Quality Remediation
SAAPI Conference
May 2019

WHEN YOU NEED TO MEET A HIGHER STANDARD

JOHN HENCHION

You can find me at
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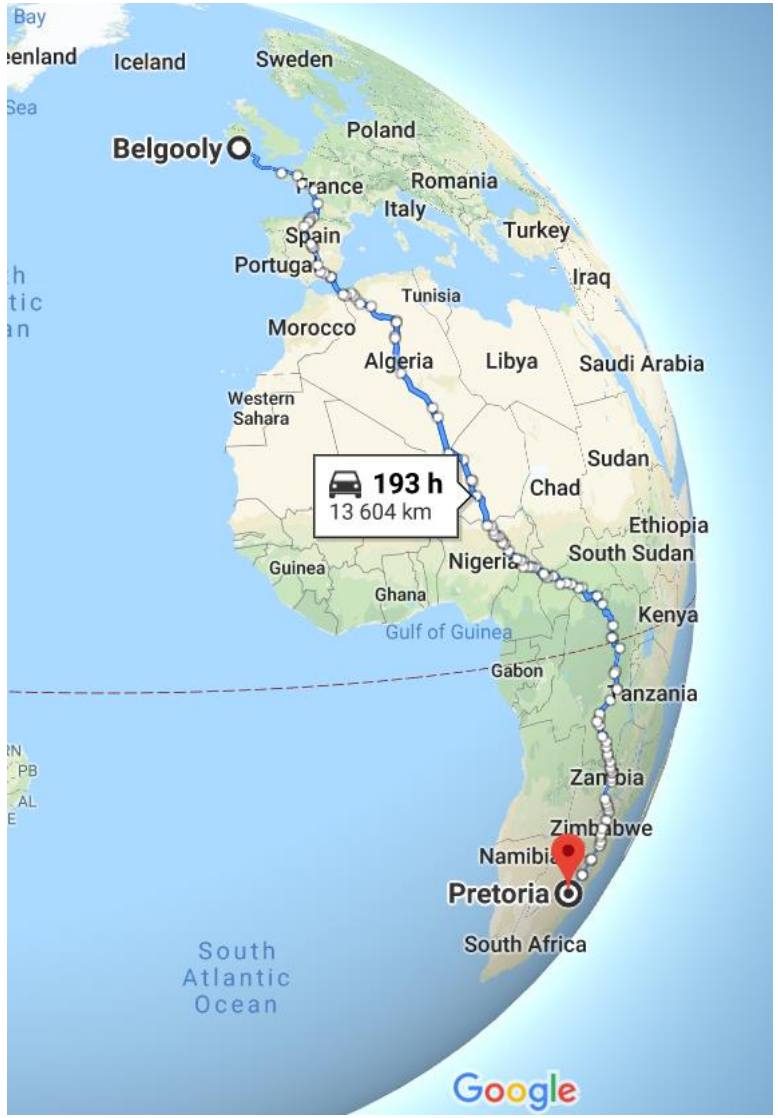
Global Director, Quality,
Compliance and Regulatory.



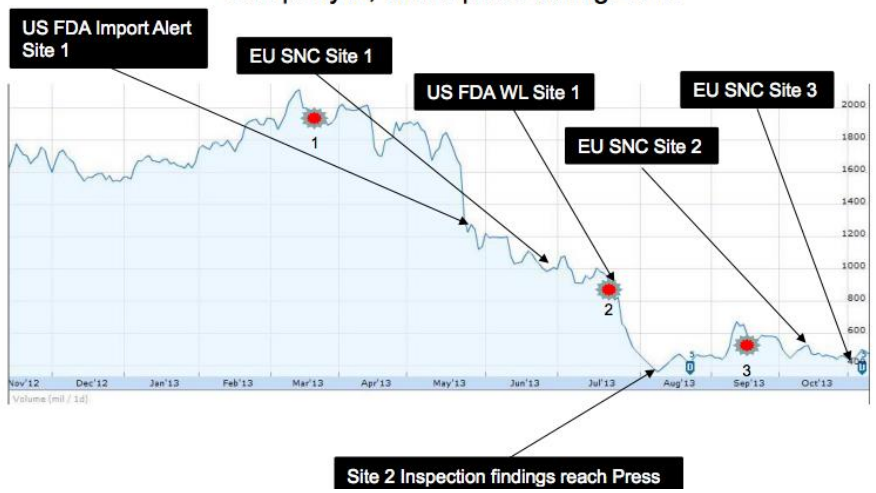
AGENDA

- Cost of Non-Compliance
- OOS
- Data Integrity
- Supply Chain
- Aseptic Manufacturing
- CAPAs/Deviations
- Quality Metrics/Culture

Cost of Non-Compliance

Company A Share Price 2012

Company A; share price during 2013



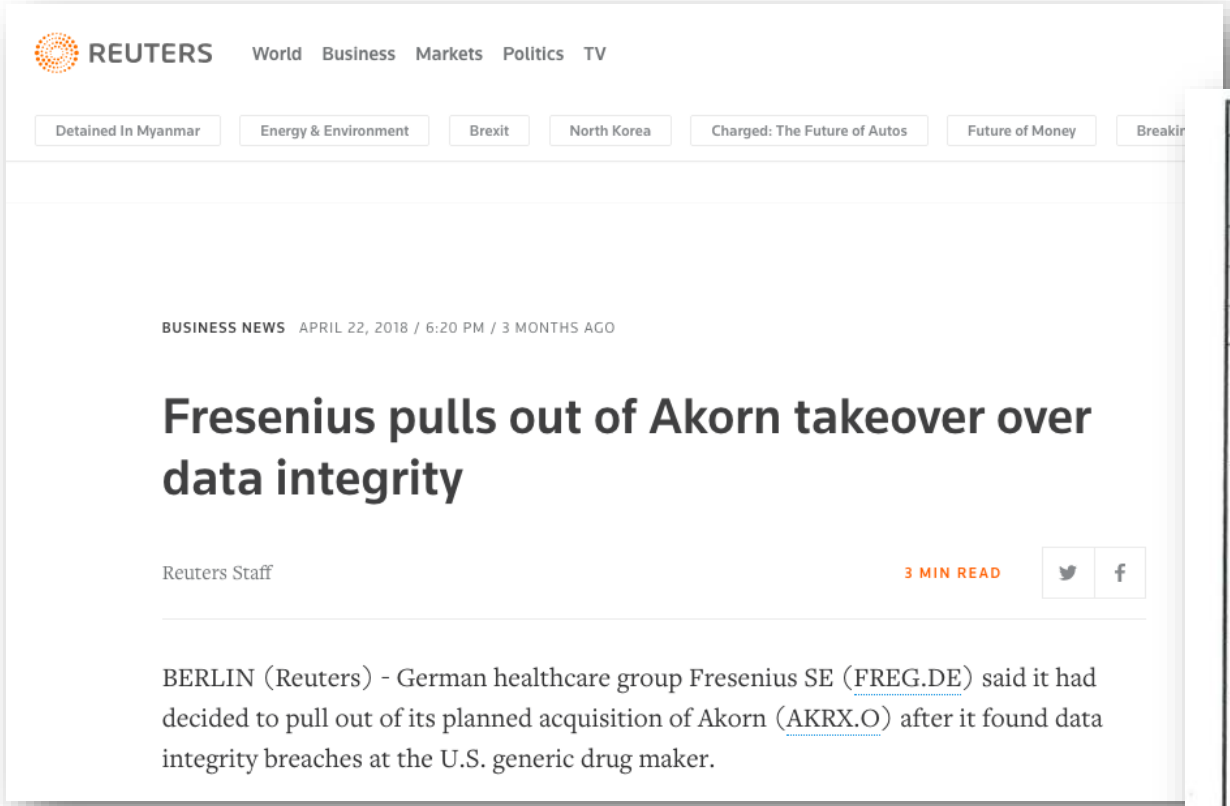
An increased focus on data integrity and governance systems has led to serious consequences for several companies

Blog Post by David Churchward at MHRA
http://ow.ly/OMfNr

Impact of organisational culture: is your company behaving well?

The impact of organisational culture and senior management behaviour on data governance must not be underestimated. Indicators with relevance to data governance provide a measure of the workforce's understanding and reporting behaviour, combined with the management's receptiveness to 'bad news'. Is error or system failure reported as an opportunity for improvement, or is there a mind-set around 'not wanting to cause trouble'? To remove the incentive to manipulate, re-create or amend data, the managerial response to 'bad news' must be fair and consistent, and not based on a fear of consequences.

'Led from the top; empowered from below'



REUTERS World Business Markets Politics TV

Detained In Myanmar | Energy & Environment | Brexit | North Korea | Charged: The Future of Autos | Future of Money | Breakir

BUSINESS NEWS APRIL 22, 2018 / 6:20 PM / 3 MONTHS AGO

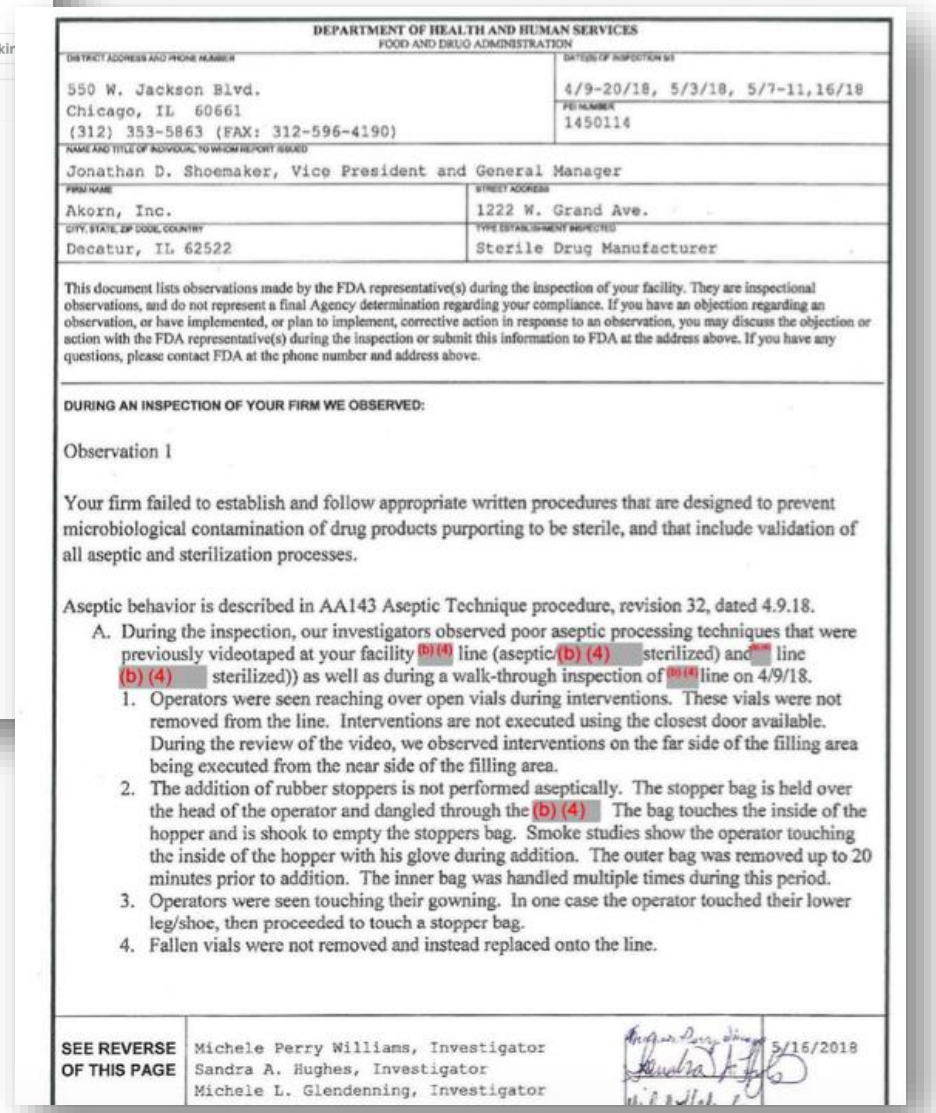
Fresenius pulls out of Akorn takeover over data integrity

Reuters Staff

3 MIN READ

BERLIN (Reuters) - German healthcare group Fresenius SE (FREG.DE) said it had decided to pull out of its planned acquisition of Akorn (AKRX.O) after it found data integrity breaches at the U.S. generic drug maker.

July 2018 – 24 page 483 published by FDA



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

550 W. Jackson Blvd.
Chicago, IL 60661
(312) 353-5863 (FAX: 312-596-4190)

4/9-20/18, 5/3/18, 5/7-11,16/18

FEI NUMBER
1450114

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Jonathan D. Shoemaker, Vice President and General Manager

FIRM NAME
Akorn, Inc.

STREET ADDRESS
1222 W. Grand Ave.

CITY, STATE, ZIP CODE, COUNTRY
Decatur, IL 62522

TYPE ESTABLISHMENT INSPECTED
Sterile 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

Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes.

Aseptic behavior is described in AA143 Aseptic Technique procedure, revision 32, dated 4.9.18.

A. During the inspection, our investigators observed poor aseptic processing techniques that were previously videotaped at your facility (b)(4) line (aseptic (b) (4) sterilized) and line (b) (4) sterilized)) as well as during a walk-through inspection of (b)(4) line on 4/9/18.
   1. Operators were seen reaching over open vials during interventions. These vials were not removed from the line. Interventions are not executed using the closest door available. During the review of the video, we observed interventions on the far side of the filling area being executed from the near side of the filling area.
   2. The addition of rubber stoppers is not performed aseptically. The stopper bag is held over the head of the operator and dangled through the (b) (4) The bag touches the inside of the hopper and is shook to empty the stoppers bag. Smoke studies show the operator touching the inside of the hopper with his glove during addition. The outer bag was removed up to 20 minutes prior to addition. The inner bag was handled multiple times during this period.
   3. Operators were seen touching their gowning. In one case the operator touched their lower leg/shoe, then proceeded to touch a stopper bag.
   4. Fallen vials were not removed and instead replaced onto the line.

SEE REVERSE OF THIS PAGE

Michele Perry Williams, Investigator
Sandra A. Hughes, Investigator
Michele L. Glendenning, Investigator

5/16/2018

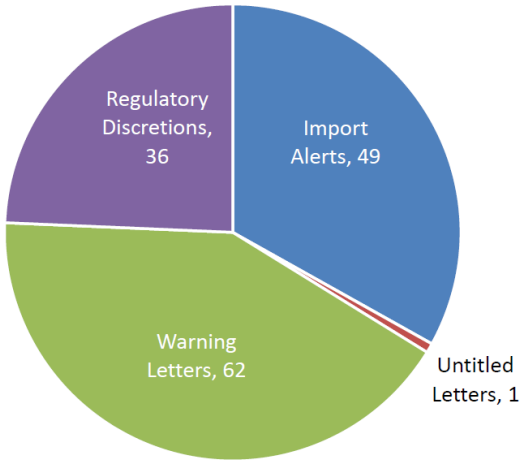
FDA CDER DATA

Recent Warning Letter Trends

1. OOS Investigations
2. Data Integrity
3. Water Systems
4. Cross Contamination
5. Lack of raw material and finished drug testing
   - More often for non-application, OTC, monograph drugs

Enforcement and advisory tools

Regulatory Meetings
Injunctions
Consent Decrees
Import Alerts
Seizures
Warning Letters
Untitled Letters
Others



1 Jan 2018 to 31 August 2018
Excludes compounding-related actions

Out Of Specification

CDER - OOS

Recent Warning Letter Trends: OOS Investigations

- 2018: more than 10 Warning Letters for deficient out-of-specification investigations
  - FDA Guidance on this topic
    - https://www.fda.gov/downloads/drugs/guidances/ucm070287.pdf
- Frequent OOS investigation issues:
  1. Not appropriately expanding scope to include manufacturing
  2. Inappropriate use of outlier tests

www.fda.gov

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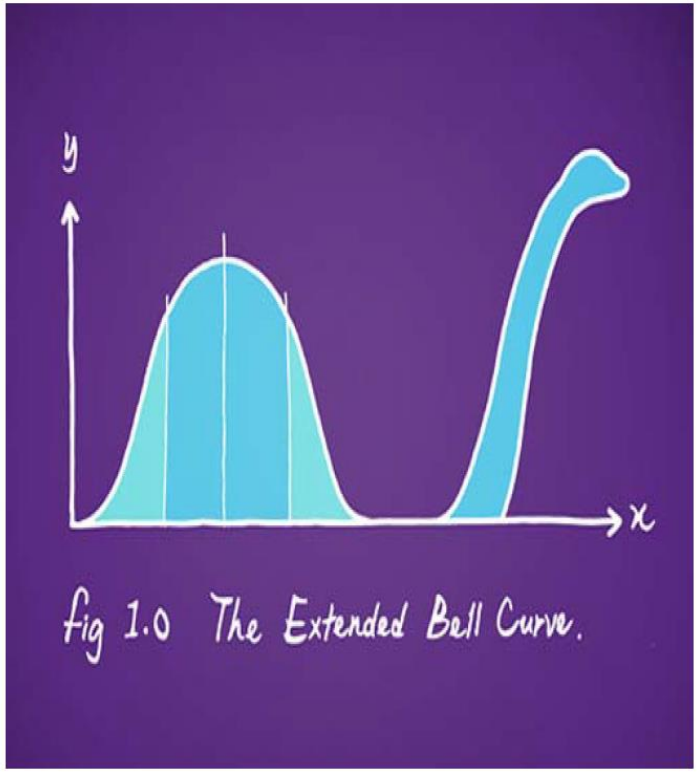
CDER - OOS

Recent Warning Letter Trends: OOS Investigations

- Inappropriate use of outlier tests:
  - *you attributed this failure to an "unknown lab error." You claimed that the low individual assay test result was an outlier and that the most probable root cause was analytical error. Outlier tests have no applicability in cases where the variability in the product is what is being assessed.*

– Recent warning letter



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OUT OF SPECIFICATION PROCEDURES

- Binary Outcome
- Phased approach

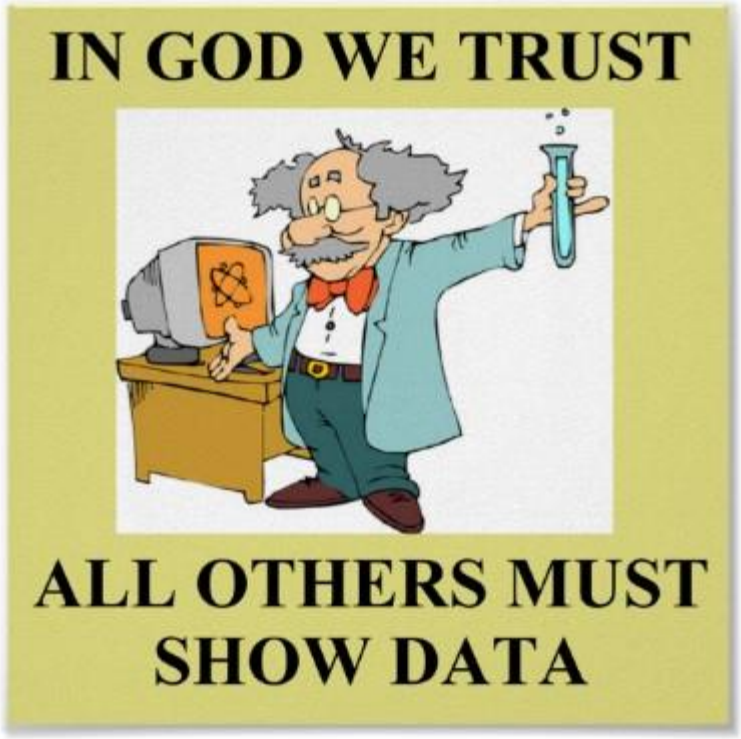
- Phase 1 – clear and obvious Lab error

- Ask yourself the question – any evidence to prove this?

DATA Integrity

DATA INTEGRITY

- Regulatory request is that Industry is designing systems where deliberate acts of fraud are impossible.
- Why the lack of trust?



CDER – DATA INTEGRITY TRENDS

Recent Warning Letter Trends: Data Integrity

- FDA continues to see a significant number of CGMP violations due to lack of data integrity.
- Numerous regulatory actions result
  - Warning Letters
  - Import Alerts
  - Consent Decrees
- But there are degrees of data integrity issues…

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CDER – DATA INTEGRITY

Recent Warning Letter Trends: Data Integrity

- Degrees of data integrity issues…
- Poor lab/data controls
  - *Our investigator observed that the audit trail feature was disabled on instruments you use for quality control testing of your API, including your high performance liquid chromatography system. Your analytical systems also lacked controls to prevent users from deleting or altering electronic data. For example, your quality assurance executive, who also performed your analytical tests, had administrator access to each system.*
- Overriding OOS findings
  - *our investigator found unreported analyses including out-of-specification (OOS) results for the same lot acquired earlier on the same date, and on the next day as the reported results*

www.fda.gov

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CDER – DATA INTEGRITY

Recent Warning Letter Trends: Data Integrity

- Degrees of data integrity issues…
- 2 sets of books
  - *Our investigator also found that you failed to document, investigate, and resolve out-of-specification (OOS) results in your laboratory. The investigator identified two sets of laboratory testing records for four [redacted] batches and five [redacted] batches: one set of records included OOS results; the second set included results within specifications.*

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CDER - DATA INTEGRITY

Recent Warning Letter Trends: Data Integrity

- Degrees of data integrity issues…
- Outright Falsification
  - *You were not able to provide analytical test data for three batches of [redacted] spray and one batch of [redacted]. We found that you created certificates of analysis for these four batches before they were manufactured and tested.*

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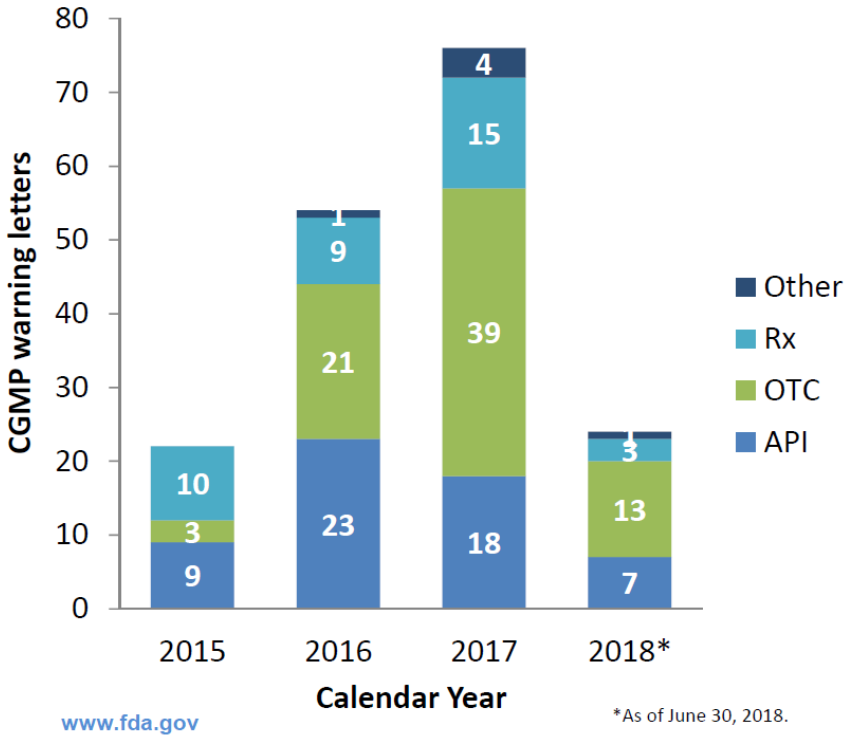
The Marketing Authorisation Holders are responsible for the integrity of their Supply Chain.

API SUPPLY

- Where are you sourcing your API from?
- How are you ensuring compliance with ICH Q7?
- Are the Regulators Inspecting based on Geographical Convenience or Risk?

FDA INSPECTION DATA

Inspectional Outcomes



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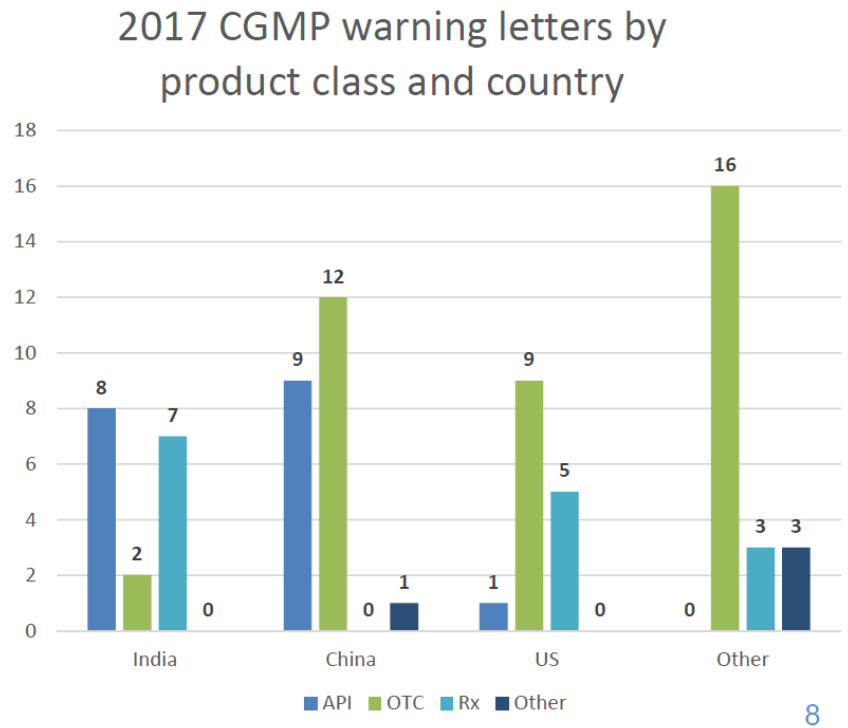
*As of June 30, 2018.



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CDER – API & RAW MATERIALS

Recent Warning Letter Trends: Raw Material and Finished Drug Testing

- 2018: more than 20 warning letters and many import alerts so far for failures to meet basic CGMP
  - No raw material testing prior to use
  - No drug product testing prior to release
- Typically non-application OTC/monograph drugs.

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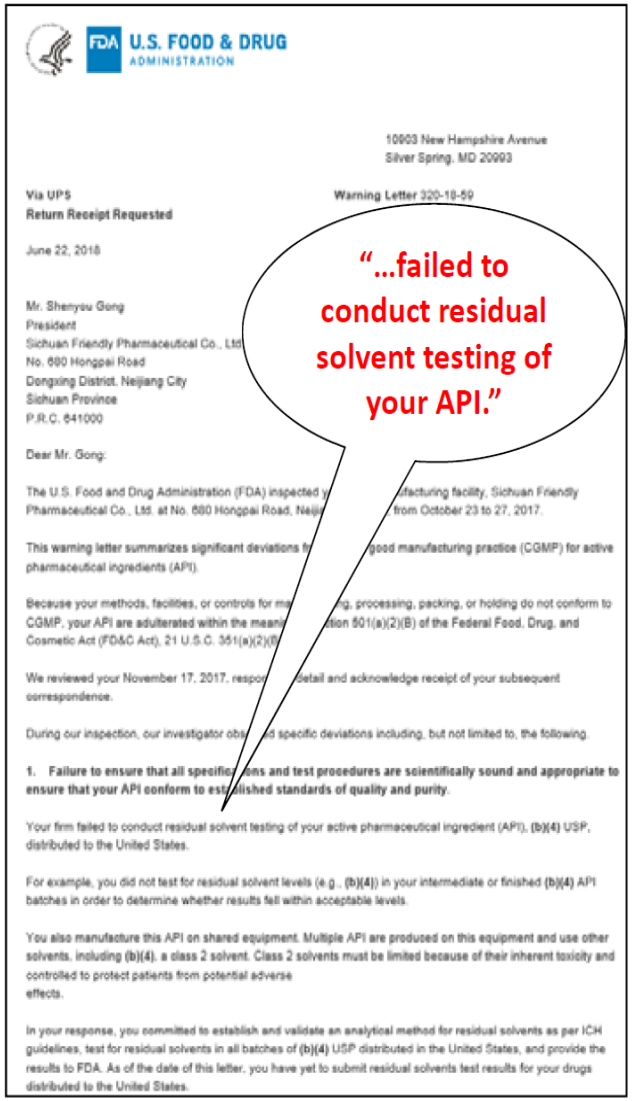
CDER – API & RAW MATERIALS

API Manufacturers

Different types of impurities

- Degradants that increase over time
- Residual solvents left over from the manufacturing process
- Elemental impurities in raw materials
- Byproducts of manufacturing chemistry reactions

www.fda.gov



U.S. FOOD & DRUG ADMINISTRATION

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS
Return Receipt Requested

Warning Letter 320-18-59

June 22, 2018

Mr. Shenyou Gong
President
Sichuan Friendly Pharmaceutical Co., Ltd
No. 680 Hongpai Road
Dongxing District, Neijiang City
Sichuan Province
P.R.C. 641000

Dear Mr. Gong:

The U.S. Food and Drug Administration (FDA) inspected y… facturing facility, Sichuan Friendly Pharmaceutical Co., Ltd. at No. 680 Hongpai Road, Neiji… from October 23 to 27, 2017.

This warning letter summarizes significant deviations f… good manufacturing practice (CGMP) for active pharmaceutical ingredients (API).

Because your methods, facilities, or controls for ma… g, processing, packing, or holding do not conform to CGMP, your API are adulterated within the meani… tion 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 November 17, 2017, respo… detail and acknowledge receipt of your subsequent correspondence.

During our inspection, our investigator obs… d specific deviations including, but not limited to, the following:

1. **Failure to ensure that all specific… ons and test procedures are scientifically sound and appropriate to ensure that your API conform to est…ished standards of quality and purity.**

Your firm failed to conduct residual solvent testing of your active pharmaceutical ingredient (API), (b)(4) USP, distributed to the United States.

For example, you did not test for residual solvent levels (e.g., (b)(4)) in your intermediate or finished (b)(4) API batches in order to determine whether results fell within acceptable levels.

You also manufacture this API on shared equipment. Multiple API are produced on this equipment and use other solvents, including (b)(4), a class 2 solvent. Class 2 solvents must be limited because of their inherent toxicity and controlled to protect patients from potential adverse effects.

In your response, you committed to establish and validate an analytical method for residual solvents as per ICH guidelines, test for residual solvents in all batches of (b)(4) USP distributed in the United States, and provide the results to FDA. As of the date of this letter, you have yet to submit residual solvents test results for your drugs distributed to the United States.

"…failed to conduct residual solvent testing of your API."

CDER – API & RAW MATERIALS

Obfuscation of supply chain information

- Failing to include the name of the API manufacturer or expiration date of the certificate of analysis
- Obscuring the name of the original API by placing their letterhead on the certificate of analysis

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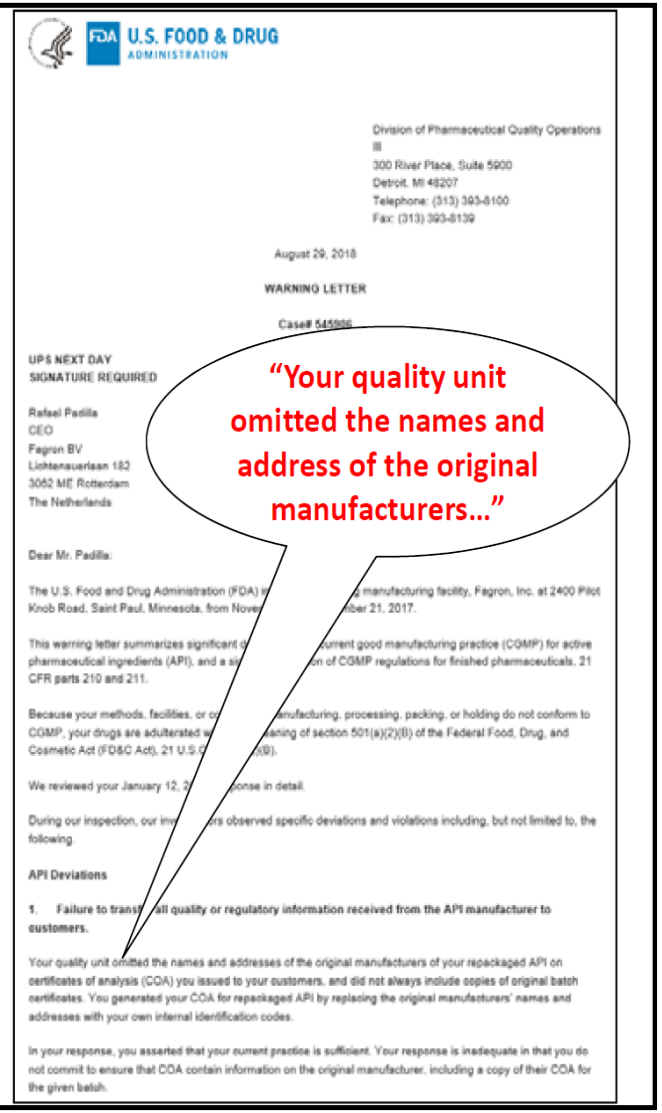

U.S. FOOD & DRUG ADMINISTRATION

Division of Pharmaceutical Quality Operations
III
300 River Place, Suite 5900
Detroit, MI 48207
Telephone: (313) 393-8100
Fax: (313) 393-8139

August 29, 2018

WARNING LETTER

Case# 545906

UPS NEXT DAY
SIGNATURE REQUIRED

Rafael Padilla
CEO
Fagron BV
Lichtenauerlaan 182
3062 ME Rotterdam
The Netherlands

"Your quality unit omitted the names and address of the original manufacturers…"

Dear Mr. Padilla:

The U.S. Food and Drug Administration (FDA) i… manufacturing facility, Fagron, Inc. at 2400 Pilot Knob Road, Saint Paul, Minnesota, from Nove… ber 21, 2017.

This warning letter summarizes significant d… urrent good manufacturing practice (CGMP) for active pharmaceutical ingredients (API), and a si… on of CGMP regulations for finished pharmaceuticals, 21 CFR parts 210 and 211.

Because your methods, facilities, or co… anufacturing, processing, packing, or holding do not conform to CGMP, your drugs are adulterated w… aning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. …(B).

We reviewed your January 12, 2… onse in detail.

During our inspection, our inv… rs observed specific deviations and violations including, but not limited to, the following:

API Deviations

1. Failure to transm… all quality or regulatory information received from the API manufacturer to customers.

Your quality unit omitted the names and addresses of the original manufacturers of your repackaged API on certificates of analysis (COA) you issued to your customers, and did not always include copies of original batch certificates. You generated your COA for repackaged API by replacing the original manufacturers' names and addresses with your own internal identification codes.

In your response, you asserted that your current practice is sufficient. Your response is inadequate in that you do not commit to ensure that COA contain information on the original manufacturer, including a copy of their COA for the given batch.

CDER – API & RAW MATERIALS

Recent Warning Letter Trends: Raw Material and Finished Drug Testing

More worrisome, there have been four Warning Letters related for glycerin testing so far in 2018.

You failed to test incoming components you use in manufacturing drug products to determine their conformance to identity, purity, strength, and other appropriate specifications....

For example, your firm did not test each lot of glycerin used as a component of your drugs to determine whether diethylene glycol (DEG) or ethylene glycol was present....

DEG contamination in pharmaceuticals has resulted in various lethal poisoning incidents in humans worldwide.

– Recent warning letter

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Aseptic Manufacturing

ASEPTIC MANUFACTURING

- Risk based EM program
  - Data driven decisions
- Operator training
  - Microbial background
  - Aseptic technique
  - Supervision
- Media Fill Qualification
  - Product Grouping
  - Discards
  - Interventions

Vaccines - MassBiologics

Tetanus and Diptheria Toxoids, Tetanus and Diptheria Toxoids Adsorbed (Td vaccine) and influenza vaccine

- Untitled Letter Issued October 2, 2017
- CGMP violations:
  - Poor aseptic technique, failure to calibrate/inspect/check equipment used in manufacture

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RTI Surgical, Inc.

- Inspection April 3 – 28, 2017
- Numerous CGMP violations: media fill issues, lack of process validation, inadequate environmental monitoring, etc.
- ***WL** issued November 8, 2017
- Firm sent many updates
- Response Review issued April 27, 2018 (continued deficiencies)

map3® Cellular Allogeneic Bone Graft Product (map3® Allograft)

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CDER - WATER

Recent Warning Letter Trends: Water Systems

Our investigator found that your firm was falsifying laboratory data. ... For multiple points of use, your analyst reported far fewer CFU than observed on the plate by our investigator....This is concerning because you use [redacted] water to manufacture products, such as [redacted] API, that are intended for use in sterile injectable dosage forms.

– Recent warning letter

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CDER - CROSS CONTAMINATION

Recent Warning Letter Trends: Cross Contamination

Import Alerts/Warning Letters for potent drugs

- **Hormones:**
  An API firm makes multiple potent drugs (including hormones) on shared equipment, but didn't validate cleaning.

- **Beta Lactams:**
  A finished-dosage firm makes OTC drugs for the US market, but uses the same facility to make beta lactam drugs.

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CAPAs/Deviations

CAPA WATCH OUTS

System

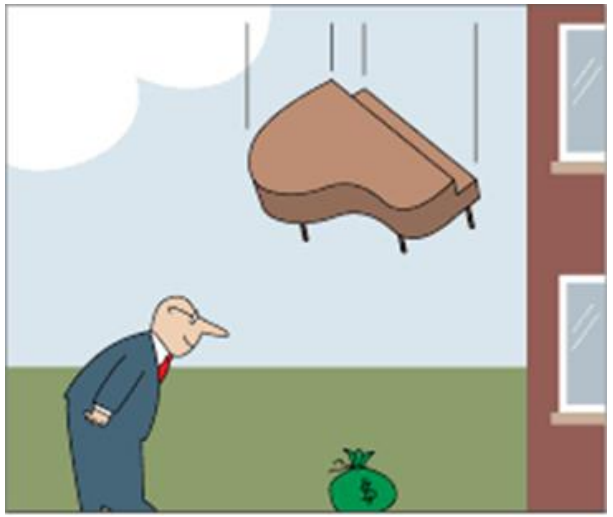
- Everything being put onto System
- Large % of overdue CAPAs
- Large % of retraining CAPAs
- Follow on CAPA's
- Impact of Metrics on behaviour
- Driven by Quality

CAPA

- Badly Defined
- Not Managed
- Not Honest
- Last minute.com
- Poor Owner Engagement

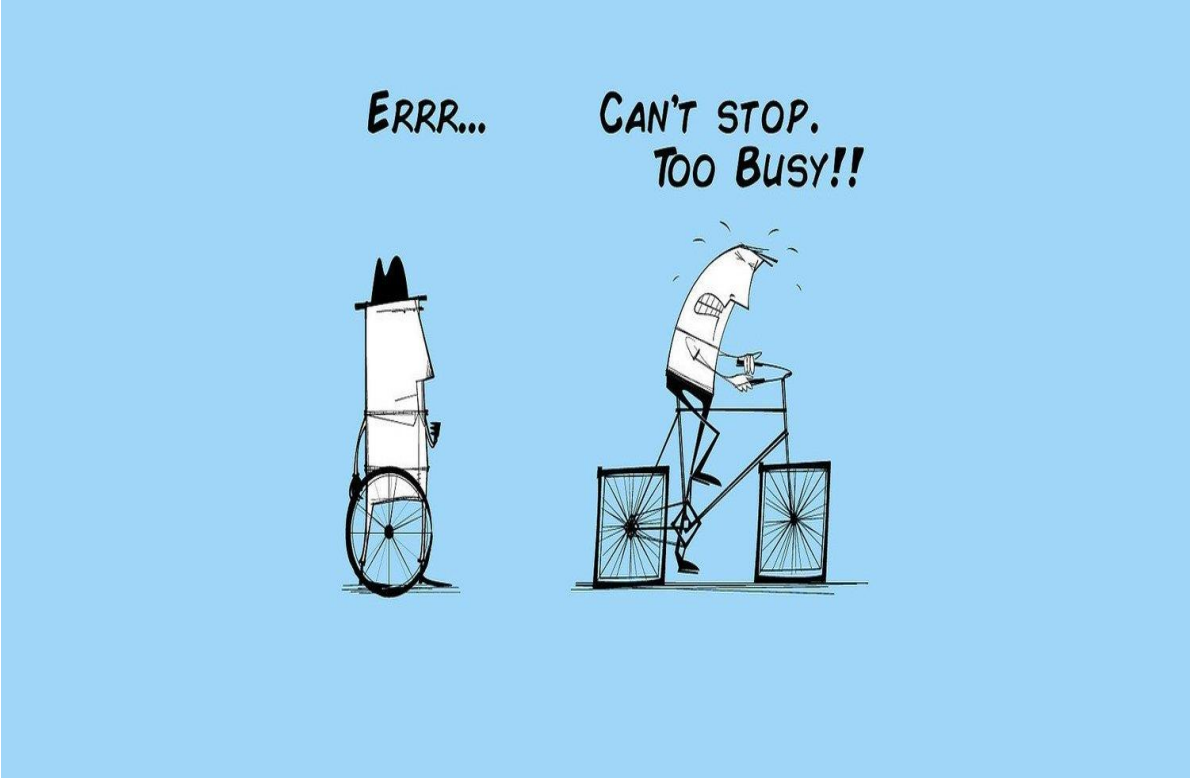
NOT ALL CAPAs ARE EQUAL

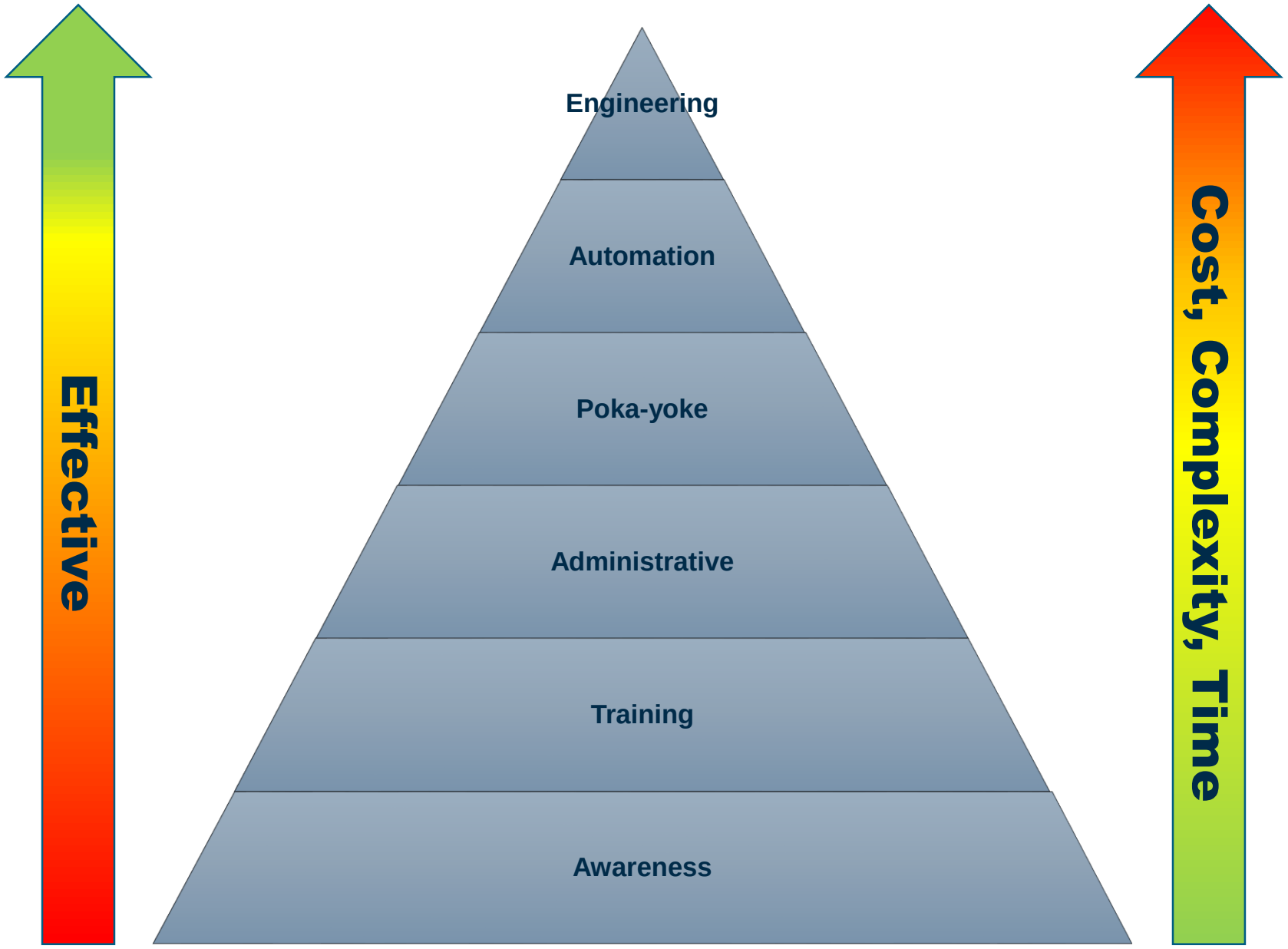
- Is CAPA commensurate with Risk/potential for occurrence?



ELEMENTS OF CAPA

- Self Contained
- Clear and Agreed Ownership
- Defined Deliverable
- Defined Time frame
- Compliance Justification for Time Frame
- Effectiveness Check





CAPA EFFECTIVENESS

EFFECTIVENESS CHECKS

- Does the Fix Work?
- Recurrence check in 6 months time?
  - Adds nothing to Quality System
  - Focused on Event not Root Cause
  - Passive
- Active Effectiveness check

Quality Metrics & Quality Culture

THE DEBATE STARTED IN 2013…

- Per ICH Q10, “Conduct management reviews of process performance and product quality and of the pharmaceutical quality system”
- Metrics are a tool designed to
  - **Drive continuous improvement** ,
  - Provide **early detection** of control drifts,
  - **Focus resources** on a particular area
  - Ensure a **stable longer term supply of drug product**.

- The development of meaningful Quantitative Quality Metrics within a company requires overcoming a number of **challenges**
- The industry (through professional society comment) is **supportive** of FDA’s efforts to utilize Quality Metrics as a potential input into FDA’s Inspectional Risk Model

Which Quality Metrics are best suited for FDA’s Inspectional Risk Model

HOW FDA INTENDS TO USE METRICS

FDA intends to use data from the quality metrics reporting program to focus the use of FDA resources on the areas of highest risk to public health (e.g., risk-based inspection scheduling).

- Establish a signal detection program as one factor in identifying establishments and products that may pose significant risk to consumers
- Identify situations in which there may be a risk for drug supply disruption
- Risk Based inspection
- Risk-based principles for reduced post-approval change reporting
- Improve the effectiveness of establishment inspections; and improve FDA's evaluation of drug manufacturing and control operations.

STARTING METRICS FDA NOV 2016

- **Lot Acceptance Rate (LAR)** as an indicator of manufacturing process performance. LAR = the number of accepted lots in a timeframe divided by the number of lots started by the same covered establishment in the current reporting timeframe.
- **Product Quality Complaint Rate (PQCR)** as an indicator of patient or customer feedback. PQCR = the number of product quality complaints received for the product divided by the total number of dosage units distributed in the current reporting timeframe.
- **Invalidated Out-of-Specification (OOS) Rate (IOOSR)** as an indicator of the operation of a laboratory. IOOSR = the number of OOS test results for lot release and long-term stability testing invalidated by the covered establishment due to an aberration of the measurement process divided by the total number of lot release and long-term stability OOS test results in the current reporting timeframe.

CULTURE – NO ONE SIZE FITS ALL

CULTURE

- What is Culture?

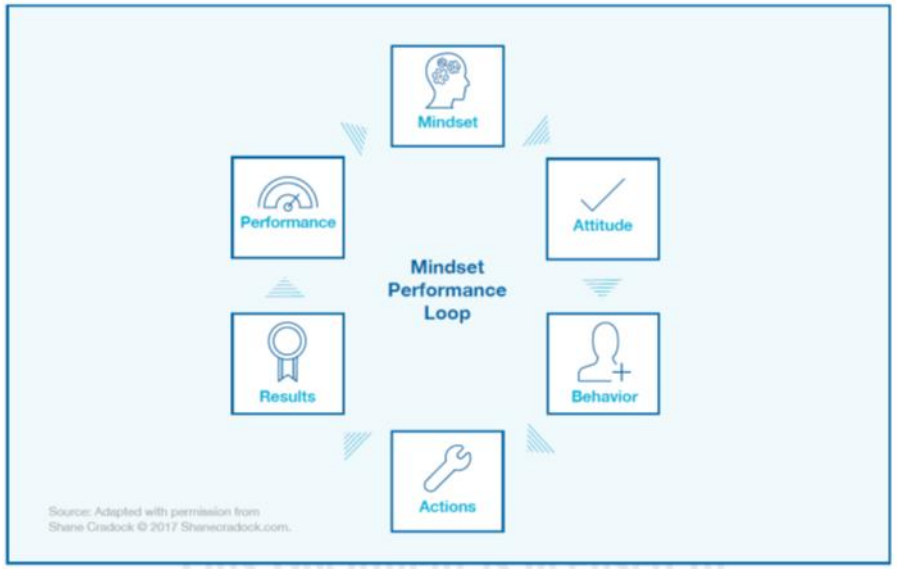
- How do you measure something like Culture?

ISPE QUALITY CULTURE EXCELLENCE

- A holistic *Quality Culture Framework* has been developed, entitled the *Six Dimensions of Cultural Excellence*

QUALITY METRICS AND CULTURE

- Metrics Drive Behaviours
- Behaviours drive Culture

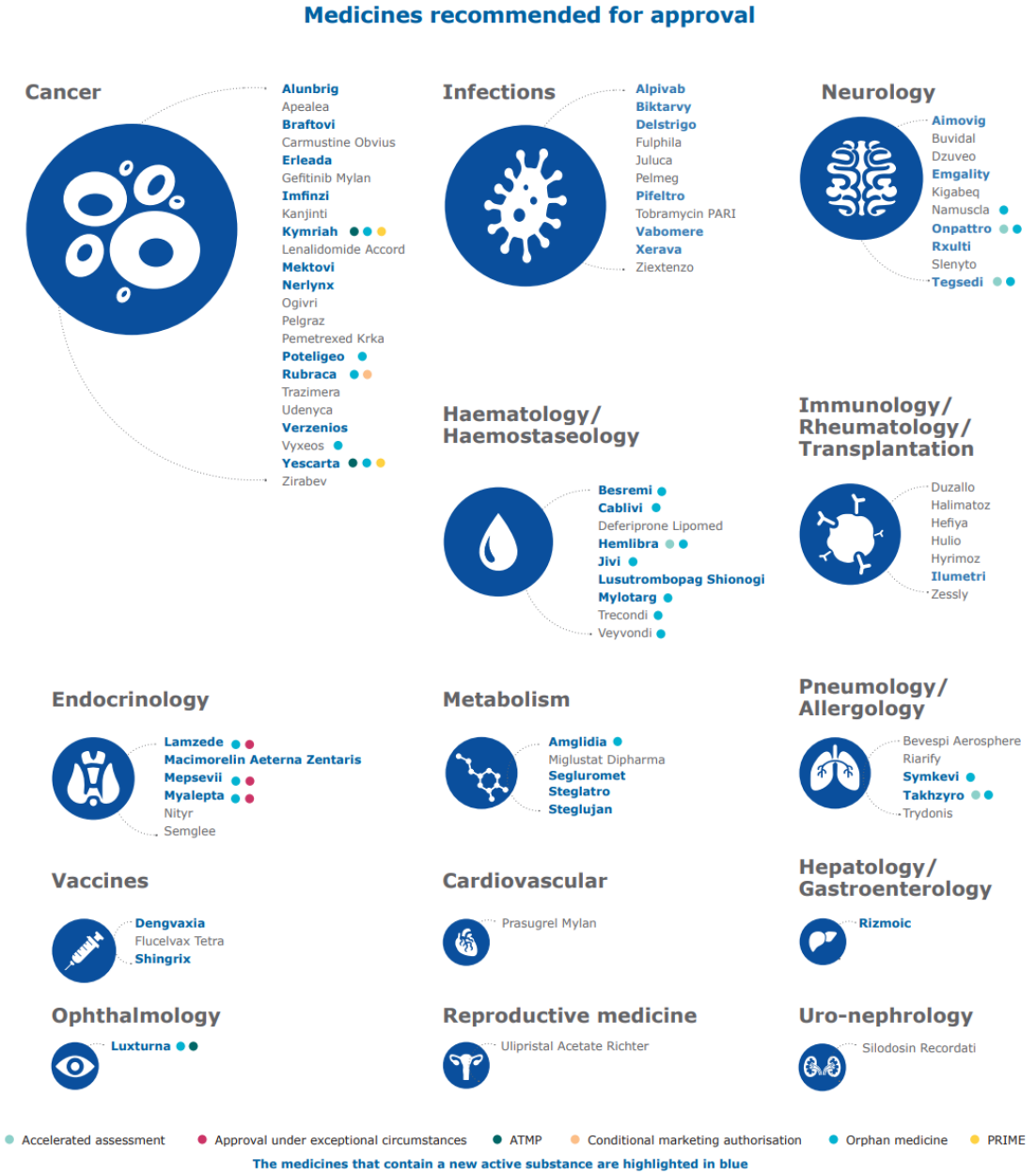


- Compliance versus Quality

- CAPA's closed on time
- No. of CAPAs overdue
- No. of Ineffective CAPAs
- No. of Killer/100 year CAPAs

New Product Trends

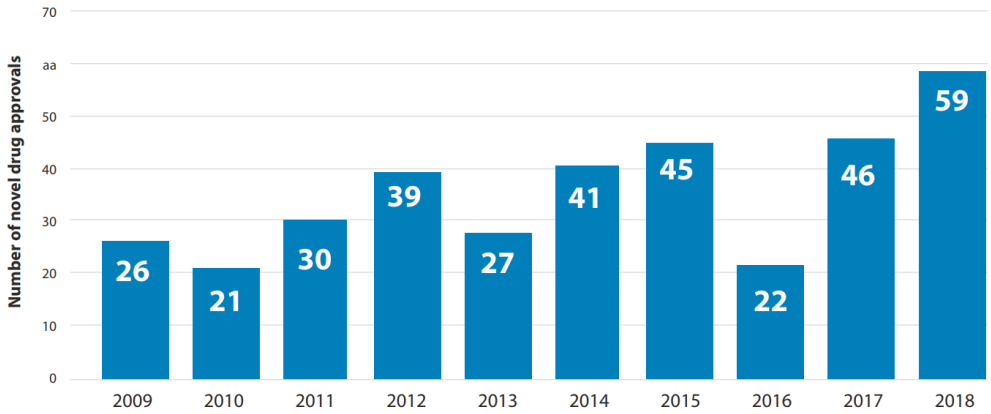
EMA - HIGHLIGHTS



FDA - HIGHLIGHTS

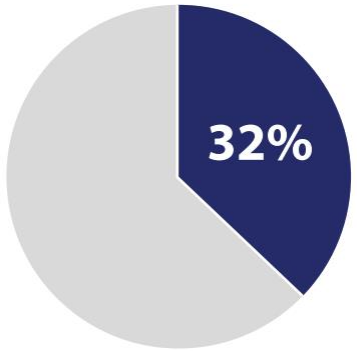
CDER's Annual Novel Drug Approvals: 2009 - 2018

In 2018, CDER approved 59 novel drugs. The 10-year graph below shows that from 2009 through 2017, CDER has averaged about 33 novel drug approvals per year.

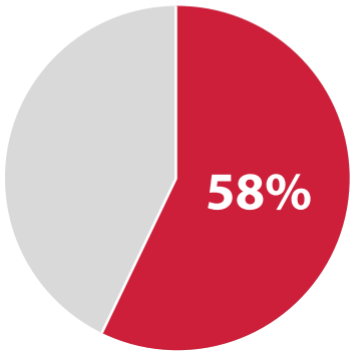


Novel Drug Approvals

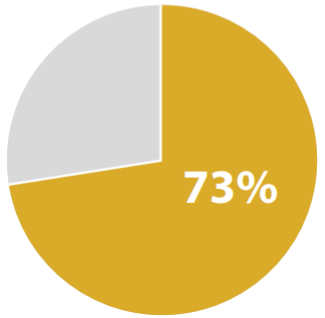
CDER identified
19 of the 59
novel drugs approved in 2018 (32%) as first-in-class.



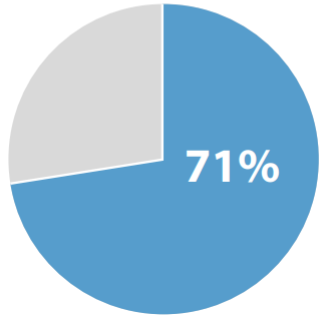
34 of CDER's 59 novel drugs (58%) were approved to treat rare or "orphan" diseases.



43 of the 59 novel drug approvals of 2018 (73%) were designated in one or more expedited categories of Fast Track, Breakthrough, Priority Review, and/or Accelerated Approval



42 of the 59 novel drugs approved in 2018 (71%) were approved in the United States before receiving approval in any other country



CAD

Project | People | Process | Facility | Quality

WHAT GOES WRONG?

- Can’t be done
- Does not fix problem
- Creates a different problem
- CAPA not accepted
- Ownership not agreed
- Timeline unrealistic

EXTENSION OR FOLLOW ON?

Extension

- Defined Process
- Current state of CAPA
- Quality impact assessment
- New agreed timeline

Follow on

- Traceability?
- Basis for Closure?

CBER

FDA Seeks Permanent Injunctions Against Two Stem Cell Clinics

"Cell-based regenerative medicine holds significant medical opportunity, but we've also seen some bad actors leverage the scientific promise of this field to peddle unapproved treatments that put patients' health at risk. In some instances, patients have suffered serious and permanent harm after receiving these unapproved products. In the two cases filed today, the clinics and their leadership have continued to disregard the law and more importantly, patient safety. We cannot allow unproven products that exploit the hope of patients and their loved ones."

FDA Commissioner Scott Gottlieb, M.D.
May 9, 2018

https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm607257.htm

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EMA - HIGHLIGHTS

CBER/CDER

Most Common Drug Citations for FY17

Among approximately 694 Drug 483s
issued 10/1/2016 to 9/30/2017

21 CFR 211.22(d)

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

Appears 185 times…

Most Common Drug Citations for FY17

21 CFR 211.160(b)

Laboratory controls do not include the establishment of scientifically sound and appropriate [specifications] [standards] [sampling plans] [test procedures] designed to assure that [components] [drug product containers] [closures] [in-process materials] [labeling] [drug products] conform to appropriate standards of identity, strength, quality and purity.

Appears 124 times…

CBER/CDER

Most Common Drug Citations for FY17

21 CFR 211.100(a)

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 possess.

Appears 91 times…

www.fda.gov 6

United States v. US Stem Cell Clinic LLC et al. (S.D. Fla.)

- Permanent injunction sought against US Stem Cell Inc., US Stem Cell Clinic LLC, CSO Kristin Comella, and Theodore Gradel
- Defendants process adipose tissue (body fat) into stromal vascular fraction (a cellular product derived from body fat) for a variety of serious diseases or conditions, including:
  - Parkinson's disease, ALS, COPD, heart disease and pulmonary fibrosis
- Products not approved for any use

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