A Fresh Take on Pre-Approval Inspection Data

Michael de la Torre

CEO, Redica Systems

Is this webinar for you?

- You're asking- What's a PAI?
- You don't like data
- You came for the Starbucks gift card (hint: there is no gift card)

You work in GxP quality for Life Sciences (or consulting) and you like data!

- ✔ Compliance
- ✔ Inspection Prep
- ✔ Vendor Quality
- ✔ Training
- ✔ …

What we will cover

1. Quick Background (2 min)
2. PAI inspection volume trends pre and post COVID
3. 483 issuance rate trends by inspection type and region
4. Differences between FDA investigators on PAI inspections
5. Top Issues cited on 483 Observations, with examples
6. Prevalence of potentially critical issues on PAI inspections
7. A short Redica commercial of how we work with Life Sciences

Who is Redica Systems?

Redica Systems - Quality and Regulatory Intelligence data analytics platform serves over 200 life sciences companies - from clinical-stage biotech to the largest global sponsors. Our customers rely on our comprehensive data sets to enable a fact-based approach to inspection preparation, vendor quality, and regulatory surveillance.

Representative customers

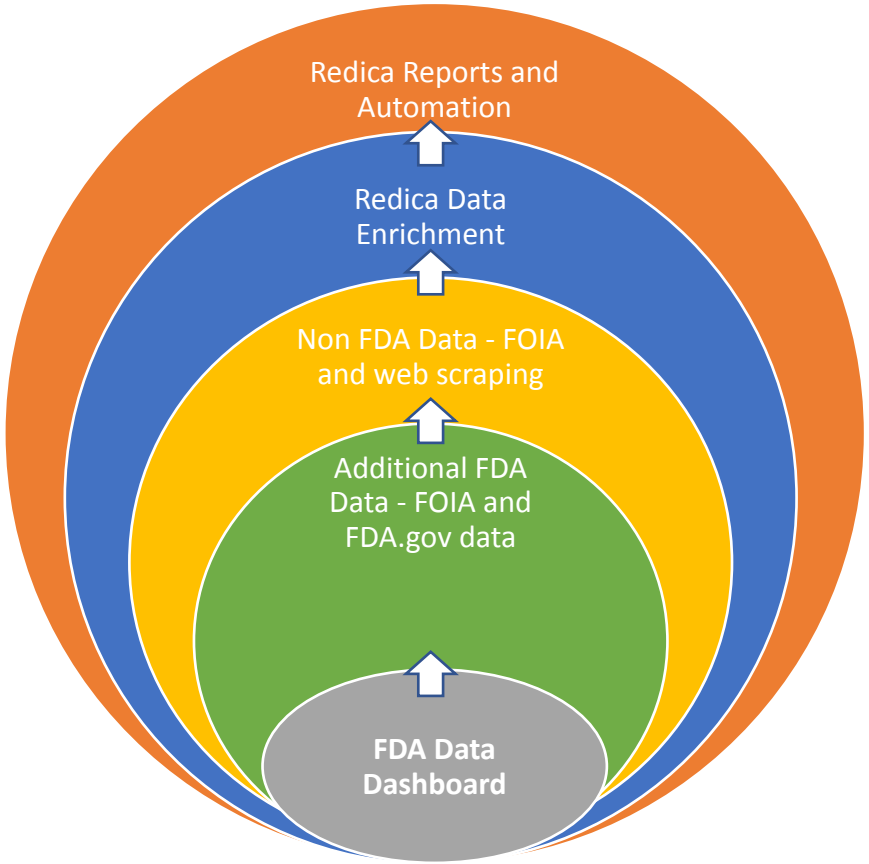
moderna, AstraZeneca, AMGEN, novo nordisk, abbvie, J&J, Seagen, Lonza, patheon by Thermo Fisher Scientific, AGC Biologics, bluebirdbio, Kite A GILEAD Company, GBT, HERON THERAPEUTICS, KRONOS BIO

Unmatched data sets

FDA, European Medicines Agency, MHRA Regulating Medicines and Medical Devices, Health Canada, ICH harmonisation for better health, ISO

- >15,000 regulatory and standards monitored daily from 200 agencies
- >1m regulatory inspections
- >25,000 Form 483s
- >17,000 Warning letters
- >16,000 EIRs and 483 Responses
- >35,000 EMA inspections and docs
- >1,500 MHRA GMP post-inspection reports
- >20,000 Health Canada inspections and docs

What you will see today: Unmatched Data



Non-FDA Data

- EMA 35k inspections and reports
- MHRA 4.5k inspection documents
- Health Canada 20k inspections and CRC Citations

FDA Data Comparison

- Inspections 256k 890k
- Inspection Documents 3k 59k
- Retyped 483 Observations 0 110k
- Inspection Reason 0 215k
- Inspector Name 0 7k

Since most of our data comes from FOIA - you are going to see data and analytics that you never knew existed…

A special thank you

Jerry Chapman – Human Dugs GMP labeling models and his sage wisdom

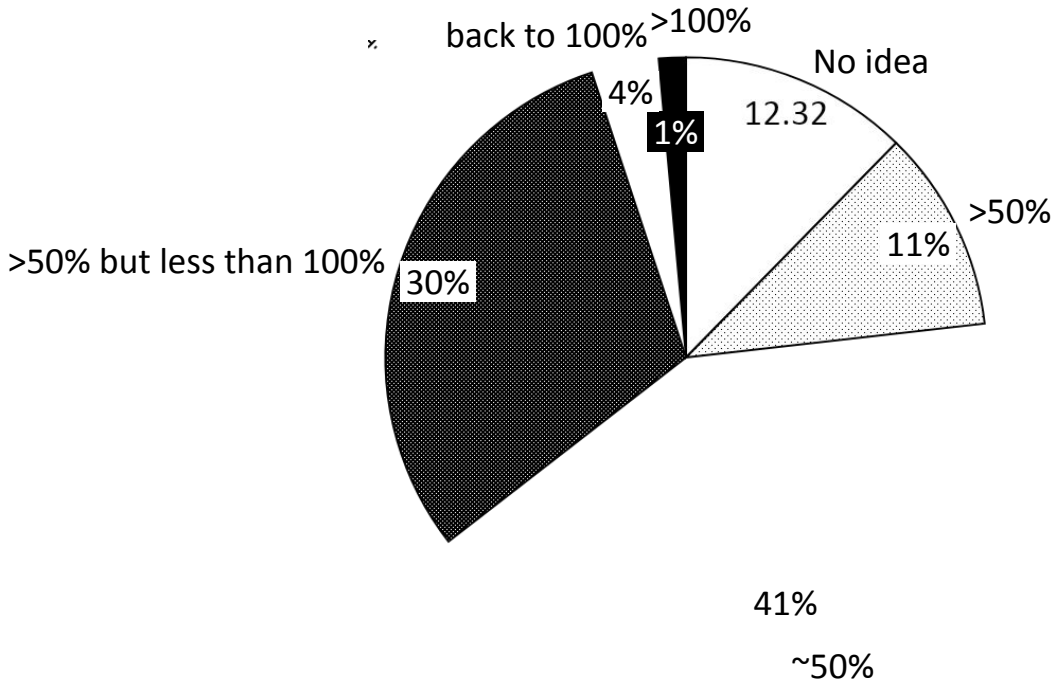
Jason Kerr – data wrangling, Inspection trends and analytics

Barb Unger – Inspection trends and analytics and mentoring

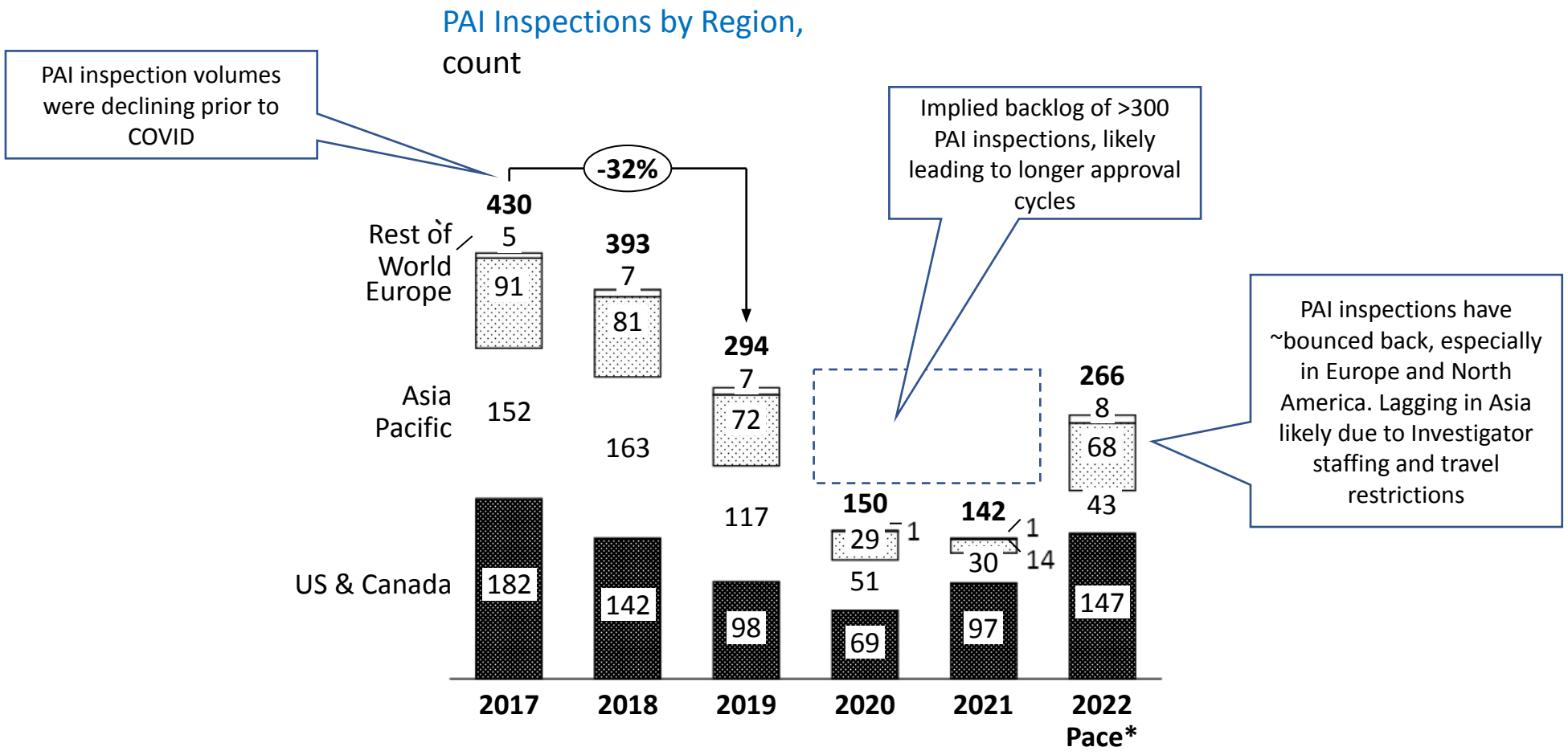
Webinar Question 1

The FDA drastically cut back PAI activity during COVID. How much do you think they bounced back? (ex: 50% back to pre-covid levels, 75% or more than pre-covid)

138 Responses



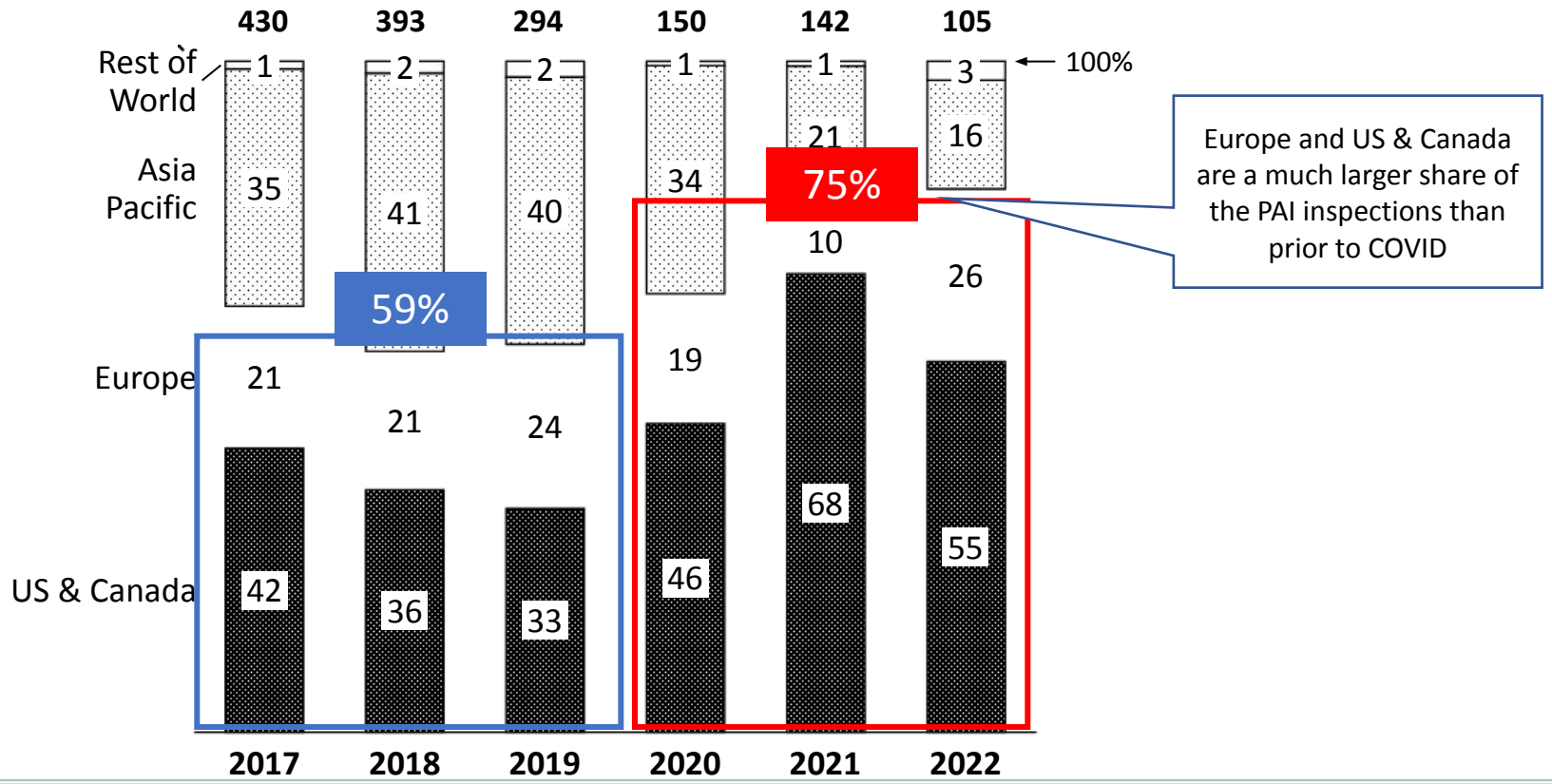
PAI Inspection volume was dropping before COVID and fully bounced back (and then some) in North America and Europe



* 105 PAI Inspections year-to-date as of 5/25/22

US & Canada is a much larger share of PAIs since COVID

PAI Inspections by Region,
percent

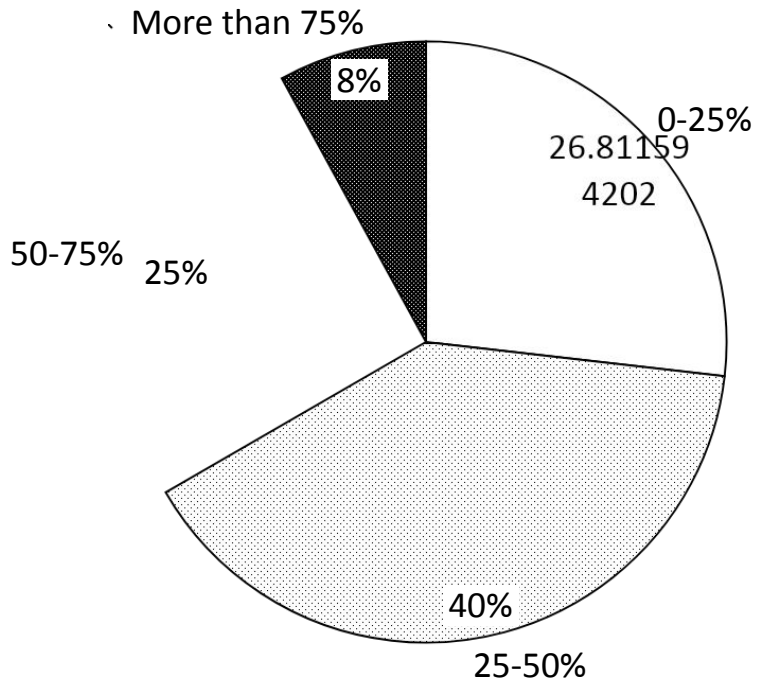


FDA - Human Drugs only, data through 5/25/22

Webinar Question 2

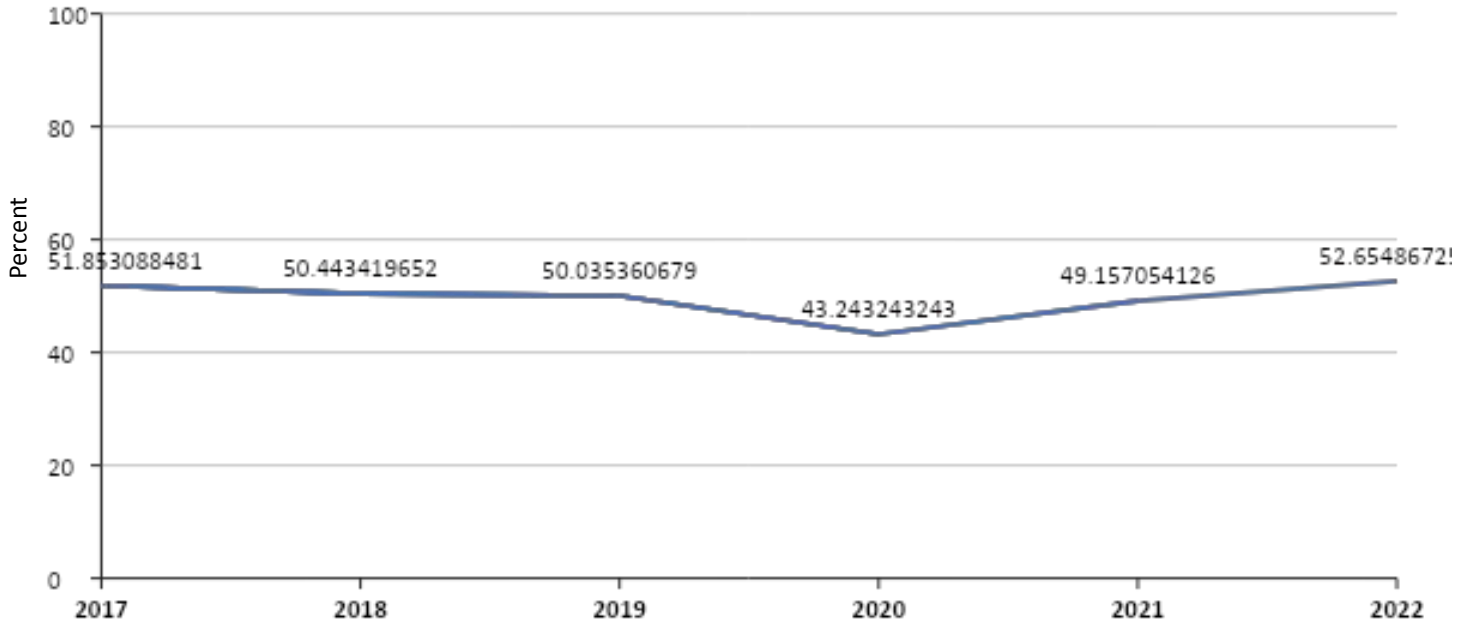
What do you think the 483 issuance rate is on PAI Inspections?

138 Responses



Not much change in 483 issuance rate… but is that all to the story?

483 Issuance Rate for Human Drug Inspections
(percent)

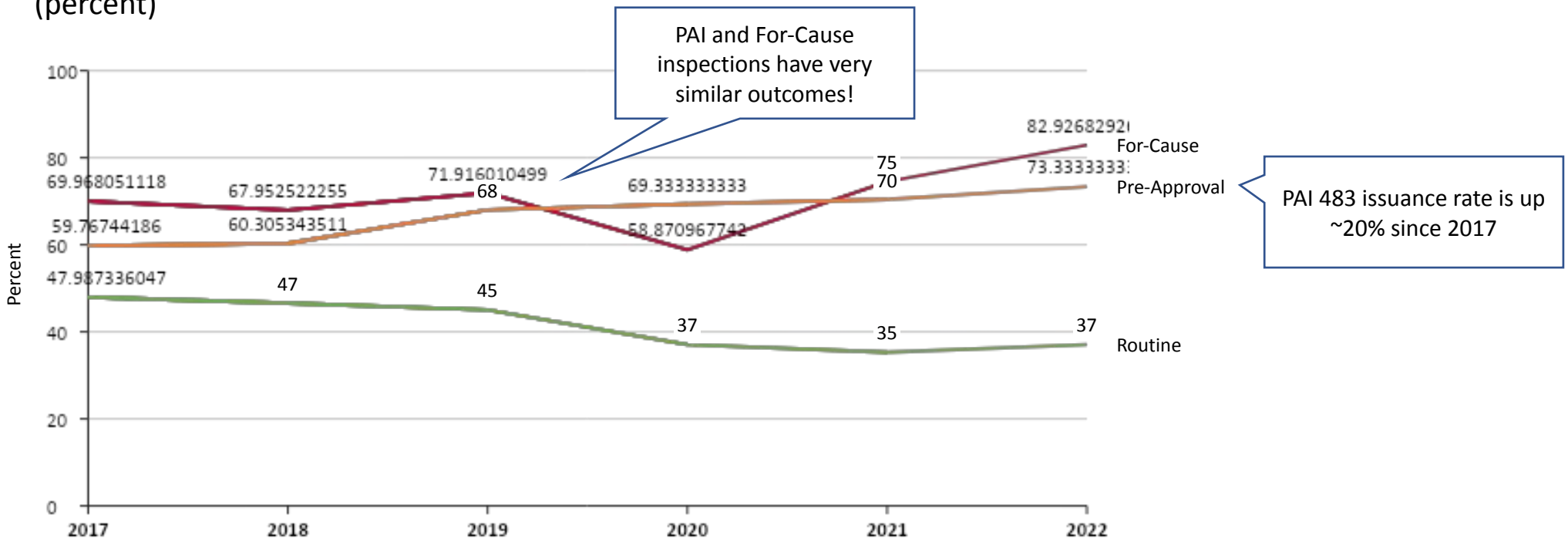


FDA - Human Drugs only, data through 5/25/22

… it is a more interesting picture when you separate the data by inspection reason!

483 Issuance Rate for Human Drug Inspections by Inspection Type

(percent)

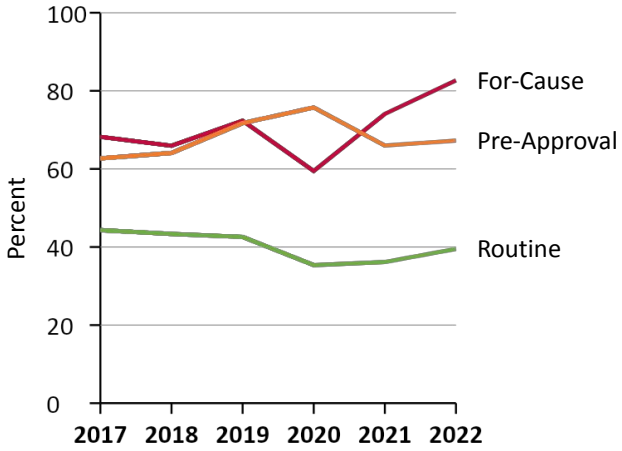


FDA - Human Drugs only, data through 5/25/22

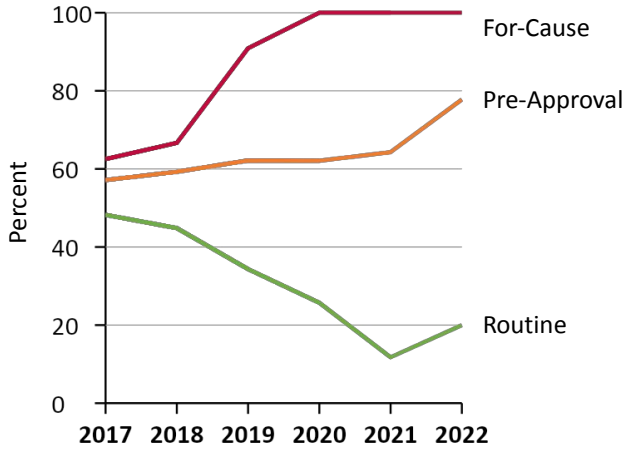
… and the trends hold across all regions

483 Issuance Rate by Inspection Type, by Region
(percent)

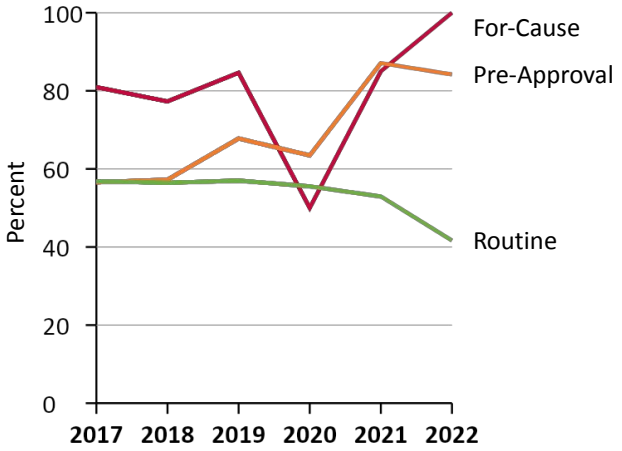
North America



Europe



Asia Pacific

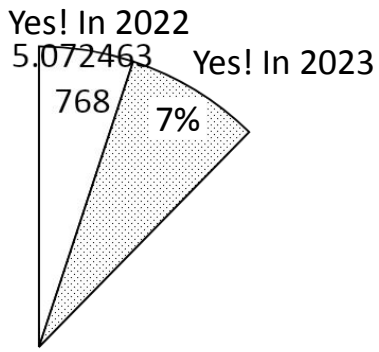


FDA - Human Drugs only, data through 5/25/22

Webinar Question 3

Do you have an upcoming PDUFA date? If so, when?

138 Responses



88%
N
o

Bonus Question 1

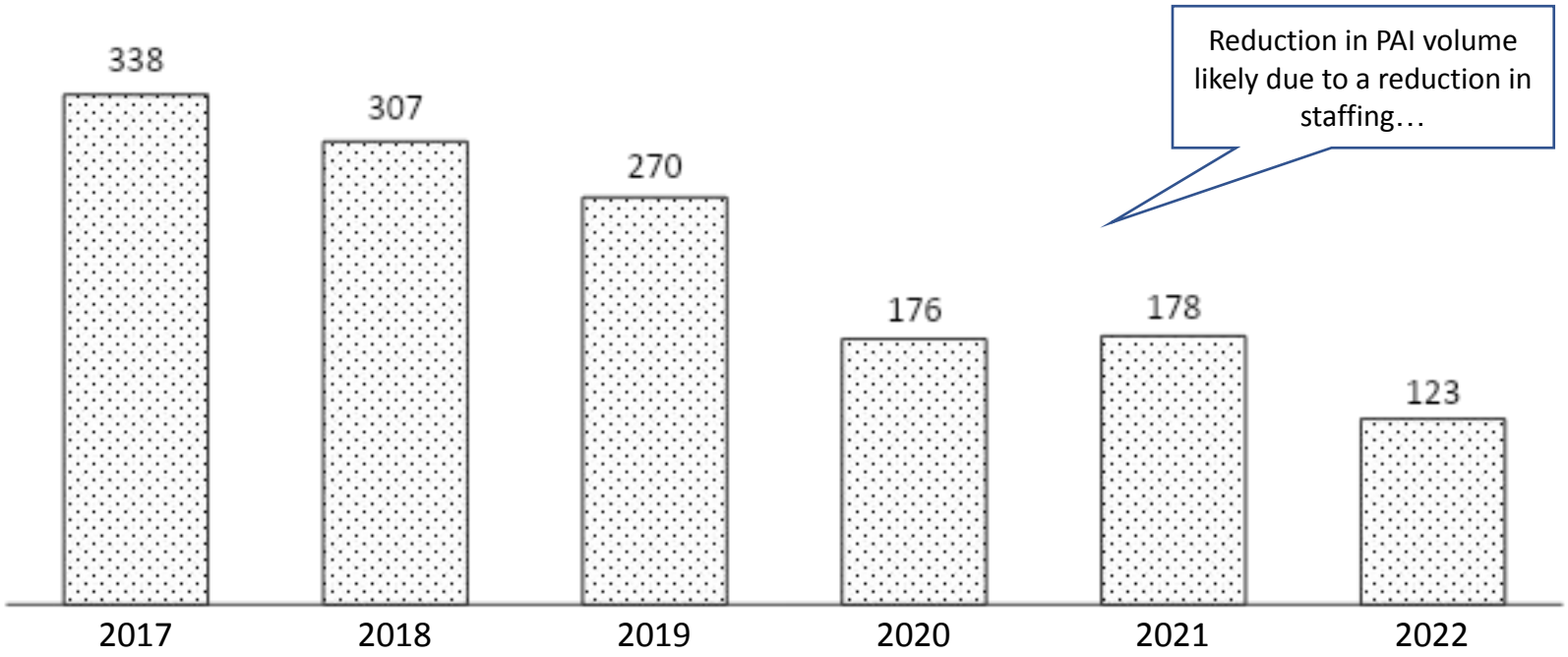
Does my specific inspector matter?

(or maybe)

How big are the differences between inspectors?

Many FDA inspectors could be your inspector, but how different could they be?

Unique FDA Inspectors active in that given year,
count

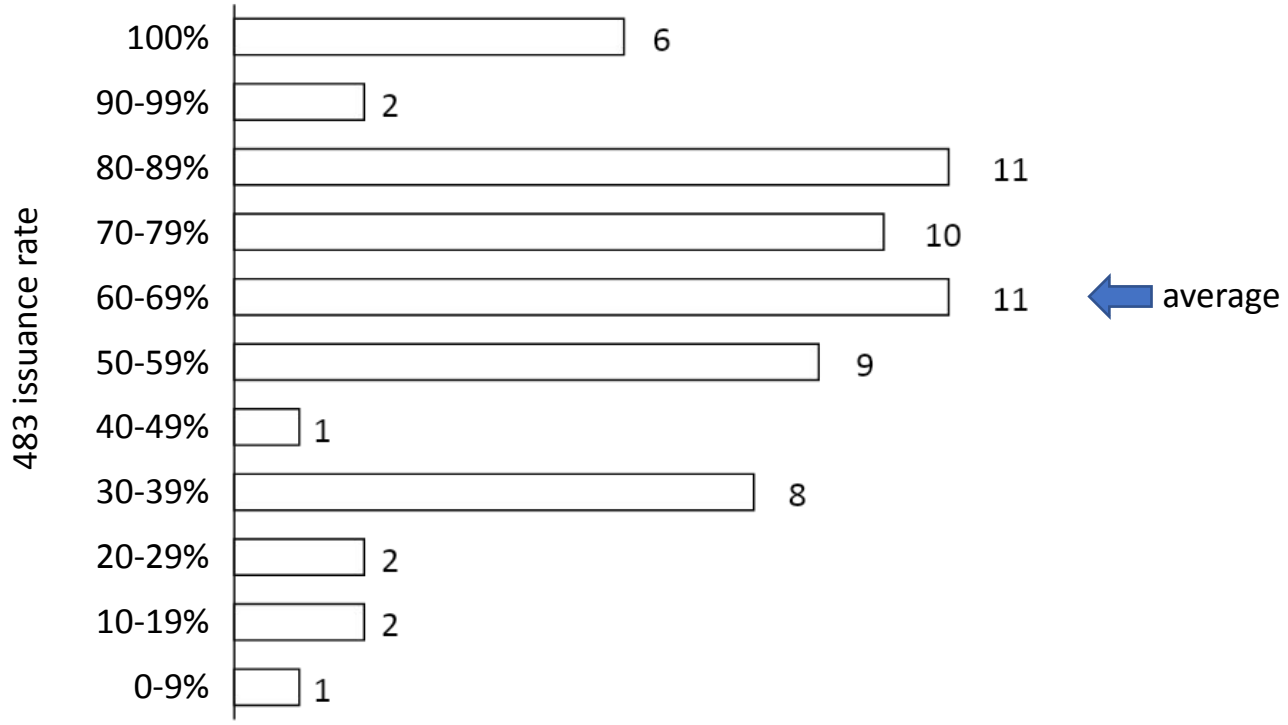


Human Drugs and Biologics inspections(with HCT/P facilities removed)

My stats professor always said to “be afraid of averages”

62 inspectors with 8+ PAIs since 2017

Top PAI inspectors by 483 issuance range (2017-2022), count



FDA - Human Drugs only, data through 5/25/22

Bonus Question 2

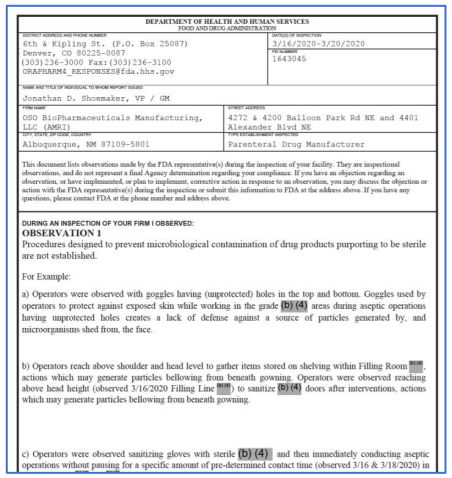
What are the top findings on PAI inspections?

(and)

Are the findings “garden variety” or potentially critical?

How did we do it? We then enriched our data with **proprietary ML models**

483 Observation/ Warning Letter Deficiency Mapping to Quality Systems



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FOOD AND DRUG ADMINISTRATION

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3/16/2020-3/20/2020

1643045

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4272 & 4200 Balloon Park Rd NE and 4401 Alexander Blvd NE

Albuquerque, NM 87109-5801

Parenteral 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 OBSERVED:

OBSERVATION 1

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established.

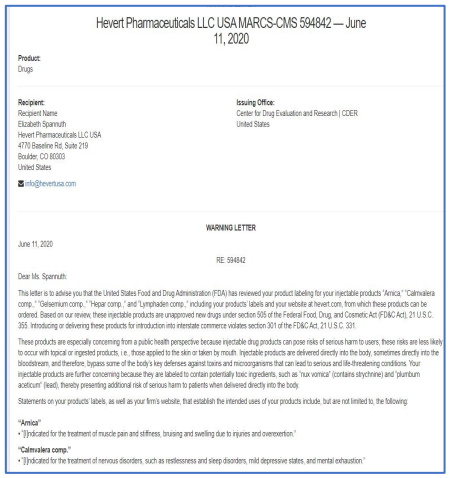
For Example:

a) Operators were observed with goggles having (unprotected) holes in the top and bottom. Goggles used by operators to protect against exposed skin while working in the grade (b) (4) areas during aseptic operations having unprotected holes creates a lack of defense against a source of particles generated by, and microorganisms shed from, the face.

b) Operators reach above shoulder and head level to gather items stored on shelving within Filling Room (b) (4), actions which may generate particles bellowing from beneath gowning. Operators were observed reaching above head height (observed 3/16/2020 Filling Line (b) (4)) to sanitize (b) (4) doors after interventions, actions which may generate particles bellowing from beneath gowning.

c) Operators were observed sanitizing gloves with sterile (b) (4) and then immediately conducting aseptic operations without pausing for a specific amount of pre-determined contact time (observed 3/16 & 3/18/2020) in

FDA 483s



Hevert Pharmaceuticals LLC USA MARCS-CMS 594842 — June 11, 2020

Product:
Drugs

Recipient:
Recipient Name
Elizabeth Spannuth
Hevert Pharmaceuticals LLC USA
4770 Baseline Rd, Suite 219
Boulder, CO 80303
United States

Issuing Office:
Center for Drug Evaluation and Research | CDER
United States

WARNING LETTER

RE: 594842

June 11, 2020

Dear Ms. Spannuth:

This letter is to advise you that the United States Food and Drug Administration (FDA) has reviewed your product labeling for your injectable products "Arnica," "Calmvalera comp.," "Gelsemium comp.," "Hepar comp.," and "Lymphaden comp.," including your products' labels and your website at hevert.com, from which these products can be ordered. Based on our review, these injectable products are unapproved new drugs under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355. Introducing or delivering these products for introduction into interstate commerce violates section 301 of the FD&C Act, 21 U.S.C. 331.

These products are especially concerning from a public health perspective because injectable drug products can pose risks of serious harm to users; these risks are less likely to occur with topical or ingested products, i.e., those applied to the skin or taken by mouth. Injectable products are delivered directly into the body, sometimes directly into the bloodstream, and therefore, bypass some of the body's key defenses against toxins and microorganisms that can lead to serious and life-threatening conditions. Your injectable products are further concerning because they are labeled to contain potentially toxic ingredients, such as "nux vomica" (contains strychnine) and "plumbum aceticum" (lead), thereby presenting additional risk of serious harm to patients when delivered directly into the body.

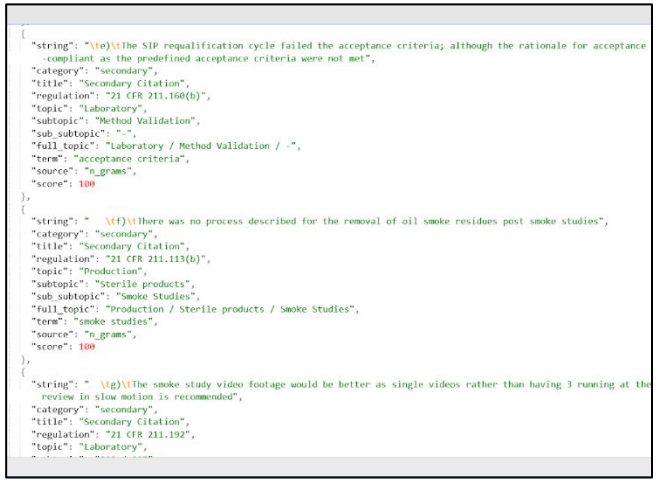
Statements on your products' labels, as well as your firm's website, that establish the intended uses of your products include, but are not limited to, the following:

"Arnica"
• "[i]ndicated for the treatment of muscle pain and stiffness, bruising and swelling due to injuries and overexertion."

"Calmvalera comp."
• "[i]ndicated for the treatment of nervous disorders, such as restlessness and sleep disorders, mild depressive states, and mental exhaustion."

FDA Warning Letters

Tagging and Scoring Models

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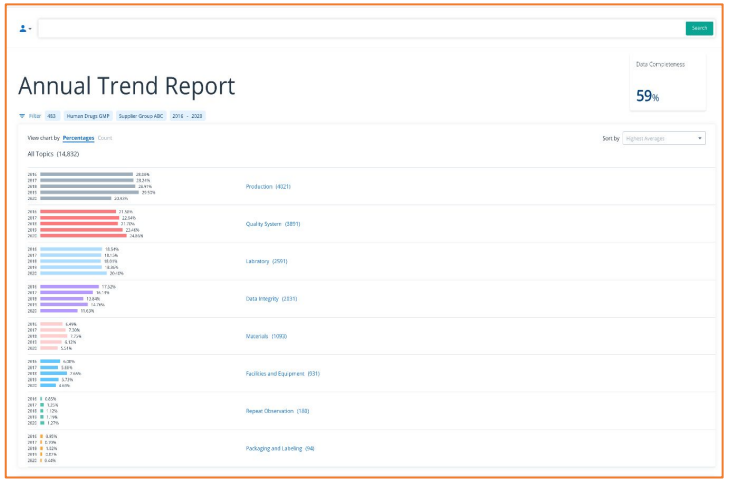
Human Drugs GMP, based on the following regulatory frameworks

- 6 Quality Systems + Data Integrity
- 21 CFR 211, EUDRALEX, HC CRC Codes, ICH Q7

Visual Output



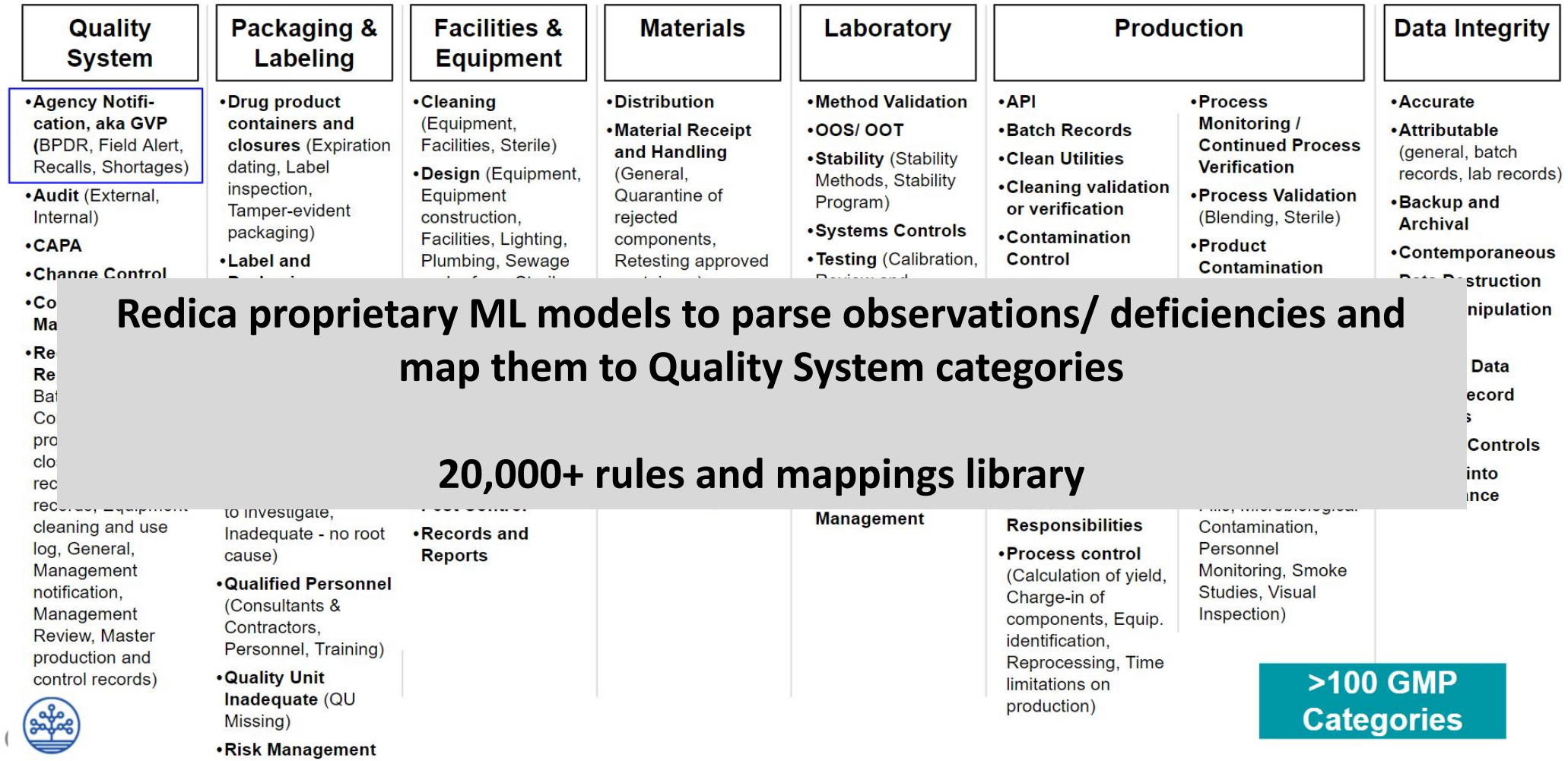
Annual Trend Report

59%

All Topics (14,832)

Redica created proprietary ML models to parse observations/ deficiencies and map them to Quality System categories

How we did it: Redica Quality System Labels for **Human Drug GMP**



How we did it: >1,500 PAI Observations analyzed (from >400 FDA 483s)

483 Observation Mapping to Quality Systems

Primary Issue(s)	Secondary Issue(s)	Primary Inferred Code(s)	Secondary Inferred Code(s)	Content
Quality System > Deviations / Investigations	Materials > Material Sampling and Testing | Production > Sterile Products > Environmental Monitoring | Quality System > CAPAs | Production > Sterile Products > Microbiological Contamination | Quality System > Deviations / Investigations | Quality System > Records and Reports > Batch Release | Laboratory > OOS / OOT | Laboratory > Stability > Stability Program | Repeat Observation	21 CFR 211.192	21 CFR 211.84(a) | 21 CFR 211.42(c)(10)(iv) | 21 CFR 211.192 | 21 CFR 211.113(b) | 21 CFR 211.192 | 21 CFR 211.192 | 21 CFR 211.113(b) | 21 CFR 211.42(c)(10)(iv) | 21 CFR 211.84(a) | 21 CFR 211.192 | 21 CFR 211.192 | 21 CFR 211.113(b) | 21 CFR 211.42(c)(10)(iv)	OBSERVATION 1 There is a failure to thoroughly review any unexplained discrepancy whether or not the batch has been already distributed. Specifically, A. Investigations into rejections of the raw material(b)(4)~~due to microbial contamination with Acinetobacter species, Klebsiella species, and Pseudomonas species have not been thorough to identify root causes and implement preventive actions to prevent the recurrence of microbial rejections of raw materials and finished drug products. 14-CAPA-005 was initiated 08/15/2014 and documented(b)(4)~~had been rejected for Acinetobacter species once in 2010, twice in 2012, four times in 2013, and six times in
Quality System > Deviations / Investigations	Production > Sterile Products > Environmental Monitoring | Laboratory > Testing > Routine Testing | Data Integrity > Original Data | Quality System > Deviations / Investigations | Quality System > Records and Reports > Procedures | Materials > Material Sampling and Testing	21 CFR 211.192	21 CFR 211.42(c)(10)(iv) | 21 CFR 211.165(a) | 21 CFR 211.194(a) | 21 CFR 211.192 | 21 CFR 211.100(b) | 21 CFR 211.194(a) | 21 CFR 211.100(b) | 21 CFR 211.192 | 21 CFR 211.84(a)	OBSERVATION 2 Investigations of an unexplained discrepancy did not extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy. Specifically, A. Nystatin Oral Solution lots LTU1110 (3/29/2019), UV1026 (2/11/2020), UV1176

SAMPLE DOWNLOADABLE OUTPUT

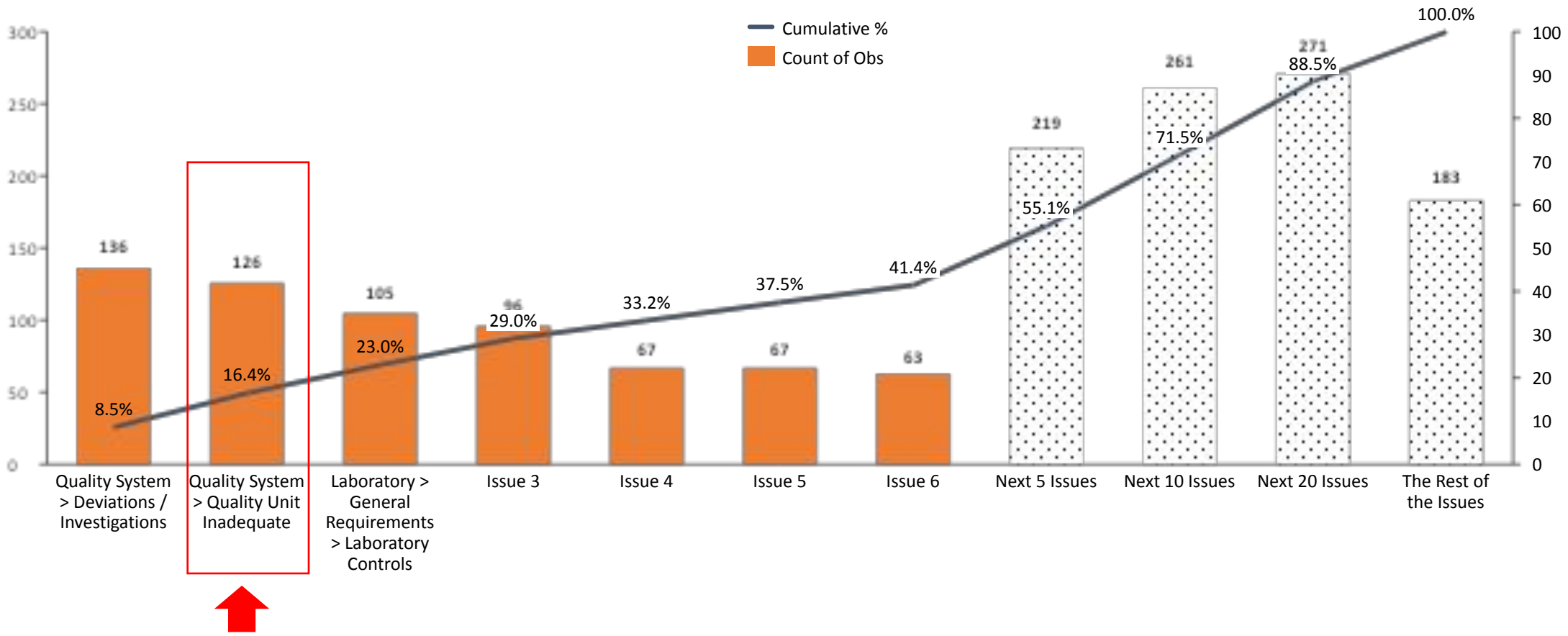
Quality System Labels

Inferred CFR codes from Observation text

Retyped Observation text

Sample: the top 6 issues account for ~41% of the Observational findings

Redica Human Drug GMP Labels on PAI Inspections (~400 483s analyzed),
Observation Count, %



FDA - Human Drugs only, data through 5/25/22

Quality Unit Inadequate!?!?

"The Quality Unit is responsible for the review and approval of all SOPs and ensuring the appropriate SOPs are in place. If there are bad SOP or do not exist, the Quality Unit is not doing its job." Jerry Chapman

Top 10 Global Sponsor

2. There are **no written procedures for production and process controls designed** to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to posses.…

Top 10 Global Sponsor/ Generics Firm

OBSERVATION 1
The **responsibilities and procedures applicable to the quality control unit are not fully followed**.

Specifically,

Your Quality Unit (QU) failed to fulfill its duties and responsibilities as outlined in SOP xxxxxxxx, Site Quality Unit Charter, as it did not provide adequate oversight and assurance that all operations, procedures, and systems were in conformance with appropriate regulations and standards.

OBSERVATION 3

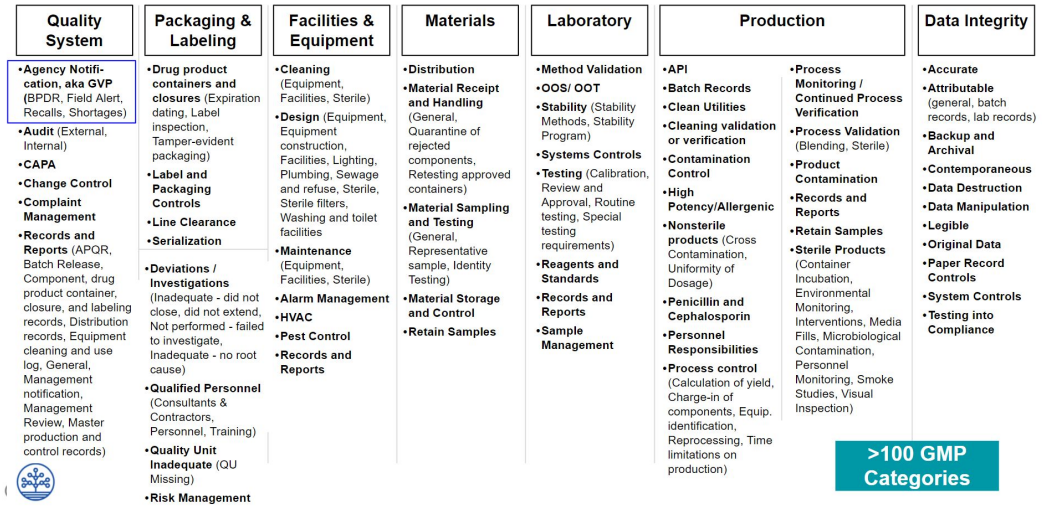
The responsibilities and procedures applicable to the quality control unit are not in writing and fully followed.

Specifically, **your quality unit failed to draft and/or adequately implement standard operating procedures related to quality assurance**, controlled issuance of production and control records and other GMP forms, qualification and approval of contract suppliers and service providers, and good documentation practices.

Top 5 CMO

OBSERVATION 3
There are no written procedures to link the process by which escalated deviations can initiate product recall or Biological Product Deviation Reporting if discovered after release of lots. …

But we decided to take it further – we overlaid additional "scoring" and categories



Potentially Critical Issues

Failures in this area **could lead to system breakdowns**, negating the checks and balances that should be in place, possibly leading to fundamental differences with the product/ processes that were registered (ex Testing into Compliance, Laboratory Controls, Quality Unit Inadequate …)

Potential Cultural Issues

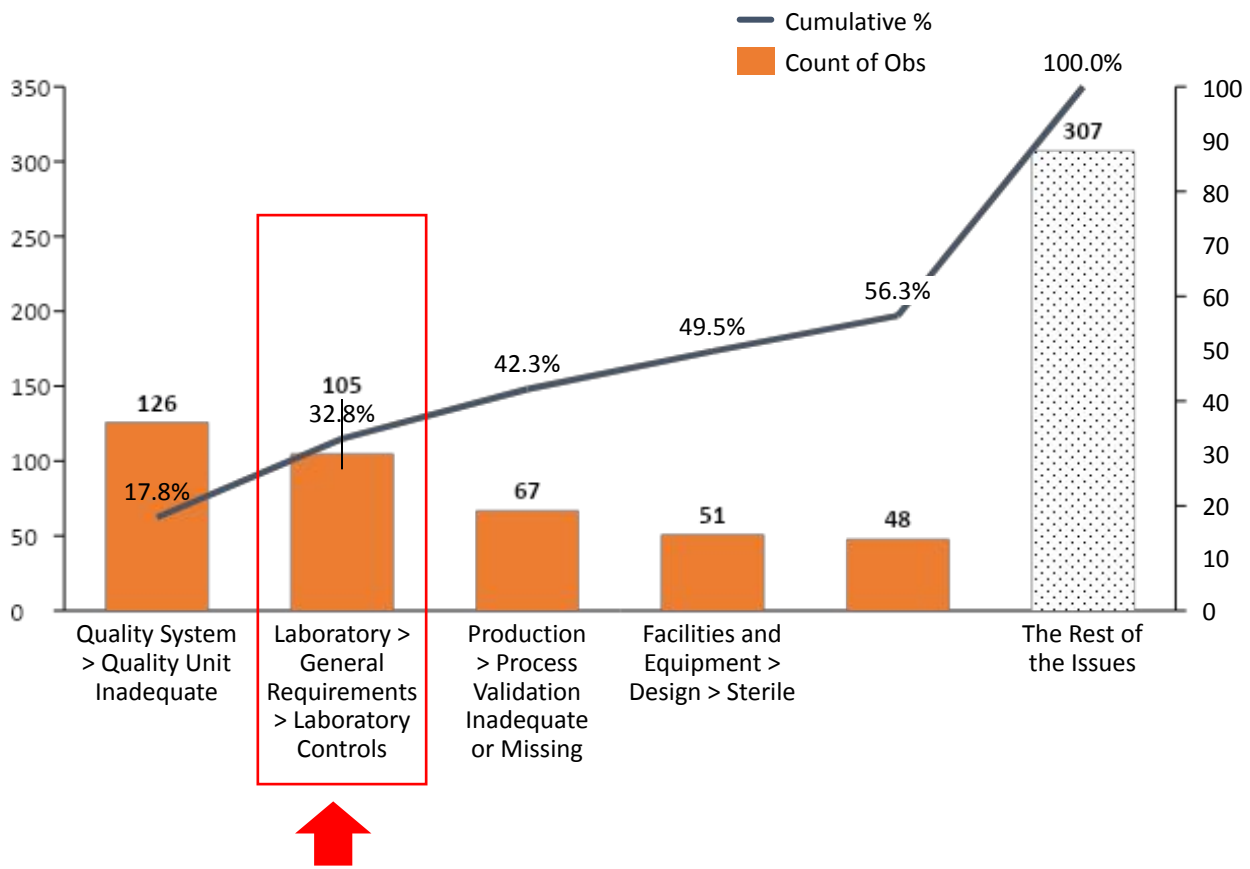
The results, consequences, or **actions resulting from cultural attitudes** of "get lots out the door" and/or "we have always done it this way so we don't need to follow these new rules" or "do what s/he does, follow the advice of a long-time operator who knows what s/he is doing" (ex Failure to Investigate, CAPAs, Training …)

Potential Product Safety Issues

There should be systems in place to **detect possible safety issues with product before it goes out the door**. But if those systems are not working properly or issues come up that systems are not in place to detect, I looked at each for possible impact to the safety of the product. (ex Sewage and refuse, pest control, microbiological or other product contamination…)

Sample: Potentially critical issues

Potentially Critical Issues - Redica Human Drug GMP Labels,
Observation Count, %



Top 5 CMO

2. **Laboratory controls are inadequate** to ensure quality of(b)(4)drug substance

Top 10 Sponsor

OBSERVATION 1
The **establishment of laboratory control mechanisms including any changes thereto, are not drafted by the appropriate organizational unit** and reviewed and approved by the quality control unit.

Top 10 CMO

1. Laboratory controls used to release (b)(4) drug substance **do not include scientifically sound and appropriate test procedures** that assure conformance to appropriate standards of quality and purity.

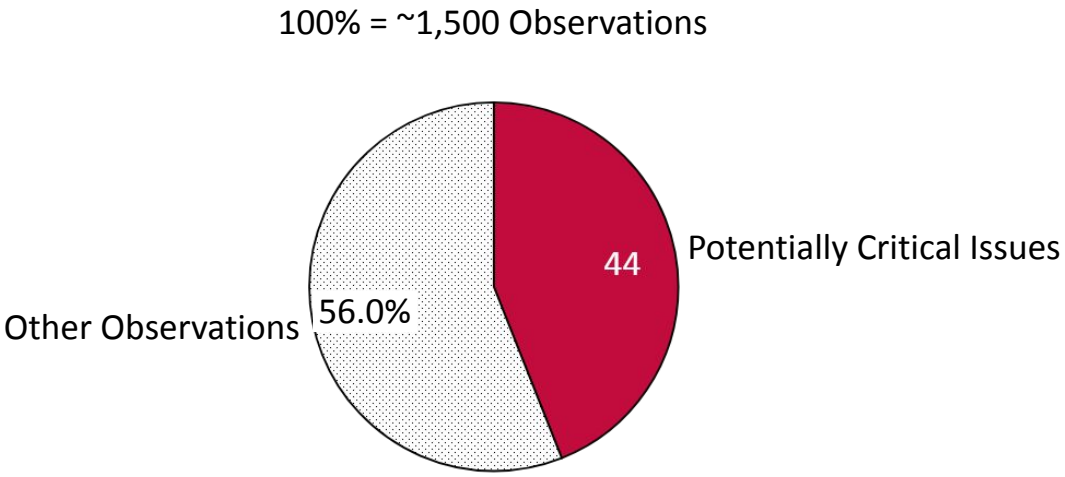
Led to GMP focused CRL

OBSERVATION 6
Laboratory controls **do not include the establishment of scientifically sound and appropriate specifications** and test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality and purity.

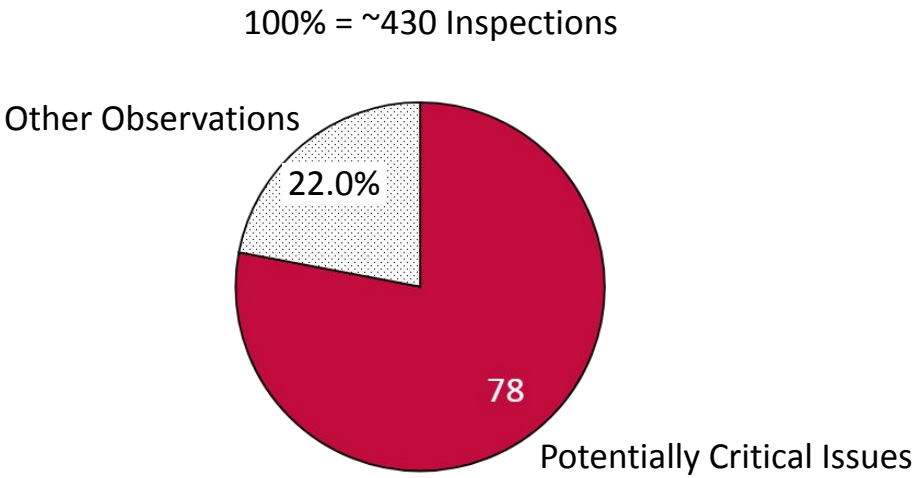
FDA - Human Drugs only, data through 5/25/22

How prevalent are these “potentially critical” issues?

Potentially Critical Issues - Redica Human Drug GMP Labels,
% of Observations



Potentially Critical Issues - Redica Human Drug GMP Labels,
% of Inspections



Potentially critical issues, like your CMO being cited with “Quality Unit Inadequate”, might be lurking on your next PAI…

Conclusions

- The FDA has ramped PAI inspections back to pre COVID levels for North America and Europe, but Asia is lagging way behind. There is likely a huge backlog.

- You are way more likely to get a 483 on a PAI than you think
  - ✔ PAI inspections receive 483s at a rate ~2x that of Routine inspections and almost at the same rate of For-Cause Inspections
  - ✔ PAI 483s are on the rise in all regions

- You specific FDA Investigator matters! How often they issue 483s and what they cite is heavily influenced by background and temperament – there is no “one size fits all”

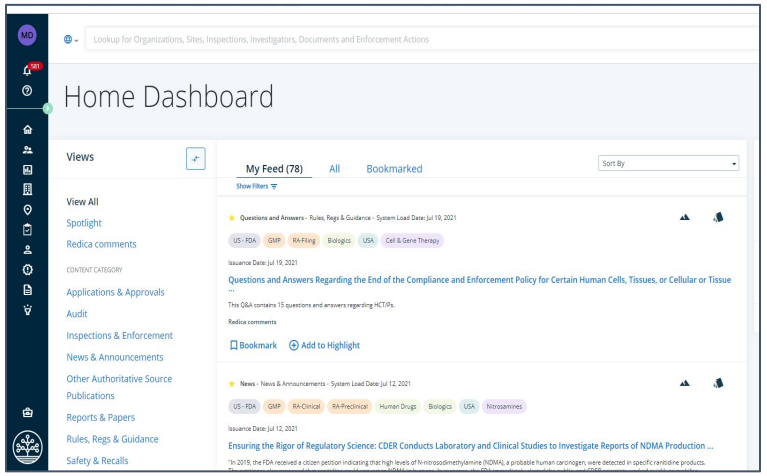
- The top items cited on PAI inspections often include “the basics” of Quality Unit responsibility, Investigations, and Laboratory Controls (… and that’s *before* we get into the Sterile environment!)

- Top Sponsors and CMOs are not immune to potentially critical issues – do your research!

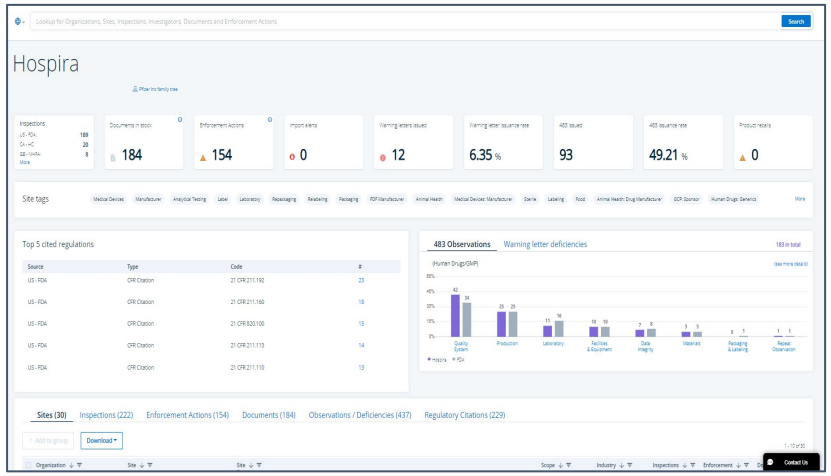
… and now a quick Redica Commercial …

Redica Systems: Our platform

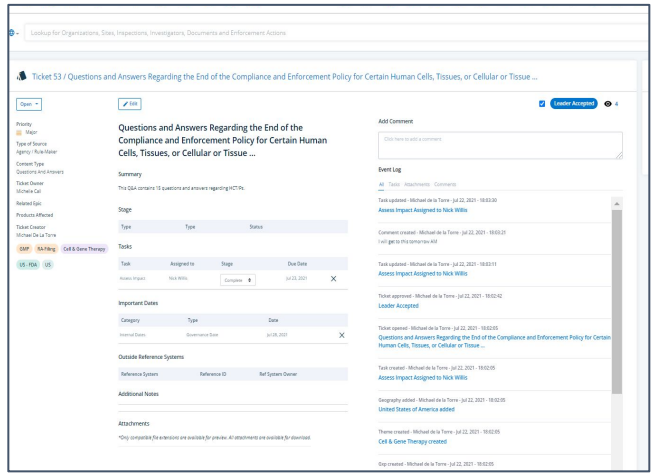
Daily Feed



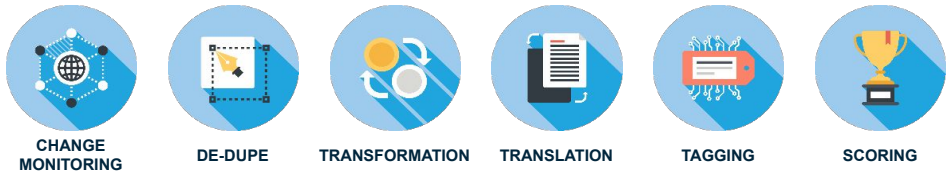
Profiles and Reports



Workflows



Intelligence Layer



Thousands of sources

FDA, NSF, World Health Organization, edqm, USDA, European Medicines Agency, Department of Justice, ISO, MEE 生态环境部, swissmedic, Australian Government Department of Health Therapeutic Goods Administration, Pmda, ICH harmonisation for better health, ANVISA, MHRA Regulating Medicines and Medical Devices, PIC/S, usp, OSHA, CDSCO, KFDA 식품의약품안전청, Cofepris

Redica Systems : How we work with Life Sciences

Inspection Preparation

- ✔ Investigator profiles
- ✔ Inspection outcomes mapped to quality system
- ✔ Inspection types
- ✔ Industry Trends mapped to GxP quality system
- ✔ Peer benchmarks

Vendor Quality

- ✔ Site and Organization profiles with full inspection history
- ✔ Monitoring and alerts for inspections and enforcement
- ✔ Vendor benchmarking

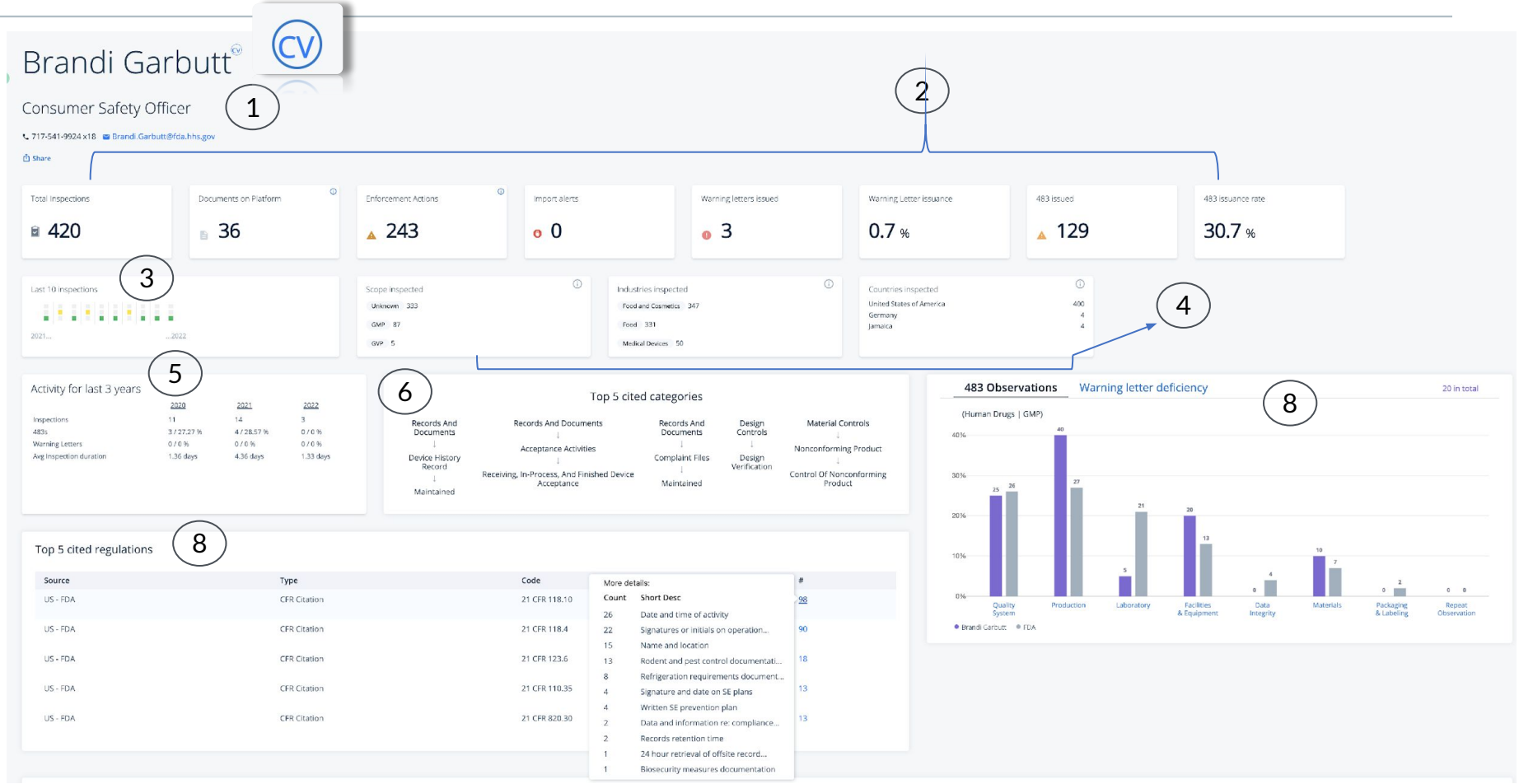
Regulatory Monitoring

- ✔ Global GxP coverage
- ✔ Unique labeling
- ✔ Simple dashboard
- ✔ Integrated workflows for triage and impact assessments

Redica **Reports, Visualizations and Automation**

FDA Inspector Profiles

1. Investigator information, including CV's in some profiles
2. View at a glance key details to quickly understand the Investigator's inspection history and outcomes.
3. Scan the inspection outcome through Inspection Patterns to easily understand outcomes
4. Quick view of the types of Scope, Industry, and Countries inspected by the Investigator
5. Spot year over year Investigator trends based on the past three years
6. A breakdown of the top five cited categories of observations based on the six quality systems
7. Compare the Investigator vs others in the FDA in Human Drugs/GMP built from the 483 observations in the six quality systems to spot trends
8. View Top 5 cited regulations given, including the count and short descriptions



The details…

Redica has complete with compete inspectional and enforcement history and benchmarks to industry averages for all FDA inspectors going back to the year 2000

Redica **Reports, Visualizations and Automation**

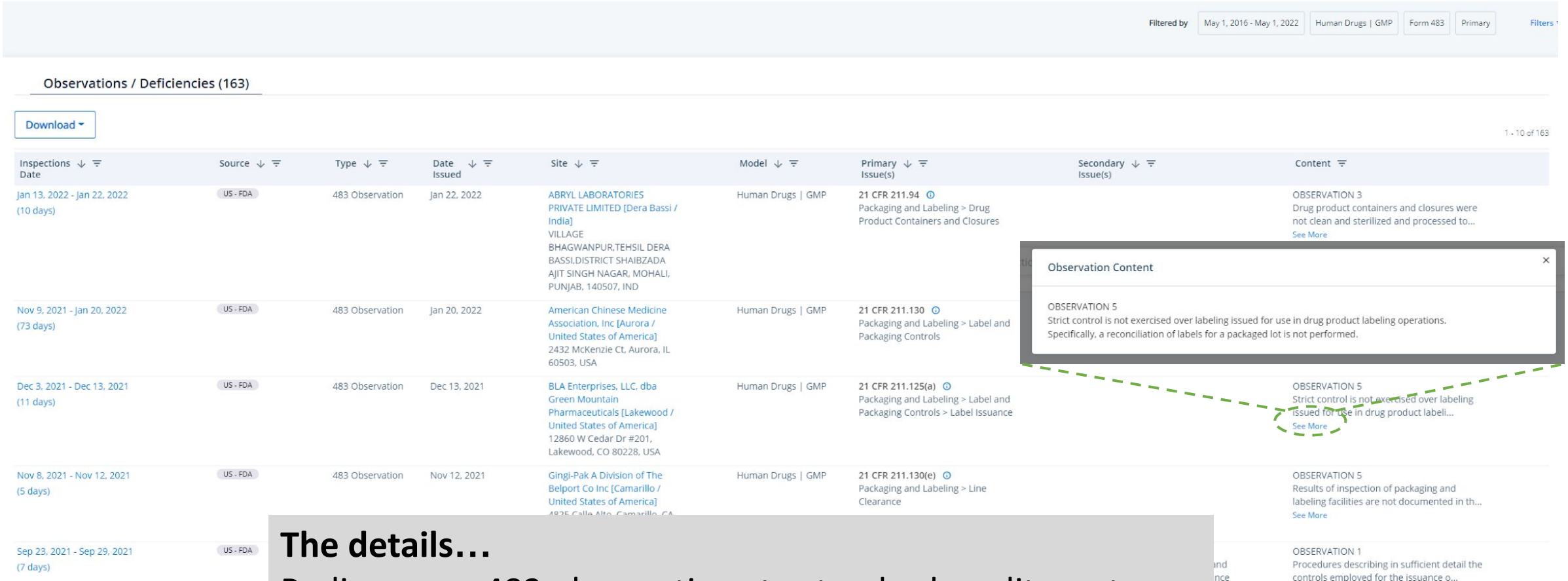
Site & Org Profiles

1. Site information, including address and Site Registry ID's
2. Family Trees provides visibility on parent and sister companies, great to keep up with mergers and acquisitions
3. At a glance key details of each Site for a quick risk assessment
4. Quickly add Sites to your Groups to run reports and be notified of activity
5. Be in the know of how the Site is registered with the FDA through Site Tags
6. View the inspection interval days to be prepared to expect a visit from the FDA
7. Top 5 cited regulations given, including count and a short descriptions
8. Compare the Site vs others in the FDA in Human Drugs/GMP built from the 483 observations in the six quality systems
9. See the count of the available data in each tab and click to drill down on the specifics

The details…
Redica has >250,000 Site profiles with compete inspectional and enforcement history and benchmarks to industry averages. Redica can send email alerts when the Site is inspected or receives an Enforcement Action

Redica **Reports and Automation**

Example 483 Observation Report –> Primary Issue = Packaging and Labeling

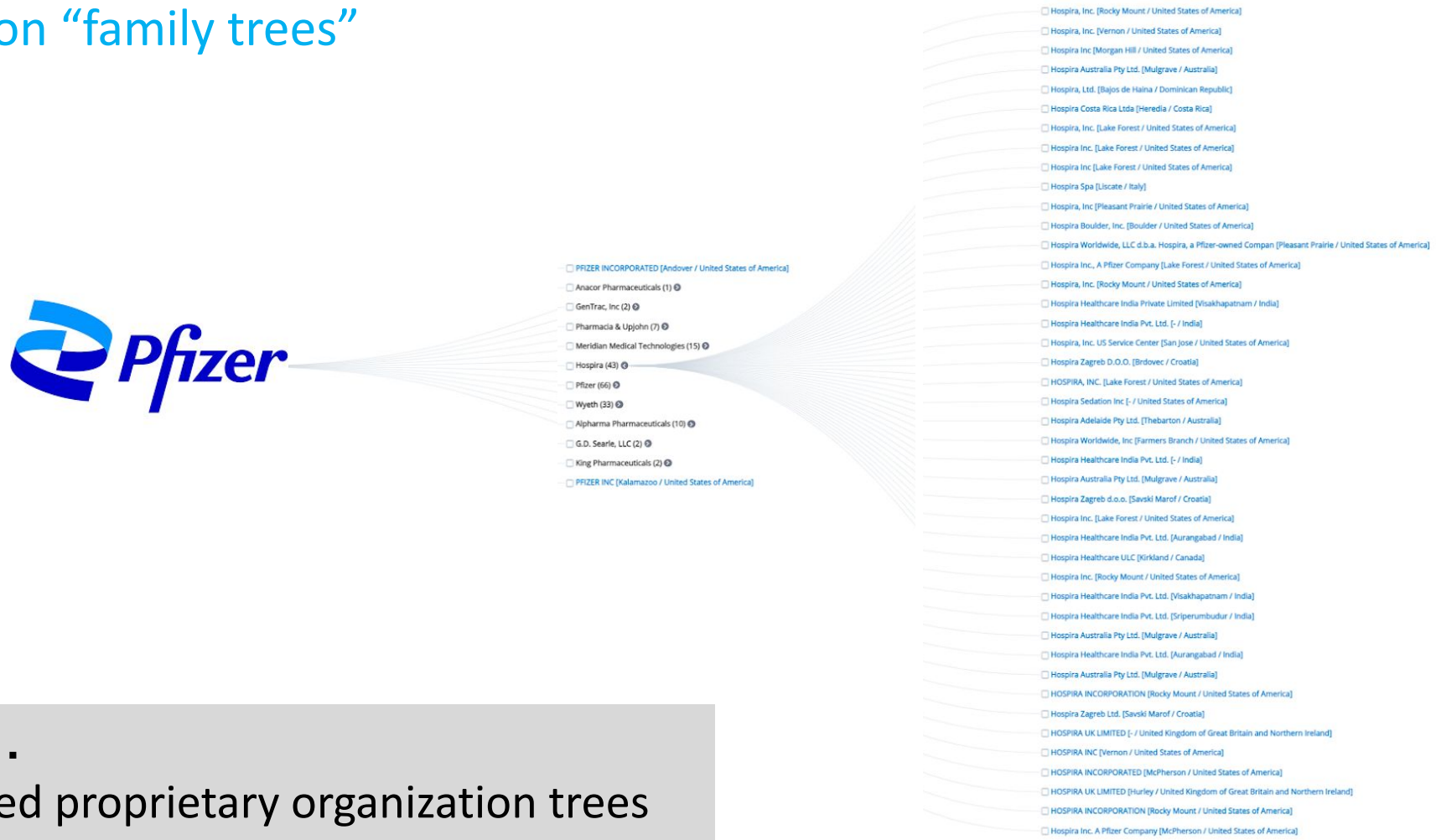


The details…

Redica maps 483 observations to standard quality system categories – taking the guess work out of 483 trends!

Redica **Reports, Visualizations and Automation**

Organization “family trees”



The details…

Redica created proprietary organization trees of the top Pharma and MedTech companies

Thank you!

Keep in touch on Twitter (@redicasystems) and subscribe to our blog or book a demo on redica.com