

# **When Risk Is Ignored: GMP Inspection Pitfalls and Compliance Impact**

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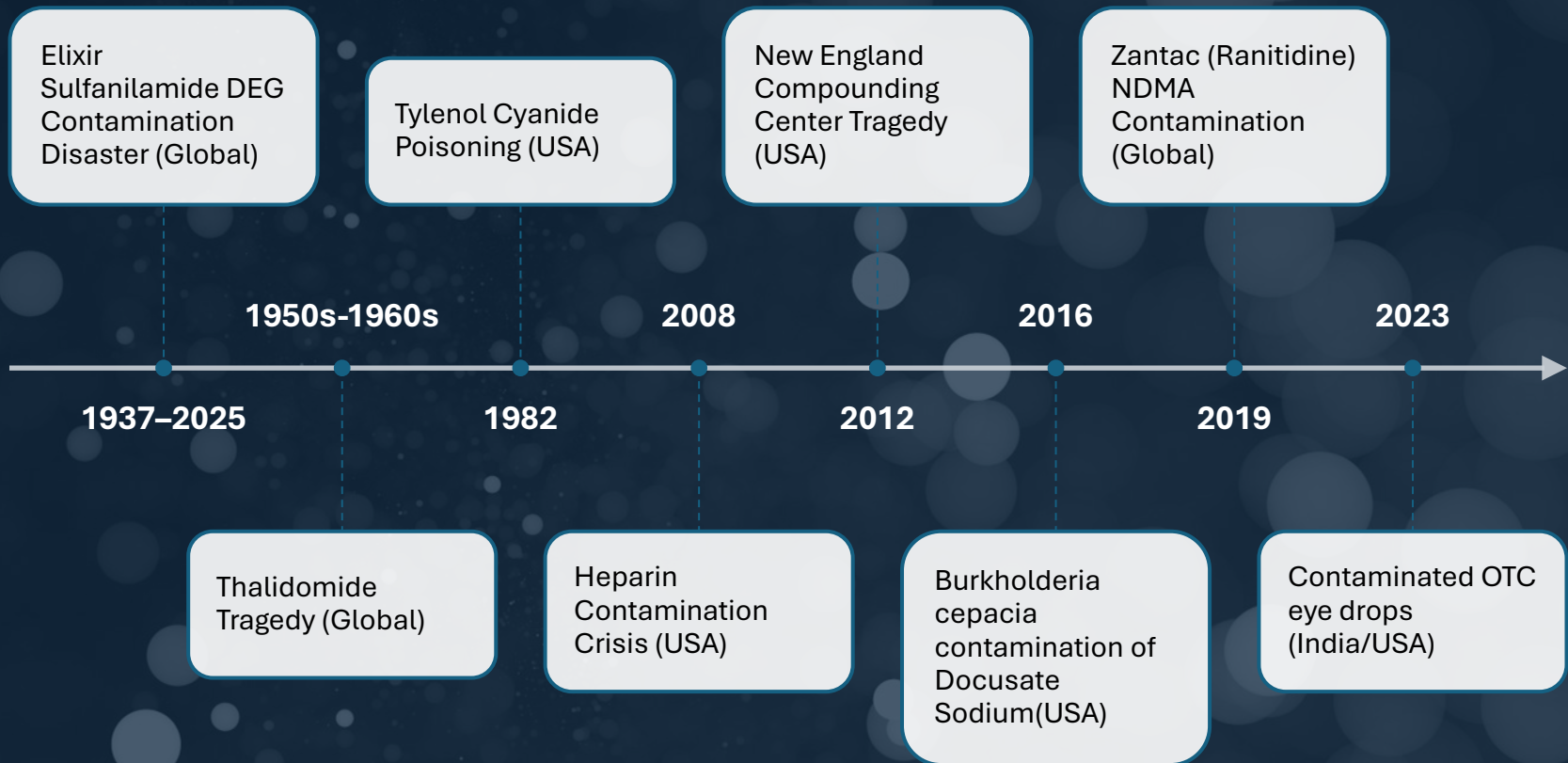


# Agenda

- Lessons Learned
- Why risk matters
- Where inspections go wrong
- Real-world examples
- Compliance & business impact
- Building a proactive quality culture



# Lessons Learned?





# DEG-Contaminated Cough Syrup (1937-2025)

## **High DEG Contamination Levels**

Certain cough syrup batches contained up to 48% diethylene glycol instead of glycerin, and causing acute kidney failure.

## **Child Fatalities and Symptoms**

Hundreds of fatalities have occurred globally after consuming tainted syrup, with symptoms progressing rapidly.

## **RISKS--Pharmaceutical Quality Failures**

Lapses in excipient testing and supply chain oversight allowed DEG contamination to enter cough syrup production. DEG, being chemically similar to glycerin yet significantly cheaper, is sometimes mistakenly or intentionally used as a substitute solvent in drug manufacturing.

## **Improved Safety Measures & Enforcement**

FDA requires stringent testing of glycerin for diethylene glycol (DEG) and ethylene glycol (EG) contamination. Manufacturers must test every container in all lots, not just rely on supplier certificates of analysis (COA), ensuring limits of 0.1% or less for these contaminants.



# Unsupported Safety Claims of Thalidomide (1950-1960s)

## **Introduction and Marketing**

Thalidomide was marketed in the late 1950s as a safe sedative and morning-sickness remedy, widely available without strict regulation.

## **RISKS--Lack of Safety Testing**

No reproductive toxicity studies were conducted, and drug effects on fetal development were not examined before widespread use.

## **RISKS--Regulatory Failures**

Weaker regulatory frameworks and inadequate clinical trials allowed thalidomide to be distributed globally without proper risk assessment.

## **Impact and Reforms**

Thalidomide's tragic consequences led to major reforms in drug development, safety evaluation, and approval worldwide.





# Heparin Contamination (2007)

- 2007–2008 crisis: Heparin contaminated with oversulfated chondroitin sulfate (OSCS), causing severe reactions and deaths.
- Contamination linked to intentional adulteration in global API supply chain.
- RISKS exposed: inadequate supplier oversight, weak raw material controls, and insufficient analytical testing.
- Regulatory response: enhanced testing, stricter supplier qualification, and reinforced ICH Q7 expectations. FDA Guidance 2013.





# NECC Contamination and Meningitis Outbreak (2012)

## **Outbreak Cause and Impact**

Contaminated steroid injections caused a fungal meningitis outbreak affecting hundreds (>700) and causing 64 deaths across 23 states in 2012.

## **Manufacturing Failures--RISKS**

NECC failed to maintain sterile conditions, with mold growth and poor environmental controls leading to contamination.

## **Regulatory Oversight Gaps & Legislative Reform**

Oversight failures between state boards and FDA allowed unsafe large-scale production of compounding pharmacies without proper enforcement. The Drug Quality and Security Act (DQSA) of 2013 clarified FDA oversight and established the outsourcing facility category for compounders.



# Contamination with *Burkholderia cepacia* (2016)

## Public Health Impact

The outbreak affected vulnerable patients (e.g., cystic fibrosis), causing severe infections (~60) and triggering a multistate health response.

## Contamination and Source Identification

*Burkholderia cepacia* contamination in docusate sodium solution (OTC stool softener) was traced to the facility purified water system.

## Regulatory Actions and Recall

FDA and CDC investigations led to voluntary recall and suspension of affected liquid docusate sodium products.

## Lessons and Compliance

The case highlights the need for strict GMP, environmental monitoring, and microbial contamination prevention in manufacturing.





# Contaminated OTC Eye Drops Tragedy (2023-2025)

- **Multistate outbreak:** antibiotic-resistant *P. aeruginosa* from OTC preservative-free, multi-dose eye drops caused 80+ infections, 4 deaths, 14 cases of vision loss.
- FDA found non-sterile batches & genetic matches between product isolates and patient infections.
- **RISKS:** lack of appropriate microbial testing, ophthalmic drugs in multi-use bottles without an adequate preservative, and lack of proper controls concerning tamper-evident packaging.
- Draft FDA Guidance (2023) Quality Considerations for Topical Ophthalmic Drug Products



## Broader Impact on U.S. Drug Oversight

- Stronger federal authority over large-scale compounding & OTC manufacturers.
- More frequent foreign-facility inspections and tighter GMP surveillance.
- Public awareness of oversight gaps in “low-priority” OTC drug category.



# RISK

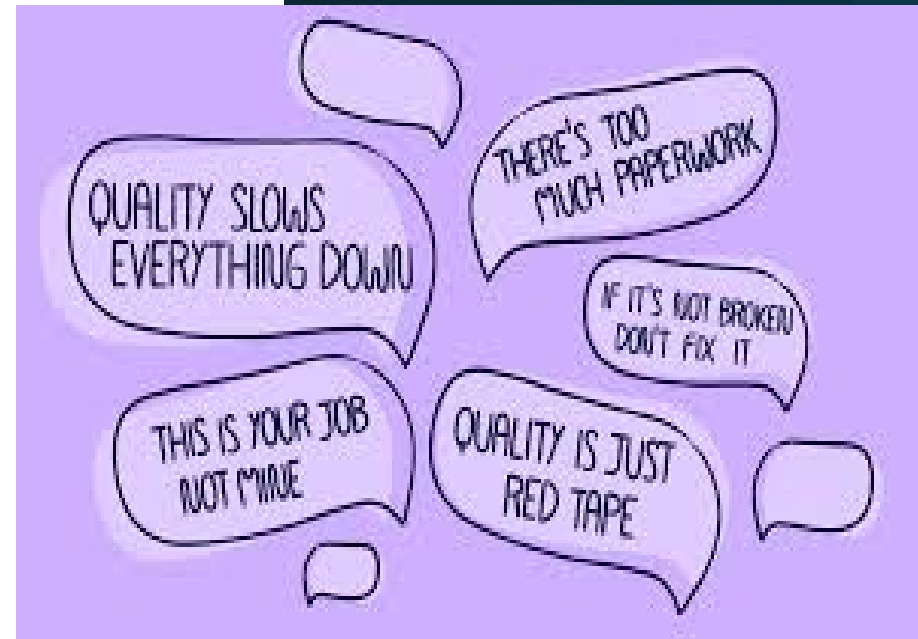
Regulatory landscape is evolving...  
Increased scrutiny on data integrity, sterile manufacturing,  
and supply chain...

Why risk blindness is still common?



# What 'Ignoring Risk' Looks Like

- Weak quality culture indicators
- Decisions made without impact assessment
- Overreliance on historical performance
- “*We’ve always done it this way*” mindset



# Weak Quality-Culture Indicators in Pharmaceutical Manufacturing



# Normalization of Deviations

## Indicators:

- Frequent minor deviations that are routinely accepted as “normal.”
- Trend of repeated deviations with no meaningful corrective action.
- Staff viewing deviations as paperwork rather than safety risks.

## Recommendations:

- Implement proactive deviation trending and routine cross-functional reviews.
- Reinforce that every deviation is a signal, not a nuisance.
- Train supervisors to model timely deviation reporting behavior.



# Fear of Reporting Errors/ Blame-Oriented Environment



## Indicators:

- Employees hide errors or avoid documenting issues.
- “*Who is at fault?*” culture instead of “*What failed in the system?*”
- Anonymous reporting channels unused.

## Recommendations:

- Adopt a Just Culture framework—focus on systems, not individuals.
- Reward transparency and emphasize learning from mistakes.
- Create confidential reporting pathways and routinely communicate outcomes.

# Poor GMP Documentation Practices/Data integrity

## Indicators:

- Backdating, missing signatures, incomplete batch records.
- Informal “rough notes” replacing controlled documentation.
- Data inconsistencies between logbooks, equipment records, and batch documents.

## Recommendations:

- Strengthen ALCOA+ training (Attributable, Legible, Contemporaneous, Original, Accurate + Complete, Consistent, Enduring, Available).
- Introduce real-time documentation controls and periodic data-integrity audits.
- Use electronic batch records (EBR) where appropriate.



# Inadequate Change Control Culture

## Indicators:

- Process or material changes implemented informally without assessment.
- Change controls perceived as slow bureaucratic obstacles.
- Recurring issues from unreviewed process adjustments.

## Recommendations:

- Train teams on risk-based change control and why it protects product quality. Categorize changes based on criticality.
- Enforce governance: no change without documented impact assessment.



# Lack of Ownership of Quality at the Floor Level

## Indicators:

- Operators rely heavily on QA to “catch problems later.”
- Little engagement in GMP housekeeping or contamination-control behaviors.
- QA seen as a policing function instead of a partner.

## Recommendations:

- Increase QA presence on the shop floor (“QA on the Floor” model).
- Use daily huddles to drive quality discussions and problem-solving.
- Make quality Key Performance Indicators (KPI) dashboards visible to all employees.



# Inadequate Training & Competency Verification

## Indicators:

- “Check-the-box” training; lack of hands-on competency assessment.
- Employees unaware of critical process parameters or contamination risks.
- High variability in execution of the same procedures.

## Recommendations:

- Implement structured OJT (on-the-job training) with qualified trainers.
- Add periodic requalification for critical tasks (aseptic, cleaning, compounding).
- Use video-based or scenario-based training to reinforce decision-making.



# Poor Cross-Functional Communication

## Indicators:

- Production, QA, QC, Supply Chain, and Engineering operate in silos.
- Critical quality signals missed due to lack of information sharing.
- Investigations stalled because departments don't collaborate.

## Recommendations:

- Establish daily or weekly cross-functional quality review meetings.
- Use digital platforms for investigation progress tracking.
- Train teams in root-cause analysis (RCA) as a shared discipline.



# Weak Management Commitment to Quality

## Indicators:

- Leadership emphasizes output, schedule, or cost over compliance.
- Quality metrics rarely discussed in leadership meetings.
- Limited investment in upgrading aging facilities or manufacturing/QC equipment.

## Recommendations:

- Include quality KPIs in leadership performance evaluations.
- Allocate budget specifically for quality improvements and modernization.
- Conduct quarterly management walkthroughs on the production floor.





# Lack of Quality Metrics Transparency

## Indicators:

- Metrics hidden within QA or presented only to upper management.
- Employees unaware of deviation rates, batch failures, or complaint trends.
- No shared KPIs for continuous improvement.

## Recommendations:

- Introduce plant-wide quality dashboards and frontline KPI boards.
- Align metrics with site performance goals (right-first-time, deviation rate, audit observations).
- Use monthly town halls to share quality performance and lessons learned.

# Ineffective Corrective and Preventive Actions (CAPAs)

## Indicators:

- Superficial root-cause investigations (“operator error”).
- CAPAs repeatedly overdue or ineffective at preventing recurrence.
- “Band-aid fixes” rather than addressing system contributors.

## Recommendations:

- Strengthen root-cause methodologies (Fishbone, 5-Whys, FMEA).
- Require effectiveness checks and post-implementation reviews.
- Trend CAPAs to identify emerging systemic vulnerabilities.





# Aseptic Failures

Quality Culture Case Studies



# Normalization of Deviations in Sterile Manufacturing

## **Routine Deviations Overlooked**

Repeated environmental monitoring excursions were dismissed as minor, preventing meaningful investigations.

## **Complacent Quality Culture**

A culture of complacency treated deviations as administrative tasks, undermining contamination risk awareness.

## **Insufficient Root Cause Analysis**

Investigations focused on operator error, ignoring systemic issues like equipment and facility design flaws.

## **Consequences and Lessons**

Normalization led to product contamination, regulatory warnings, and highlighted the need for scientific risk mitigation.





## Case Study: Data Integrity Weaknesses



# Uncontrolled Documentation Practices

## Shadow Documentation Risks

Unofficial worksheets led to transcription errors, unrecorded adjustments, and data omissions undermining accuracy.

## Audit Trail Findings

Audit trails revealed overwritten entries, missing metadata, and unauthorized retrospective data modifications.

## Cultural and Training Gaps

Emphasis on timelines over accuracy and minimal data integrity training normalized poor documentation practices.

## Consequences on Quality

Poor documentation caused batch delays, regulatory issues, and loss of trust in lab or manufacturing data integrity.

$$15 \times 4.2 = 63$$

$$\begin{array}{r} 210 \div 9 \\ \hline 23,3 \end{array}$$

$$\begin{array}{r} 543 \\ - 189 \\ \hline 354 \end{array}$$

$$210 \div 9$$



# Audit Trail Red Flags and Regulatory Impact

## **Audit Trail Inconsistencies**

Unexplained entry deletions, repeated overwriting, and missing audit-trail entries indicate critical system weaknesses.

## **System Control Weaknesses**

Insufficient system controls and poor user access management undermine data integrity and review processes.

## **Regulatory Impact**

Regulators demand corrective actions including system revalidation, audit-trail enhancements, and staff retraining.

## **Data Governance Importance**

Embedding strong governance and a culture valuing accuracy ensures data integrity in everyday operations.

# Case Study: Training and Competency Gaps





## Inconsistent Execution Due to Poor Training



### **Inconsistent Cleaning Procedures**

Operators performed cleaning inconsistently, causing recurring contamination risks and production stoppages.

### **Ineffective Training Methods**

Training relied mainly on reading procedures rather than structured on-the-job training, leading to skill gaps.

### **Cultural and Competency Gaps**

Lack of trainer qualifications, performance checks, and feedback channels revealed deeper organizational issues.

### **Need for Competency-Based Training**

Emphasizing competency-based programs and quality culture supports continuous learning and process ownership.

# Impact of Competency Gaps on Product Quality

## Effect on Product Quality

Competency gaps cause failures in sensitive processes, leading to contamination risks and production delays.

## Operator Awareness

Lack of understanding of process rationale results in shortcuts and procedural errors by operators.

## Building a Quality Culture

Investing in training programs and ongoing evaluation builds competency and reduces compliance risks.





# Improvement Strategies Across Case Studies

## **Promoting Just Culture**

Encouraging open issue reporting without fear fosters transparency and builds a Just Culture within organizations.

## **Robust Training Programs**

Comprehensive training and competency verification ensure personnel can reliably perform GMP activities.

## **Strengthening Data Integrity**

Reinforcing ALCOA+ documentation and using electronic systems enhances data reliability and decision confidence.

## **Leadership in Quality**

Effective leadership defines quality expectations, allocates resources, and emphasizes metrics organization-wide.

## **Cross-Functional Communication**

Structured CAPA programs and scientific problem-solving foster sustainable improvements through collaboration.

# Impact of Ignoring RISKS





Poor  
Product  
Quality  
and High  
Safety  
Risk to  
Patients



## Regulatory Impact



**WARNING  
LETTER**



**IMPORT  
ALERT**



**INCREASED  
INSPECTION  
FREQUENCY**



**DELAYED  
APPROVAL**



## Operational Impact

- Batch failures
- Production downtime
- Supply chain disruption/drug shortages
- Cost of remediation

# Key Takeaways

- Most GMP failures stem from ignored risks
- Proactive QRM reduces compliance exposure
- Strong quality culture is the best defense
- Inspection readiness must be continuous





Thank You



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