QYOBO

Navigating Compliance Post-COVID with AI and Big Data

DRGA Jahreskongress– Bonn, June 20/21, 2024

Contents

Aurobindo lost 5 million USD per week due to a single non-compliant inspection

- **Eugia Unit-3 stopped production** of terminally sterilized products following a Form 483 issued by the USFDA on **February 2, 2024**
- Production **resumed February 29, 2024**
- **Unit-3** contributes 40% to Eugia's revenue, implying **US sales contribution of USD 140-150 million** (9-10% of overall US sales)
- Aurobindo expects quarterly revenues will be **impacted by 20 million USD** (~ 1 month production stop + ramp-up times)

USFDA Issues 9 Observations To Aurobindo Pharma's Injectable Arm Which Could Dent US Sales | ET Now

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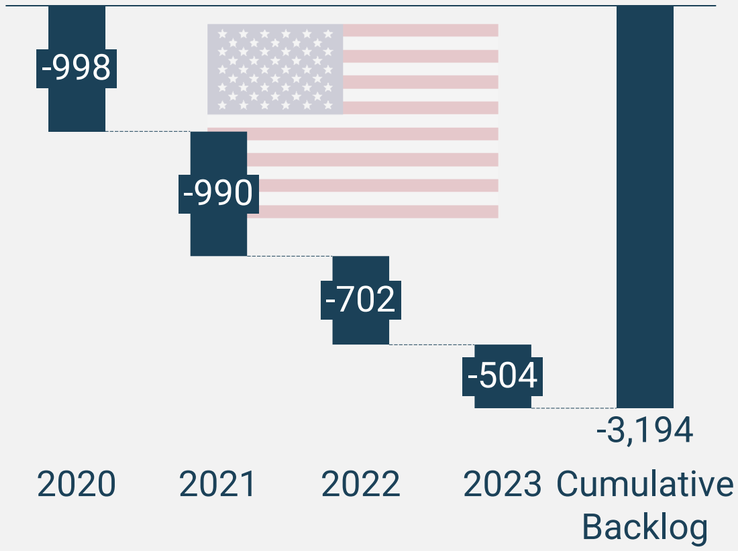
Source: IIFL securities; NSE India, YouTube/ETNOW

Contents

Regulatory agencies have a substantial inspection backlog from the pandemic, resulting in a higher share of non-compliance

Agency	Inspections of API and FDF manufacturing sites[1], # of inspections						Share of "non-compliant" inspections, %	
	2018	2019	2020	2021	2022	2023	2018	2023
Anvisa[2]	158	103	31	5	223	291	0.0%	5.2%
EDQM	566	654	407	593	605	452	0.5%	0.4%
USFDA	1,419	1,387	405	413	701	899	3.0%	4.4%
Health Canada	806	884	403	561	610	281	1.4%	2.1%
WHO[3]			38	27	55	29	*---n/a---*	

USFDA – Cumulative backlog[4], # of inspections



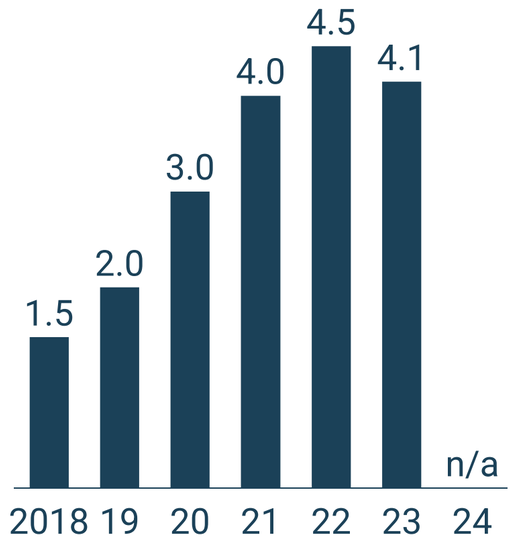
Cumulative backlog is equivalent to 2.3 years of inspections conducted by FDA pre-COVID

1 Covering a total of N = 3,447 confirmed API and FDF manufacturing sites mapped on the QYOBO platform – excluding offices, packaging, logistics or testing sites without commercial manufacturing operations. 2 Preliminary results, filtered for actual inspections only, risk assessment and other acceptance types were removed. 3 WHO only publishes compliant inspection certificates 4 Comparing the average number of inspections in 2018 and 2019 (1,403 inspections per year) against the actuals in the years 2020 through 2023.

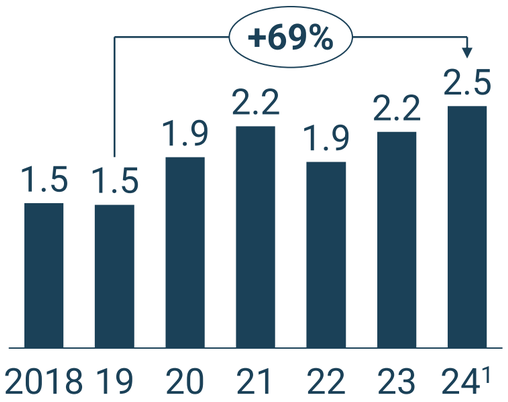
Source: QYOBO platform, filtered for API, FDF or API + FDF manufacturing that have been inspected in the past 10 years (2015-2024)

The time since the last inspection vastly increased for all regulatory agencies during the pandemic

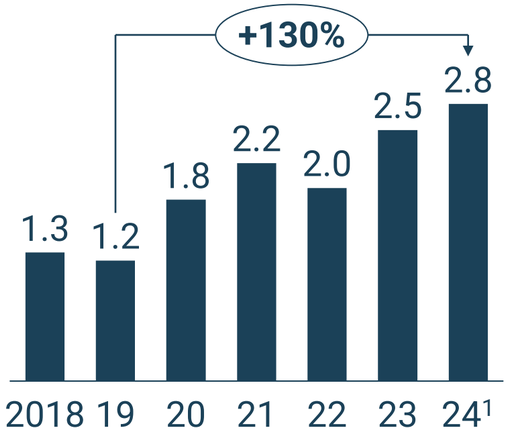
Median time since last inspection per manufacturing site (N = 3,447 sites), years



Anvisa

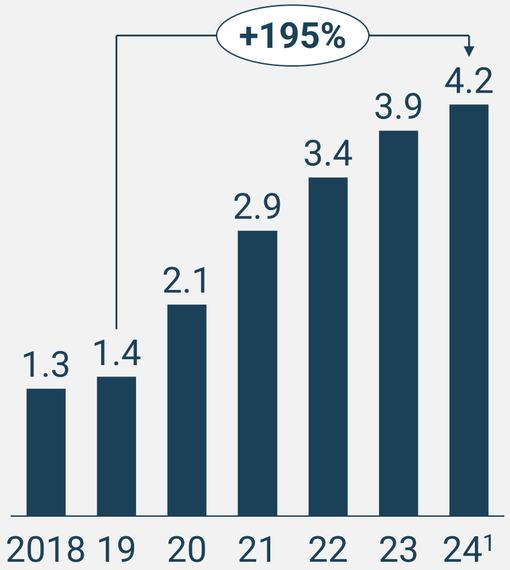


EDQM



Health Canada

Deep-dive follows



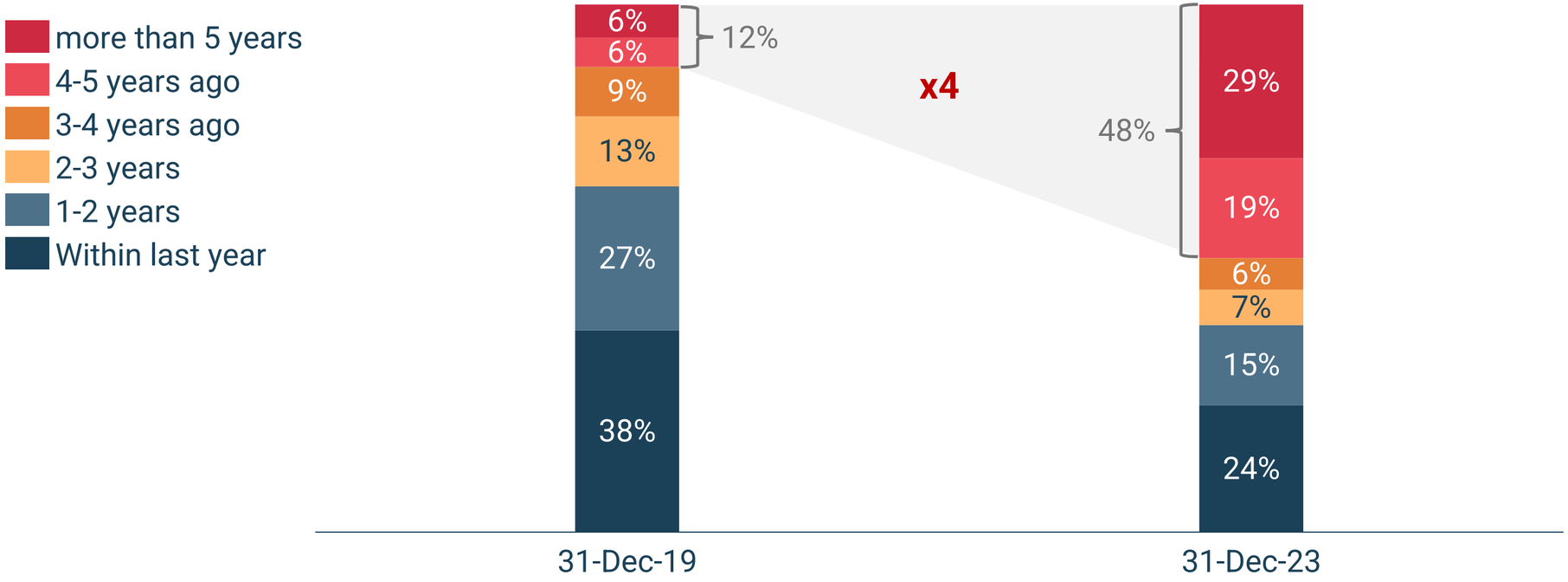
USFDA

1 “Time since last inspection” calculated for each year on December 31, except for the ongoing year 2024 where April 5 was used

Source: QYOBO platform

At the end of 2023, four times more manufacturing sites had not been inspected in over 4 years compared to 2019

Time since last US FDA inspection, # of manufacturing sites

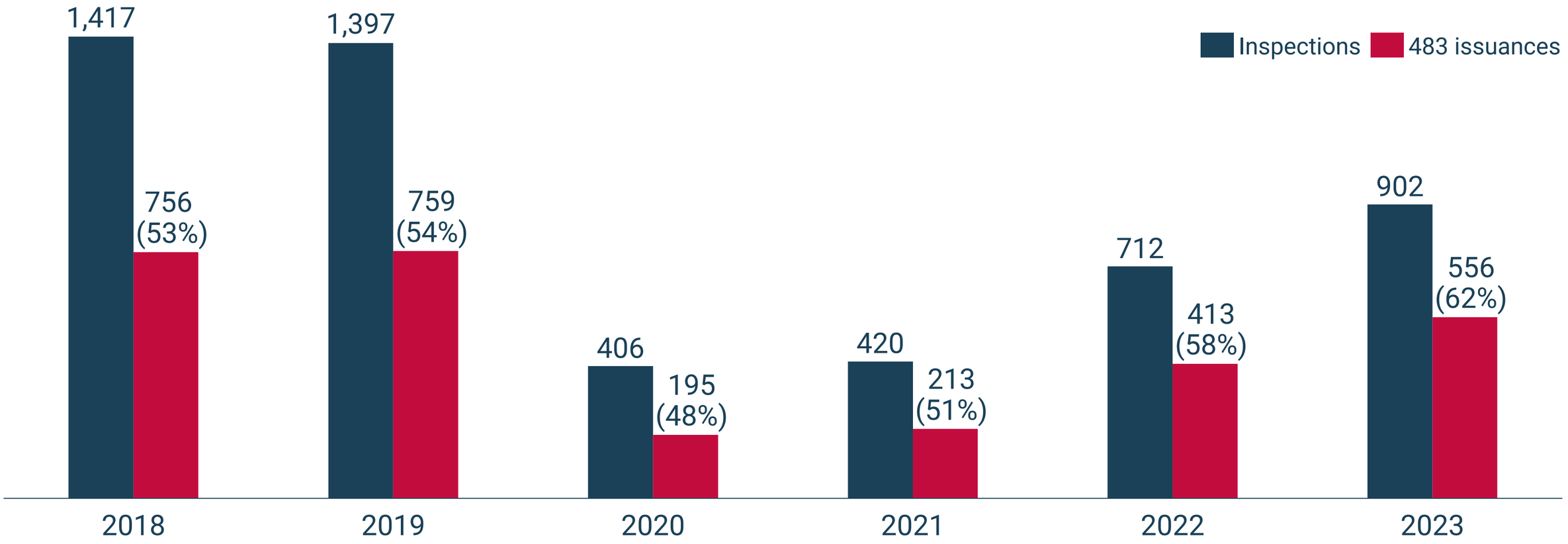


1 The total site count differs between 2019 (N = 3,204 API and FDF manufacturing sites) and 2023 (N = 3,447 manufacturing sites) as further sites were added/registered with the FDA.
Source: QYOBO platform

US FDA inspections

In 2023, Form 483s were issued at a higher rate than ever before

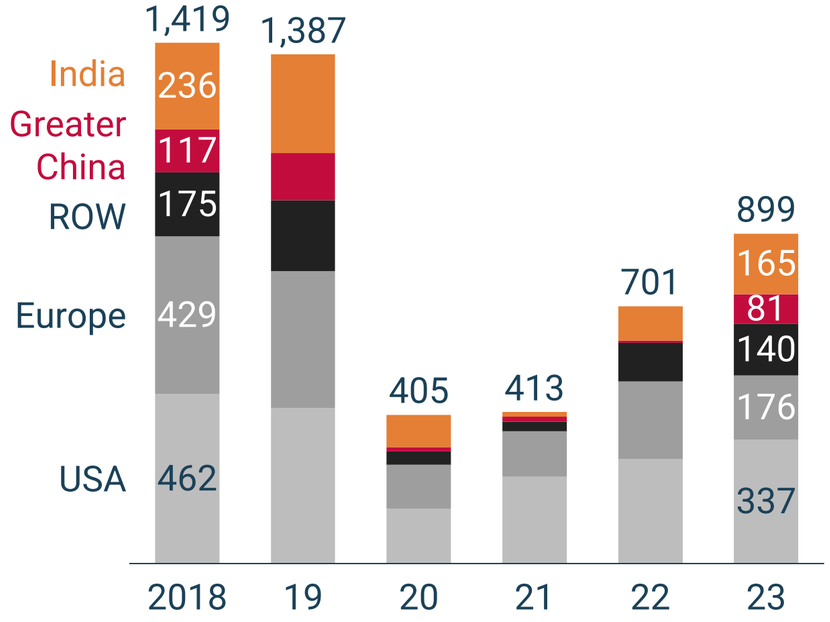
Total number of inspections vs. total number of 483 issuances, #



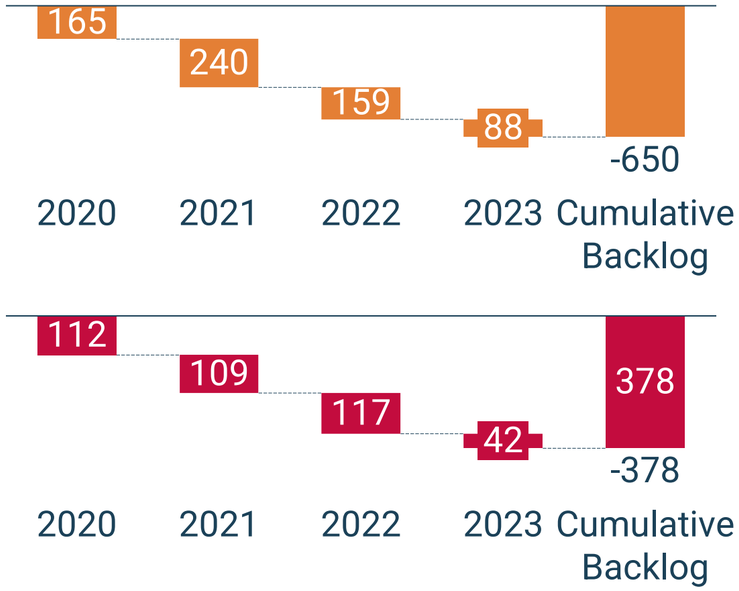
Source: QYOBO platform

Geographic focus – Inspections of Indian and Chinese sites will soon surpass pre-COVID levels to mitigate 2-3 year backlog

US FDA inspections per country or region,



USFDA – Cumulative backlog by country, # of inspections



Backlog is equivalent to 2.6 years of inspections conducted pre-COVID

Backlog is equivalent to 3.1 years of inspections conducted pre-COVID

Background (mounting political pressure)

"The Committee is particularly concerned about foreign drug inspections conducted in India and China… we are worried that the United States is overly reliant on sourcing from foreign manufacturers with a demonstrated pattern of repeatedly violating FDA safety regulations."
House Energy and Commerce Oversight and Investigations Subcommittee, July 2023

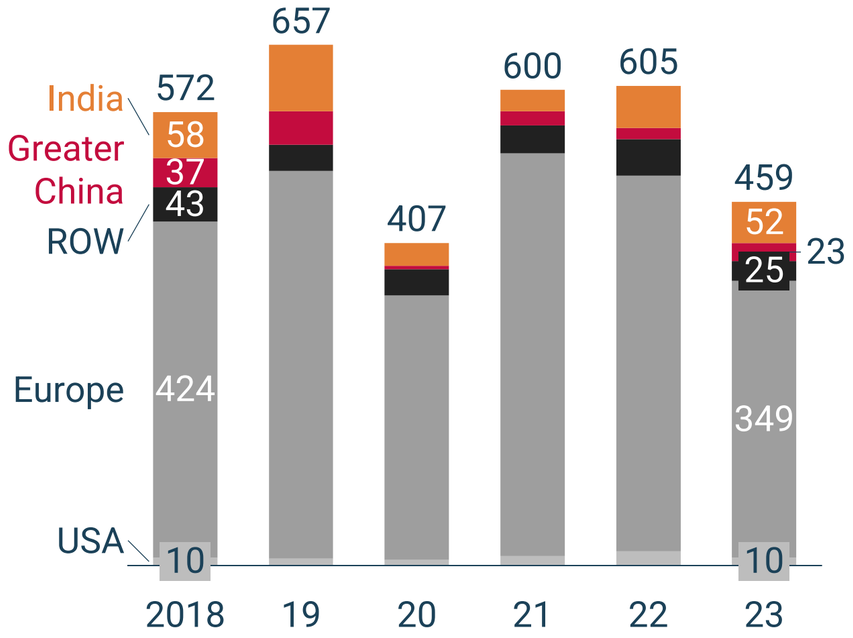
"What steps is the FDA taking to increase the number of foreign inspections overall?"
Marco Rubio + 8 Rep. U.S. Senators, December 2023

"I'm concerned that the FDA is failing in its mission. It is not adequately executing its foreign inspection program, which was questionable before the pandemic, became non-existent during the pandemic, and has seen little improvement since."
Cathy McMorris Rodgers, U.S. House Representative, February 2024

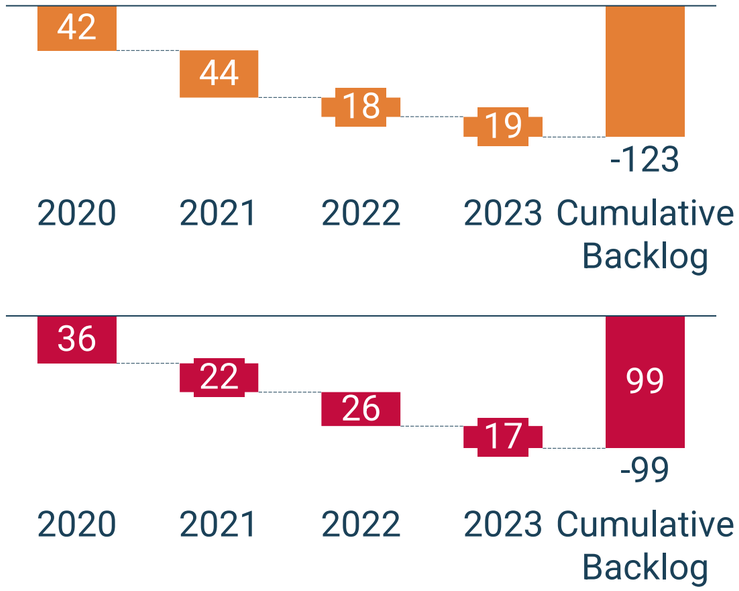
Source: QYOBO platform, U.S. Congress, U.S. Senate, U.S. Congress - HECOI Subcommittee,

Geographic focus – EDQM has a backlog of 1.7 and 2.5 years of inspections in India and China respectively

EDQM inspections per country or region, #



EDQM – Cumulative backlog by country,
# of inspections



Backlog is equivalent to 1.7 years of inspections conducted pre-COVID

Backlog is equivalent to 2.5 years of inspections conducted pre-COVID

Source: QYOBO platform

Contents

How can big data analysis and AI boost regulatory compliance?

1. **Understand** – impact analysis
   - **Quantify your risk accurately** – on a market and product level

2. **Anticipate** – plan ahead
   - **Predict** how/whether a non-compliance event will impact your business or result in regulatory action (e.g. a warning letter prediction)
   - **Assess and monitor –** Set up an automated process to monitor when manufacturing sites have last been inspected

3. **Mitigate –** when things don’t go by plan
   - **Test and improve –** Proactively reach out to suppliers with overdue inspections
   - **Prioritize and communicate –** Make regulatory compliance a top-line responsibility to ensure the organization is made aware of the financial risk associated with it

1 USFDA issued a Form 483 noting 9 observations at Aurobindo's EUGIA pharma site in February 2024

SITE PROFILE

EUGIA PHARMA SPECIALITIES LTD (TELANGANA - UNIT 3)

Corporate Group: AUROBINDO PHARMA LTD

OVERVIEW | NEWS | FDF PRODUCTS | API PRODUCTS | API DEMAND | REGULATORY | SITE INSPECTIONS | ESG

Compliance score

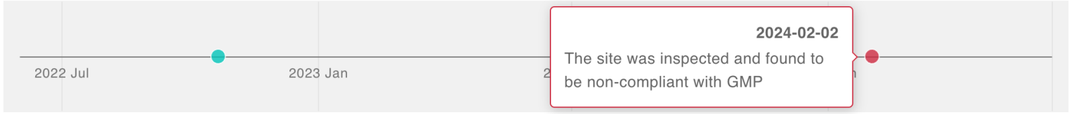
Overall score: 47

- Last inspection (50%): 0
- Inspection baseline (30%): 89
- Time between inspections (20%): 100

Global rank: Bottom 10% (8,785 of 9,494 sites)

Country rank: Bottom 20% (678 of 824 sites)

Inspection timeline



MAX | 2 YEARS | 1 YEAR

Inspections

Search

Description	Date	Source
The site was inspected and found to be non-compliant with GMP	2024-02-02	USFDA 1228546
The site was inspected and found to be compliant with GMP	2023-06-26	Health Canada 81070
The site was inspected and found to be compliant with GMP	2022-10-21	EDQM FT007/MH/003/2023 (RN 164254)
The site was inspected and found to be non-compliant with GMP	2019-11-13	USFDA 3008461619-2019-11-13
The site was inspected and found to be compliant with GMP	2019-11-04	Health Canada 78734

Observations include:

- **Inadequate product quality controls**
- **Inadequate documentation** of tests, examinations, production and process controls, etc.
- **Inadequate procedures to prevent microbiological contamination** of drug products, e.g., "When glass breakage occurred and generated glass particulate during this intervention, the operator did not remove surrounding vials that could have been contaminated with glass particles."

1 Eugia Unit 3 manufactures injectables and eye drops for the US market

SITE PROFILE

EUGIA PHARMA SPECIALITIES LTD (TELANGANA - UNIT 3)

Corporate Group: AUROBINDO PHARMA LTD

OVERVIEW | NEWS | FDF PRODUCTS | API PRODUCTS | API DEMAND | REGULATORY | SITE INSPECTIONS | ESG

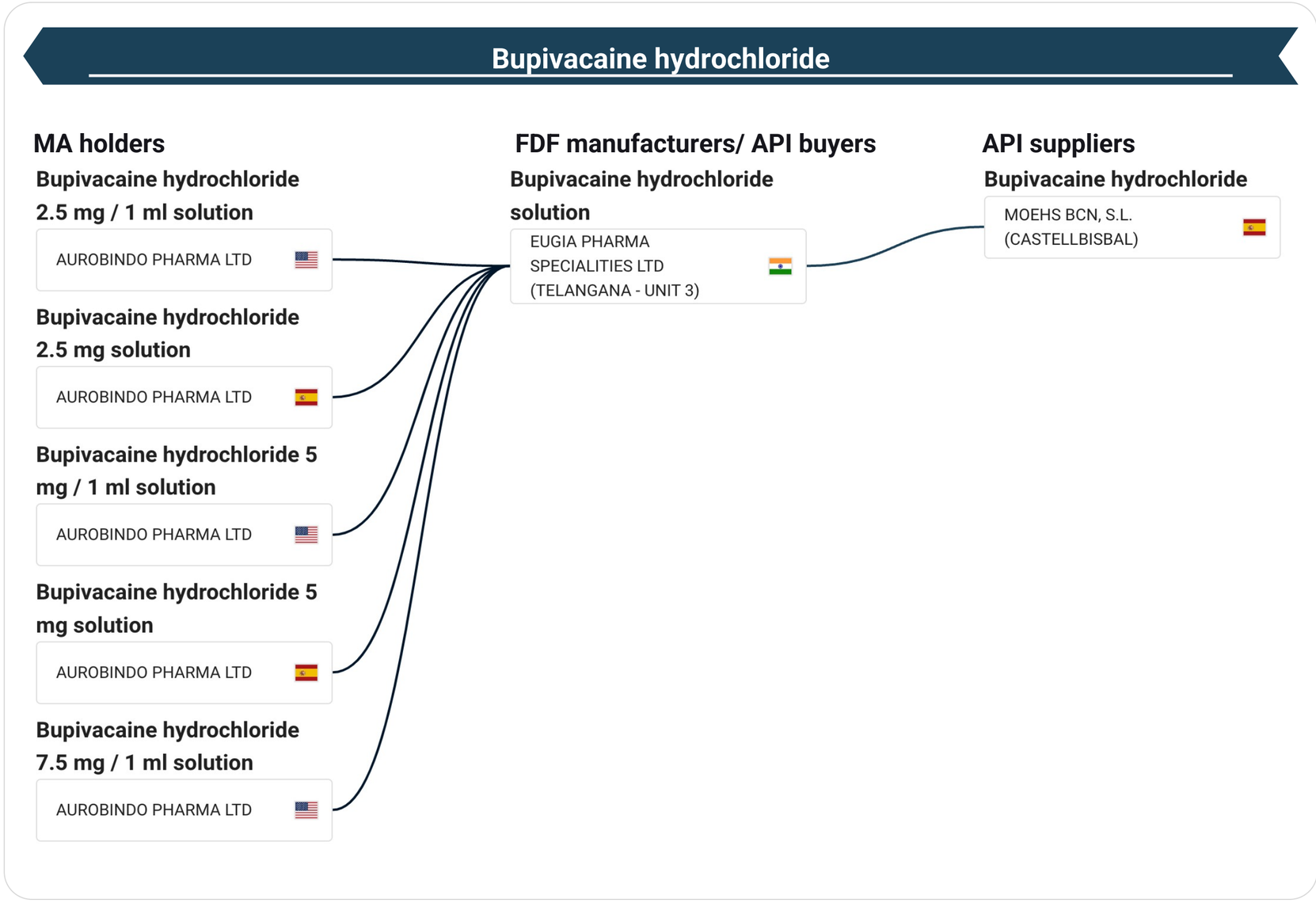
FDF Product list

Search

Active ingredients	Administration route	Dosage form	Strength	Properties
Acyclovir sodium	parenteral use	injectable solution	1 gm / 20 ml	
Acyclovir sodium	parenteral use	injectable solution	500 mg / 10 ml	
Alcaftadine	ocular use	eye drop	2.5 mg / 1 ml	
Amiodarone hydrochloride	parenteral use	injectable solution	150 mg / 3 ml	
Amiodarone hydrochloride	parenteral use	injectable solution	450 mg / 9 ml	
Amiodarone hydrochloride	parenteral use	injectable solution	900 mg / 18 ml	
Atracurium besylate	parenteral use	injectable solution	100 mg / 10 ml	
Atracurium besylate	parenteral use	injectable solution	50 mg / 5 ml	
Azithromycin monohydrate		powder for injectable solution/suspension	500 mg	
Bivalirudin		powder for injectable solution/suspension	250 mg	

The site predominantly manufactures eye drops and liquid injectables with a few exceptions (solutions for inhalation, powder for injection)

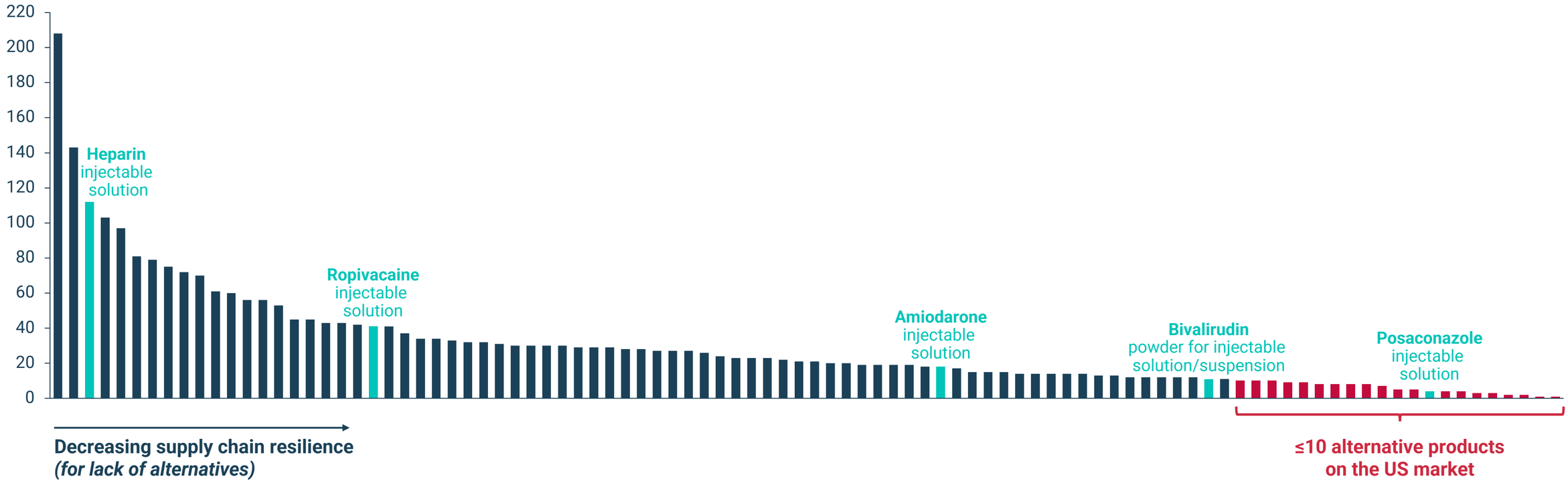
1 Impact assessment: QYOBO platform helps customers to understand which markets are affected…



1 … and which products: most have various alternatives on the market, but 21 products have 10 or less alternatives

US market

Alternative products[1] on the US market, total #



1 Products with same active ingredient and dosage form as those manufactured by Eugia Unit 3 for Aurobindo and other companies.

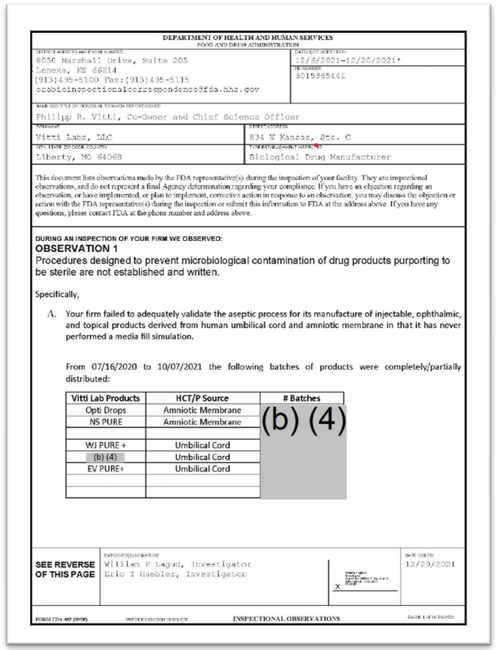
Source: QYOBO platform (FDF module)

2 Based on 10,000+ FDA offline documents, global inspection data of 8,000+ manufacturing sites and past warning letters…

Input Data: over 50,000 compliance documents

Pre-processing

QYOBO requested 10,000+ Form 483 documents from USFDA via FOIA (Freedom of Information Act)



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

8050 Marshall Drive, Suite 205
Lenexa, KS 66214
(913)495-5100 Fax:(913)495-5115
orablelnspectionalAccordenceResponse@fda.hhs.gov

12/6/2021-12/20/2021*
3015365441

Phillip R. Vitti, Co-Owner and Chief Science Officer

Vitti Labs, LLC
834 W Kansas, Ste. C
Liberty, MO 64068
Biological 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 WE OBSERVED:
OBSERVATION 1
Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established and written.

Specifically,

A. Your firm failed to adequately validate the aseptic process for its manufacture of injectable, ophthalmic, and topical products derived from human umbilical cord and amniotic membrane in that it has never performed a media fill simulation.

From 07/16/2020 to 10/07/2021 the following batches of products were completely/partially distributed:

Vitti Lab Products	HCT/P Source	# Batches
Opti Drops	Amniotic Membrane	(b) (4)
NS PURE	Amniotic Membrane	
WJ PURE +	Umbilical Cord	
(b) (4)	Umbilical Cord	
EV PURE+	Umbilical Cord	

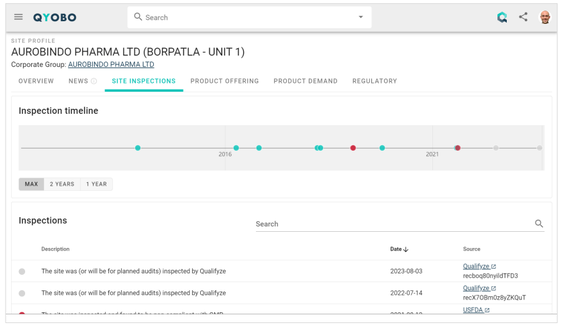
SEE REVERSE OF THIS PAGE

William F Lagud, Investigator
Eric T Haebler, Investigator

12/20/2021

INSPECTIONAL OBSERVATIONS

Global inspection data for over 8,000 manufacturing sites*



QYOBO

Search

SITE PROFILE
AUROBINDO PHARMA LTD (BORPATLA - UNIT 1)
Corporate Group: AUROBINDO PHARMA LTD

OVERVIEW NEWS SITE INSPECTIONS PRODUCT OFFERING PRODUCT DEMAND REGULATORY

Inspection timeline

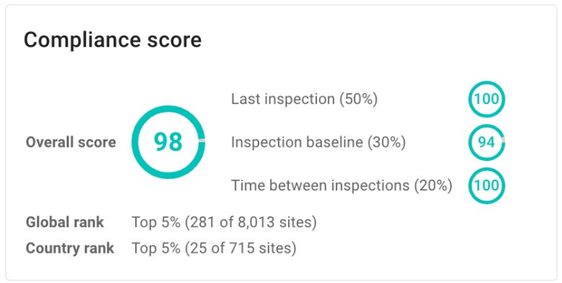
2016 2021

MAX 2 YEARS 1 YEAR

Inspections

Search

Description	Date	Source
The site was (or will be for planned audits) inspected by Qualityze	2023-08-03	Qualityze recbocq8OnyIidTFD3
The site was (or will be for planned audits) inspected by Qualityze	2022-07-14	Qualityze recK7OBm0z9yZXQuT
		USFDA



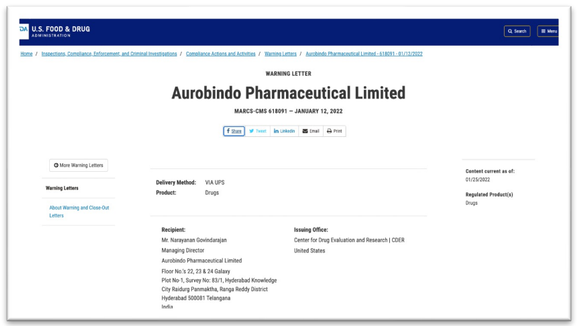
Compliance score

Overall score 98

Last inspection (50%) 100
Inspection baseline (30%) 94
Time between inspections (20%) 100

Global rank Top 5% (281 of 8,013 sites)
Country rank Top 5% (25 of 715 sites)

Past warning letters from the USFDA



U.S. FOOD & DRUG ADMINISTRATION

Home / Inspections, Compliance, Enforcement, and Criminal Investigations / Compliance Actions and Activities / Warning Letters / Aurobindo Pharmaceutical Limited - 618091 - 01/12/2022

WARNING LETTER

Aurobindo Pharmaceutical Limited

MARCS-CMS 618091 – JANUARY 12, 2022

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More Warning Letters

Warning Letters

About Warning and Close-Out Letters

Delivery Method: VIA UPS
Product: Drugs

Content current as of: 01/25/2022

Regulated Product(s): Drugs

Recipient:
Mr. Narayanan Govindarajan
Managing Director
Aurobindo Pharmaceutical Limited
Floor No's 22, 23 & 24 Galaxy
Plot No 1, Survey No: 83/1, Hyderabad Knowledge City Raidurg Panmakhta, Ranga Reddy District
Hyderabad 500081 Telangana
India

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

Step 1:

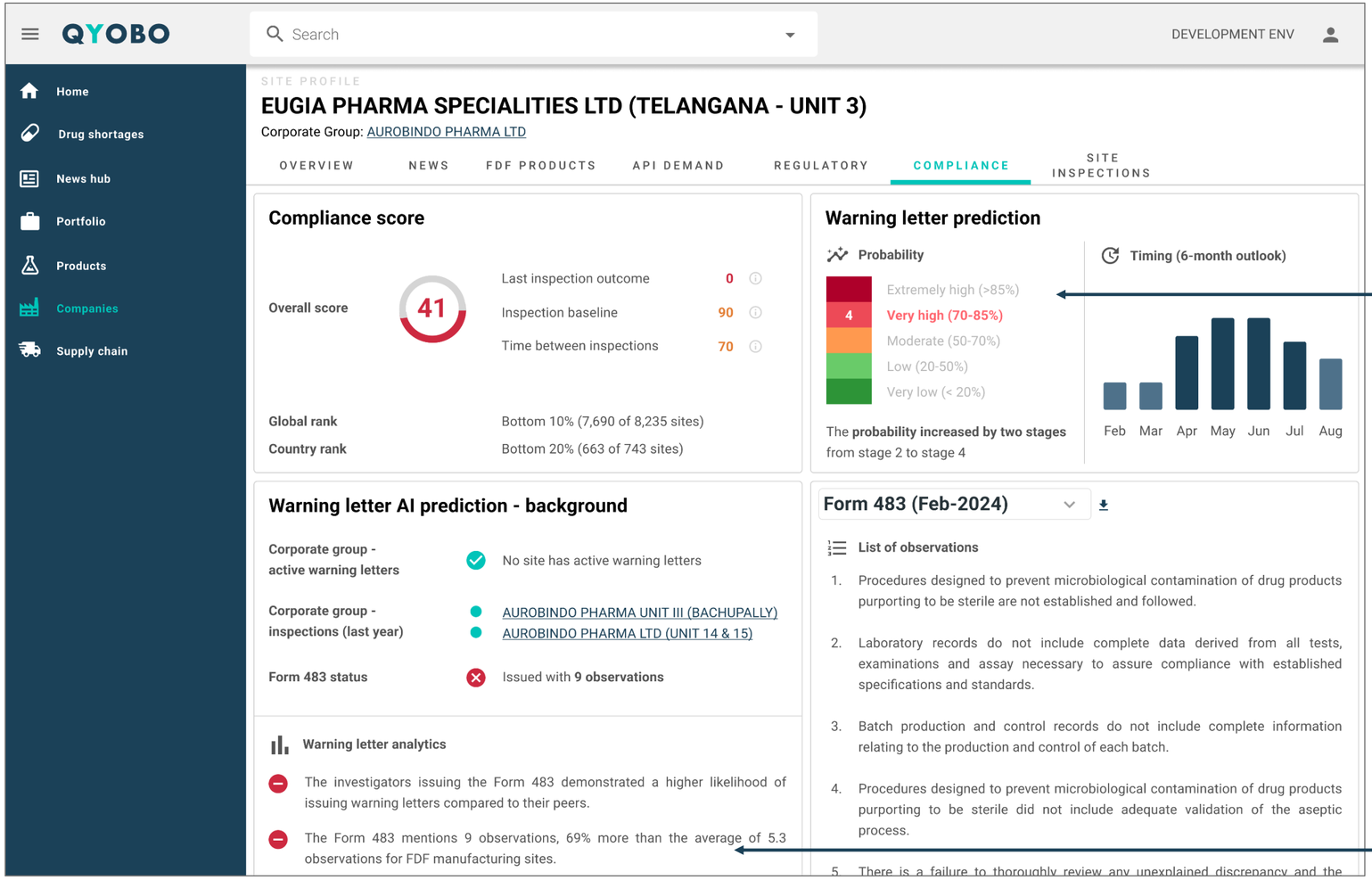
QYOBO is processing these documents via **OCR (Optical character recognition)** and converts it into structured text

Step 2:

Subsequent **pattern recognition extracts meaningful features** (overall document sentiment, tagwords, inspectors, etc.)

* work in progress

2 … our AI model indicates a “very high” probability for a warning letter for Eugia Unit-3



Screenshot cropped for brevity

The warning letter prediction model indicates a very high probability of a warning letter between April and July 2024

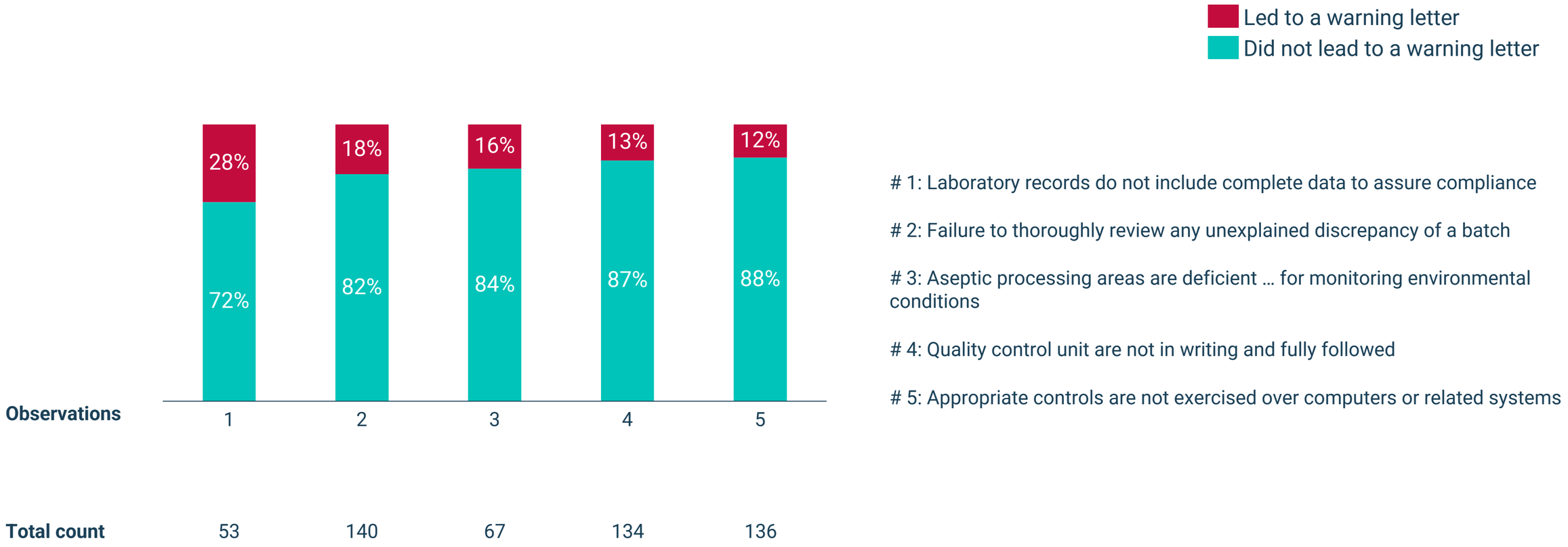
To make this assessment, the model uses over 50,000 compliance documents for 8,000 manufacturing sites and their corporate relationships

Warning letter analytics provide data-driven statistics and background to help understand the prediction

Source: QYOBO platform (Compliance module)

2 The model itself decides which features are best suited for the prediction (example for observations)

Severeness of observations, %



1: Laboratory records do not include complete data to assure compliance

2: Failure to thoroughly review any unexplained discrepancy of a batch

3: Aseptic processing areas are deficient … for monitoring environmental conditions

4: Quality control unit are not in writing and fully followed

5: Appropriate controls are not exercised over computers or related systems

2 Systematically anticipate upcoming inspections in the supply chain - Example for Aurobindo (1/2)

Active in US Market[1]	Operation type	Dosage form	Manufacturing site	Time since last USFDA inspection[2], years	Time since last EDQM/HC inspection[2], years
✓	API		APITORIA PHARMA LTD (KISTAIPALLY, UNIT 8)	4.2	3.8
✓	API		APITORIA PHARMA LTD (BORPATLA - UNIT 1)	2.4	2.4
✓	API		APITORIA PHARMA LTD (PASHAMYLARAM, UNIT 5)	1.9	
✓	API		APITORIA PHARMA LTD (PYDIBHIMAVARAM, UNIT 4)	1.4	1.7
✓	API		APITORIA PHARMA LTD (GUNDLA MACHANUR - UNIT 9)	1.1	1.1
✓	API		APITORIA PHARMA PRIVATE LIMITED (E-BONANGI, UNIT-VI)	0.6	
✓	API + FDF	💊	EUGIA PHARMA SPECIALITIES LTD (BHIWADI)	1.5	1.5

Inspected > 3 years ago
Inspected 2-3 years ago
Inspected < 2 years ago

1 GDUFA fees paid for 2024 or active CDER (Current Drug Establishment Registration) 2 Calculated on 31.12.2023
Source: QYOBO platform

2 Systematically anticipate upcoming inspections in the supply chain - Example for Aurobindo (2/2)

Active in US Market[1]	Operation type	Dosage form	Manufacturing site	Time since last USFDA inspection[2], years	Time since last EDQM/HC inspection[2], years
✓	FDF		EUGIA SEZ PVT LTD (MAHABUBNAGAR)	4.8	4.9
✓	FDF	💉	EUGIA PHARMA SPECIALITIES LTD (TELANGANA - UNIT 3)	4.1	0.5
✓	FDF	💉	AUROBINDO PHARMA LTD UNIT 12 (MIYAPUR)	3.9	0.8
✓	FDF	💊	AUROLIFE PHARMA LLC (2400 ROUTE, DAYTON)	2.1	
✓	FDF	💊	AUROBINDO PHARMA LTD (JEDCHERLA MANDAL, UNIT 7)	1.6	5.6
✓	FDF	💊	AUROLIFE PHARMA LLC (DURHAM)	1.3	
✓	FDF	💊	AUROBINDO PHARMA UNIT III (BACHUPALLY)	0.5	0.5
✓	FDF	💊	EUGIA PHARMA SPECIALITIES LTD. (KOLTHUR)	0.4	1.1
✓	FDF		APL HEALTHCARE LIMITED (MENAKURU - UNIT IV)	0.3	
✓	FDF	💊	AUROBINDO PHARMA LTD (CHITKUL, UNIT 6)	0.3	
✓	FDF	💊	APL HEALTHCARE LIMITED (JADCHERLA , GREEN IND AREA)	0.1	
✓	FDF	💊	EUGIA US MANUFACTURING LLC (HIGHTSTOWN)	0.0	

Inspected in 2024

Inspected > 3 years ago
Inspected 2-3 years ago
Inspected < 2 years ago

1 GDUFA fees paid for 2024 or active CDER (Current Drug Establishment Registration) 2 Calculated on 31.12.2023
Source: QYOBO platform

Summary

- The **COVID-induced backlog** poses an **increasing risk to a safe and reliable drug supply**, as inspection data suggest a higher degree of non-compliance.
- **Indian and Chinese manufacturing sites** are particularly **in focus** for inspections.
- Leveraging **big data and AI models**, **sites at risk** can be identified using **globally connected data**.
- **Quantifying and systematically monitoring** compliance risks can provide the means to **anticipate and mitigate** non-compliance events.