Qualio

Pharmaceutical quality in 2024:
An overview

Table of Contents

2024 will be a big year for pharmaceutical quality professionals.

New technology, fresh legislation, innovative drug and trial delivery formats, and evolving expectations of quality best practice will all shape the profession in the coming year.

This guide breaks down the key drivers and developments you need to be aware of. Forewarned is forearmed – careful preparation now will reap rewards for your business in the months to come.

Meg Sinclair
Quality Operations Manager

Chapter 1

The drivers

We asked our Qualio+ team of industry experts about the key developments and trends they anticipated impacting the pharmaceutical industry in 2024 and beyond. Here's what they said.

Shortages – and preventing them

Drug shortages are a lingering, damaging threat to both patients and the status quo of the pharmaceutical industry. Responding to them and preventing future shortages is a problem occupying the attention of regulators across the globe.

The FDA noted 305 continuing drug shortages at their 2023 PDA/FDA Joint Regulatory Conference, and this isn't a new problem. After all, it was their 2019 Interagency Drug Shortages report which birthed the concept of their upcoming Quality Management Maturity program (more on that below, and in our dedicated QMM guide!) 40-50 new shortages have sprung up in the United States like clockwork for the past 5 years.

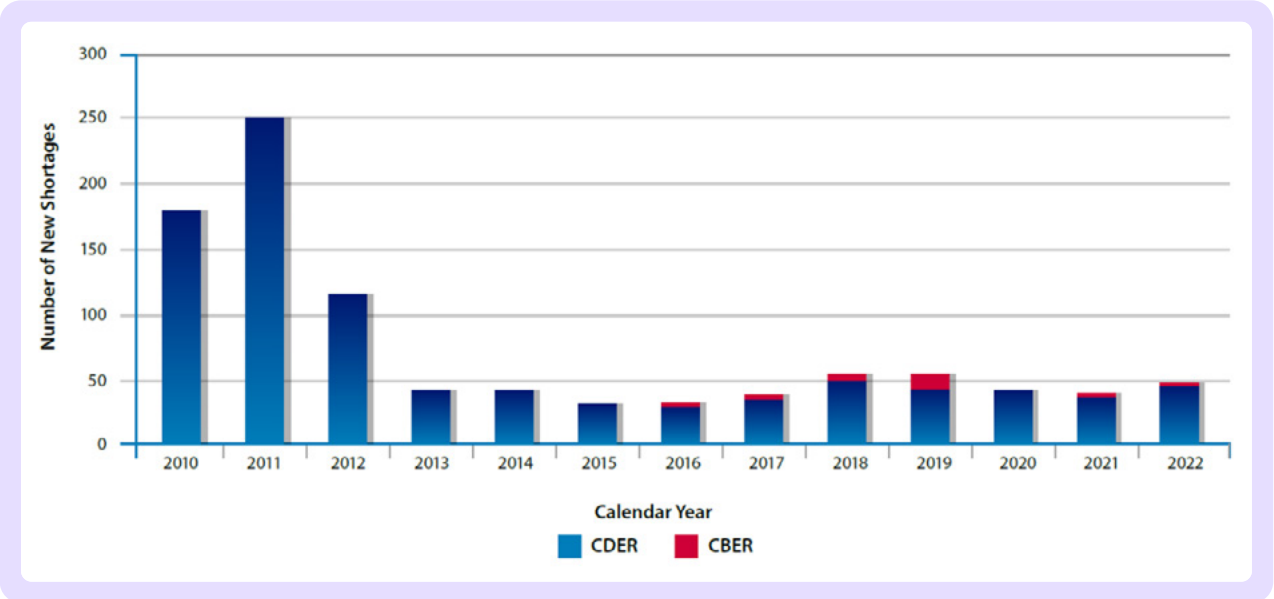


Figure 1. Number of New Drug Shortages Per Calendar Year, (from CY 2010 to CY 2022)

Unsurprisingly, the 2019 report was followed up in 2022 by the FDA's draft guidance: Risk Management Plans to Mitigate the Potential for Drug Shortages. A key requirement of this guidance was the recommendation for stakeholders and key actors in the supply chain to build and collaborate on risk management plans. These supply chain RMPs should consider, evaluate and mitigate supply risks to insulate the broader supply chain from the risk of shortages.

The shortage problem is currently being amplified by low industry engagement with the drug amount reporting required by the 2020 CARES Act. Despite the federal requirement for manufacturers to make an annual report of manufactured product volumes to the FDA, the pitiful engagement levels of around 25% of NDCs in the Act's first year have steadily declined to less than 20% since.

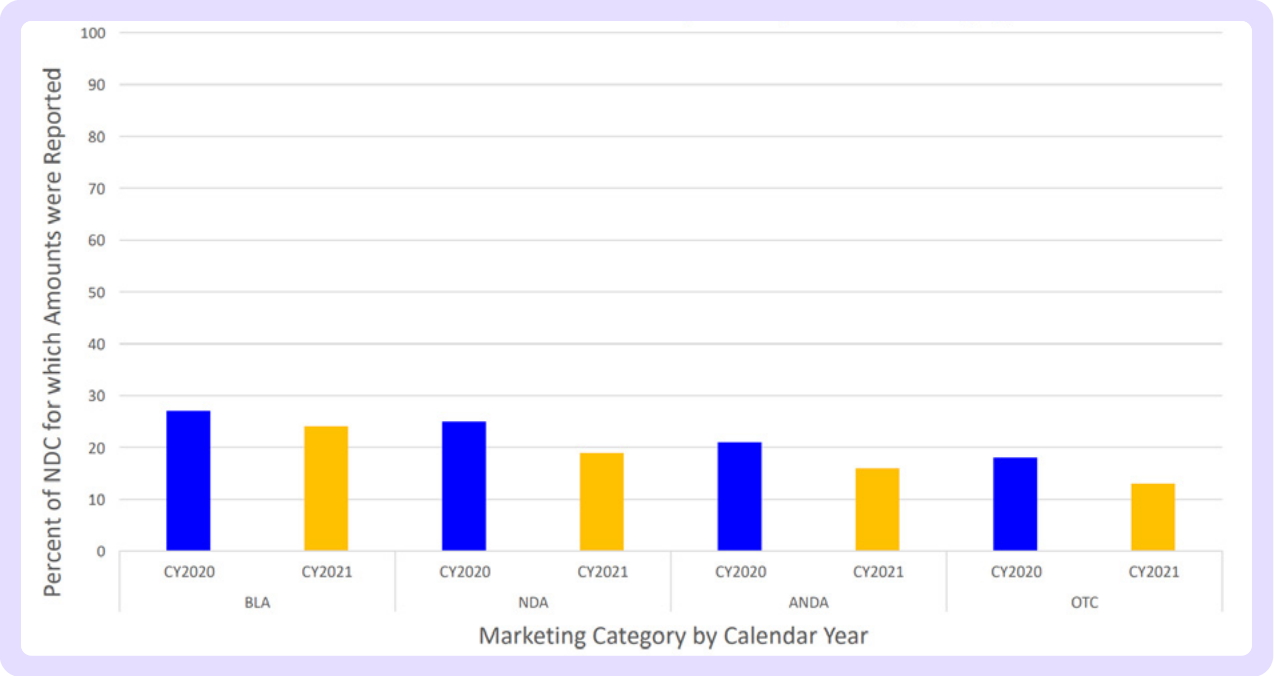


Figure 2: Percent of NDCs for which amounts were reported by marketing category

On top of all this, a key regulatory requirement for American pharmaceutical companies will go live in 2024.

The Drug Supply Chain Security Act was originally launched in 2013 by President Obama, mandating end-to-end drug traceability requirements at the package level to further insulate against drug supply disruption. The Act was scheduled for enforcement in

November 2023, before being delayed to a final enforcement date of November 27, 2024.

This recent regulatory nail-biting about supply chain risk isn't restricted to the States. In 2023, the EU proposed its new Human Medicines Regulation. It suggests that future marketing authorization (MA) holders should build and maintain a shortage prevention plan for any product they place on the European market.

A Critical Medicines Alliance of national authorities, manufacturers, civil society representatives and EU agencies is expected to go live in early 2024, with a possible Critical Medicines Act to follow.

And EU Regulation 2022/123, going live in early 2025, gives the EMA a new role to monitor and protect medicinal supplies. A new European Shortages Monitoring Platform (ESMP) will go live simultaneously.

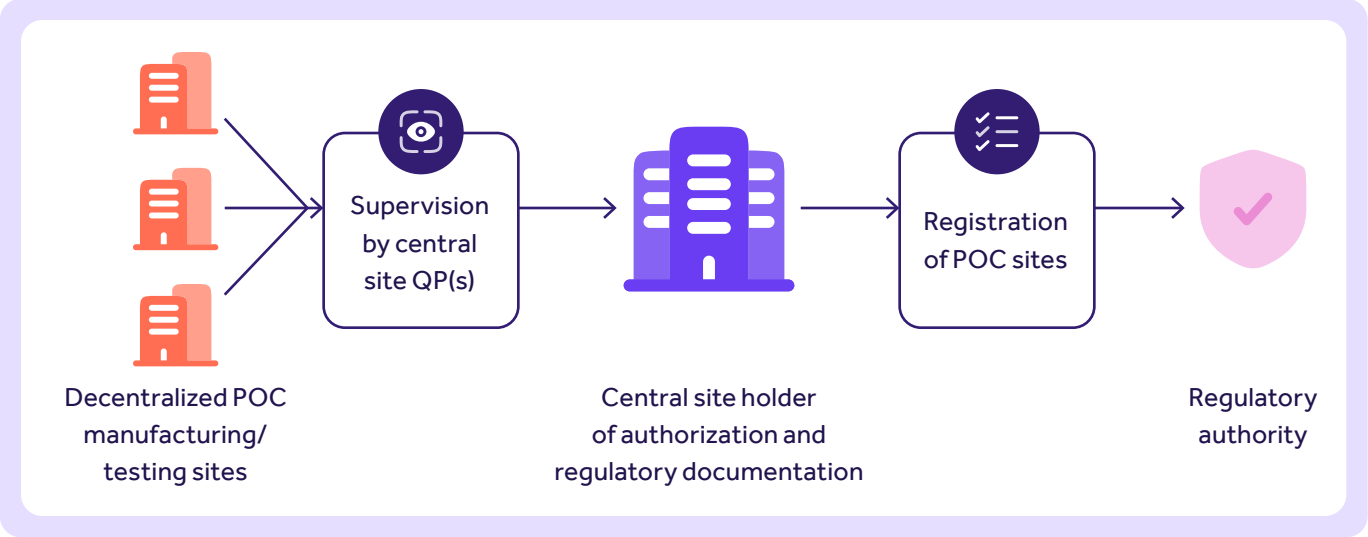
The takeaway: drug shortages continue to rumble on. Regulators are paying attention, and new legislative requirements and expectations will take further shape in 2024. Pay attention to your own output, and focus your quality efforts on consistency as well as quality of supply.

New manufacturing, distribution and clinical trial methods

Between 2021 and 2023, the UK, EU and US all proposed models in that order of a new decentralized point-of-care manufacturing model.

The objective? Build an operational framework for short-life medicines and therapies to be produced at the point of care – such as a hospital or clinic – allowing treatments to be administered rapidly with no delivery and storage phase.

These distributed just-in-time sites would be connected by an overarching 'control site' responsible for regulatory liaison and creation of documents like a master file.



This format has found voice in 3 key ways:

- **The original UK proposal:** August 2021 (94% of surveyed respondents supported the model)
- **US FDA consultation:** October 2022 (part of the FRAME project)
- **EU Human Medicines Directive:** April 2023 (practically identical to the UK model)

Point-of-care manufacturing isn't the only industry innovation gathering pace.

Decentralized clinical trials (DCTs) are also being explored. The FDA has, in recent years, published both its Framework for the Use of Digital Health Technologies in Drug and Biological Product Development and Decentralized Clinical Trials for Drugs, Biological Products, and Devices Guidance for Industry, Investigators, and Other Stakeholders.

But this prospective model is currently being hamstrung in both the USA and EU by the clashing of federal and state requirements.

In the EU, clinical sites are only authorized to deliver experimental trial drugs to patients within the same national territory. While in the States, direct-to-patient trial drug delivery is classed as a pharmacy dispensing activity, forcing trial operators to register as out-of-state pharmacy bodies before DCTs can begin.

This brings a whole slew of pharmacy requirements to integrate into your regular PQS operations, blocking many from being able to realistically take part.

DCTs are one to watch for the future, then, but we expect that the regulatory landscape will require some tweaking to make them realistic operational prospects.

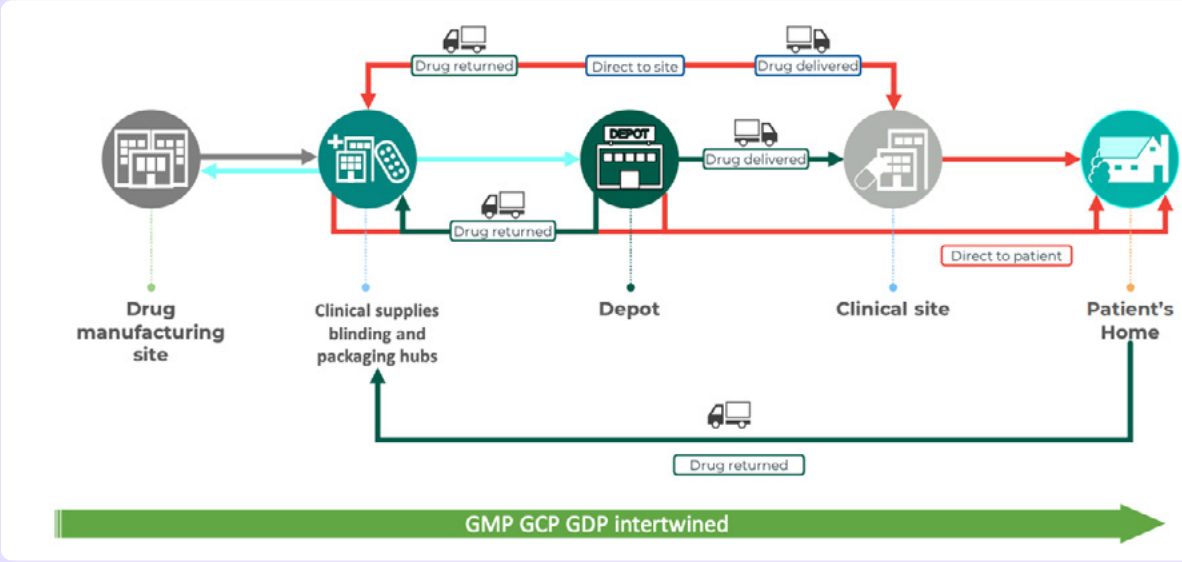


Figure 3: Potential DCT model. Credit: NSF

The takeaway: POC manufacturing and decentralized trials are still in the theoretical stage, but are gradually finding favor in multiple key markets as a way to deliver more agile, personalized therapeutics. Decentralizing operations and moving trial and medicinal delivery closer to the patient, we should imagine, would also help to tackle the supply chain and shortage issues noted above – while bringing new quality challenges to tackle. Keep an eye on developments in this space, particularly if you're involved in especially compatible areas like ATMP production!

Quality management maturity: a new approach to pharmaceutical quality

Arguably the most important industry development for pharmaceutical companies in 2024 is the ever-nearing Quality Management Maturity program from the FDA.

We saw above how it emerged as a response to the continuing drug shortage problem in the US, but its implications go far beyond just insulating drug supply.

A 2019 FDA drug shortage investigation report pitched 3 solutions to the shortage problem:

1 — Cultivating a shared, industry-wide understanding of the impact of drug shortages and the importance of guarding against them

2 — Promoting sustainable private contracts across the pharmaceutical industry to foster consistent supply of pharmaceutical product

3 — Establishing a quality management maturity 'rating' system that rewards companies reaching those 'more advanced levels of quality management'

Of these 3, it's the final point which has formed the heart of the QMM program and generated the most attention.

In short, pharmaceutical companies will be rewarded for the first time for moving beyond the baseline of bare-minimum cGMP compliance. Companies that can demonstrate commitment to continuous improvement, through practices like the adoption of new technology,

quality-cultural initiatives, leading quality metrics and proactive senior management support, will be given a public-facing quality 'score'.

Quality-centric pharma businesses will then enjoy boosted brand equity in front of industry purchasers, regulators and – most importantly – the drug-purchasing American public.

It's unlikely that the program will go live in 2024, but we can expect it to come closer into focus and towards its final form as the FDA finishes its consultation period.

The QMM program represents a dramatic overhaul of industry attitudes to quality management, and we predict international echoes once the FDA has rolled it out. 2024 will be the year when this watershed moment draws nearer.

Read our quality management maturity guide for more details

Chapter 2

Regulatory updates

The past few months have seen the roll-out of a string of new regulatory documents from both the FDA and ICH.

Do your research on all those applicable to your business and ensure you're prepared for evolving regulatory and quality expectations.

Upcoming FDA documents

Pharmaceutical quality/CMC

- Advanced manufacturing technologies designation program, designated technologies in drug and biological products
- Stability considerations for drug substances and drug products in NDAs, ANDAs, and BLAs and associated labeling statements for drug products
- Use of alternative tools to assess manufacturing facilities named in pending applications
- Post-approval manufacturing changes to biosimilars and interchangeable biosimilars questions and answers

Framework for Regulatory Advanced Manufacturing Evaluation (FRAME)

- Approaches to meeting cGMP requirements for distributed manufacturing
- Considerations for complying with 21 CFR 211.110

Upcoming ICH documents (in development or revision)

- ICH Q3E impurity: assessment & control of extractables and leachables for pharmaceuticals and biologics
- ICH Q5A (R2): Viral safety evaluation of biotechnology products derived from cell lines of human or animal origin
- M4Q (R2) CTD on quality
- ICH Q2/Q14: Analytical procedures
- ICH Q1A-E/Q5C (revision): stability testing

The MHRA

The UK MHRA has no new therapeutic regulatory documents in the pipeline for 2024. But a key consideration to anticipate is their replacement of the European Commission Decision Reliance Procedure (ECDRP) with a new post-Brexit International Recognition Procedure (IRP). In short, the MHRA will in 2024 recognize international drug licensing utilizing pre-existing MA decisions from the following territories:

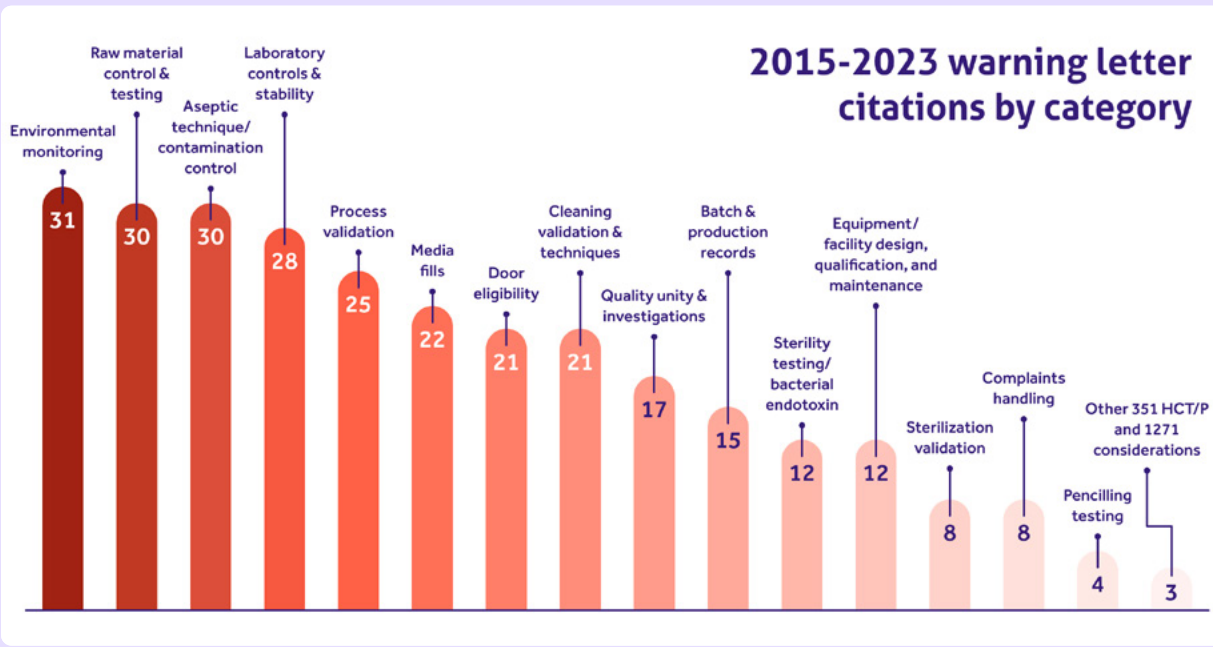
- Australia
- Canada
- The EU
- Japan
- Switzerland
- Singapore
- The US

Chapter 3

Quality and regulatory trends

Where are pharmaceutical businesses going wrong with their PQS activities as we head into 2024?

A key message from the FDA at the PDA/FDA Joint Regulatory Conference in late 2023 was that lazer focus on manufacturing quality and cGMP adherence is causing other adjacent quality issues to go unnoticed and unfixed. This is borne out in the data:



Environmental monitoring	› 21 CFR 211.113(b): Control of Microbiological Contamination › 21 CFR 211.42(c)(10): Design and Construction Features – Aseptic Processing
Raw material control & testing	› 21 CFR 211.80: General Requirements › 21 CFR 211.84: Testing and Approval/Rejection of Components, Containers, and Closures › 21 CFR 211.113(b): Control of Microbiological Contamination
Aseptic technique and contamination control	› 21 CFR 211.113(b): Control of Microbiological Contamination › 21 CFR 211.42(c)(10): Design and Construction Features – Aseptic Processing
Laboratory controls and stability testing	› 21 CFR 211.160: General Requirements › 21 CFR 211.166: Stability Testing
Process validation	› 21 CFR 211.100: Written Procedures: Deviations

Environmental monitoring and control of both raw materials and contamination topped the leading causes of warning letters for the 2015-2023 period.

Contaminations loomed large in recall data too, with three of the five most recalled products for 2016-2020 triggered by nitrosamine and methanol contamination.

What does this mean?

cGMP is important - but so is the environment your drug must pass through on its way to patients. Pay close attention to your adjacent environment, including your supply chain - as supply chains grow in length and complexity, the importance of robust contamination, material and environmental monitoring systems only grows.

The FDA's other key recurring quality concerns as we head into 2024 include:

- Continued marketing of unapproved products without an approved BLA or IND
- Inadequate microbial control
- Lack of adequate aseptic process validation and media fills
- Poor aseptic processes
- Lack of adequate environmental monitoring procedures
- Inadequate cleaning techniques and validation
- Inadequate quality control and screening systems
- Inadequate donor eligibility determination
- Inadequate investigations and material control from QC teams
- Lack of adequate batch and production records
- Inadequate testing programs
- Lack of stability data to support expiration dates
- Lack of appropriate testing for raw materials

If you've not recently reviewed, assured and optimized your quality and compliance in these areas, add them to the top of your internal auditing list. They represent the most common, current weaknesses in pharmaceutical operations.

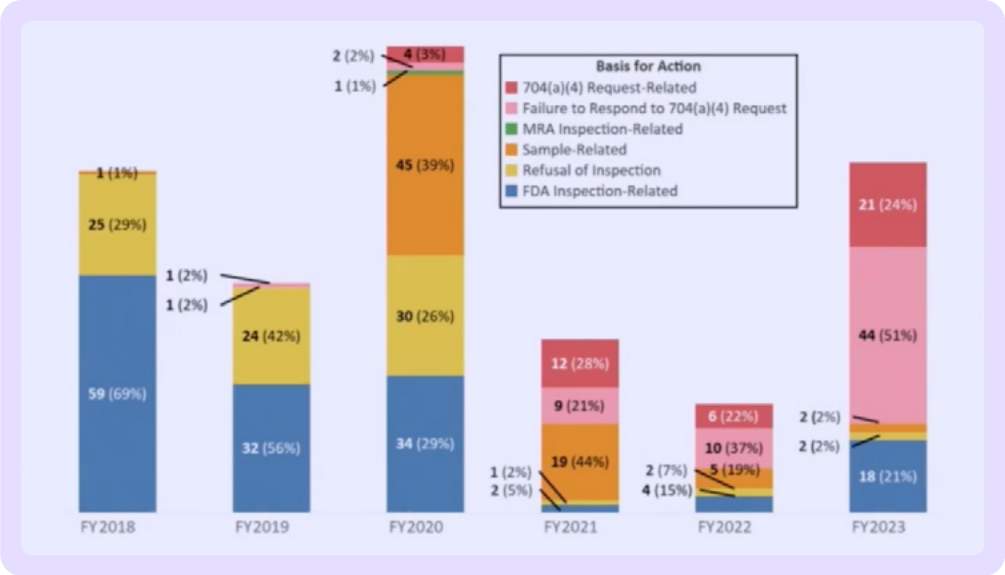


Figure 4: Shift in basis of action for drug adulteration import alert cases FY18-FY23 (as of 8/31/2023). FDA.

One final trend to be aware of is the increasing shift towards hybrid inspections, particularly in the US. The shift to 'remote regulatory assessments' and information requests that took place in the pandemic days of 2020-21 doesn't seem to be going anywhere as we head into 2024.

In fact, where inspections – or companies refusing to be inspected – drove 98% of drug adulteration import alert cases in 2018, that figure was only 23% in 2023.

Strikingly, three-quarters of the import alerts last year were triggered by either information uncovered during remote 704(a)(4) record requests, or by companies failing to respond adequately to those requests.

The FDA, in short, is relying more and more on remote inspections and record requests to keep tabs on drugmakers. The implication is that remotely accessible, cloud-based and digitized PQS documentation is now expected by default. Organizations that still rely on mountains of paper records will have to be physically inspected, and will therefore miss out on the faster, less burdensome hybrid approach which the FDA is starting to favor.

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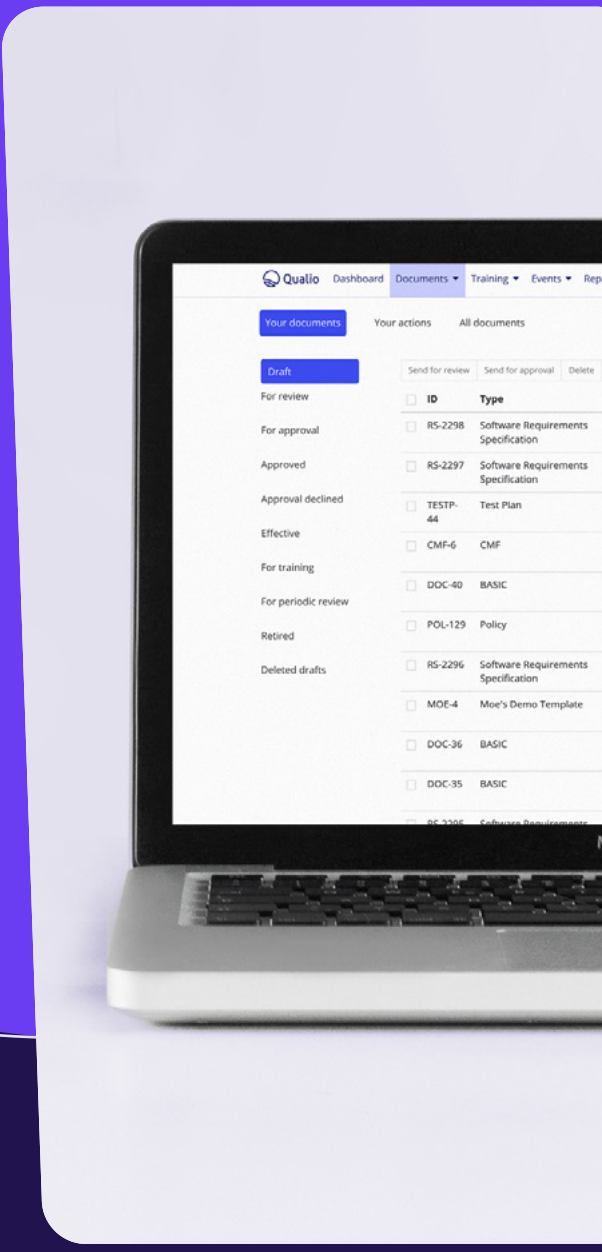
Prepare for 2024 with optimized, digitized quality

Learn more



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