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GMP Compliance, Quality Assurance, and Business Synergy

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Editor's Note:

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Hello. I am very happy to join you today virtually for the TU Dublin Quality Business Leadership Summit to share an FDA perspective on the quality/business synergy. I will begin today's presentation by briefly discussing the concept of GMP compliance, and why it is synonymous with quality assurance.

I will then discuss the importance of making sound lifecycle decisions to assure a continuing state of control. We will then look at senior management accountability for effective quality systems and how that ultimately manifests in the capability of your manufacturing facilities. Finally, I will highlight the quality and business synergies of assuring capable manufacturing facilities.

Concept of Compliance

Let's start with the GMPs and the practical importance of complying with this legal requirement.

What exactly is compliance? By definition, compliance means 'the act or process of adhering to a pre-established regimen, and even more precisely, the degree of constancy and accuracy with which a prescribed regimen is followed.'

The concept of compliance is, of course, relevant in many diverse everyday contexts. For example, in a clinical context, patient compliance refers to adherence to a prescription. If the patient does not comply by taking medicines as prescribed, a favorable health outcome will be less likely. The therapy will likely be ineffective, and perhaps even unsafe, if the drug is not taken according to its labeled instructions, and the doctor's prescription. This is especially true if the patient widely diverges from the prescription.

In the context of drug manufacturing, when the process or procedure used differs from that shown to be reliable, acceptable manufacturing output is not assured, and there is a higher probability that

consumers will be exposed to defective medicines. And again, significant deviations are especially worrisome.

So, the essence of compliance and quality assurance is developing robust procedures and processes and then executing them reproducibly every day. In my experience, companies that have quality and compliance failures often have a misconception of what CGMPs really are and often fail to address manufacturing quality issues until it is too late.

Designing for Quality

Fortunately, a great proportion of facilities are compliant because they understand that CGMP compliance is a legal requirement underpinned by the core theme of prevention – prevention of errors, defects, loss of process control, contamination, etc.

It is a holistic system of design, control, and oversight that assures drug quality each day at a facility. And to drill down deeper into how that is accomplished in a tangible way, this slide discusses two basic elements at any company that maintains a continuing state of control, being strong quality systems and highly capable manufacturing facilities.

Likewise, companies who have resolved their persistent non-compliance have transformed by emphasizing these two ingredients as core to their comprehensive CAPA [corrective and preventive actions] plan.

For **quality systems**, this means quality systems benchmarking to learn from others who have robust quality systems, improving governance to quality systems by senior executives where attention, routine meetings, ad hoc escalation where needed of emerging quality issues, and visible commitment to quality from the senior executives. That is what a lot of people call establishing the right quality culture.

[Also], increasing operations accountability for identifying capability performance gaps and opportunities for quality improvement – not just QA doing that, operations taking co-ownership, and of course, improved QA oversight of facility processes, quality performance, and properly functioning systems.

The second piece here, the **highly capable facility piece**, is changing from lower-capability processing lines to more capable lines, upgrading using automation, isolation technology, closed systems, or continuous manufacturing opportunities.

So, just an example in the sterile industry because we have seen the sterile industry start to change significantly over the years due to some well-publicized sterility problems. Many sterile drug manufacturers have transformed operational reliability and are now consistently CGMP compliant after they converted from low capability, inefficient equipment, manually intensive, to highly capable isolator technology, with automation – and often that automation these days includes robotics.

Quality System Improvement

I already mentioned the core theme of prevention in GMPs. Ultimately, GMPs exist as a standard for companies to follow to prevent consumers from exposure to harm.

Regulatory agencies like FDA and HPRA are in the business of prevention. This means we cannot react only once consumers are harmed before we take an action.

Of course, the quality system at a drug company shares the same objective: to ensure lifecycle quality vigilance and prevent distribution of defective medicines.

On this slide, you can see many of the elements that comprise a competent quality system, including supply chain oversight, a patient-centric mindset, data integrity, ongoing pursuit of lifecycle continual improvements, and the CAPA program, just to name a few. In the upper left-hand corner, you see the words 'state of control,' which is our next topic.

Figure 1 Elements of a Competent Quality System

Assuring an Ongoing State of Control

Senior management has a critical ongoing oversight role to ensure a continued state of control in their manufacturing operations. This is not only a GMP requirement in the United States, but also the focus of our inspection program efforts in the U.S. – a state of control.

The term is not new. Maintaining a stable and robust operation is a basic goal of producers of goods throughout the industries.

FDA publications have used this state of control terminology since at least the early 1980s, and FDA's process validation guidance explains the requirement as follows: 'after establishing and confirming the process, manufacturers must maintain the process in a state of control over the life of the process.'

This is necessary 'even as materials, equipment, production environment, personnel, and manufacturing procedures change' over the lifecycle. It also notes that to accomplish this, a company must have a strong program for collecting and analyzing process performance and product quality data. And this data must be used to evaluate the performance of the process and identify problems

and any actions needed to correct, anticipate, and prevent problems so that the process remains in control.

As many of you know, just like our process validation guideline and our inspection program, ICH Q10's quality system also has the same basic goal of establishing and maintaining a state of control. So, you see this dovetail between all of these different guidelines and our inspection program.

I will also point out that 'state of control' is defined in the ICH Q10 glossary if you would like to see a definition.

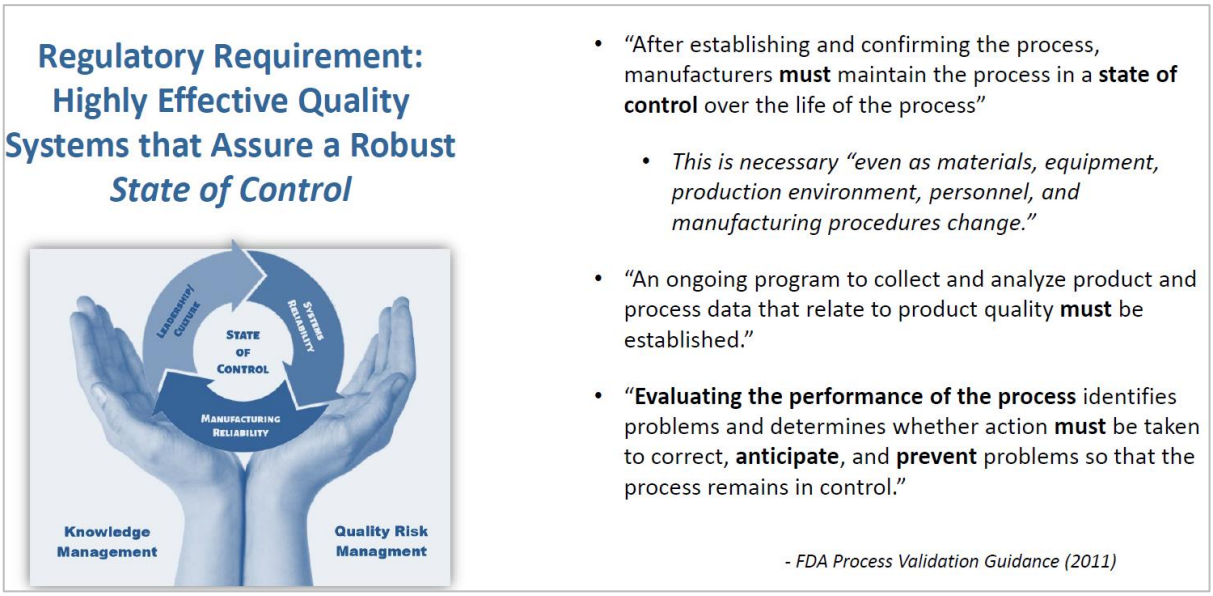

Figure 2 Regulatory Requirement for a Quality System Assuring a State of Control

Examples of a Loss of State of Control

This slide summarizes some tangible examples from recent FDA inspections of the loss of a state of control. Our inspections have found major medicinal quality issues due to deficient supplier management, inadequate facility design, facilities in a state of disrepair, insufficient investigations of drug quality failures, ineffective cleaning – including many cases of visible drug residuals on equipment marked as clean – and inadequate aseptic processing operations.

As a consequence of these GMP deficiencies, we have seen significant quality defects like recurring assay and content uniformity failures, non-sterile ophthalmics and parenterals, objectionally contaminated non-sterile dosage forms, including some well-publicized *B. cepacia* contaminations, products made of poor-quality excipients and APIs, and various other direct impacts to product quality.

And in the upper right-hand corner, you see that FDA has found some alarming data integrity issues, including several companies that have repeatedly fabricated manufacturing or laboratory data. We have also observed too many systems that are vulnerable to data integrity breaches and can be better fortified against ALCOA deviations, security breaches, and record retention issues.

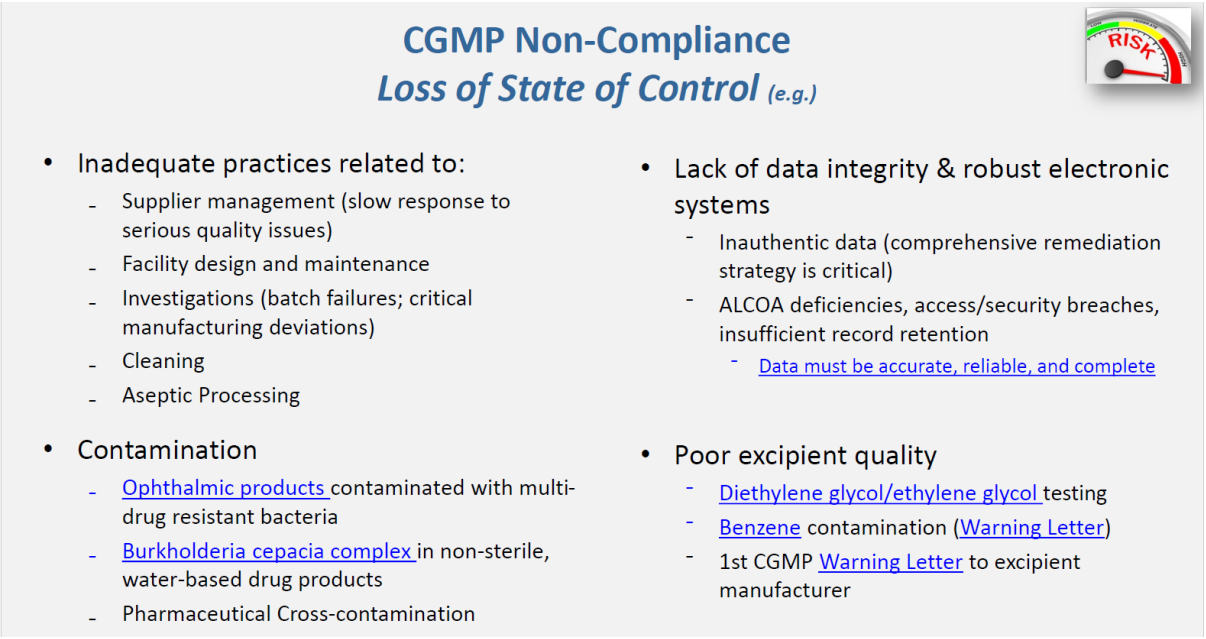

Figure 3 Examples of Loss of State of Control

Senior Management Accountability for Quality

I think it is pretty clear that those facilities had some major lapses in management oversight. So I thought this would be a good time in the presentation to take a closer look at senior management responsibilities for assuring a robust quality system and higher capability manufacturing facilities.

One of the true objective quantitative tests of whether top management is sufficiently overseeing quality is in the capability of its manufacturing operations.

A **low-capability** manufacturing process creates the conditions for excessive variation in the quality of finished products. It may yield acceptable products on some days, but when that operation experiences its inherent capacity for excessive variation on any given day, the quality of finished units will suffer.

A company often has early signals of this high variability, but in some cases, senior management does not act quickly enough to improve the manufacturing operation, and needed improvements are, in fact, only made after there have been negative quality and regulatory outcomes.

In contrast, **highly capable** processes use robust manufacturing operations that yield high-quality output each day throughout processing.

So going back to my two ingredients of sustainable compliance, it is possible that a company may have a good quality system on paper, and in practice, this may also prove true in many ways. However, quality assurance is fundamentally undermined if a facility is not suitable for its intended use.

Happily, there are quantitative measurements for laboratory methods and manufacturing unit operations to show their capabilities and areas for improvement. And there are a lot of quality tools like Six Sigma out there and process capability indexes to help identify and target those efforts.

FDA Warning Letters to Senior Management

FDA has increasingly been addressing management oversight responsibilities in our warning letters. This first letter notifies a company that it cannot maintain robust operations without steadfast support for quality from top executives in the company.

> **Warning Letter Excerpt: Executive Management**
>
> *"Describe how **top management** supports quality assurance and reliable operations, including but not limited to timely provision of resources to proactively address emerging manufacturing/quality issues and to assure a continuing **state of control**."*

The letter asks the company to describe how **top management supports quality** assurance and reliable operations, including but not limited to, timely provision of resources to proactively address emerging manufacturing and quality issues and assure a continuing state of control. So, there are those keywords again. And keep the provision of resources in mind for the latter part of this presentation.

Another warning letter. Here again, you see an emphasis on **operations leadership responsibility**. There has been increased emphasis in the last 10 years on this front.

> **Warning Letter Excerpt: Operations Responsibility**
>
> *"In your response, provide:*
>
> *Your corrective action and preventive action (CAPA) plan to implement routine, vigilant operations management oversight of facilities and equipment. This plan should include, but not be limited to, improved oversight to ensure prom**pt detection of equipment and facilities performance issues**, timely **upgrades to equipment and facilities**, adherence to appropriate preventive maintenance schedules, **effective execution of repairs**, appropriately personnel competencies, and improved systems for ongoing management review of potential quality risks.*
>
> *Your plan should also ensure appropriate actions are taken throughout the company network."*

Particularly we will include this type of paragraph in warning letters where we find low capability operations, whether it is because a facility has degraded due to lack of attention and upkeep over the years and it is in a state of disrepair, or the equipment and facilities are low capability at the outset and have been operating on the edge of failure for years – and upgrading has always been something that should have been considered just by sheer borderline capability of the operation. You are only as good as the equipment capability.

So, in this example, the warning letter stresses the need for improvements, including more prompt detection of equipment and facilities and any performance issues that are arising, and better execution of repairs. It has been an issue. There [have been some] very interesting CMO and generics cases in particular, but also the innovator sector – better systems for detection and review of manufacturing quality risks, and timely upgrades of equipment and facilities.

The **operations and quality partnership** is critical here and that is what you are talking about today. Operations owns quality along with the quality assurance department, and that partnership is key.

This letter is a more high-level focus on the **failure of a quality system** to meet GMP standards.

Warning Letter Excerpt: Non-Compliant Quality System

Ineffective Quality System: *"Significant findings in this letter demonstrate that your firm **does not operate an effective quality system in accord with CGMP**. In addition to the lack of effective management oversight of your production and laboratory operations, we found **your quality unit is not enabled** to exercise proper authority and/or has insufficiently implemented its responsibilities. **Executive management** should immediately and comprehensively assess your company's global manufacturing operations to ensure that your systems, processes, and products conform to FDA requirements."*

It notes that the lack of effective management oversight in production and laboratory operations and ineffective quality assurance function was present at this company. It concludes by emphasizing again, the executive management role and asks the company to respond with an 'immediate and comprehensive assessment' of the firm's global manufacturing operations to ensure that systems, processes, and products conform to FDA requirements.

This is how we are asking the CEO to respond to FDA. The warning letters are addressed to the CEO or managing director of a company….

This last warning letter excerpt addresses a critical function in all quality systems, the CAPA program.

Warning Letter Excerpt: Executive Management Support for QA

*"Provide an independent assessment and remediation plan for your CAPA program, including whether your firm assures CAPA effectiveness, regularly reviews investigations trends, implements improvements to the CAPA program when needed, ensures appropriate quality assurance unit decision rights, and is fully **supported by executive management**."*

The letter states that a third-party assessment of the firm's CAPA program is needed, and it names several aspects of a competent CAPA program. You see how it ends here by noting the need for appropriate quality assurance unit decision rights and that there is a demonstration by executive management of the full support for the CAPA program.

Strong Quality Management Oversight

I mentioned the importance of the quality/operations partnership, but there is also the critical responsibility of the quality leaders in an organization to develop a good relationship with top executives at the company and for the executives to be engaged and visibly involved in quality matters.

Where that is strong in a company – and it is usually manifested today with a CQO, Chief Quality Officer, who reports directly to the CEO – those companies have integrated quality into business decisions, and they tend to have stellar compliance records.

Our CDER Center Director, Dr. Patrizia Cavazzoni, has also noted the fundamental role of strong quality management oversight. At the PDA/FDA conference in September of last year, she discussed the importance of quality ownership throughout the entire organization, strong management oversight and accountability, and highly capable facilities.

She also stressed the need for pharmaceutical quality systems to vigilantly monitor the state of control and proactively identify emerging quality hazards. So you see these same sustainable compliance themes of:

- prevention
- state of control
- management oversight, and
- improved manufacturing capabilities

communicated by our center director, Dr. Cavazzoni, at this venue PDA/FDA, as well as many others.

Figure 4 CDER Director Patrizia Cavazzoni's 'Call to Action' at PDA/FDA 2023

The Quality/Business Synergy

Now, we sometimes encounter companies that are reluctant to invest in quality system and manufacturing facility improvements. Practically speaking, all organizations have budgets and need to decide how to allocate resources.

Deming found that when executives saw the long-term economic benefits of making quality improvements, they became much more interested in making those relevant investments.

As Deming noted, investing in quality will pay off with cost reductions accrued from reliable operations that reduce the cost of failures, low yields, long inventory times, complex investigations, delayed batch disposition decisions, and many other high costs associated with low capability factors.

ISPE Pharma 4.0 Survey

ISPE's Community of Practice has done some great work researching the benefits, challenges, and maturity of Pharma 4.0 with the industry.

This slide is from their recent survey, and it shows that 'no business case and high cost' is the second highest perceived challenge. In their most recent survey, it is clear that more work can be done to fully quantify the benefits of infrastructure modernization in the pharmaceutical industry.

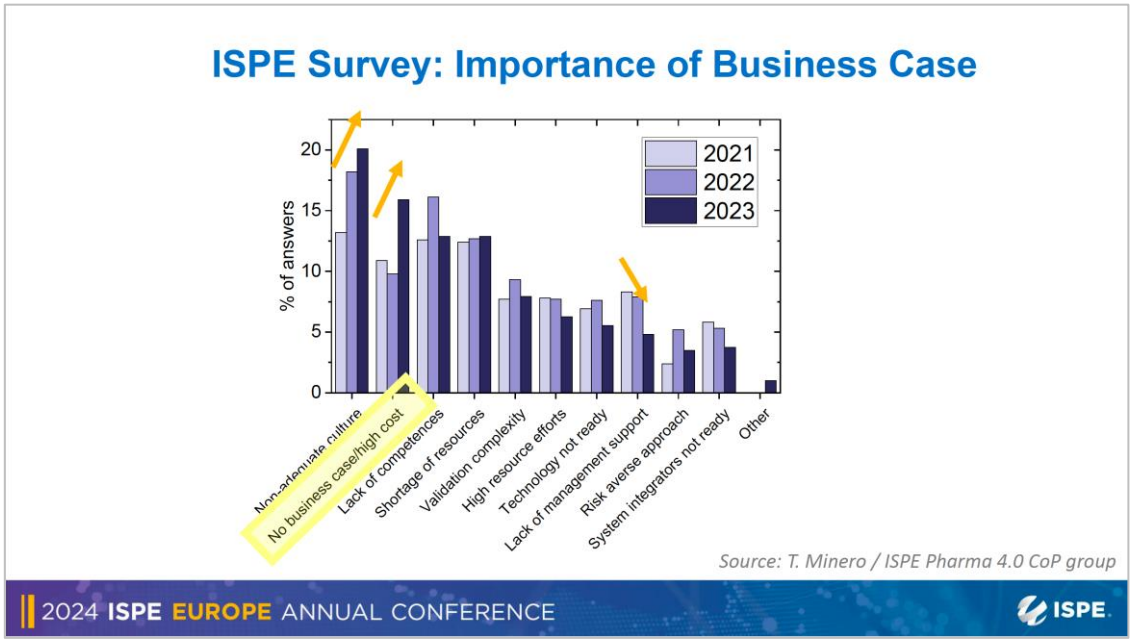

Figure 5 ISPE Survey on business case importance

But there is good news on that front. Many industries have data demonstrating the value gained from improving manufacturing capabilities from both quality and business perspectives. From discussions with many industry professionals, it appears that the pharmaceutical industry could learn from other industries and the more comprehensive models used by those industries.

Lessons Learned from Other Industries

I am personally very interested in this issue and co-authored a paper in PharmTech earlier this year that shares lessons learned from other industries that have shown the value created by improved production capabilities.

This slide summarizes some of the **nonpharmaceutical models** that have shown the business benefits of investing in quality. You can see the myriad industries, including agricultural, aviation, healthcare, semiconductor, hotel, and automobile.

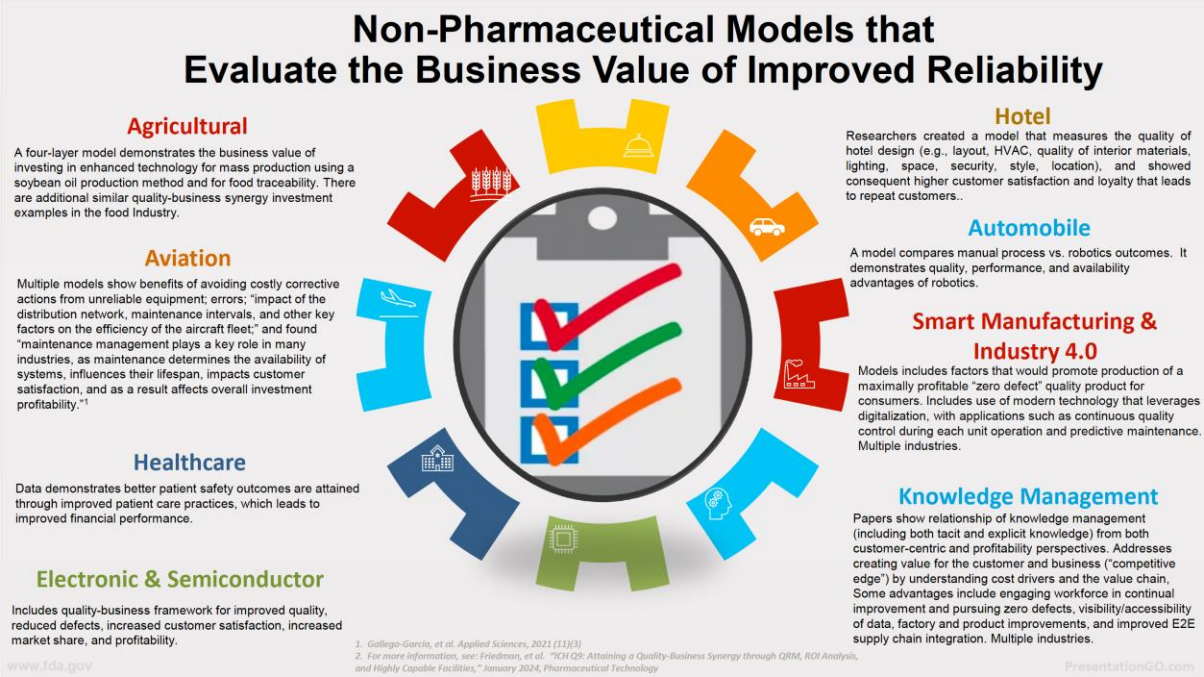

Figure 6 non-pharmaceutical models that have shown business benefits of investing in quality

Various industries have also developed return-on-investment models for smart manufacturing and industry 4.0 – we call it Pharma 4.0 for our industry. Knowledge management has also shown end-to-end benefits for supply chain integration and communications with customers and with service and supplier entities.

Here are some **universal concepts** that are further elaborated in the PharmTech paper I mentioned from January of this year. This graphic includes many universal benefits that can be better quantified and can be pivotal in supporting needed technological upgrades, better yield, throughput benefits, faster turnaround, personnel efficiencies moving from manual to automation, earlier detection and averting unexpected downtime, and faster market launches.

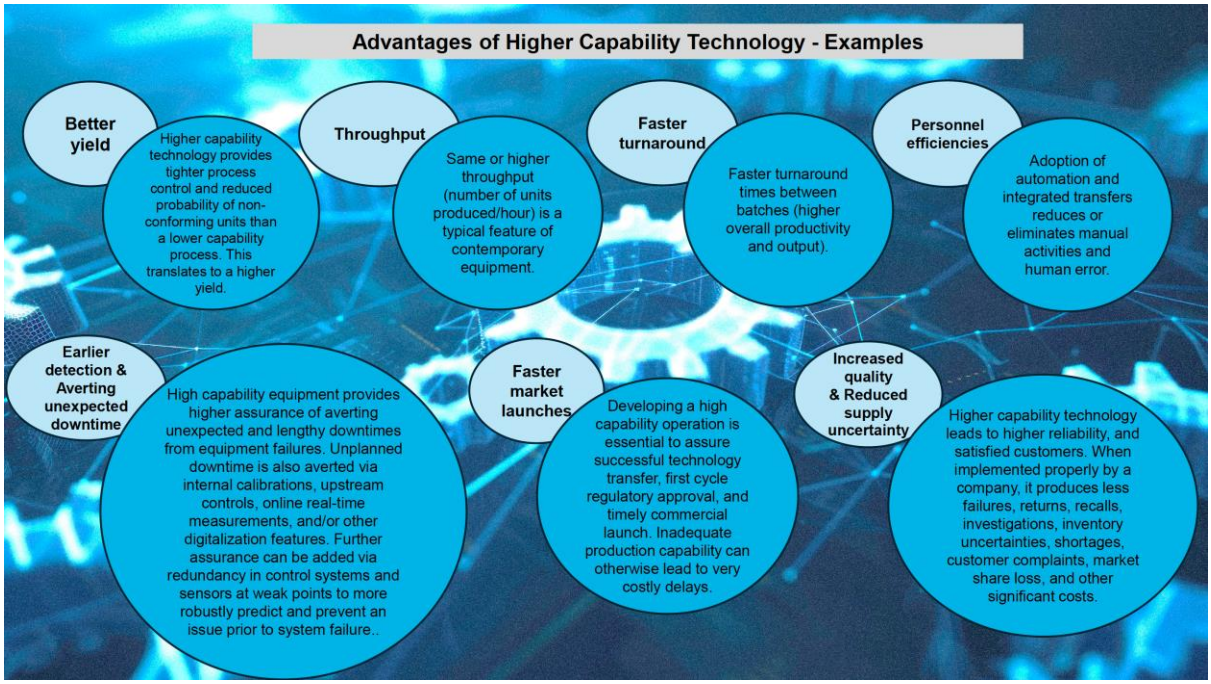

Figure 7 Advantages of higher capability technology

First-cycle regulatory approval is among those benefits in terms of commercial launch, increased quality, and reduced supply uncertainty, to name just a few.

Limited ROI Analyses on Quality Improvements

Related to this was an industry survey by Temple University a couple of years back, which asked industry professionals whether companies typically capture the business benefits of a manufacturing quality improvement proposal in a comprehensive and effective way.

73% of respondents stated that only basic return on investment analyses were done. It was relatively rare for companies to perform comprehensive ROIs that calculate the total cost of ownership benefits of modernizing technology in comparison to the status quo operation.

It is clear that business costs and benefits that distinguish manufacturing choices are not always sufficiently understood. So perhaps this emerging realization will stimulate companies to start developing more comprehensive ROI models to support manufacturing upgrades that benefit both quality and efficiency – and of course, are the foundation for sustainable compliance.

It appears to me that senior quality leaders in the industry can do a better job of showing the value of quality improvements by adopting such comprehensive models to show these to top executives in an organization, and that should explain the high cost of not addressing inconsistent, unreliable manufacturing operations and poor-quality outcomes.

Summary Comments

In summary:

- Manufacturing capability determines the quality of outputs.
- Daily attention to CGMPs prevents patient harm through robust quality systems and facilities. These CGMPs are not reducible to a checkbox approach.
- Quality assurance and operations leaders have a critical daily role in assuring a continuing state of control through vigilant lifecycle review and oversight. Executive managers are ultimately accountable for the quality of medicines, which is enabled via visible support for quality, a strong quality system, and the provision of needed resources.
- Highly capable technology is essential to ensure pharmaceutical quality, and fortunately, it also has substantial cost-of-ownership benefits. Lower-capability manufacturing operations will continue to receive extra FDA scrutiny.

I wish you a most excellent Quality Business Leadership Summit.