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Constructing an Intelligent Tomorrow

EFFECTIVE QUALITY APPROACH IN LIFE SCIENCE - REIMAGINING THROUGH SUCCESSFUL STRATEGIES

CHARTING A NEW COURSE TO A SMART QUALITY SYSTEM

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Abstract

There is a high level of dissatisfaction by Life Science Industry leaders in the effectiveness of their efforts on Quality and Regulatory investments. This paper will look at the approach to Quality Systems across two different industries to understand different strategies, the foundational drivers that inform each industry's approach, and their effectiveness.

Introduction

There is clear recognition that the Quality Systems implementation in Life Sciences needs to be revised to achieve better compliance and better quality. Looking at another industry can be instructive in observing differences in the approach for formulating and implementing Quality Systems and their subsequent outcomes. Both Semiconductor and Life Science industries have made significant technological progress but the drivers for quality systems are very different for valid reasons. Reviewing them can lead to areas of cross learning.

For the Life Science industry to reframe its approach to quality, perhaps a reframing of the quality objective should guide the system formulation. The intended objectives are very clear for a quality system to drive:

- Provide the framework to deliver value to the company, its people, and its customers while being fully compliant to regulations.
- Drive continuous improvement in business performance (metrics).
- Improve the capacity of an organization.

Note the order of the list above, delivering value, followed by compliance. However, in practice, the order is to drive compliance first.

Viewing the standards or regulatory documents of these two industries, they are quite similar in intent:

- “Do what you say, say what you do.”
- Control your processes to assure that the product meets the functional requirements consistently and safely.
- Provide full traceability.

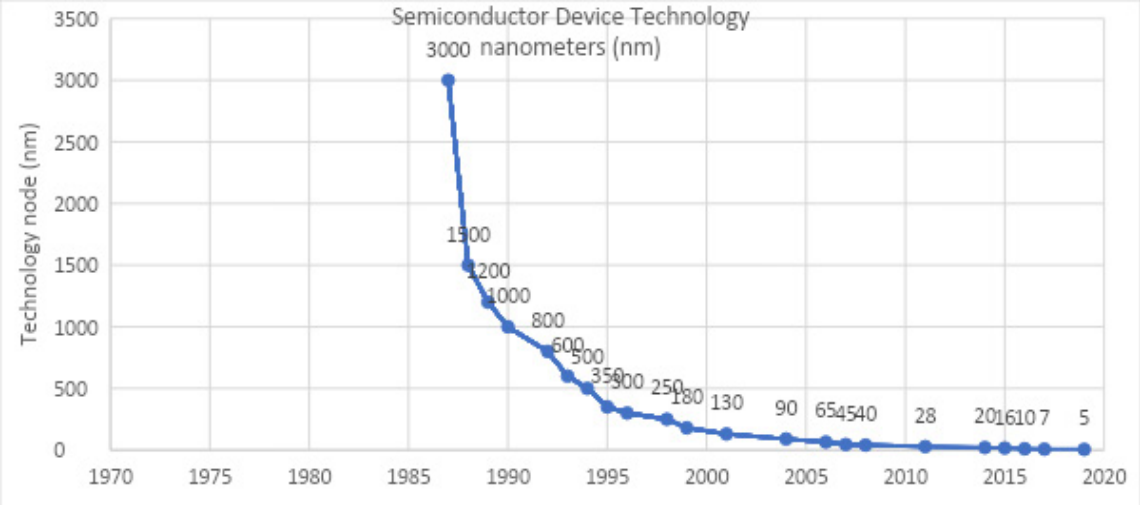
But the implementation and practice of the systems is quite different.

Advances in Technology

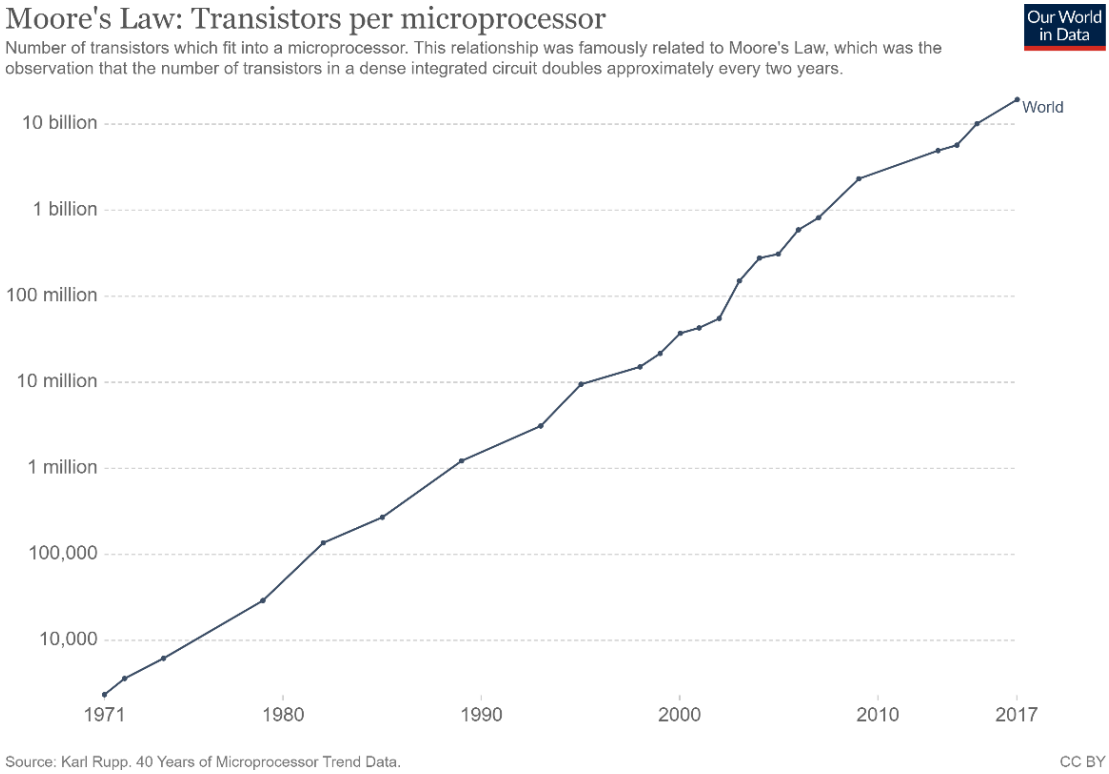
Both industries have achieved significant progress over time. A few charts indicating the advances are shown below.

SEMICONDUCTOR INDUSTRY

Growth in Semiconductor technology is shown below, a 200x improvement since 1990.

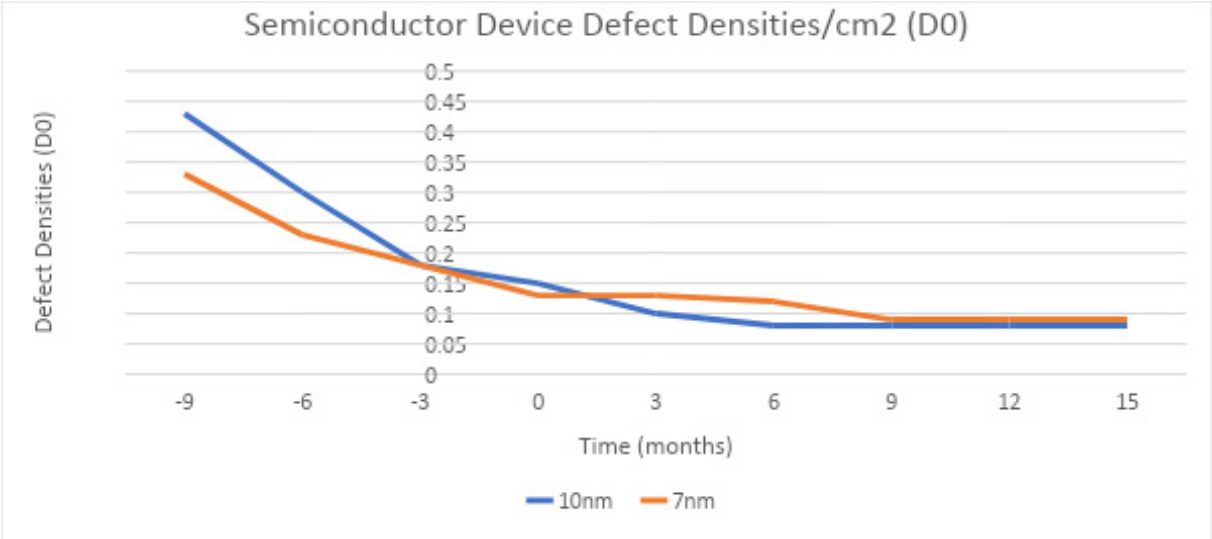


The above improvement has led to the exponential increase in transistors per microprocessor as shown below.



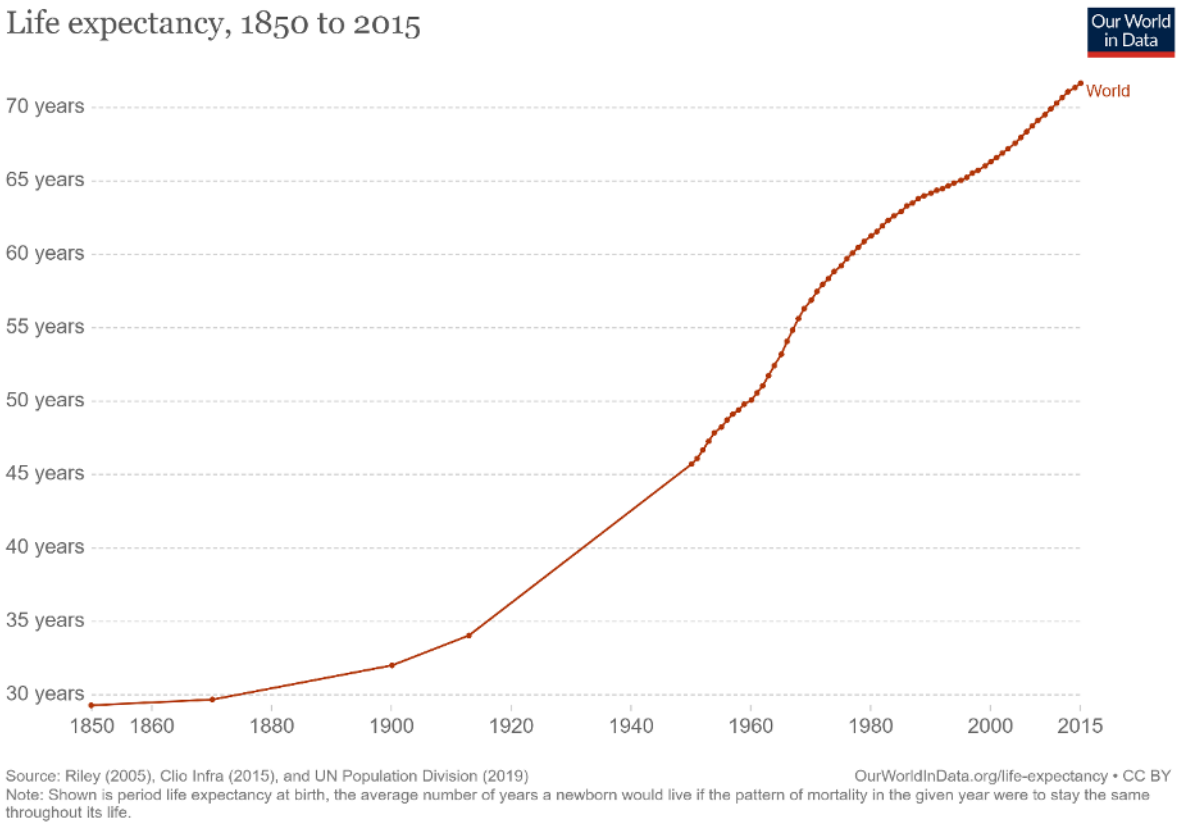
Semiconductor Quality (Yield) is best described in terms of Defect Densities (D0), or defects per square centimeter. This normalizes the quality for all devices chip sizes and a D0 of less than 0.1 would be >90% for a chip size of 87mm2 (typical cell phone processor).

Taking the recent technologies of 10nm and 7nm, their yield improvement, as measured by reduction in D0 Defect densities, the graph below shows the improvement over time, with time "0" being released for production. Reducing defect densities are the drivers for quality operating systems.

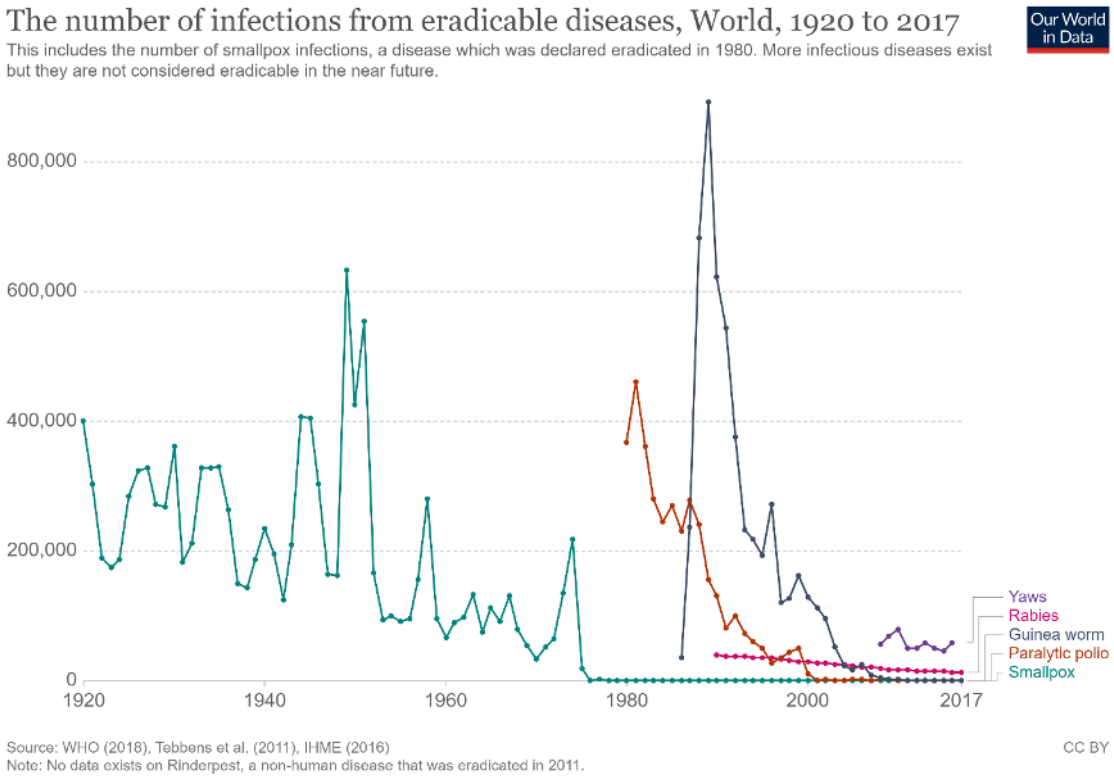


LIFE SCIENCE INDUSTRY

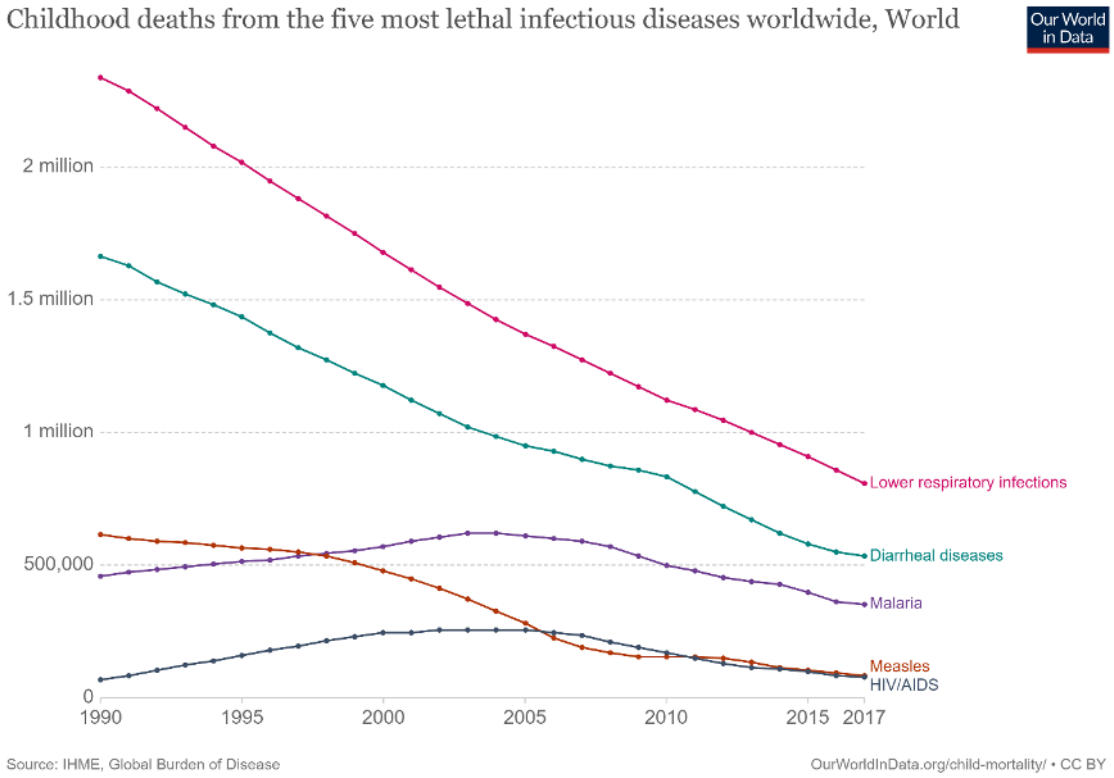
The impact of technological progress in the Life Science is best seen in the life expectancy over time, doubling in 100 years on average globally.



Another measure of the significant technological progress is shown by the following reduction in infections from eradicable diseases.

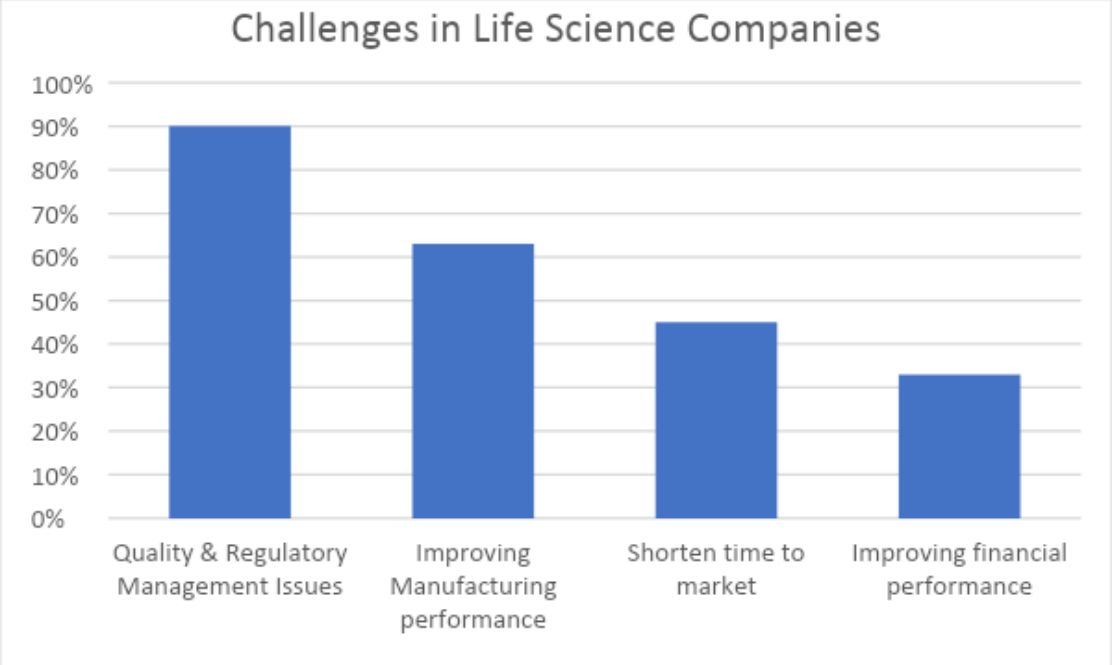


Another metric is the reduction in childhood deaths from the most lethal infectious diseases.



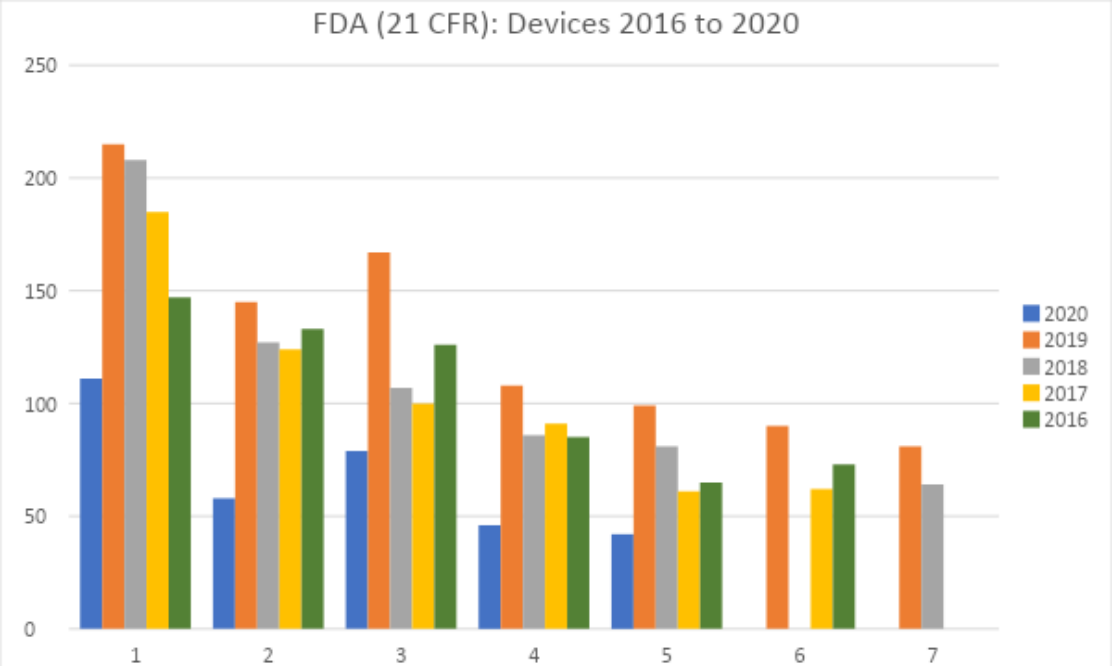
Concern

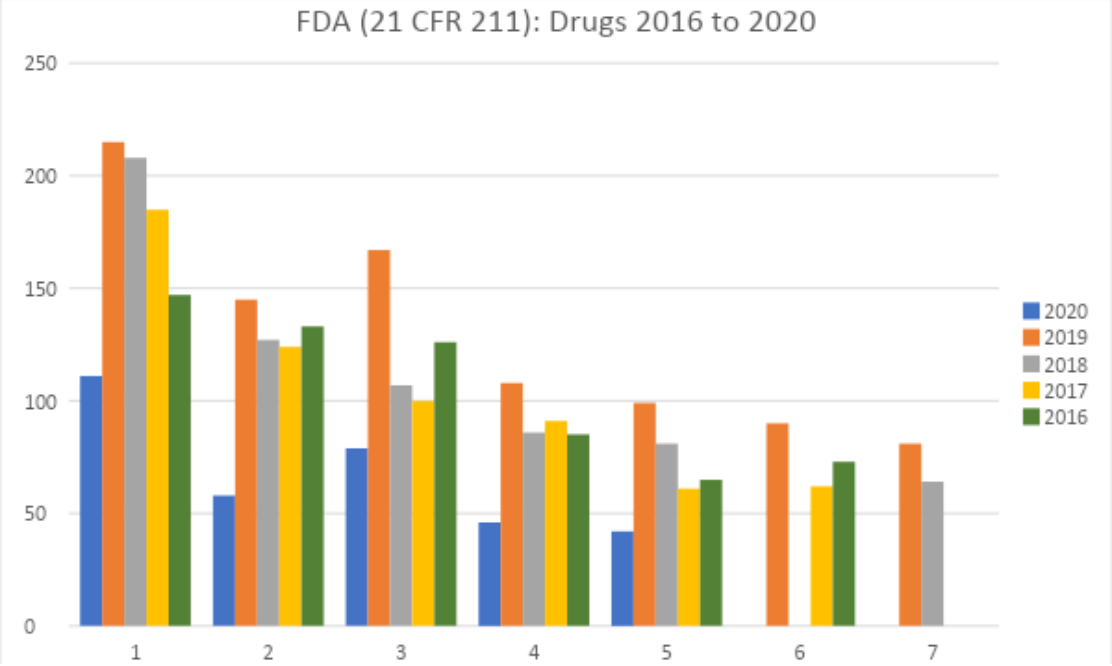
Yet, there is significant concern inside the industry around Quality Management. Multiple surveys of Life Science companies have indicated the following top challenges within the industry.



The surprising element of this is the amount of effort that has been invested in improving Quality and Regulatory systems.

The available data of the Quality & Regulatory effectiveness in Life Science industry is seen in terms of FDA Office of Pharmaceutical Quality and inspection results. The data is shown below for Medical Devices and for Drugs over the recent 5-year period from 2016 to 2020. Both show a consistency in terms of the top issues, and the quantity of findings within each issue. They do not show an improvement. Note that 2020 quantity data is lower due to the lower level of FDA inspections during the Covid19 time.





The implication is the lack of progress in these issues over the years despite the effort placed, and the dissatisfaction inside the industry on its own performance.

The Why vs What

One may begin by asking how should Quality Systems be defined and evaluated? Quality should be a **value-added** partner and **coach** that helps integrate compliance into regular operations while enabling speed and effectiveness. A fundamental requirement to achieve this in practice is to reframe how the Quality System is defined and structured for the organization.

In Semiconductor practice, the quality systems provide the framework to implement, with the guiding principle that specifications and procedures must be directly proportional to the product quality needs which drives an assessment of all steps in terms of "**Value Add**" for the process. This is a Quality **Operating** System in practice.

In Life Science, the quality systems provide the framework to implement procedures to be directly proportional to meet compliance first, then product quality. This is a Quality **Management** System in practice.

The key here is the practice within these two industries where an **operating** system leans towards directly controlling the production – building in quality, while a **management** system leans towards building in inspection – checking for compliance.

Operating systems tend to drive controls that directly affect the product quality. Management systems allow controls that indirectly affect product quality. The impact on engineering in practice is clearly understanding the "Why" first in an operating system, and the "What" first in a management system.

- *Do your quality controls affect products Directly or Indirectly: are they designed to build in quality (the why), or designed to build in inspection (the what)?*
- *Quality Operating System vs. Quality Management System in practice.*

Understanding some of the differences that drive the industries helps inform the frameworks that influence the different approaches. Both industries have competitive pressures, but the Life Science industry has an additional pressure of regulatory requirements for good reasons, and the regulatory requirement takes a dominant role.

INDUSTRY	SEMICONDUCTOR	LIFE SCIENCE
DRIVER	Competitive pressures drive the need to achieve (Poisson D0) <0.1 defects/cm2 (or >90% product yields) ISO standards	Regulatory pressures & competitive pressures – allowing variable product yields CGMP Regulations
PERSPECTIVE	"As good as you are today, it will not be good enough tomorrow"	Manufacture in accordance with cGMP
CONTROLS	"Does it improve Quality?" = Is it Value Add? Do your systems improve performance?	"Does it meet Compliance?"
IMPACT	Quality Lowers Costs	Quality is a Cost of doing Business

Semiconductor manufacturing process have well over 1000 process steps and if the processes are not within 3 sigma control, the yield will be extremely low. This led to the start of 6 sigma techniques (Motorola, 1986) for driving 99.99966% of the steps to be defect free, or 3.4 defects per million steps. This forces all quality elements to be directly related to process control and the need to utilize statistically based controls that the engineers analyze daily and adjust as appropriate.

The above two elements drive a difference in the implementation:

INDUSTRY	SEMICONDUCTOR	LIFE SCIENCE
MINIMUM	(SPC) Statistical Process Control (output control, sensor data) – electronic records Correlation of physical, electrical and material data	Paper or electronic records of Process parameters
ADVANCED	Input control: Fault Detection Control (FDC) Run-to-Run control, Advanced data analytics Predictive (Maintenance, Performance)	Electronic records of process parameters Process equipment automation
QUALITY VIOLATION	Product yield affected, Actively correlated to parameters	Product yield may or may not be affected, Not actively correlated to process parameters
CONTROLS PRACTICE	Direct at each operation. Electronic data (iOT) to enable SPC, FDC Practice: Data driven implementation	Indirect & Direct: Automation controls & instrumentation tolerances Practice: Interpretive & data driven implementation
EVIDENCE	Statistics (6 Sigma) CpK trends, Control Limits at 3 Sigma at all process steps. Tracking In-process yield, final yield	cGMP records, Process parameters, setpoints, alarm tolerances
INTERPRETATION	Not Interpretive – Objective Mature QbD	Interpretive – Subjective Early QbD
STANDARDS	ISO (ie. 9001) Effectiveness of the quality systems to drive improvements in quality, efficiency and customer satisfaction.	CGMP Regulations to drive safety and efficacy of products.
INTERPRETATION	Not Interpretive – Objective Mature QbD	Interpretive – Subjective Early QbD
SMART QUALITY	Implementation Mature	Early stages

This is the basis for which Quality Systems have been established in the semiconductor industry and demonstrating the value for the business.

In terms of "Smart Quality" implementation, below is a short (incomplete) table of the quality framework analytics that is typical in the semiconductor manufacturing process. None of this is forced on the industry by any regulatory body but is driven by the need to continuously improve and drive towards predictable and stable production quality. Although, automotive customers have driven this expectation (requirement) onto their semiconductor suppliers.

SEMICONDUCTOR QUALITY FRAMEWORK		
DATA COLLECTION	**EQUIPMENT +**	**PROCESS & EQUIPMENT CONTROL**
FACTORY LOGISTICS: WIP: By batch, by wafer Start & Finish day/time stamps Equipment: By chamber	**EQUIPMENT HEALTH MONITORING:** Monitoring equipment parameters to assess performance as a function of deviation from normal.	**FAULT DETECTION**: Monitoring and analyzing variations to detect anomalies with univariate and multivariate techniques.
EQUIPMENT: Availability, Utilization Batch/wafer processing data Control Data: SPC, FDC Error logs	**PREDICTIVE MAINTENANCE:** Analysis of process and equipment parameters to predict when equipment components need maintenance, and as a driver to improve maintenance.	**FAULT CLASSIFICATION:** Determining root cause of faults. **FAULT PREDICTION:** Monitoring and analyzing variations to predict anomalies
MATERIALS: Batch Analytics (Cert. of. Compliance) Batch usage qualifications Batch changes SPC of material (Cert of Comp) Correlation to product performance	**PREDICTIVE SCHEDULING:** Analysis of current and future factory demands to optimize scheduling (WIP, Maintenance)	**RUN-TO-RUN CONTROL:** Adjusting process parameters between runs to maintain statistical process
FACILITY: HVAC Gas, Chemicals Process Products Process recipes, variations Performance of Electrical, Physical Statistical performance		**STATISTICAL PROCESS CONTROL:** Statistical methods to analyze trends and define control adjustments and continuously improve process capability.
PROCESS: Products Process recipes, variations Performance of Electrical, Physical Statistical performance		**YIELD PREDICTION:** Big Data & Analytics to predict quality

Success in implementation requires addressing the **Roles & Responsibility for ensuring quality**. The two industries utilize a different approach with the key difference being the level of ownership at the manufacturing level.

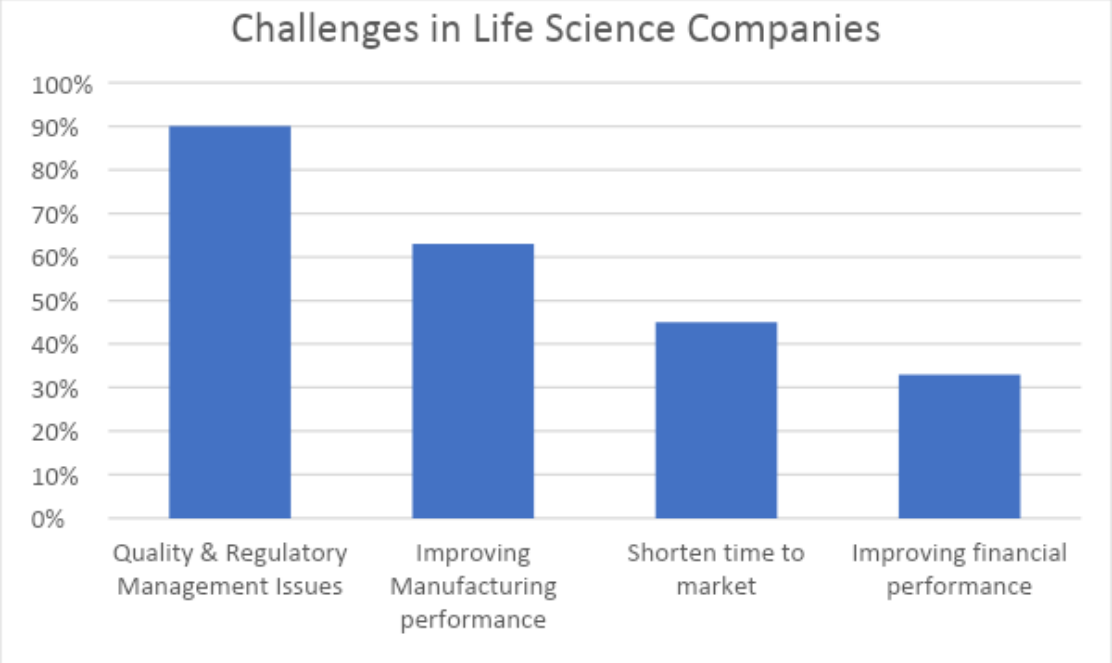
INDUSTRY	SEMICONDUCTOR	LIFE SCIENCE
QUALITY FRAMEWORK	Quality Group	Quality Group
DEFINE CONTROLS	Engineers: Process & Equipment	Quality Group & MSAT
PRIMARY RESPONSIBILITY	Engineers & Technicians	Engineers & Technicians
REVIEW & OVERSIGHT	Manufacturing Management	Quality Group
CAPA PROCESS OVERSIGHT	Manufacturing	Quality Group

The Roles & Responsibility drive a difference in the Quality Organization makeup in the industries.

INDUSTRY	SEMICONDUCTOR	LIFE SCIENCE
TYPICAL QUALITY TEAM SIZE AS A % OF ORGANIZATION	1%	>10%
QUALITY GROUP ROLE	Guide, Coach Create quality systems, coach quality methods Statistical methods Design of Experiments Define SPC and FDC strategies Track CAPA trends	Police, Guide Drive CAPA's Define regulatory compliance Define quality systems Track CAPA trends
CAPA RESPONSIBILITY	Manufacturing	Quality
ENSURE COMPLIANCE	Manufacturing	Quality
PRODUCT QUALITY ACCEPTANCE	Manufacturing	Quality

Conclusion: Cross learning of Quality: Semi & Life Science

To address the primary challenges that industry leaders define, a change in perspective may be helpful. Quality as an operating system may be the fundamental difference in perspective and implementation.



Quality owned by the manufacturing organization to implement (quality) controls that are data based, and readily evaluated statistically. Controls must provide demonstrable value (Value-Add). There should be relentless efforts on continuous improvement that are fundamentally based on Lean/Six Sigma methods. CAPA's are owned by manufacturing. Quality does not own the quality controls but provides the quality systems framework. The Lean principles drive the evaluation of each requirement to demonstrate the value provided directly to quality.

It is a shift to establishing Quality as an enabler of value creation and the foundation for practical formation of a Smart Quality approach that provide demonstrable value (Value-Add).

Quality as an operating system has driven measurable improvement in:

- Operational Excellence
- Efficiency, Quality, Agility & Flexibility
- Organizational efforts that are integrated & aligned.

Such quality systems will follow CGMP by building in compliance rather than inspecting in compliance.

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