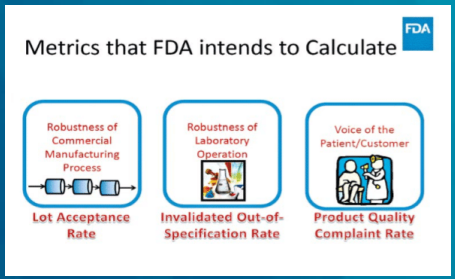
PDA
Parenteral Drug Association



Quality Metrics

Metric type	CAPA timeliness	Recurring deviations	Temporary changes
Description/ calculation of metric	% CAPAs closed on time	% recurring of all deviations	% temporary changes of all Change Control cases
Limit to be considered in compliance/ in control	High (>90 %)	Low (<10 %)	Low (<10 %)
Site 1	94	22	9
Site 2	91	8	7
Site 3	67	5	21

- *PDA Israel*
- *March 20th 2022*

Gil Pharma
Consulting

- *Gil Zomber*
- *Gil Pharma*

Instructor

- Dr. Gil Zomber, freelance quality consultant and Senior Associate in the Compliance Practice at Lachman Consultants.
- Quality Systems, Internal and external audits and mock inspections, GMP audits of CMO's and supplier audits, support in preparation for and during FDA inspections.
- Member of the Executive Committee Members of the Israel Chapter of PDA.
- In the past:

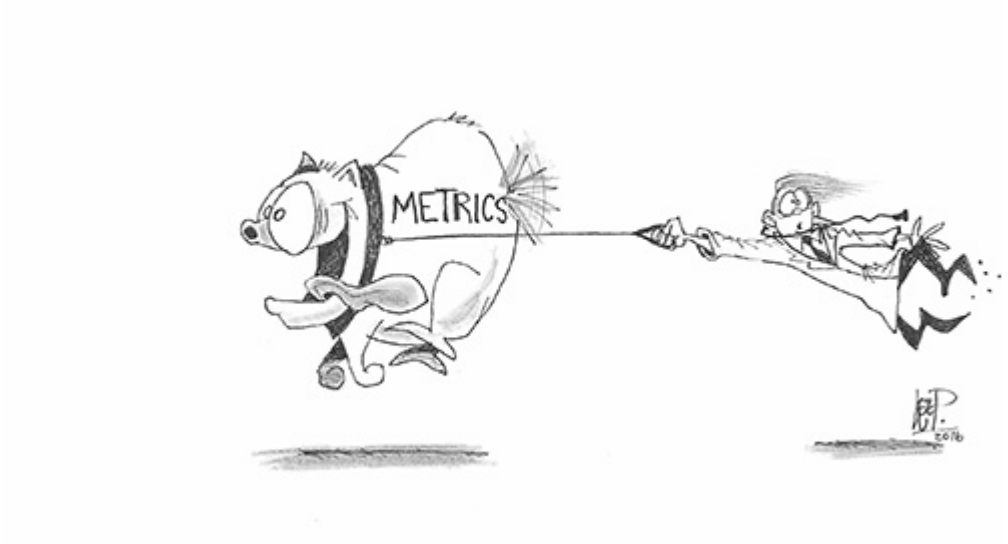
Vice President, Quality – Ayana pharma

Teva, Senior Director, Quality Assurance, R&D Biologics

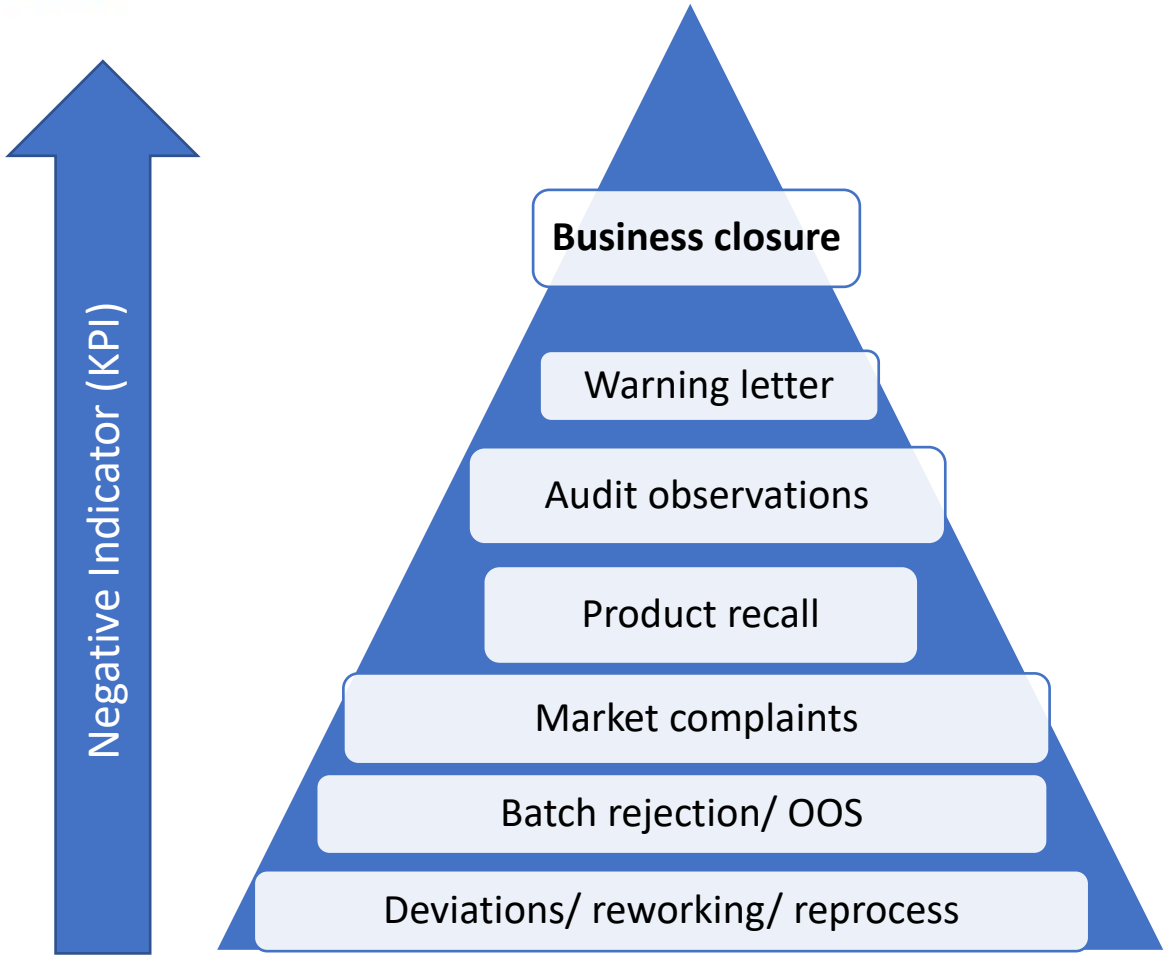
Israel Institute for Biological Research (Israel)

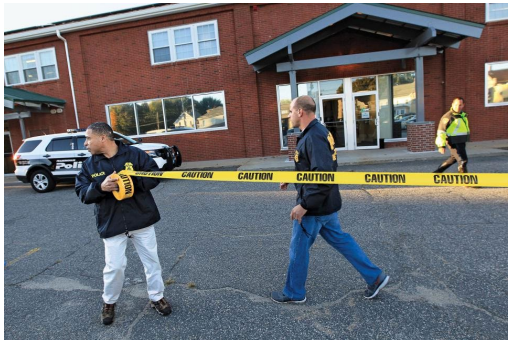
Presentation Overview

- Negative Indicator influence
- Drug Shortage and quality metrics
- ISPE (International Society for Pharmaceutical Engineering) quality metrics pilot program
- Quality metrics for CMO's (Contract manufacturing organizations)



Negative Indicator influence





International Journal of Current Research, Vol. 08, Issue, 01, pp.25285-25288, January, 2016

FDA – March 2022

- An effective Pharmaceutical Quality System (PQS) ensures both sustainable CGMP compliance and supply chain robustness. Quality metrics data can contribute to a manufacturer's ability to develop an effective PQS because metrics provide insight into manufacturing performance and enable the identification of opportunities for updates and innovation to manufacturing practices. Quality metrics also play an important role in supplier oversight and can be used to inform the oversight of outsourced activities and material suppliers as well as appropriate monitoring activities to minimize supply chain disruptions.

WARNING LETTER
Toyobo Co. Ltd.
MARCS-CMS 614177 — AUGUST 19, 2021

You did not adequately investigate significant particulate defects in your sterile drug product, including recurring incidents of extrinsic particle contamination.

During 2019 and 2020, multiple batches of (b)(4) injection solution were found to have significant particulate contamination defects, many of which are defined in your procedure and response as "foreign" (i.e., extrinsic). When extrinsic particulates were identified within batches, you failed to initiate a timely investigation to determine root causes and assess the drug product impact. Our review revealed that your in-process quality standards, limits, categories, and triggers for investigations do not sufficiently differentiate intrinsic from extrinsic particulate contamination.

A recent investigation update, submitted to FDA on June 18, 2021 (four months after FDA's inspection), indicates that you have improved your procedures and are performing supplier audits. While your investigation concluded that it is "highly possible" that your washing and sterilization processes could not remove certain particles adhered to the (b)(4) stoppers or vials, you failed to adequately address the upstream root causes of the contamination and implement timely corrective action and preventive actions (CAPA).

However, your stopper supplier indicated that their process was not the cause of the problem at the time, and your CAPA was inadequate to resolve the problem.

לא תיחקרתם כראוי בעיית חלקיקים משמעותית במוצר סטרילי כולל מיקרים חוזרים ונשנים של בעייה זאת

נכשלתם בפתיחת חקירת חריגה בזמן ובהגעה לסיבת השורש

החקירה שלכם הגיעה למסקנה שהבעייה נובעת מספק הפקקים שלכם אך לא יישמתם פעולות מתקנות ומונעות סבירות

ספק פקקי הגומי שלכם ציין שבעיית החלקיקים לא מגיעה מהטיפול שלהם בפקקי הגומי

WARNING LETTER

Your response is inadequate. You failed to adequately investigate both extrinsic and intrinsic particulate contamination issues. You did not determine the root cause and implement a timely and effective CAPA to address persistent incidents of extrinsic particulate contamination in your sterile injectable product. Extrinsic particulate contamination should occur infrequently and be fully investigated.

CGMP Consultant Recommended

Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for resolving all deficiencies and systemic flaws to ensure ongoing CGMP compliance.

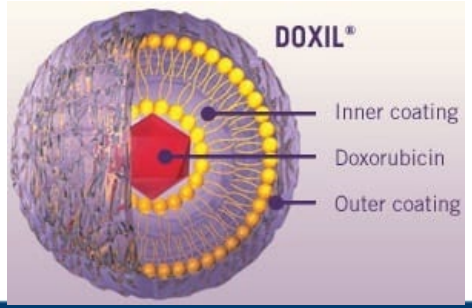
In response to this letter, provide:

- A comprehensive, independent assessment of your overall system for investigating deviations, discrepancies, complaints, out-of-specification results, and failures. Provide a detailed action plan to remediate this system. Your action plan should include, but not be limited to, significant improvements in investigation competencies, scope determination, root cause evaluation, CAPA effectiveness, quality unit (QU) oversight, and written procedures. Address how your firm will ensure all phases of investigations are appropriately conducted.

Doxil Shortage

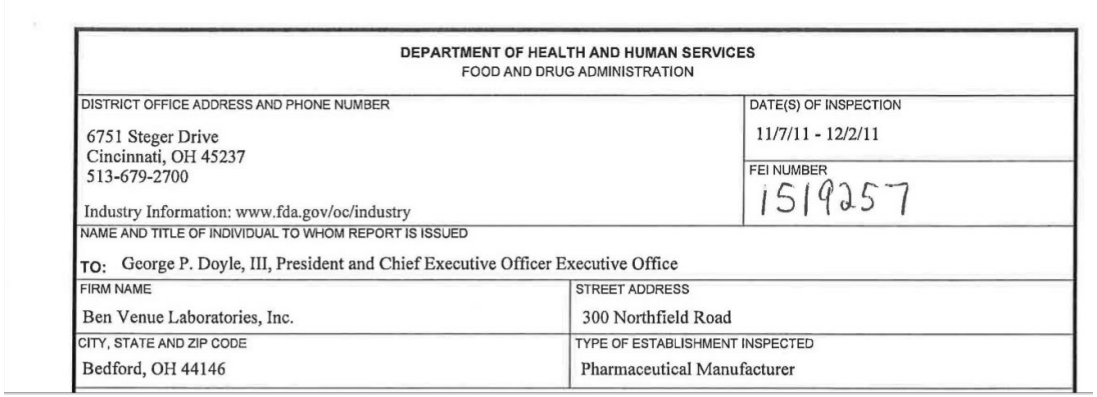
The Ben Venue lab was the sole manufacturer of Doxil in the nation. It voluntarily shut down in November 2011.
A May 2011 FDA inspection found a string of problems, including inadequate oversight and metallic particle shards in some of the drugs produced on site.

November 2011 inspection by FDA and EMA found "ongoing quality and manufacturing issues,



Doxil Shortage

The root of Doxil's shortages is a "voluntary shutdown" of an Ohio facility run by Ben Venue Laboratories, a contract manufacturer working for J&J, after a November 2011 inspection by FDA and EMA found "ongoing quality and manufacturing issues," reported RAPS. The Doxil shortage left as many as 2,700 patients on a waiting list for the drug last year, though J&J has since squeezed out enough supply to clear the waiting list.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
6751 Steger Drive Cincinnati, OH 45237 513-679-2700 Industry Information: www.fda.gov/oc/industry	11/7/11 - 12/2/11
	FEI NUMBER 1519257

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: George P. Doyle, III, President and Chief Executive Officer Executive Office

FIRM NAME	STREET ADDRESS
Ben Venue Laboratories, Inc.	300 Northfield Road
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Bedford, OH 44146	Pharmaceutical Manufacturer

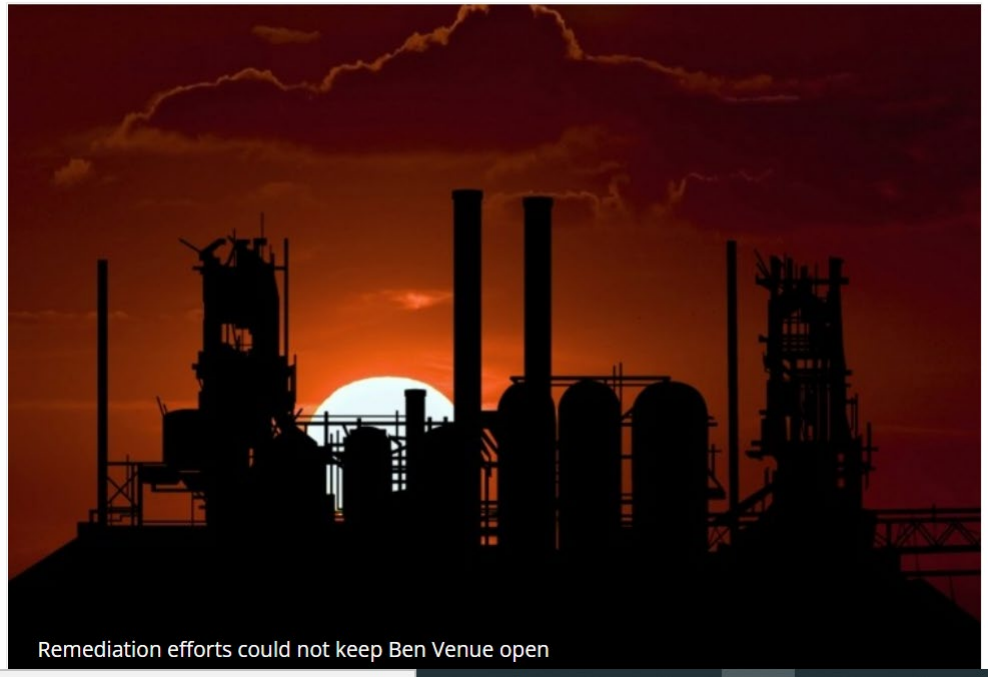
Quality Issues
Poor CMO control (J&J)
Failure in inspection
Drug Shortage
voluntary shutdown

FDA says approval of generic Doxil will ease cancer drug shortage

- *Allows Sun Pharma to manufacture its own version of the medicine*
- **US regulators have taken the unusual step of fast-tracking approval of a generic version of Johnson & Johnson's cancer drug Doxil in order to try and alleviate nationwide shortages of the medicine tha stem back to June 2011.**
- At the time, J&J's subsidiary Janssen placed the blame on delays at its third-party contract manufacturer Ben Venue Laboratories, but these problems were later compounded when Ben Venue issued a temporary suspension of manufacturing and distribution of drug products due to a series of violations in standards.
- The FDA has now approved India-based Sun Pharma's generic version of Doxil (doxorubicin hydrochloride liposome injection), which is protected by orphan drug marketing exclusivity until May 2014, but only in a multiple myeloma indication. Generic patent protection for its other indications expired in 2009.

Boehringer CMO Ben Venue Labs to close permanently, layoff 1,100

By Zachary Brennan
03-Oct-2013 - Last updated on 04-Oct-2013 at 12:35 GMT



Remediation efforts could not keep Ben Venue open

Shortage by reason

ov/media/131130/download

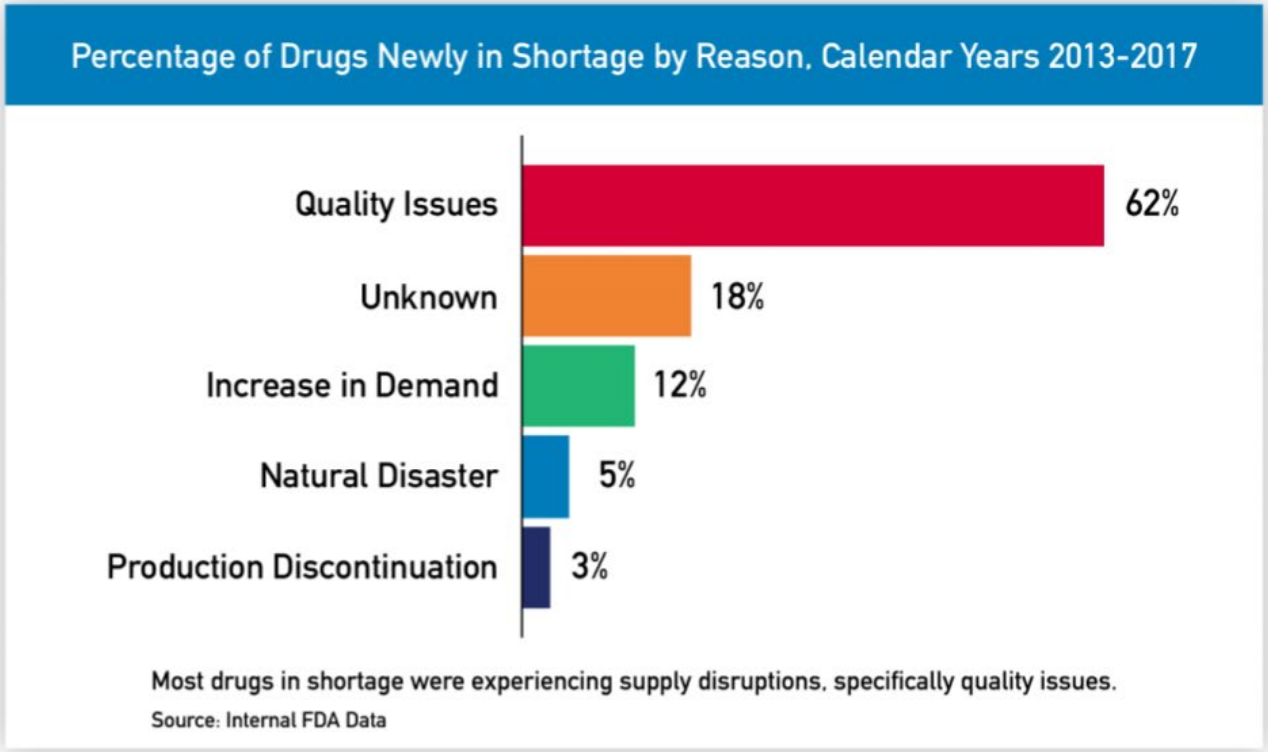
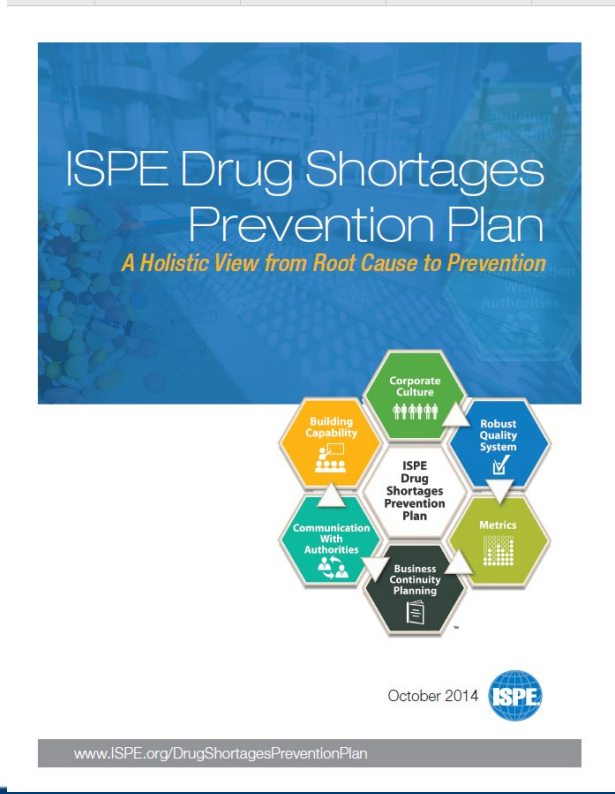


Figure 6. Of 163 drugs that went into shortage between 2013 and 2017, 62 percent went into shortage after supply disruptions occurred that were associated with manufacturing or product quality problems.

ISPE Drug Shortage Prevention Plan

- The International Society for Pharmaceutical Engineering is a not-for-profit association serving its Members by leading scientific, technical, and regulatory advancement throughout the entire pharmaceutical lifecycle.




Corporate Culture
Building Capability
Robust Quality System
ISPE Drug Shortages Prevention Plan
Communication With Authorities
Metrics
Business Continuity Planning
™

ISPE Drug Shortage prevention Plan

Corporate Quality Culture describes the importance of organizations being designed in such a way as to foster cross-functional ownership of quality so that quality is not viewed as a hindrance for success, but an absolute necessity for the company to collectively make decisions to best benefit patients [2]. The Plan suggests that avoiding supply disruptions requires not just a compliant quality system, but one that helps drive the overall quality of the product throughout its lifecycle by integrating it and focusing on a number of key processes. These processes include:

- Cross-functional cooperation
- Management controls and problem escalation
- Communication and transparency

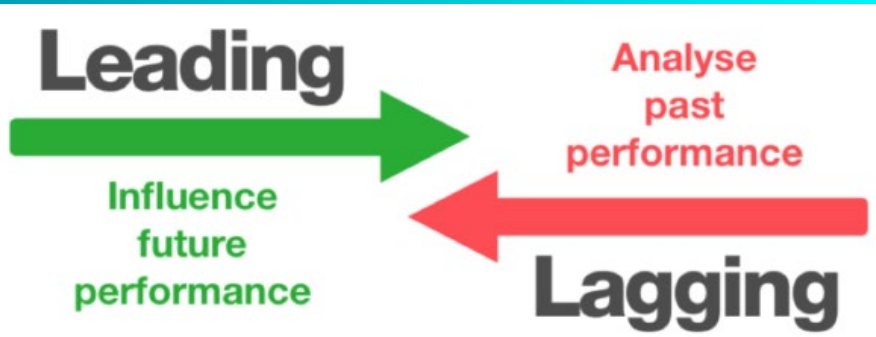
Robust Quality System – highlights the ability of the company's quality system to integrate applicable Good Manufacturing Practice (GMP) regulations and complements ICH Q9 [3]. This integration is a necessary foundation for companies to create more and better opportunities for the "the delivery of products with the quality attributes appropriate to meet the needs of patients, health care professionals, and regulatory authorities."

In order to achieve a robust quality system, the Plan proposes structuring the approach to developing strategies across a few key elements, including governance, culture, and management controls, as well as improvements to overall production and process-related factors contributing to shortages. The Plan argues that this integration will enable stronger and more consistent decisions that will ultimately drive higher levels of quality. These decisions, in turn, may help drive the following improvements:

ISPE Drug Shortage prevention Plan

Metrics – are measures put in place to determine the performance of not just the quality system, but also of other operational elements – such as supply chain and culture – that may indicate the potential for a drug shortage. Depending on the site quality system, some quality metrics and other indicators can be predictive of the overall ability to reliably supply quality products.

Leading Indicator and Lagging indicator



4.2 Quality Metrics

Categorizing a measure is highly subjective. Any given metric can be either leading or lagging based on how it is used. In order to ensure selected metrics are proactive rather than reactive in identifying potential shortages, companies have adopted measures that are leading indicators rather than lagging indicators. The definitions for leading and lagging are:

- A leading indicator may be predictive of future performance.
- A lagging indicator identifies or signifies past and up-to-the present performance.

Similar definitions can be found in various texts (for example, ICH Q10) [4].

ISPE Drug Shortage prevention Plan -Metrics

Metrics generally assigned as leading indicators:

- *Lot acceptance rate* – total lots released for shipping out of the total finally dispositioned lots for commercial use in the period.
- *Right first time (rework/reprocessing)* – total lots that have not been through rework or reprocessing out of the total finally released lots for commercial use in the period.
- *APQR completed on time* – number of APQRs in the period that were completed by the original due date normalized by all products subject to APQR.
- *Recurring deviations rate* – number of deviations that have occurred during the preceding 12 months period with the same root cause within the same process and/or work area out of all deviations in the reporting period.
- *CAPA effectiveness rate* – number of CAPA evaluated as effective (the quality issue subject of the CAPA was resolved and/or has not reoccurred, and there have been no unintended outcomes from the CAPA implementation) out of all CAPAs with effectiveness check in the reporting period.
- *Technology specific* – Media fill (for sterile) – number of media fills dispositioned as successful out of all media fills to support commercial products dispositioned during the period.

Annual Product Quality Review (**APQR**)

ISPE Drug Shortage prevention Plan -Metrics

Metrics generally assigned as lagging indicators:

- *Complaints rate (total and critical)* – total complaints received in the reporting period related to the quality of products manufactured in the site normalized by the number of products released. Critical complaints (indicating a potential failure to meet product specifications, impact product safety and/or lead to regulatory actions), normalized by the number of products released.
- *Confirmed Out-of-Specification (OOS)* – total confirmed OOS (test results that fall outside the specifications or acceptance criteria) out of all lots tested during the period.
- *Recall events.*
- *Stability Failure rate* – total confirmed OOS related to stability testing out of all stability lots.
- *Invalidated OOS rate* – total unconfirmed OOS out of all lots tested by the lab during the period.
- *Environmental monitoring (sterile aseptic sites)* – total sterile lots with investigations related to action limit excursions out of all sterile lots dispositioned. Total sterile lots rejected due to action limit excursions out of all sterile lots dispositioned.

3.2.3 Quality culture indicators

Wave 1 Pilot provided some key insights in relation to the prevailing quality culture within an organization that merited further exploration. The Quality Culture sub team, therefore, included in Wave 2 a series of additional Cultural Indicators to probe the relative importance of these indicators of quality culture. These Indicators were:

- Corrective Actions and Preventive Actions (CAPAs) with Preventive Actions (%)
- Planned Maintenance Rate (%)
- Employee Turnover Rate (%)
- Human Error Deviations (%)
- Deviations with No Assigned Root Cause (%)

הגורם האנושי

- טעות אנוש יכולה להעיד בהרבה מיקרים סימפטום לבעיה אחרת
- טעויות יכולת להיגרם כאשר תהליך לא מתוכנן כראוי ואינו ולידי, בעיות בהוראות עבודה, או נהלים שלא כתובים לוגית או לא מתוכננים כראוי או כאשר מימשק מפעיל – מכונה לא מתוכנן כראוי או קשה לשימוש.
- לכן חיוני לבדוק את הגורמים מסביב לפני שחורצים "טעות אנוש"

FDA

Human Factor

- Sciences of human factors engineering and human reliability analysis can provide valuable tools
- Human error may be more a symptom of an underlying problem rather than its cause.
- "...Errors can occur when a manufacturing process has not been sufficiently designed and validated... Also, problems may arise when work instructions, procedures, or policies are poorly written or designed,

- ... or when the operator-equipment or ***operator-process interface is poorly designed or difficult to use***.
- Therefore, it is useful to explore whether the existing manufacturing or other process may have contributed to the error or incident before assigning human error as the [primary] cause of the deviation or incident."

❖ *[O'Donnell, K. "Human Error and Retraining," IVT Journal, 2009]*

Quality Metrics Pilot Program

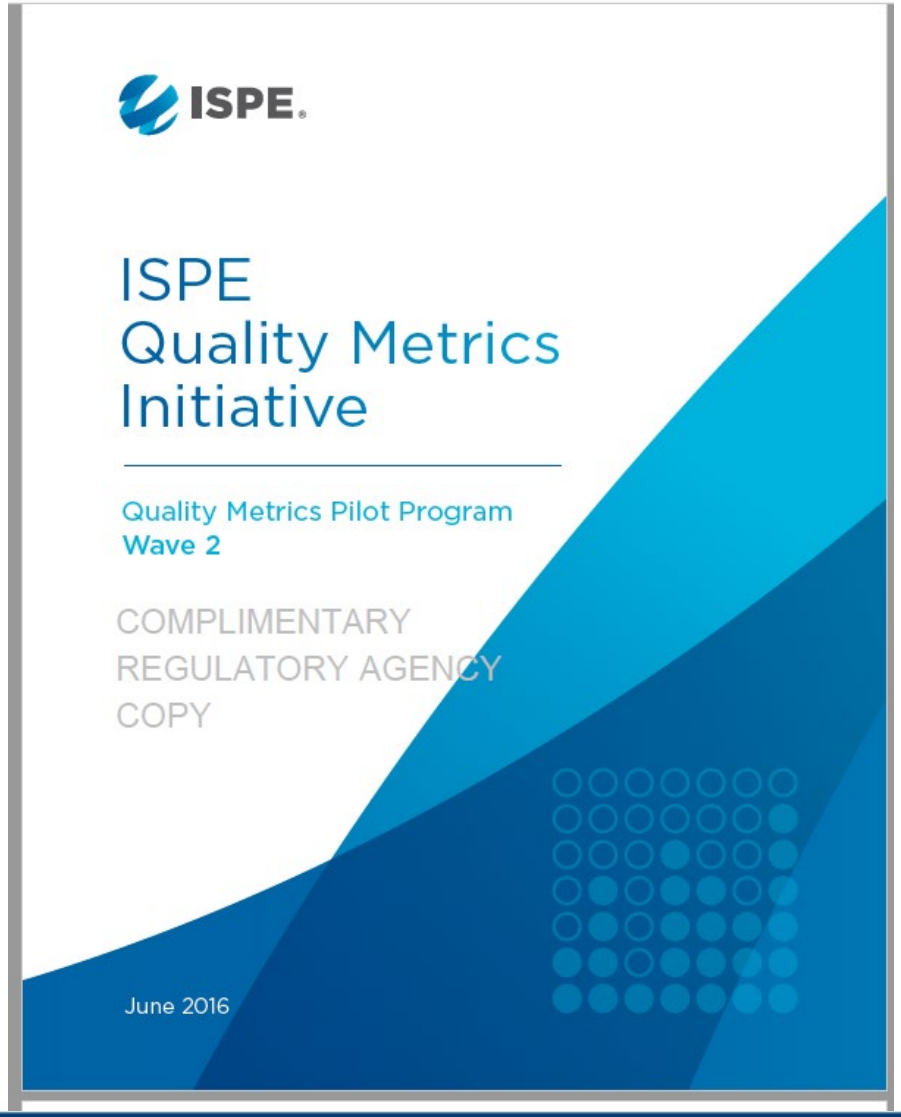
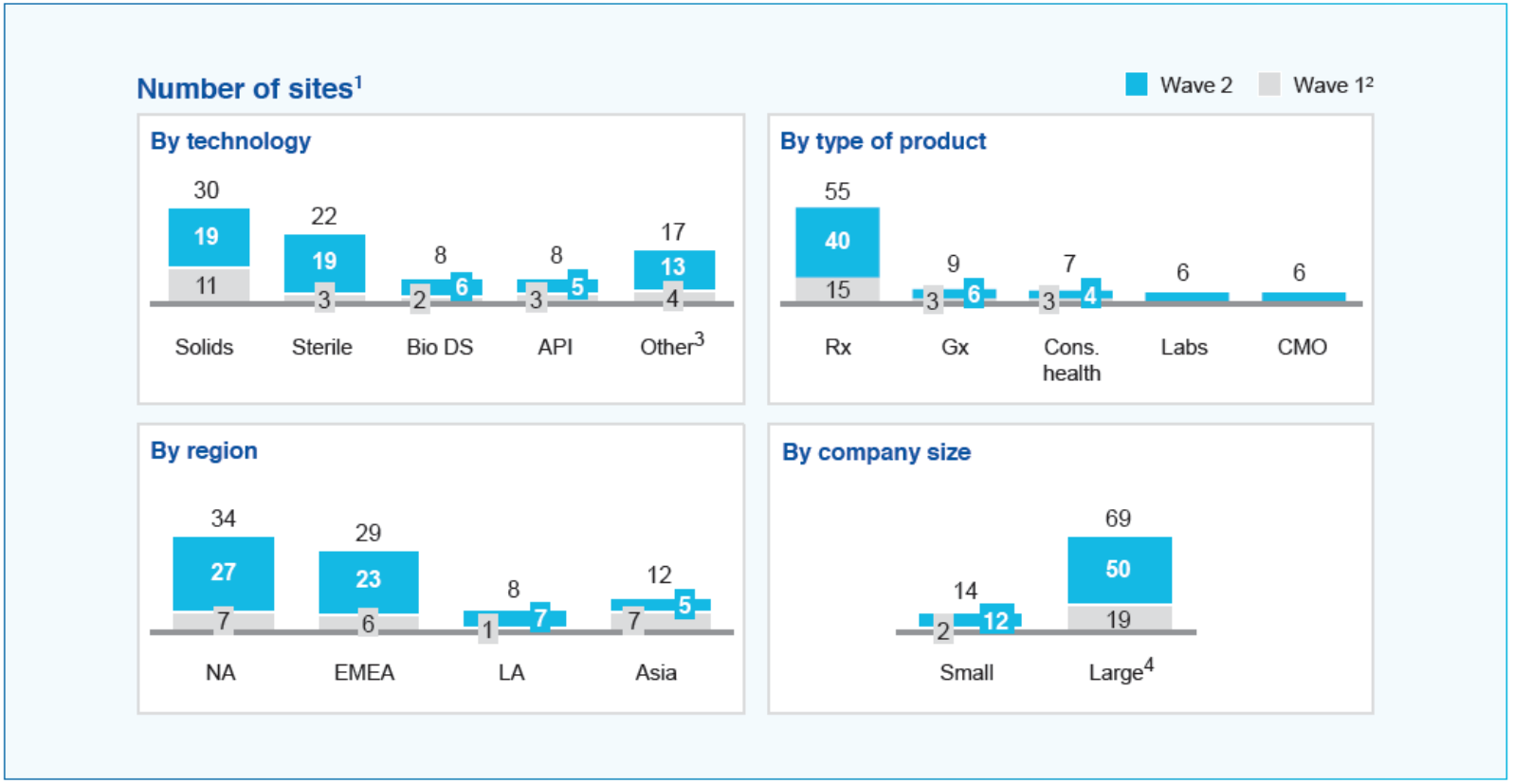


Figure 4: Combined enrollment for Wave 1 and Wave 2



1 If a site has more than one technology we count the number of separate templates they will fill, usually one per technology
2 Sites that participated in both Wave 1 and Wave 2 are reported under Wave 2 only
3 e.g., soft gels, transdermal
4 Over $1 billion in annual revenue

Figure 11: Median values of metrics by technology

		Solids	Steriles	Liquids/Creams	API	Bio DS
External Quality Outcomes	Total Complaints Rate, incl. lack of effect (per million packs)	18	41	49		
	Total Complaints Rate, incl. lack of effect (per '000 attempted lots released)	131	369	1,861	0	0
	Total Complaints Rate, ex. lack of effect (per million packs)	14	45	46		
	Total Complaints Rate, ex. lack of effect (per '000 attempted lots released)	116	311	1,752	0	0
	Critical Complaints Rate (per million packs)	0	0	1		
	Critical Complaints Rate (per '000 attempted lots released)	3	11	27	0	0
	Total Recall Events (Recalls per year)	0	0	0	0	0
Internal Quality Outcomes	Lot Acceptance (per finally dispositioned lots, percent)	99	99	99	100	99
	Lot Acceptance (per attempted lots, percent)	100	100	100	100	99
	Lots pending disposition more than 30 days (per attempted lots, percent)	6	7	1	67	181
	Right First Time Rate (%)	89	76	98	79	0
	Invalidated OOS Rate (per '000 lots tested)	4	6	2	11	21
	Invalidated OOS Rate (per '000 test performed)	1	0	1	1	2
	Deviations Rate (per '000 attempted lots)	123	186	15	386	8,326
	Deviations Rate (per '000 finally dispositioned lots)	143	283	77	616	7,043
	Recurring Deviations Rate (%)	11	9	19	6	11
Culture indicators	Deviations with No Assigned Root Cause (%)	5	4	0	7	6
	Human Error Deviations Rate (%)	33	20	36	27	32
	CAPAs with Preventive Actions Rate (%)	26	20	31	53	35
	Planned Maintenance Rate (%)	59	74	82	35	70
	Employee Turnover Rate (%)	7	6	13	4	7
	CAPAs Requiring Retraining Rate (%)	9	8	8	9	9

Based on full sample of Wave 2 data and Wave 1 data for sites that did not participate in Wave 2, no outliers excluded.

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Figure 11: Median values of metrics by technology

		Solids	Steriles	Liquids/Creams	API	Bio DS
Internal Quality Outcomes	Lot Acceptance (per finally dispositioned lots, percent)	99	99	99	100	99
	Lot Acceptance (per attempted lots, percent)	100	100	100	100	99
	Lots pending disposition more than 30 days (per attempted lots, percent)	6	7	1	67	181
	Right First Time Rate (%)	89	76	98	79	0
	Invalidated OOS Rate (per '000 lots tested)	4	6	2	11	21
	Invalidated OOS Rate (per '000 test performed)	1	0	1	1	2
	Deviations Rate (per '000 attempted lots)	123	186	15	386	8,326
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PDA
Parenteral Drug Association

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	Total Complaints Rate, ex. lack of effect (per million packs)	14	45	46		
	Total Complaints Rate, ex. lack of effect (per '000 attempted lots released)	116	311	1,752	0	0
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	Critical Complaints Rate (per '000 attempted lots released)	3	11	27	0	0
	Total Recall Events (Recalls per year)	0	0	0	0	0

PDA
Parenteral Drug Association

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		Solids	Steriles	Liquids/Creams	API	Bio DS
Culture indicators	Deviations with No Assigned Root Cause (%)	5	4	0	7	6
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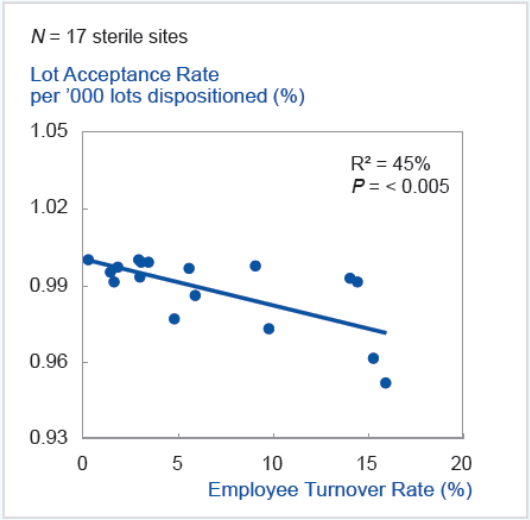
	CAPAs with Preventive Actions Rate (%)	26	20	31	53	35
	Planned Maintenance Rate (%)	59	74	82	35	70
	Employee Turnover Rate (%)	7	6	13	4	7
	CAPAs Requiring Retraining Rate (%)	9	8	8	9	9

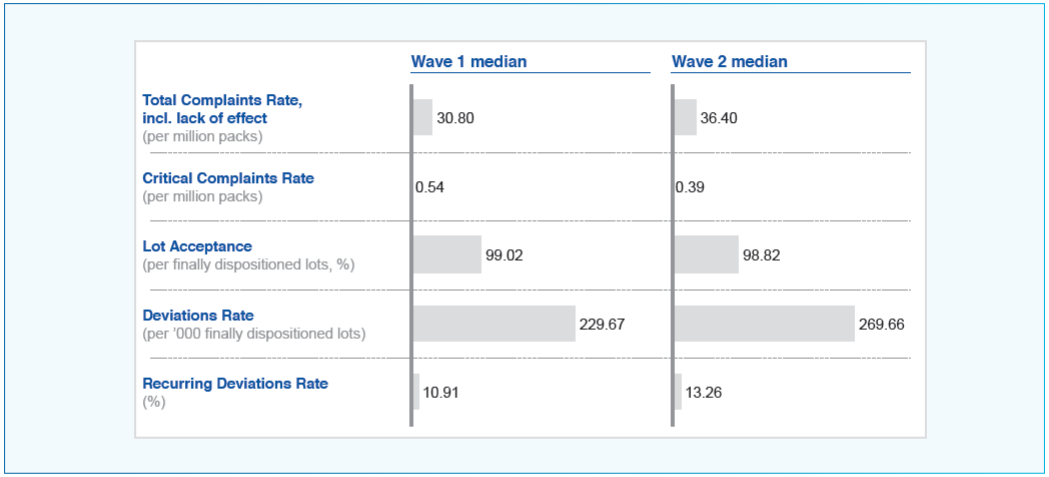
Employee Turnover

Figure 35: Relationship of Lot Acceptance Rate and Employee Turnover Rate



Note: Outliers more than two standard deviations away from sample mean were excluded: One on Employee Turnover Rate (US-based Rx site), and one on Lot Acceptance Rate (India-based Rx site).
R^2 measures to what extent metric Y (dependent variable) is explained by the variability of metric X (independent variable).
p value is probability that correlation between X and Y is zero, value below 0.05 indicates statistically significant results.

Figure 12: Median values of Wave 1 and Wave 2 metrics

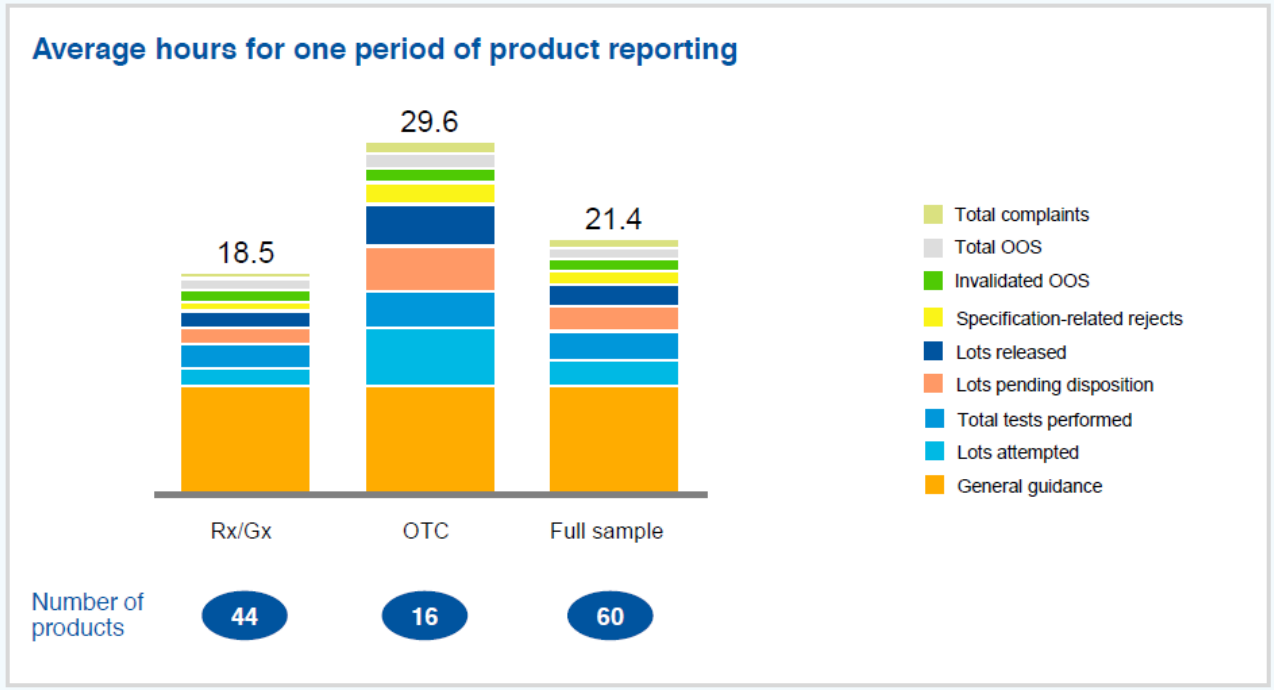


Based on full sample of Wave 2 data and Wave 1 data for sites that did not participate in Wave 2, no outliers excluded.

This comparison shows that Wave 1 and Wave 2 median values are similar, with consistent data in both.

Data Collection Effort

Figure 5: Data collection effort



ICH guideline Q10 on pharmaceutical quality system

- Performance indicators that measure progress against quality objectives should be established, monitored, communicated regularly and acted upon as appropriate

2.7. Management of outsourced activities and purchased materials

The pharmaceutical quality system, including the management responsibilities described in this section, extends to the control and review of any outsourced activities and quality of purchased materials. The pharmaceutical company is ultimately responsible to ensure processes are in place to assure the control of outsourced activities and quality of purchased materials. These processes should incorporate quality risk management and include:

a) Assessing prior to outsourcing operations or selecting material suppliers, the suitability and competence of the other party to carry out the activity or provide the material using a defined supply chain (e.g., audits, material evaluations, qualification);

b) Defining the responsibilities and communication processes for quality-related activities of the involved parties. For outsourced activities, this should be included in a written agreement between the contract giver and contract acceptor;

c) Monitoring and review of the performance of the contract acceptor or the quality of the material from the provider, and the identification and implementation of any needed improvements;

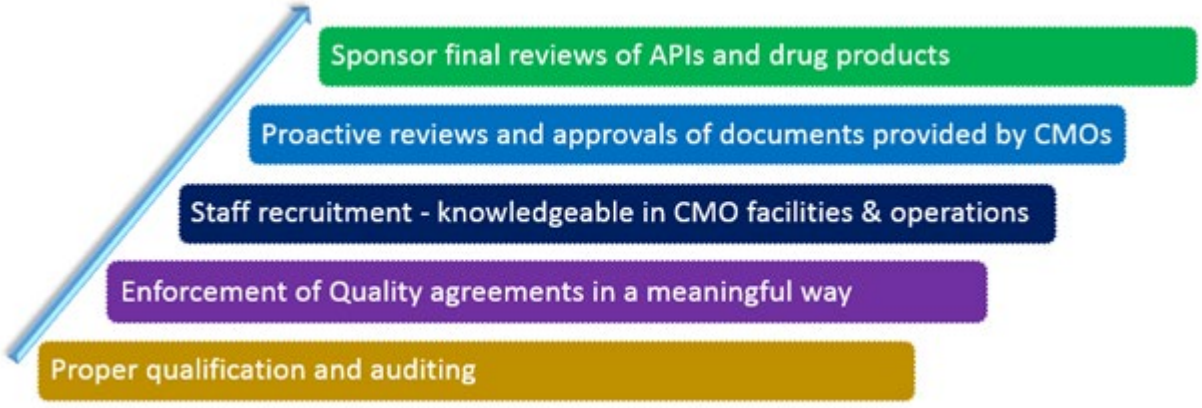
d) Monitoring incoming ingredients and materials to ensure they are from approved sources using the agreed supply chain.

Managing Metrics With Your CMO

CMO- Contract Manufacturing Organization

ICH Q10 clarifies that the sponsor bears ultimate responsibility for outsourced activities and for the quality of the product. A CMO is an extension of a sponsor's operation.

As sponsors are increasingly placing greater responsibility for quality and compliance on their outsourcing partners, they are also increasingly being held ultimately responsible by regulatory agencies for issues that may occur.



ISPE – CMO perspective

- Many sponsors wish to report metric data from their CMOs
- CMOs in ISPE's Pilot programs indicate that they wish that sponsors submit quality metric data. A CMO may have a complex range of products, for example there may be some at the in-process, bulk and packaged stages of manufacture, which constitute only parts of a supply chain
- CMOs want clear, consistent definitions so that they provide the same information to all their clients without the requirement for customization due to different interpretations by their clients
- Nevertheless, some sponsors think there could be an incentive for CMOs to focus on site reporting so that their performance is fully and clearly visible. This could lead to duplicate reporting, for example when some clients wish to report by product and the CMO wishes to include all its product range in a site report since a CMO cannot be absolutely sure their performance will be highlighted.

While each partner will have internal metrics, together they must set metrics for the sponsor's program and understand the terms and definitions. Additional operational and quality metrics, typically with less detail, are set at the site level and shared by both partners.

Discussing metrics at the outset helps ensure that the right metrics will be evaluated. While each partner will have internal metrics, together they must set metrics for the sponsor's program and understand the terms and definitions.

Communication systems should incorporate a quality agreement for proper responsibility and accountability.
Partners should also have current data-sharing systems and periodic meetings and reviews.

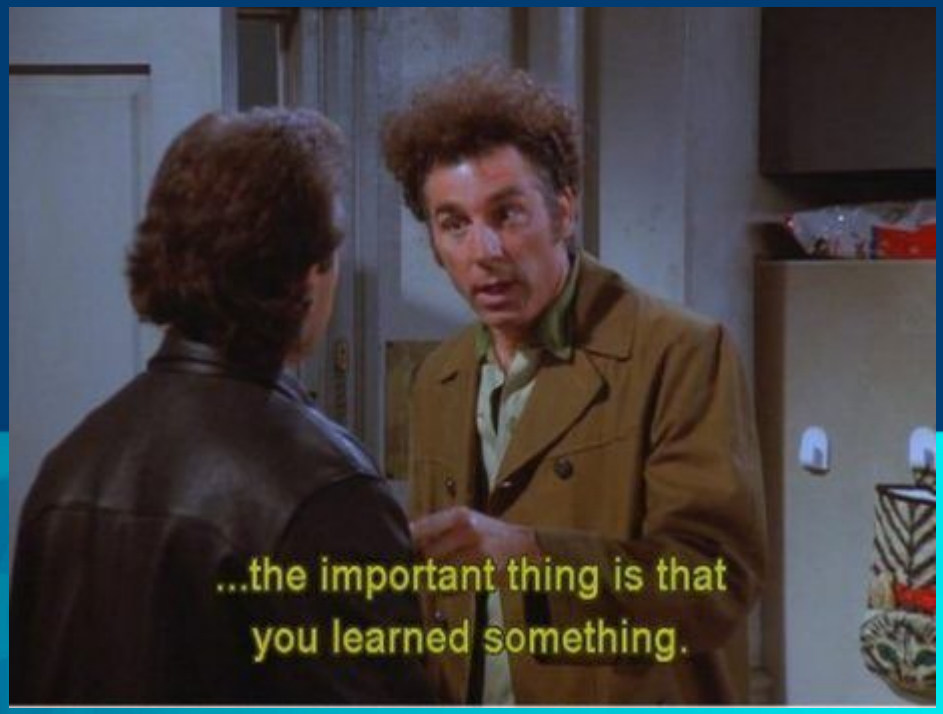
When preparing and utilizing a metric, we advise following seven steps:

1. Define the objective. State what you are measuring, how and how frequently you collect and measure data, goals, who is responsible for gathering the data, how they are recorded and when they are reviewed.
2. Define the metric – ensure that there is a clear understanding of the definition.
3. Set targets.
4. Collect data.
5. Assess the data in a timely manner and communicate the status internally and between sponsor and contract service provider
6. Modify or change metrics according to the data.
7. If the target is easily achieved, raise the bar.

Sample for acceptance criteria

Performance Indicator	Information	< Expected	Accept-able	Objective	> Expected
Authority Inspections	# Authority Inspections passed # Total Authority Inspections received	< 85%	85% - 99%	100%	100% passed <= 2 major
Customer Audits	# Customer Audits with NO critical observations # Total Customer Audits received	< 80%	80% - 90%	91% - 95%	96% - 100%
Internal Audit	# Completed # Total planned	< 70%	70% - 80%	80% - 84%	85% - 94%
Repeat Deviations	# Repeat Deviations # Total Deviations	> 20%		< 20%	<10%
Overdue Deviations	# Overdue Deviations # Total Deviations	> 10%		<= 10%	<1%
Human Deviation Reduction	# Human Error Deviations # Total Deviations	> 30%		<= 30%	<= 10%
Overdue CAPA's	# Overdue CAPAs # Total CAPAs	> 10%		<= 10%	<= 1%
On Time PQR	# completed on time # Total	< 85%		>= 85%	100%
Overdue SOPs	# Overdue # Total	< 95%		>= 95%	100%
Reprocessing rate (API, FP)	# Batches NOT conforming with specification # Total batches produced	> 5%		<= 5%	0%
OOS rate	# Confirmed OOS # Total batches produced	> 5%		<= 5%	0%

Adapted from Klaus Pitterschatscher, personal communication



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- BACK UP

Food and Drug Administration Quality Metrics Reporting Program; Establishment of a Public Docket; Request for Comments

- **Manufacturing Process Performance**
- *Process Capability/Performance Indices (Cpk/Ppk):* A measure that compares the output of a process to the specification limits and can be calculated as a proportion (*e.g.,* total number of attributes with Ppk greater than 1.33 divided by total number of attributes where Ppk is used). It is important to consider standard deviation measurements using a reasonable sample size.

Process capability

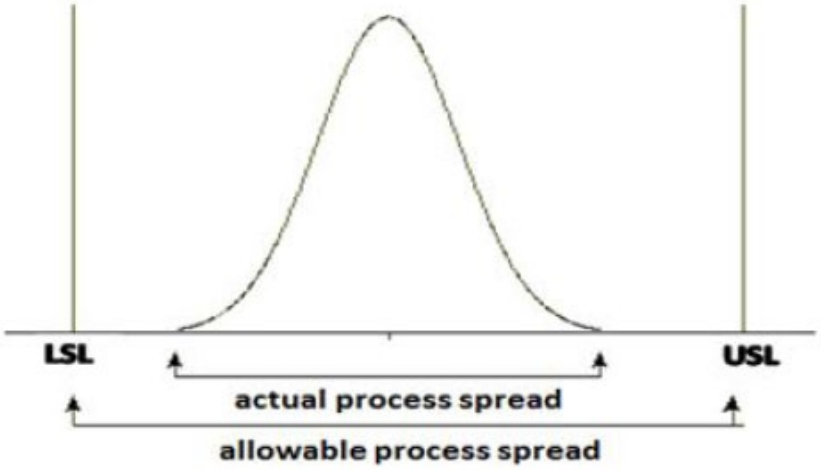

Fig. 3. Gaussian curves with USL and LSL [6]

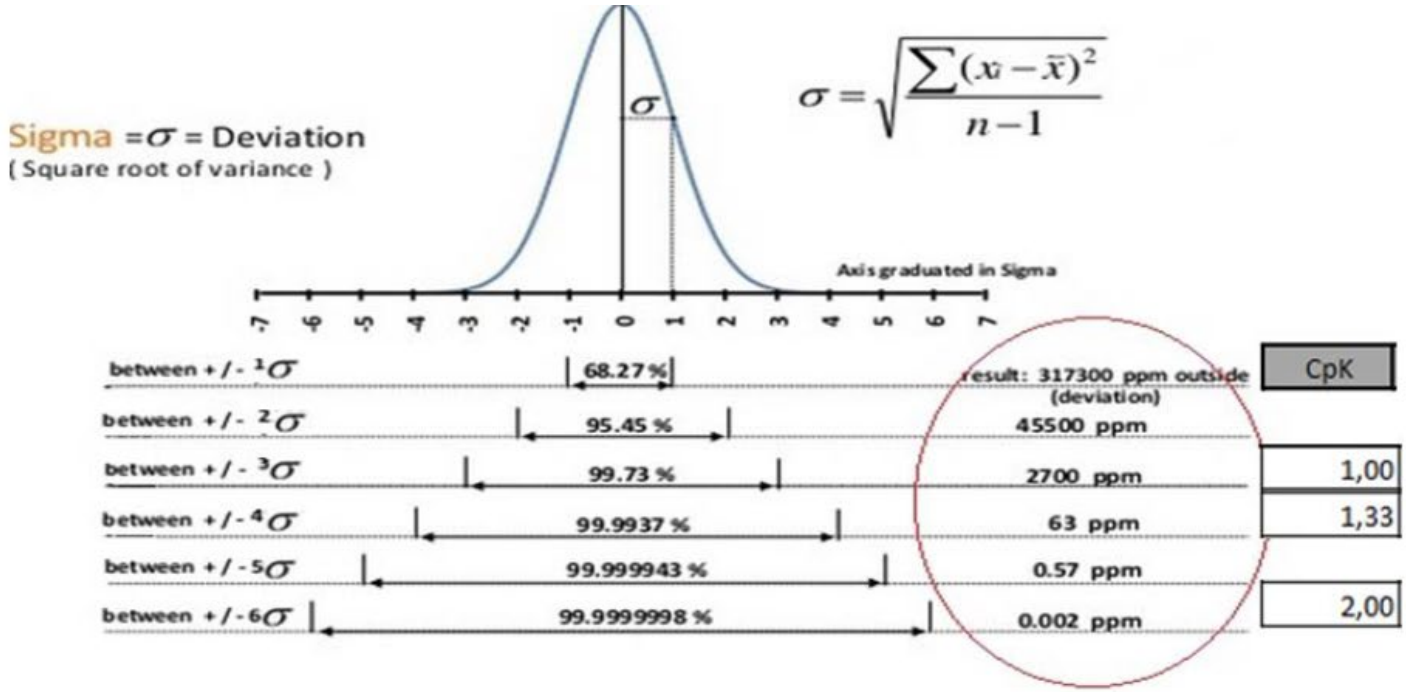

Fig. 7. Rule 6 Sigma indicating indicator ppm and c_{pK} [12]

כושר תהליך - Process Capability Index
תפוקת הפריטים התקינים בתהליך נורמאלי

$$C_{PK} = \min \{ (USL-\bar{x})/3\sigma, (\bar{x}-LSL)/3\sigma \}$$