OOS/ OOT
- Stability (2 subs)
- Systems Controls
- Testing (4 subs)
- Reagents and Standards
- Records and Reports
- Sample Management

Production

- 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)
- Process Monitoring / Continued Process Verification
- Process Validation (2 subs)
- Product Contamination
- Records and Reports
- Retain Samples
- Sterile Products (8 subs)

Data Integrity

- Accurate
- Attributable (3 subs)
- Backup and Archival
- Contemporaneous
- Data Destruction
- Data Manipulation
- Legible
- Original Data
- Paper Record Controls
- System Controls
- Testing into Compliance

NOTE: Different models will have different categories: drugs use FDA quality systems

Building and Applying the Models

Build the parser and the model

- Process FDA warning letters, 483s – NLP tools

- Run the algorithm against them

- 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 in addition to those listed by CFR

“Hiding in plain sight”

Model Insights

Redica Systems data can be used for a variety of purposes to support our mission:

“Empowering the champions of quality and safety with actionable data intelligence”

Sam Klooster from SIMCO will present insights his company has been working on using our systems and data platform

Specifically, he used the Human Drug GMP model to look at data integrity issues related to Part 11 compliance

Maintaining FDA Compliance is a Top Industry Challenge

90% of Quality Leaders say maintaining compliance is their top challenge

Recent Inspection Citations Manufacturers Received from the FDA:

- ”Written procedures are not established and followed for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing or holding of a drug product.”
- ”The calibration of instruments and apparatus is not done at suitable intervals.”
- ”Electronic records are used, but they do not meet systems validation, system access limitation, audit trail, operational system check, authority check, device check, personnel qualifications, employee accountability/responsibility policy, systems documentation control, open systems control, signature manifestation and signature to record linking requirements to ensure that they are trustworthy, reliable and generally equivalent to paper records.”

About 21 CFR Part 11 Compliance

What is FDA 21 CFR Part 11?

- FDA Regulation governing the use of electronic records and digital signatures to store, track and transfer records pertaining to the manufacture of products
- Defines the criteria under which electronic records and e-signatures are considered trustworthy, reliable, and equivalent to paper records
- Electronic systems are not required, but increasingly used by manufacturers to improve compliance faster and at lower cost

Benefits of using electronic systems for 21 CFR Part 11 compliance:

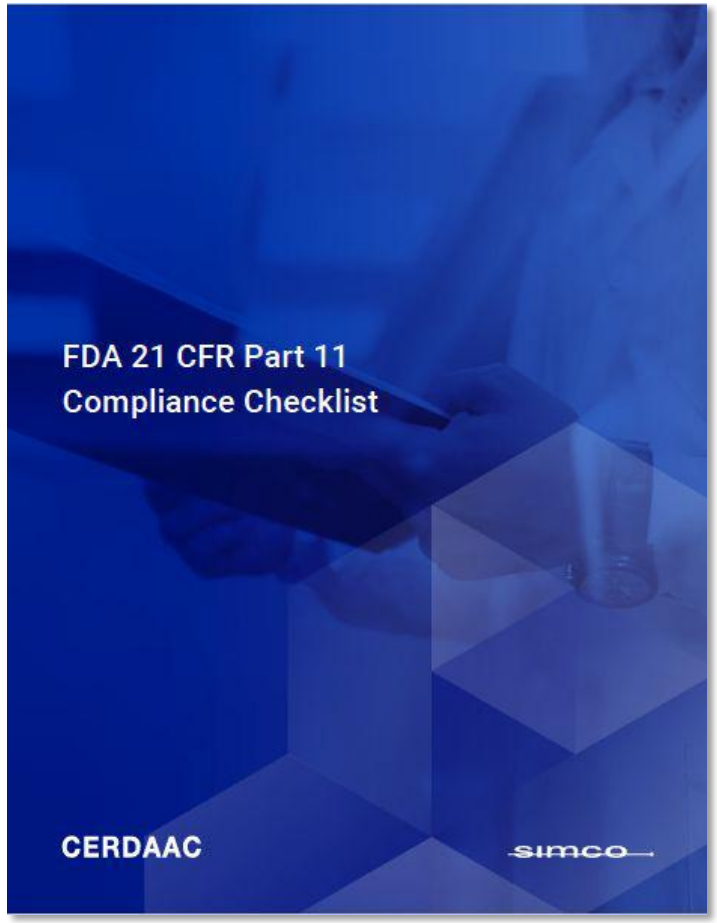
- Reduced errors
- Increased data confidentiality, integrity, and accessibility
- Faster information exchange
- Increased cost savings

Penalties for non-compliance can include:

- FDA Form 483, a warning letter, an injunction (which can include a market recall or ban on importation), or a consent decree.
- Criminal penalties, fines, etc.

Five Key Areas of the Regulation

- **Systems Compliance**: are the electronic systems being used to store records in compliance
- **Audit Trails**: are records kept of alterations and changes, with previous versions stored and available?
- **Electronic Signatures**: who can sign, are signatures validated?
- **Access and Control**: are roles and permissions properly defined and controlled?
- **System Validation**: the difference between “validatable” and prevalidated, and key requirements

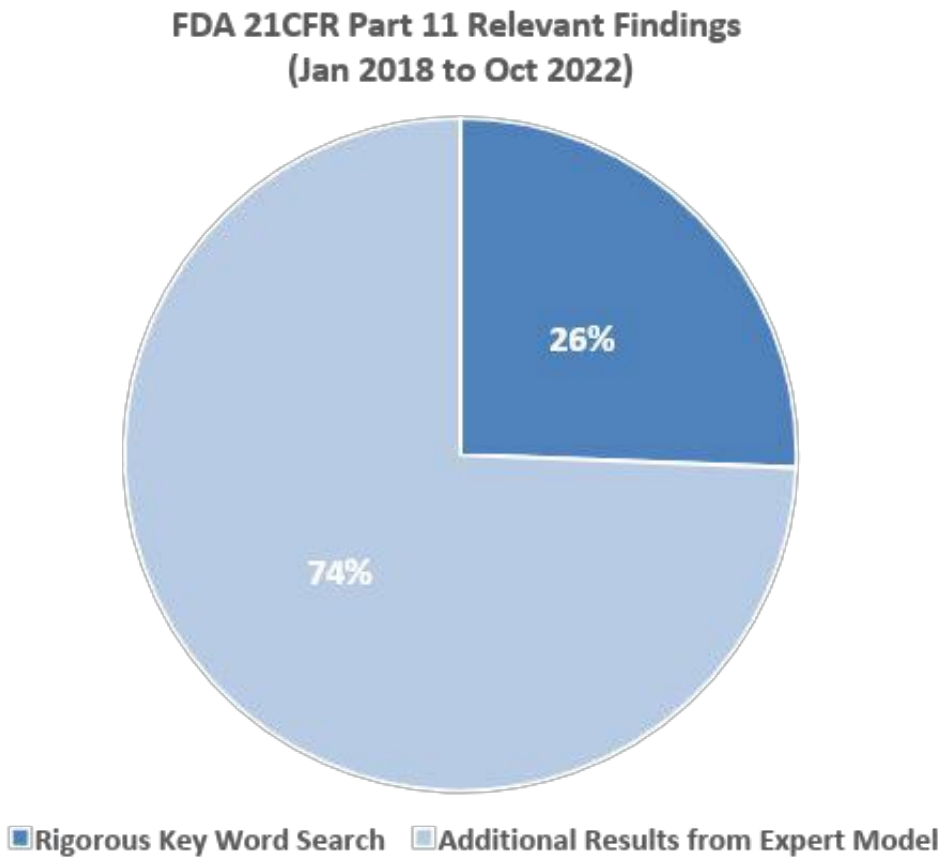


Systems Compliance

- Does the system include workflows that enforce compliance?
- Control and limit delete capabilities included?
- Are proper sequence of steps and processes enforced?
- Are roles and permissions properly controlled?
- Can results be altered, and if so, are changes easily tracked and identified?
- Is training provided and documented?

Rigorous Keyword Search vs Expert Model

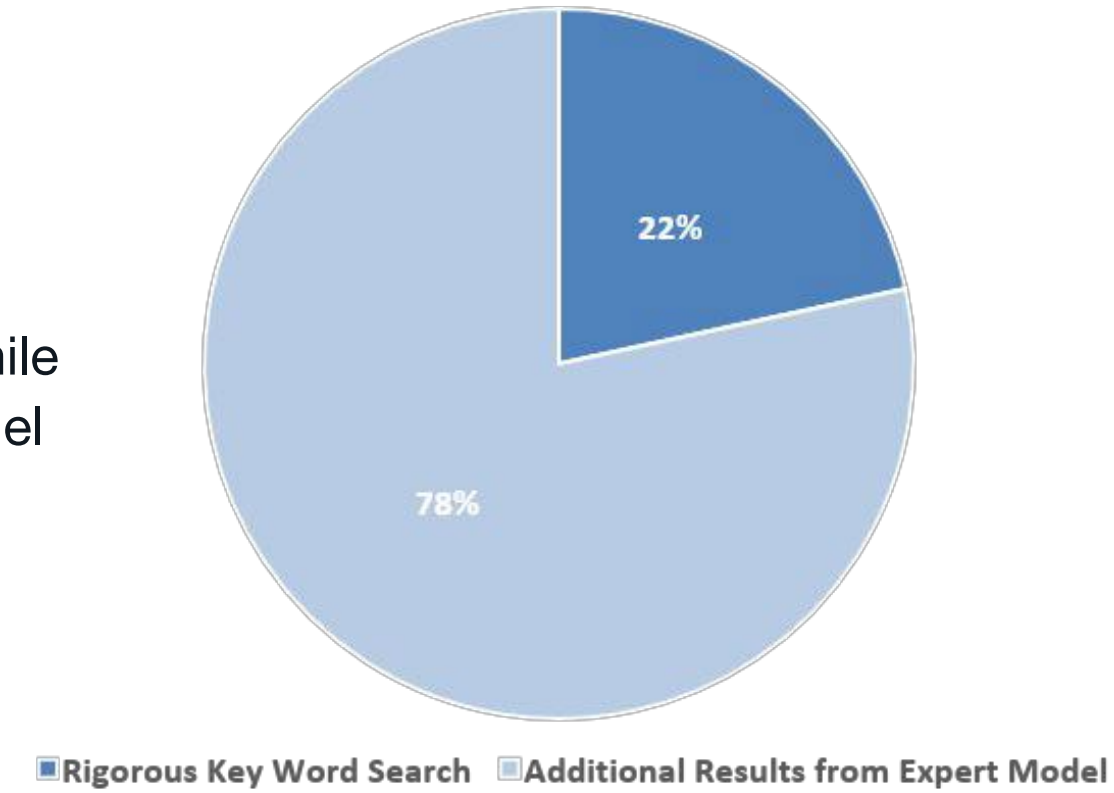
- Redica Systems' Human Drug model was used as the expert model to review data over the last 5 years
- A rigorous key word search was also used to identify relevant 483 observations as it relates to FDA 21 CFR Part 11 compliance
- The key word search only identified ¼ of the observations across the data



5 Years of “Systems Compliance” Observations

- Redica Systems’ Human Drug model shows nearly 1500, 483 observations focused on “Systems Compliance” in the last 5 years

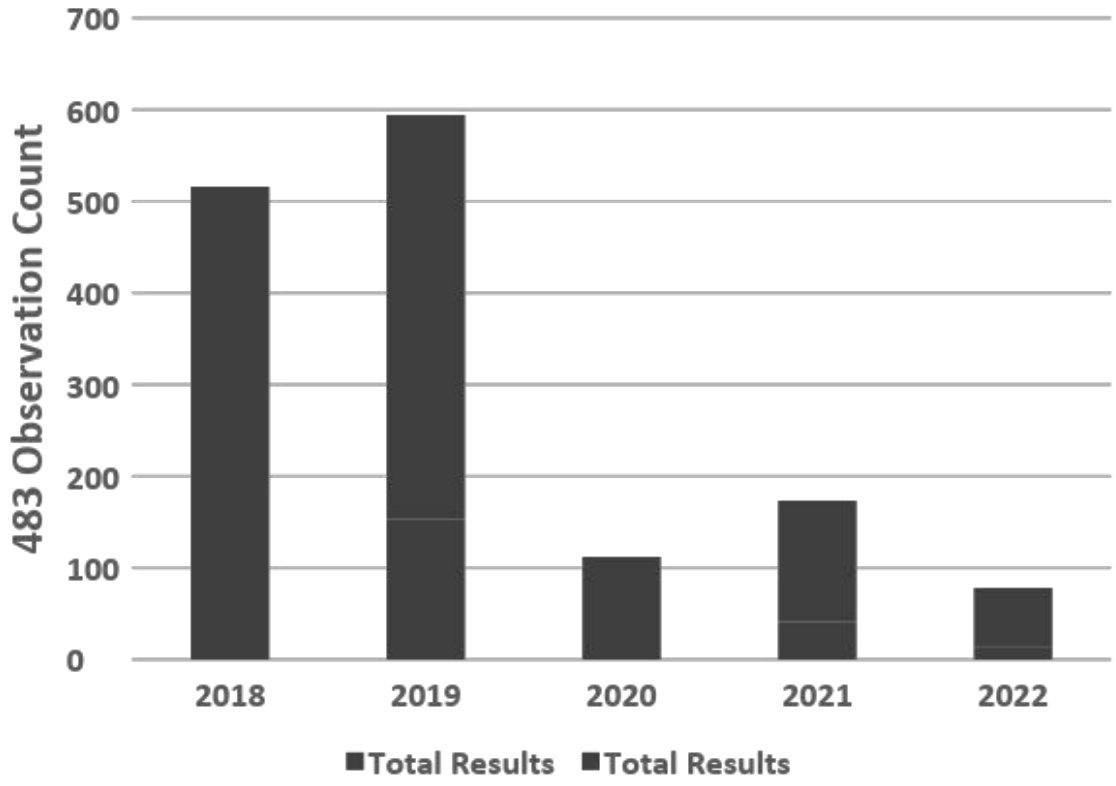
- 22% of “Systems Compliance” 483 observations were identified by a rigorous key word search, while 78% more were only identified by the expert model



5 Years of “Systems Compliance” Observations

- “Systems Compliance” referenced 483 observations decreased 74% due to COVID

- USA vs International observations were fairly even with 55% cited US companies while 45% cited International companies



FDA “Systems Compliance” Citation Example

WARNING LETTER

Clinicon Corp

MARCS-CMS 582801 – JUNE 20, 2019

Share | Tweet | Linkedin | Email | Print

Delivery Method: United Parcel Service
Product: Medical Devices

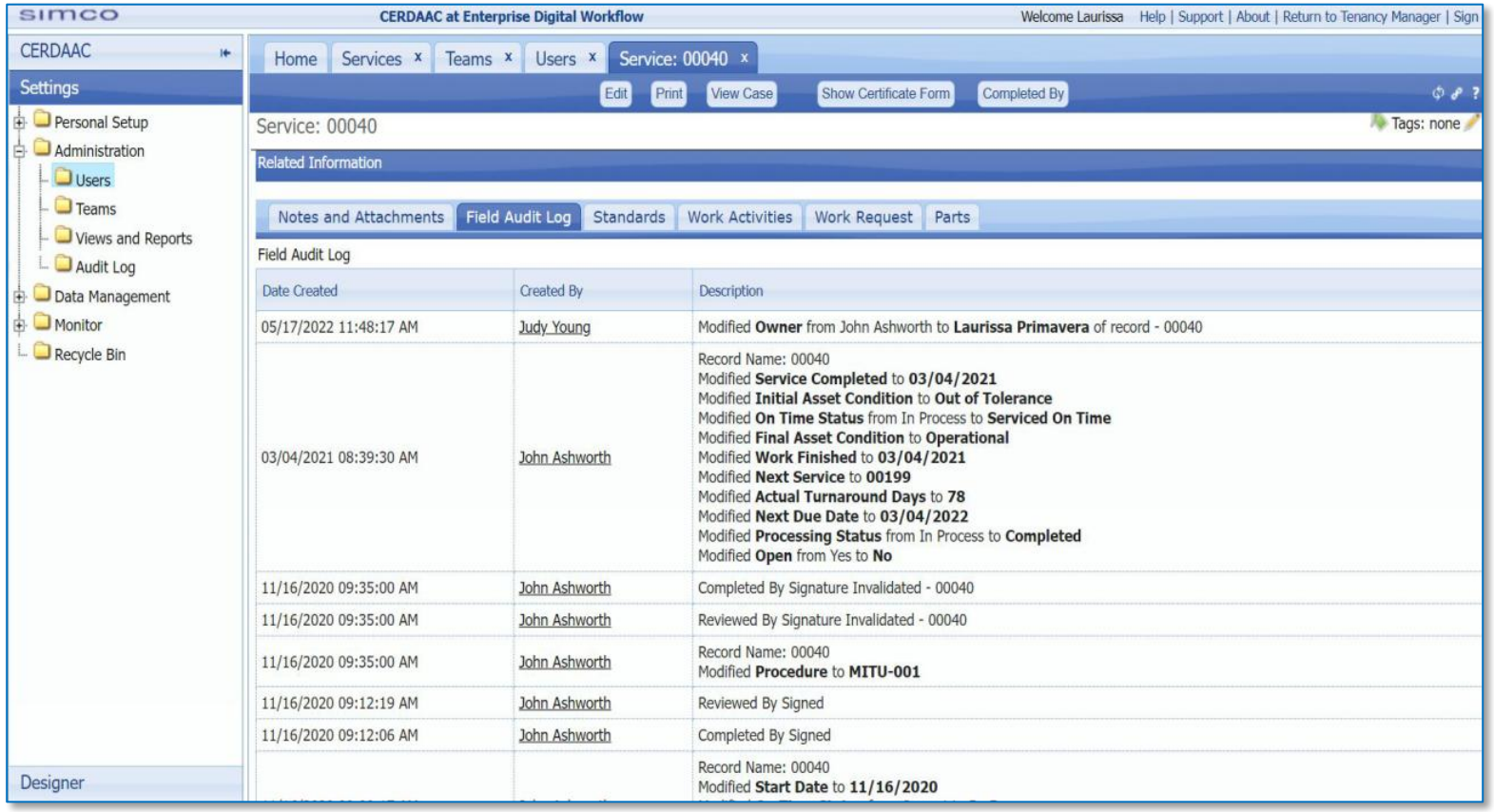
Recipient:
Mr. Fritz A. Brauer
President and CEO
Clinicon Corp
3025 Industry St., Ste. A
Oceanside, CA 92054
United States

Issuing Office:
Division of Medical Device and Radiological Health Operations West
19701 Fairchild
Irvine, CA 92612-2506
United States

The documentation maintained by your firm does not demonstrate a validation has been maintained for the **(b) (4)** process, or performed for your packaging process. Please review the requirements of 21 CFR Part 820.75 and provide information as to how you are ensuring sterilization and maintaining the sterile barrier for your products currently being distributed and in future. We also request that you review your procedures to ensure they meet the requirements, and implement those procedures to include retention of applicable records. Please provide our office a timeframe for when this can be completed, a copy of the procedure if it is updated, and records such as the final report showing results of each validation.

Audit Trails

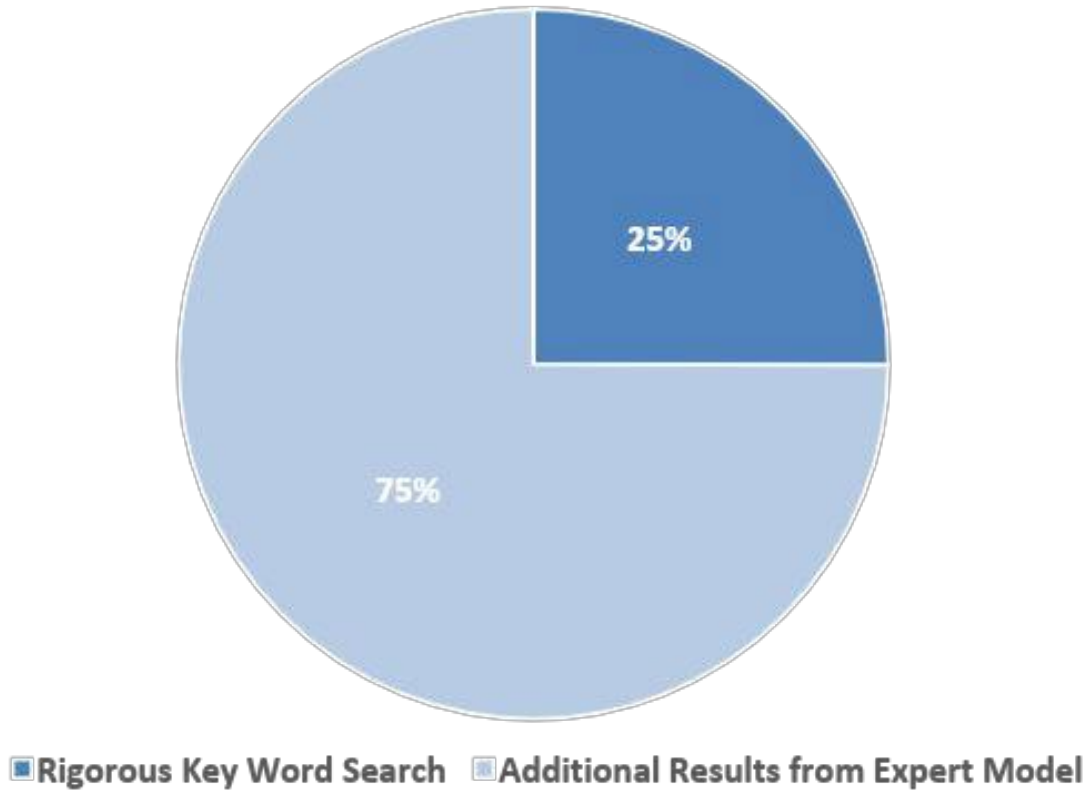
- Time stamped audit trails with complete histories?
- Are change histories available, and previous versions stored?
- Audit trails retrievable and available for review?
- Device checks to confirm source data validity?
- Evidence of system checks?
- Written policies that deter record and/or e-signature falsification?



5 Years of “Audit Trails” Observations

- Redica Systems’ Human Drug model shows nearly 2150, 483 observations focused on “Audit Trails” in the last 5 years

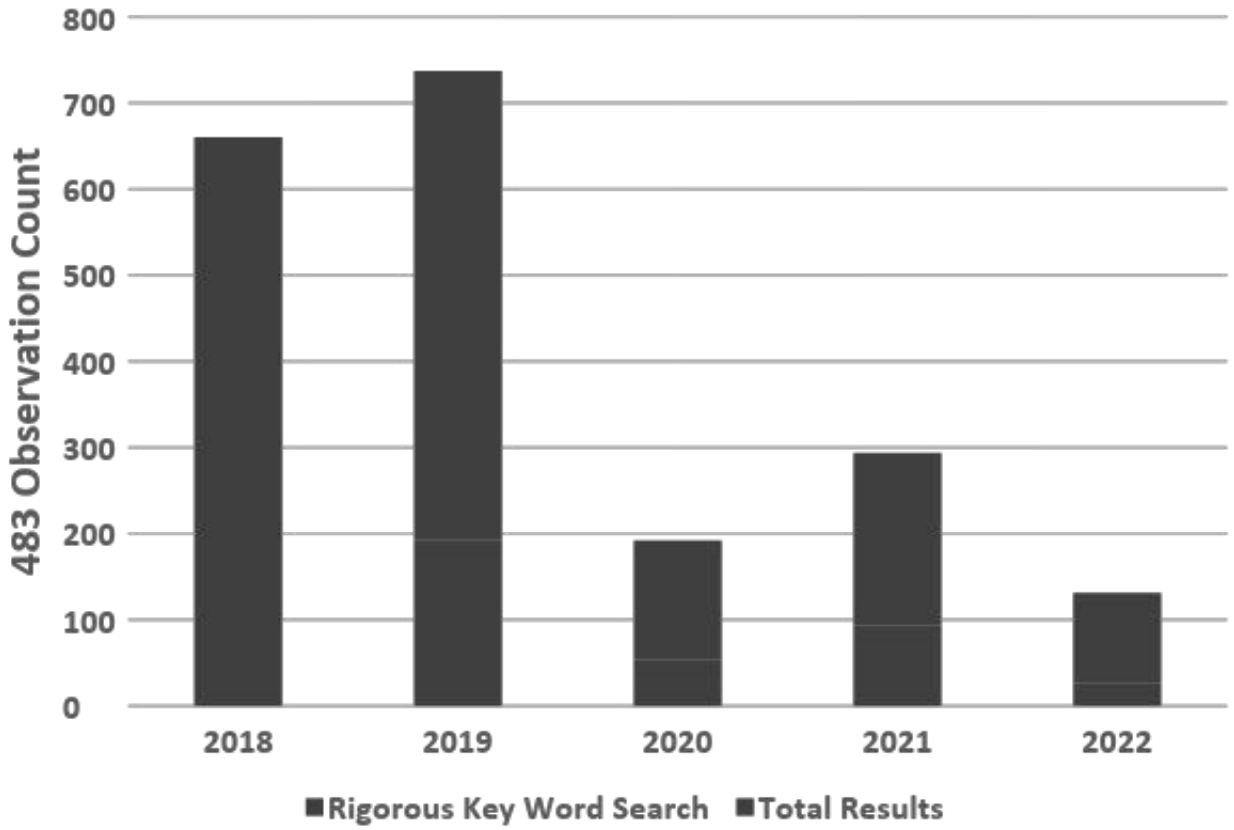
- 25% of “Audit Trails” 483 observations were identified by a rigorous key word search, while 75% more were only identified by the expert model



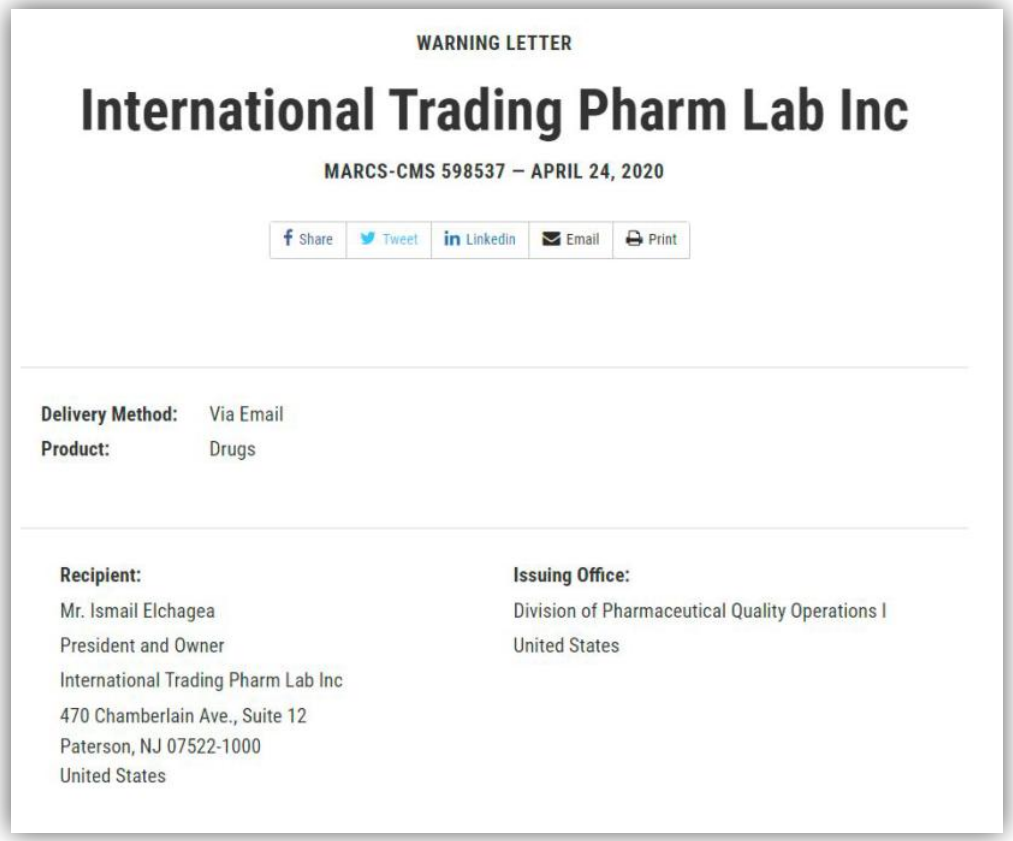
5 Years of “Audit Trails” Observations

- “Audit Trails” referenced 483 observations decreased 65% due to COVID

- USA vs International observations were slightly skewed towards the US with 62% cited US companies while 38% cited International companies



FDA “Audit Trails” Citation Example



WARNING LETTER

International Trading Pharm Lab Inc

MARCS-CMS 598537 — APRIL 24, 2020

Share Tweet Linkedin Email Print

Delivery Method: Via Email
Product: Drugs

Recipient:
Mr. Ismail Elchagea
President and Owner
International Trading Pharm Lab Inc
470 Chamberlain Ave., Suite 12
Paterson, NJ 07522-1000
United States

Issuing Office:
Division of Pharmaceutical Quality Operations I
United States

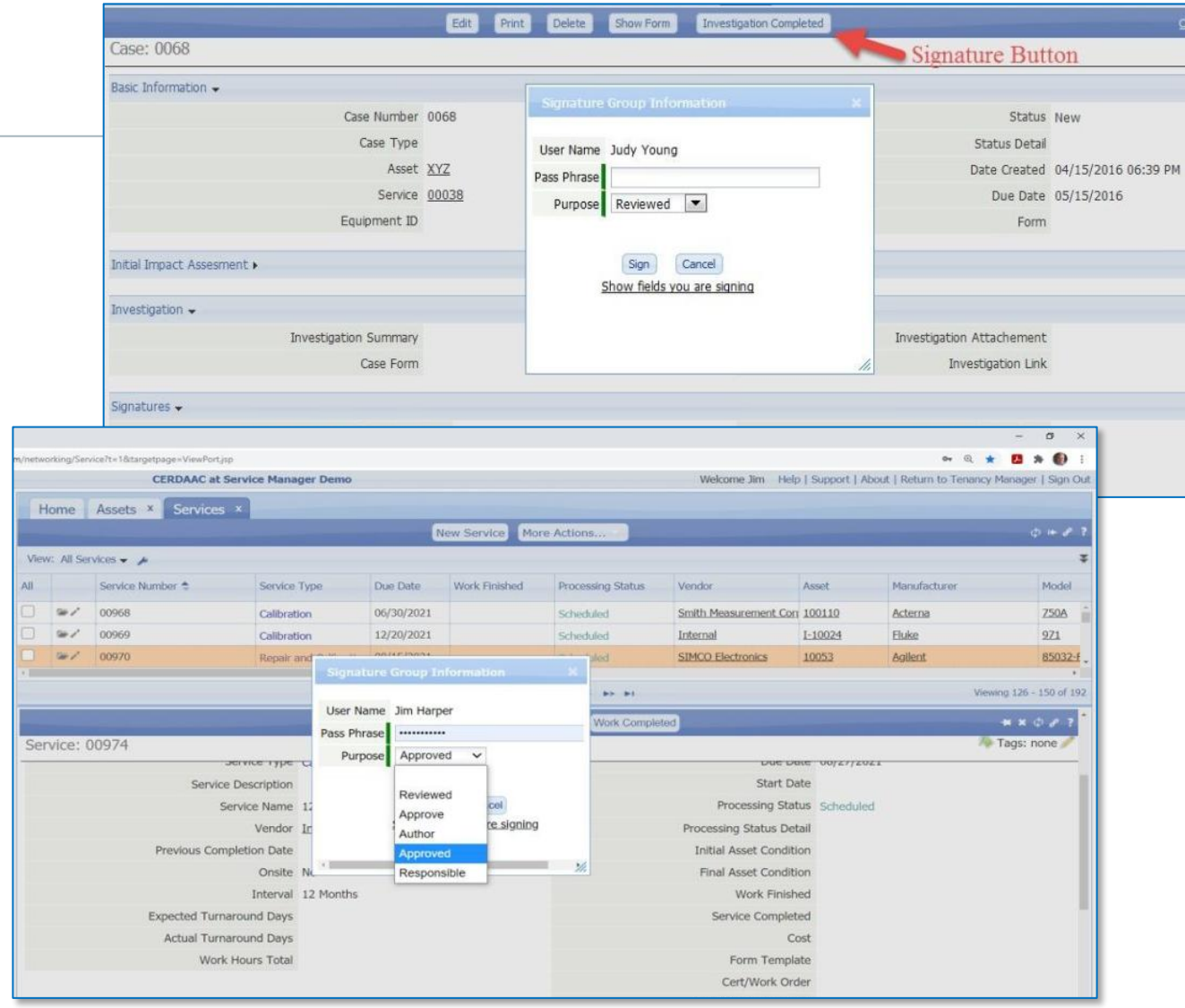
4. Failure to exercise sufficient controls over computerized systems to prevent unauthorized access or changes to data, and failure to have adequate controls to prevent omission of data.

Your firm lacks controls to assure the integrity of electronic test data generated by high performance liquid chromatography (HPLC) and gas chromatography (GC) systems. For example, during the inspection our investigator observed that stand-alone computers used to run an HPLC and a GC allowed analysts who test drug samples the ability to delete raw data files and alter date and time stamps. In addition, audit trails were not enabled, so there would be no way to determine whether analysts manipulated data.

Electronic Signatures

E-signatures can accelerate review and approval processes, BUT there are key requirements for FDA regulated manufacturers to make sure e-signatures are compliant:

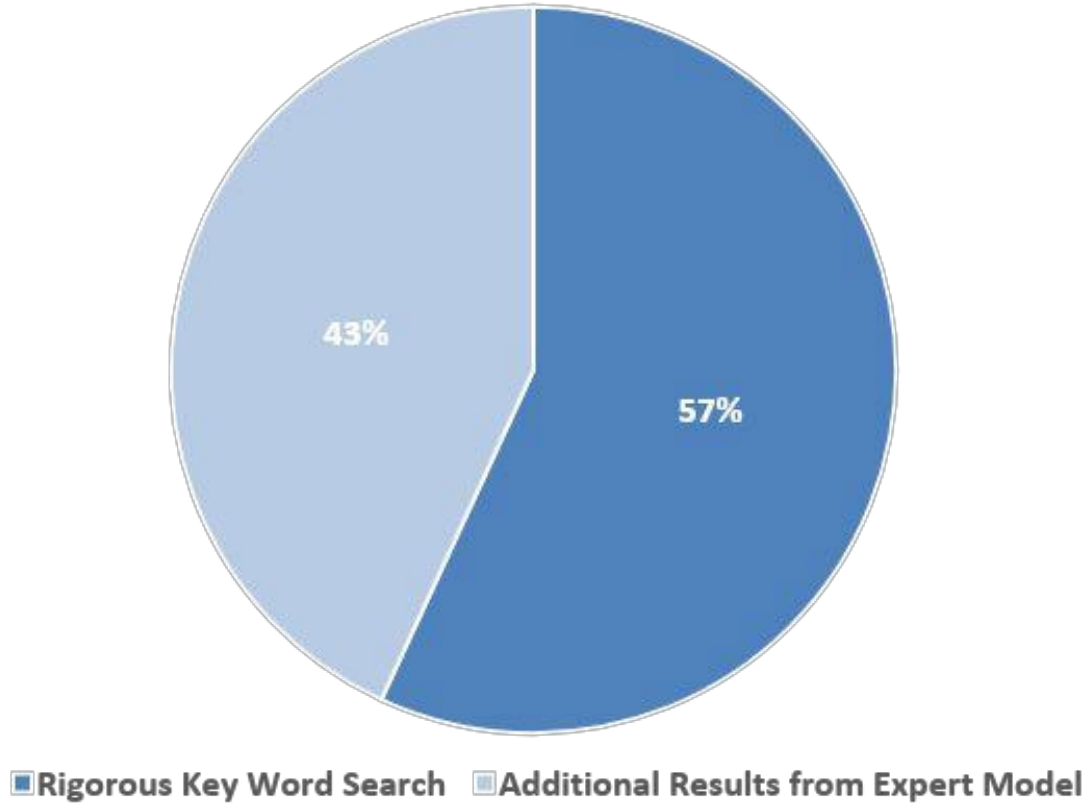
- Include printed name and date, as well as signature?
- Meaning of signature included? (review, approval, etc.)
- Are e-signatures linked to their respective electronic records?
- Cannot be cut, copied, falsified?
- Verification of signer's identity?
- Cannot be reused or reassigned?



5 Years of “Electronic Signatures” Observations

- Redica Systems’ Human Drug model shows nearly 300, 483 observations focused on “Electronic Signatures” in the last 5 years

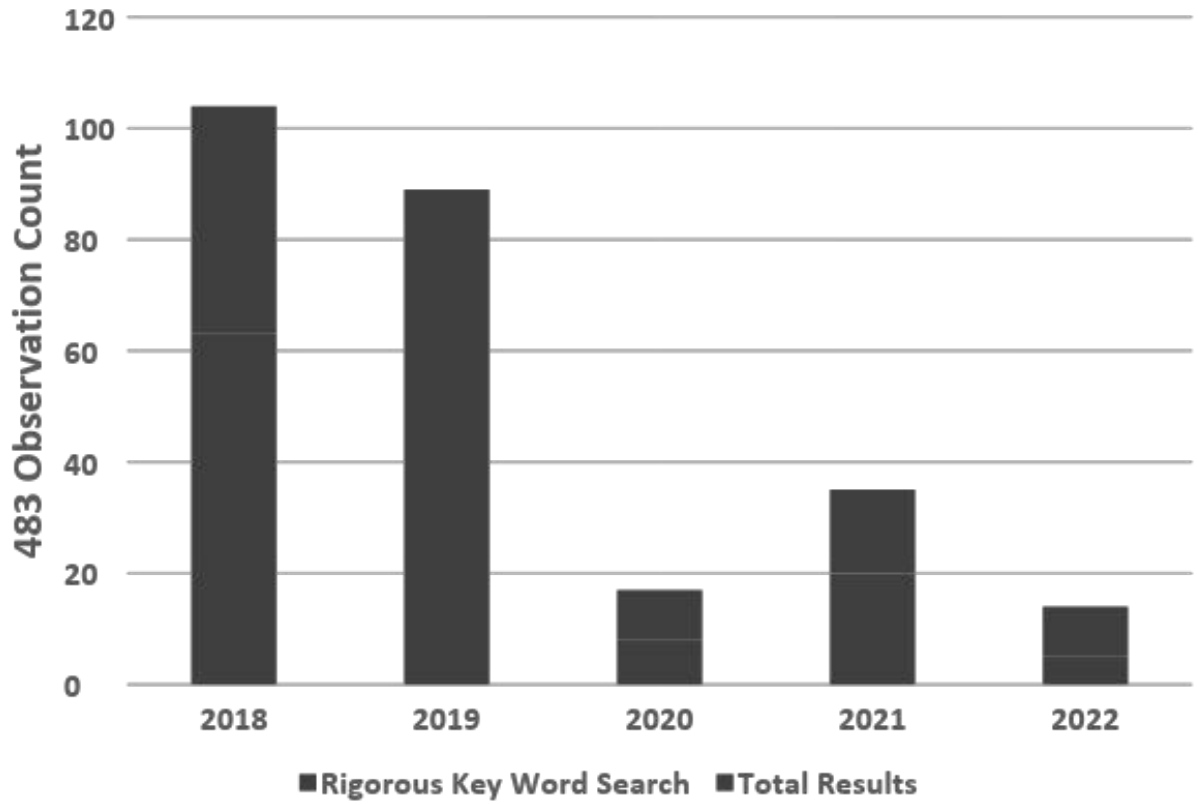
- 57% of “Electronic Signatures” 483 observations were identified with a rigorous keyword search, while 43% more were only identified by an expert model. This split is significantly higher than the other observations.



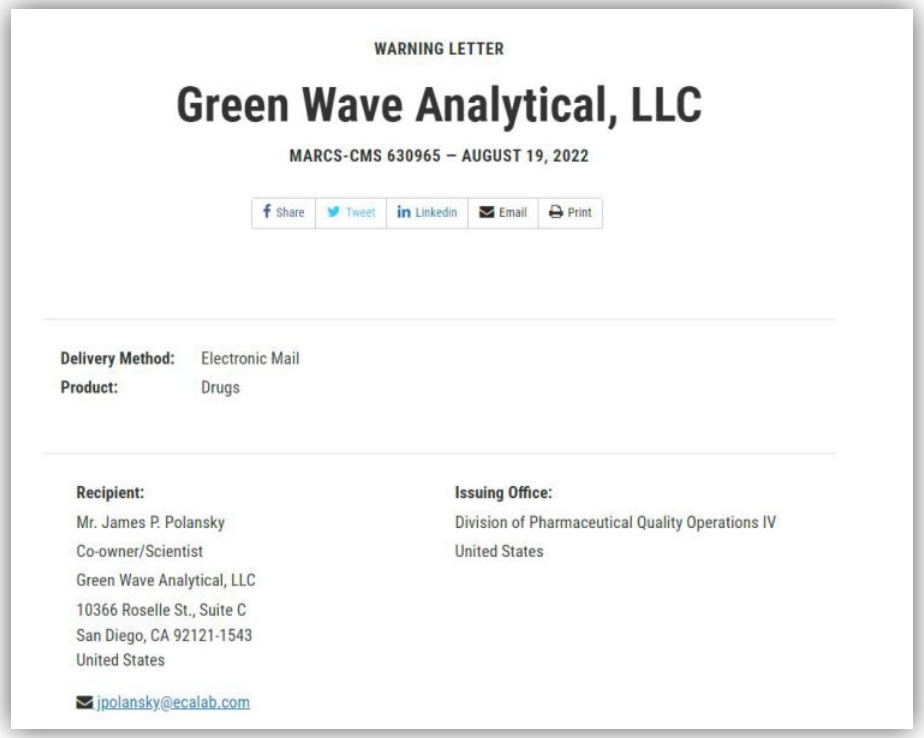
5 Years of “Electronic Signatures” Observations

- “Electronic Signatures” referenced 483 observations decreased 73% due to COVID

- USA vs International observations were even with 49% cited US companies while 51% cited International companies



FDA “Electronic Signature” Citation Example



WARNING LETTER

Green Wave Analytical, LLC

MARCS-CMS 630965 – AUGUST 19, 2022

Share Tweet Linkedin Email Print

Delivery Method: Electronic Mail
Product: Drugs

Recipient:
Mr. James P. Polansky
Co-owner/Scientist
Green Wave Analytical, LLC
10366 Roselle St., Suite C
San Diego, CA 92121-1543
United States

jpolansky@ecalab.com

Issuing Office:
Division of Pharmaceutical Quality Operations IV
United States

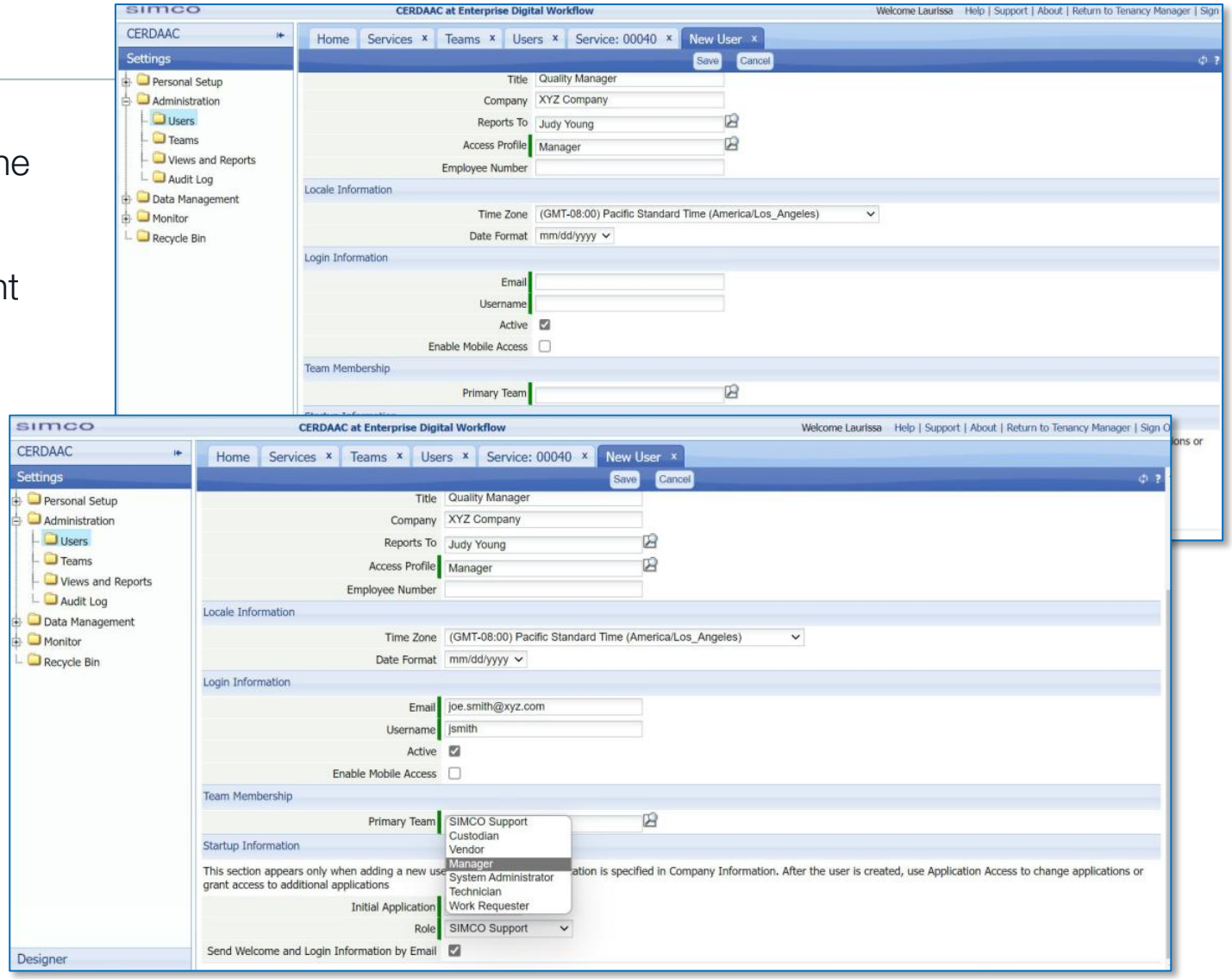
In addition, the HPLC instrument was found to be operating in the absence of an activated audit trail to record information about each analytical test, such as:

- Type of injection
- Date and time
- Identity of analyst
- Nature of action taken and reason

You also stated that data from the HPLC was not securely backed up and you did not review the HPLC audit trail data. In addition, you failed to validate electronic signatures used to approve analytical testing records for release testing of drugs performed from at least January 2020, to September 2021.

Access and Control

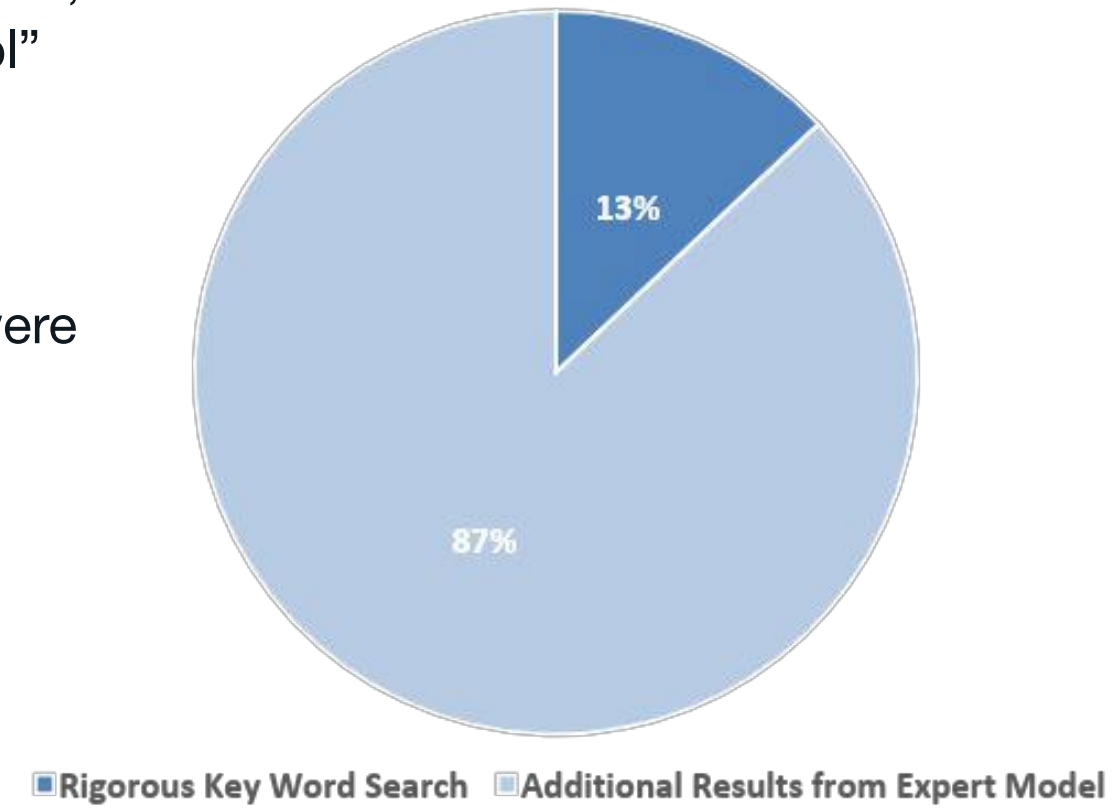
- Individual access control to confirm the identity of the person accessing the system?
- Sophisticated password security measures, frequent password updates, password expirations
- Procedures for recalling passwords
- Unauthorized access attempt notifications
- Loss management procedures for devices
- Controls for testing of devices



5 Years of “Access & Control” Observations

- Redica Systems’ Human Drug model shows 500+, 483 observations focused on “Access & Control” in the last 5 years

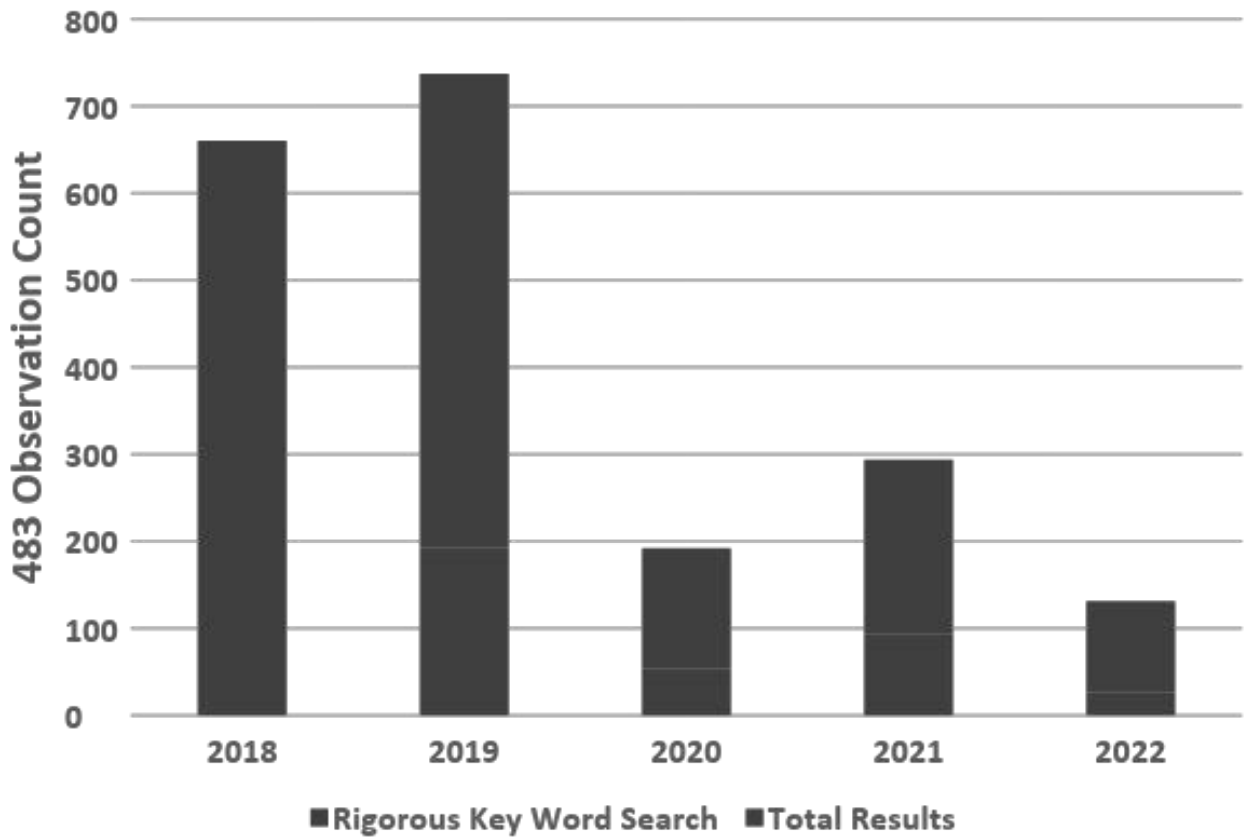
- 13% of “Access & Control” 483 observations were identified by a rigorous key word search, while 87% more were only identified by the expert model. This is the lowest number of keyword results across all 5 sections



5 Years of “Access & Control” Observations

- “Access & Control” referenced 483 observations decreased 71% due to COVID

- USA vs International observations were skewed with 71% cited US companies while 29% cited International companies



FDA “Access and Control” Citation Example

WARNING LETTER

Vi-Jon, LLC

MARCS-CMS 622087 – MARCH 31, 2022

Share Tweet Linkedin Email Print

Delivery Method: VIA UPS
Product: Drugs

Recipient:
Mr. Richard Koulouris
Chairman and CEO
Vi-Jon, LLC
8800 Page Avenue
St. Louis, MO 63114
United States

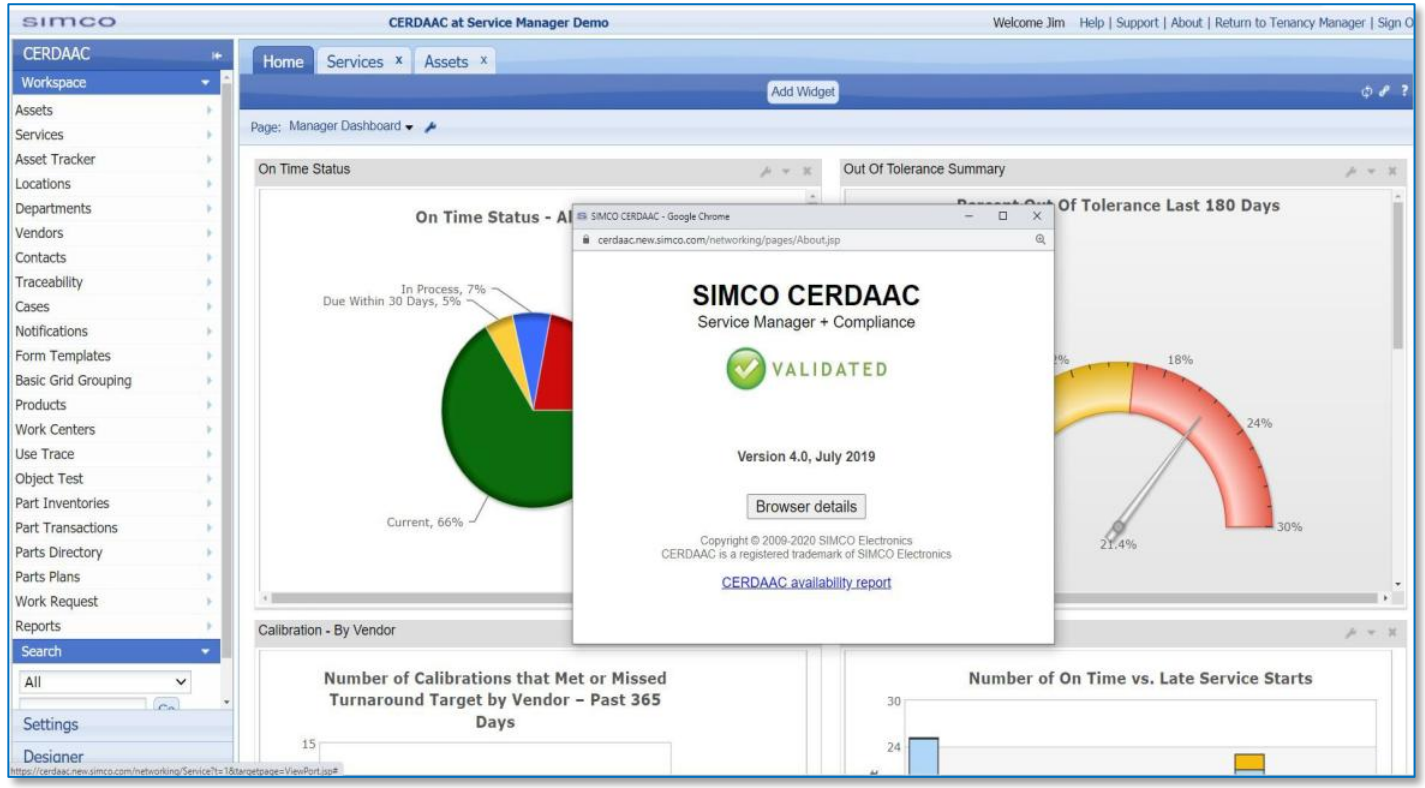
Issuing Office:
Division of Pharmaceutical Quality Operations III
United States

4. Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in the master production and control records, or other records (21 CFR 211.68(b)).

Your firm failed to implement adequate controls to support the integrity of your electronic data and to ensure that only appropriate individuals had administrative rights. For example, your **(b)(4)** microbiological testing instrument used for drug product release testing is controlled by a stand-alone computer which does not have appropriate controls in place to prevent deletion of raw laboratory data. All QU users utilized a shared generic account to access the computer which had administrative privileges capable of changing and deleting files. During the inspection, one of your employees opened the computer's recycle bin and noted that approximately **(b)(4)** files and folders were deleted. Further, these deleted items included at least **(b)(4)** files of the “**(b)(4)**” format which your personnel stated were most likely **(b)(4)** data files. The names of **(b)(4)** of those deleted files were similar to drug product formulas produced since 2017.

System Validation

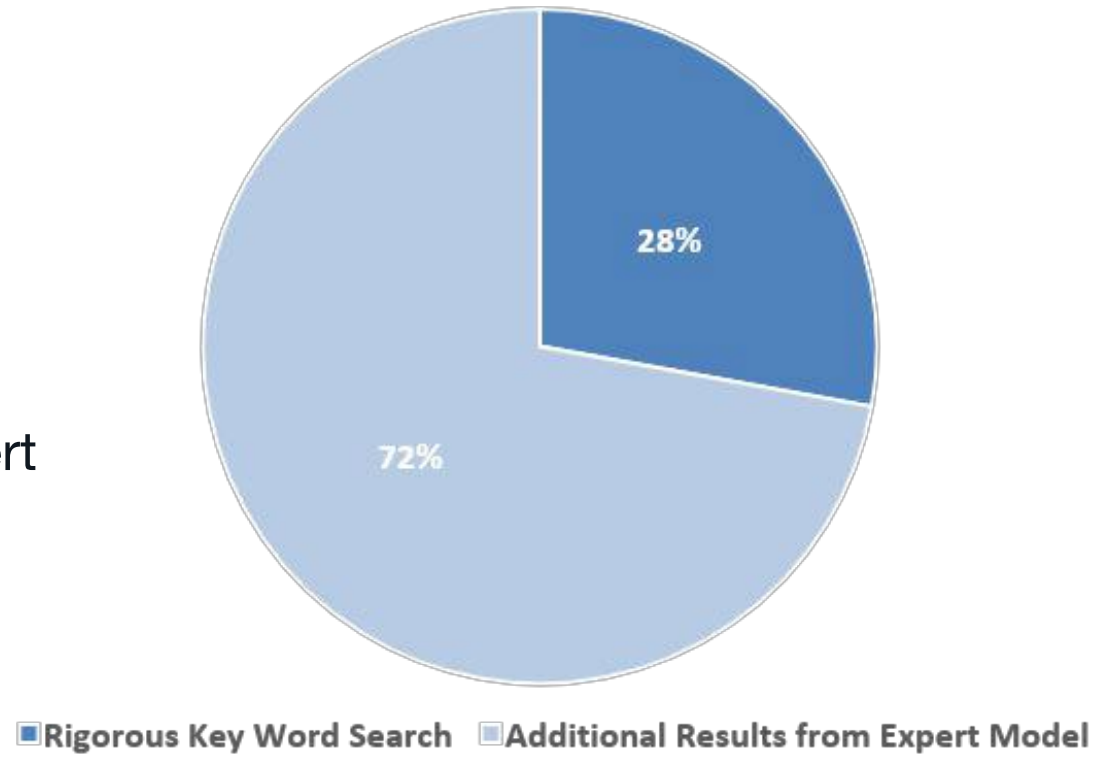
- Has the system been validated?
- The difference between "*validatable*" or *pre-validated?* The answer can save you considerable time and money!
- Does the system validate for:
  - IQ (Installation Qualification)
  - OQ (Operational Qualification)
  - PQ (Performance Qualification)—"Does This Process Produce the Right Result"? "Is This Process Safe and Consistent?"



5 Years of “System Validation” Observations

- Redica Systems’ Human Drug model shows nearly 2000, 483 observations focused on “System Validation” in the last 5 years

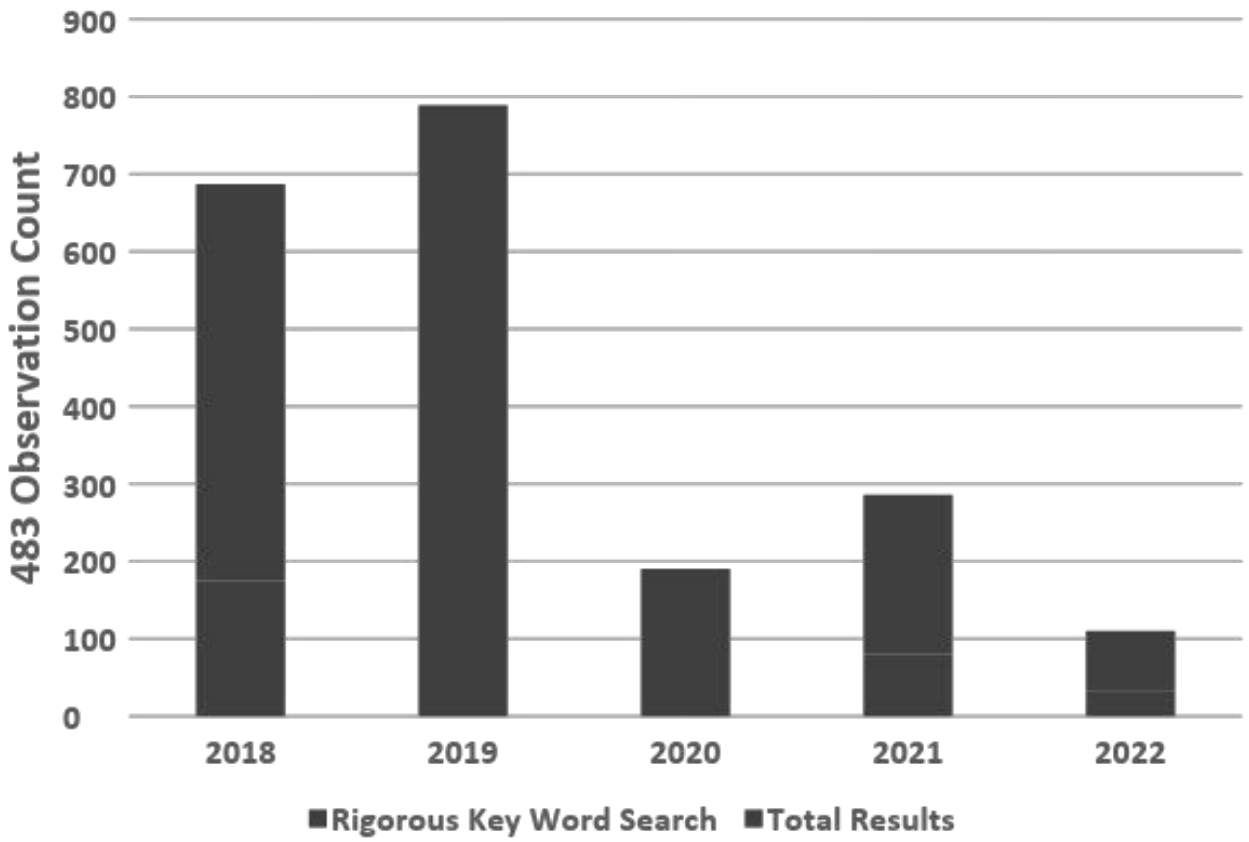
- 28% of “System Validation” 483 observations were identified by a rigorous key word search, while 72% more were only identified by the expert model



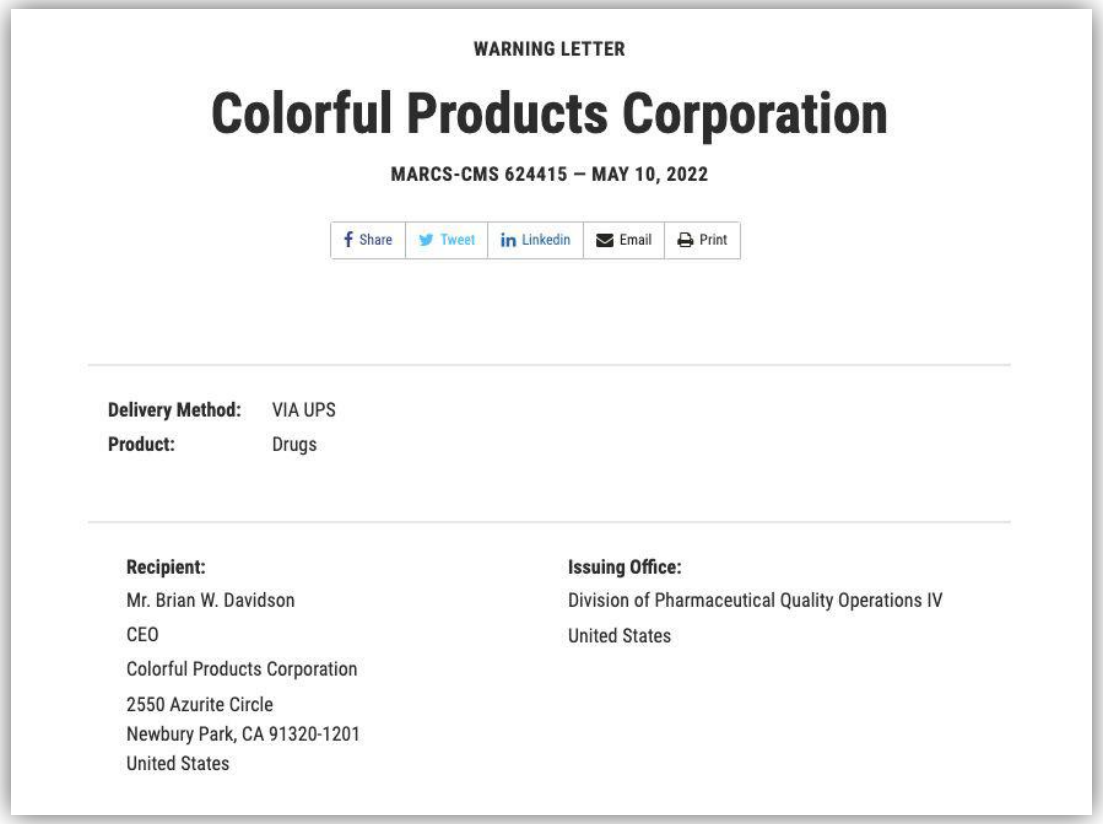
5 Years of “System Validation” Observations

- “System Validation” referenced 483 observations decreased 68% due to COVID

- USA vs International observations were slightly skewed with 60% cited US companies while 40% cited International companies



FDA “Software Validation” Citation Example



WARNING LETTER

Colorful Products Corporation

MARCS-CMS 624415 – MAY 10, 2022

Share | Tweet | Linkedin | Email | Print

Delivery Method: VIA UPS
Product: Drugs

Recipient:
Mr. Brian W. Davidson
CEO
Colorful Products Corporation
2550 Azurite Circle
Newbury Park, CA 91320-1201
United States

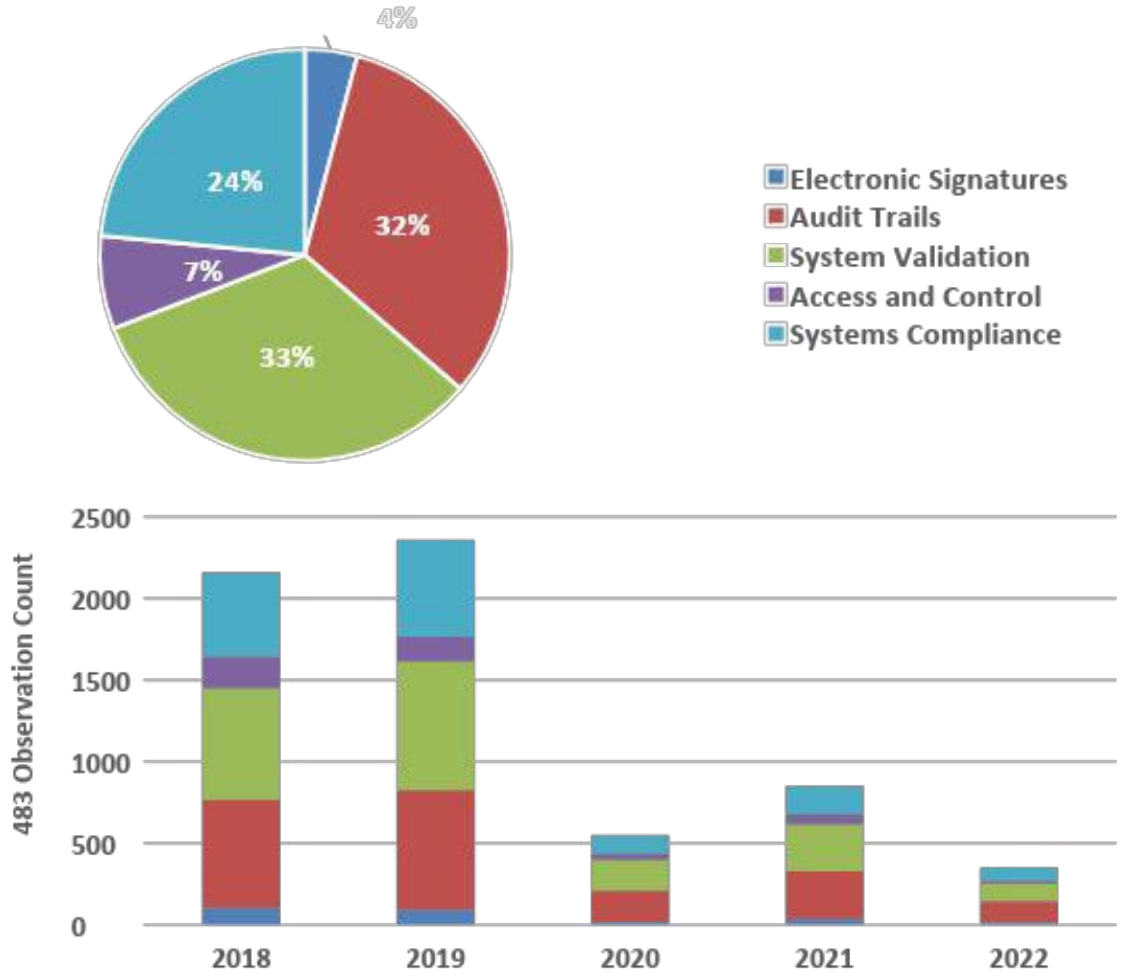
Issuing Office:
Division of Pharmaceutical Quality Operations IV
United States

4. Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records. (21 CFR 211.68(b)).

Your firm lacked controls to assure the integrity of **(b)(4)** used in the manufacturing of your drug products. For example, your firm utilized software (i.e., **(b)(4)**) for the retention of data, including your drug product formulations and the quarantine and release status of drug products. This software is also used to document the completion of manufacturing steps on batch records, including **(b)(4)** amounts, manufacturing activities, and calculations. You stated to our investigator that this **(b)(4)** software was not validated and lacked audit trails.

Summary of 5 Years of 483 Observations

- FDA 21 CFR Part 11 Compliance was cited more than 6,250 times in the last 5 years
- “System Validation” and “Audit Trails” were observed the most frequent
- “Electronic Signatures” was cited the least
- COVID caused a 69% decrease in Human Drug 483 observations



CERDAAC: Ensures FDA 21 CFR Part 11 Compliance without Increasing Costs:

Purpose-built for highly regulated industries:

- 16 of the top 20 global life sciences companies
- 14 of the top 20 global aerospace & defense companies
- 60 years in business
- 15M+ services performed

- FDA 21 CFR Part 11 Compliant: e-signatures, workflows, records, data, etc.
- **Prevalidated** system saves you time and money
- Manage quality and compliance of assets, people and processes
- Cloud solution makes it easy to access, deploy, and maintain
- Highly configurable to your business needs
- Easy to use
- Secure, controlled access

Thank you for attending!
“The Insider’s Guide to Audit Readiness”

Jerry Chapman
Senior GMP Quality Expert,
Redica Systems
jerry.chapman@redica.com

Sam Klooster
VP of Software,
SIMCO
sam.klooster@simco.com

Does anyone have any questions?