Institute of Technology Management

University of St.Gallen

UNIVERSITY OF GEORGIA

Building Quality Management Science to Improve Drug Manufacturing

48th International GMP Conference

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March 5, 2024

Athens, GA

Funding for some of the research contained in this presentation was made possible, in part, by the Food and Drug Administration through BAA contracts [#75F40121C00161, #75F40119C10121] and grants [#5U01FD005675-02, #1U01FD005675-01]. The views expressed in written materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services; nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government

"From insight to impact"

Agenda

1. Introduction
2. FDA BAA: RiskSurve - Overview and Results
3. Continuous Improvement and Compliance
4. Outlook

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Operational Excellence @ University of St.Gallen

The Pioneer for OPEX in Pharma Research

18+ years of experience OPEX Benchmarking in pharma!

- We launched the first large scale international pharmaceutical manufacturing benchmarking in 2004
- Our OPEX database consists of more than 400 production sites from over 148 different companies in 2023

St. Gallen books are mandatory reading when it comes to OPEX in pharmaceutical production!

- We published five books that help executives to set-up improvement initiatives
- St. Gallen literature is under the Top 25% downloaded eBooks published by SpringerLink

FDA has been collaborating with St.Gallen since 2016!

- Three years of collaborative research in the context of FDA's Quality metrics initiative (2016-2019)
- D&B – St.Gallen Quality Benchmarking Study (2019-2020)
- RiskSurve (2021-2023)
- PCIA (2023-2025)

Pharma associations collaborate with St.Gallen!

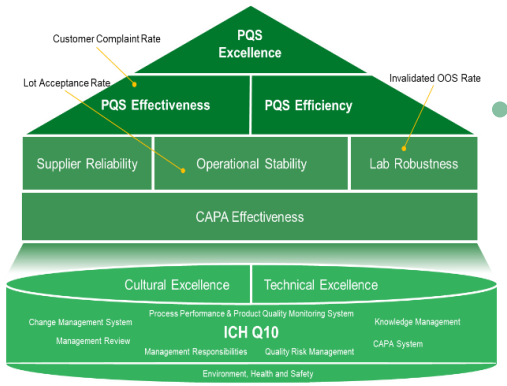
- We have been speaking at numerous conferences such as ISPE Annual Meetings in Atlanta, San Diego & Philadelphia; PDA Conferences in Bethesda; GMP Conference in Georgia; POMS Conferences in Houston & Washington DC

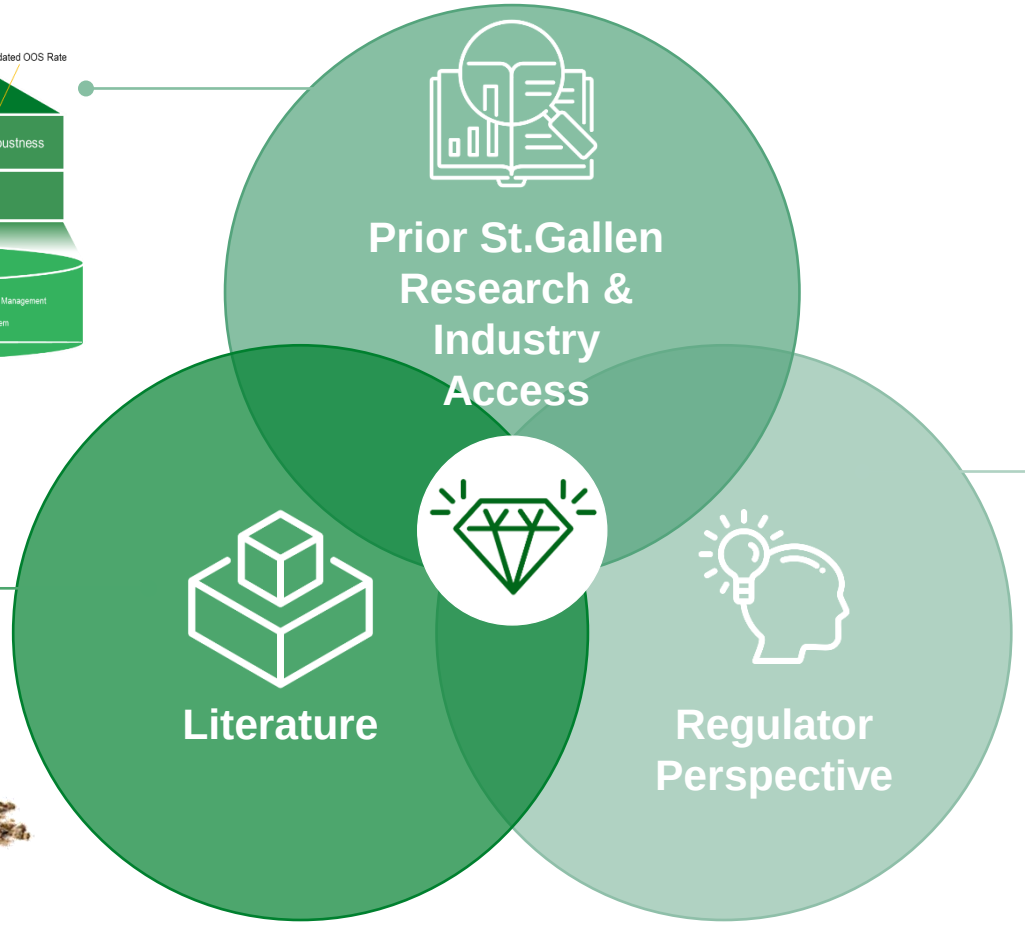
Leading companies consult St.Gallen to improve their operations!

- All Top-Five pharmaceutical companies (measured by revenue) have been participating in the St. Gallen Exchange Platforms to learn from our research
- Numerous individual improvement projects (e.g. Production System Implementation, Maturity Assessments Design, Quality Risk Prediction) performed in pharmaceutical companies

Where we are coming from

From Insight to Impact





FDA (2022). Quality management maturity: essential for stable U.S. supply chain of quality pharmaceuticals
Ferdows & de Meyer (1990). Lasting improvements in manufacturing performance: in search of a new theory. Journal of Operations Management
Friedli et al. (2019). FDA quality metrics initiative – third year report.

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FDA’s ongoing efforts to characterize site quality in the context of a broader surveillance strategy motivated the goal of our recently concluded BAA

This project aims to create a comprehensive Remote Site Risk Surveillance Model consolidating data from the four dimensions Outcome Metrics, Maturity Indicators, Compliance History, External Signals embedded in their relevant Context.

RiskSurve relies on a conceptual framework to drive our analysis and develop the predictive compliance model

Conceptual Framework - Overview

Relationship Additional Info *e.g. Product Inherent Risk, ….

We operationalized the input dimensions scientifically

Outcome Metrics – 9 Metrics in 4 categories

***Maintenance**: e.g. Unplanned Maintenance*

***Quality**: e.g. Rejected Batches*

***Delivery**: e.g. On Time In Full*

***Efficiency**: e.g. Maintenance FTEs/ Overall FTEs*

Compliance History – 2 Perspectives

***Site Perspective**:*

- *Past compliance Information from the manufacturing facility*

***Corporate Perspective**:*

- *Identification of network wide quality failures to rise flag alerts related to the manufacturing network*

Maturity Indicators – 13 Items in 3 categories

Performance Measurement & Continuous Improvement

Collaboration Culture & Organization

Training & Skills

External Signals – Proxies for Performance & Maturity Indicators

:

- *Collection of publicly available data from the web to calculate proxies for:*

***Employee Culture** – Site vs. Corporate, Low vs. High tiers*

***Performance & Complexity** – Financial & Product related information*

After comparing the accuracy of three different classification models, we selected the Light Gradient Boosting Machine (LightGBM)

During the model development, we observed **how tree-based** models (LightGBM and Random Forest) **outperformed** the Support Vector Machine model. The **quicker computation time and accuracy** of the result made us **selecting the LightGBM** over the RF

LightGBM Multiclass Classification

	Dimension & Context Factors			
	$Accuracy_{avg}$	$F1_{NAI}$	$F1_{VAI}$	$F1_{OAI}$
FIR0	56%	40%	70%	0%
FIR1	61%	50%	71%	0%
FIR2	**65%**	**50%**	**74%**	**57%**

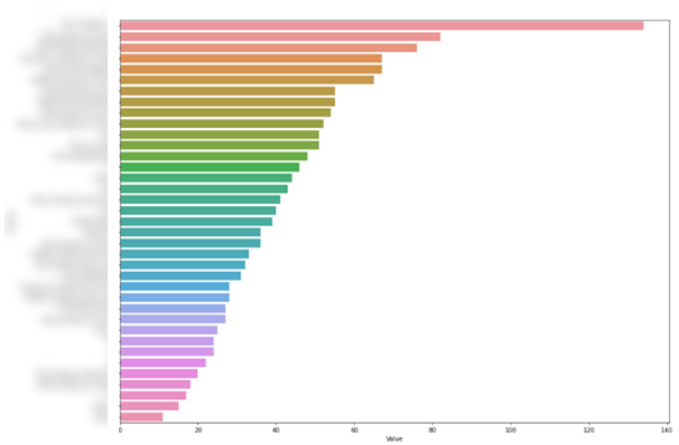
LightGBM Sequentially Binary Classification

	Step 1: NAI vs VAI & OAI			Step 2: VAI vs. OAI		
	$Accuracy_{avg}$	$F1_{NAI}$	$F1_{Rest}$	$Accuracy_{avg}$	$F1_{VAI}$	$F1_{OAI}$
FIR0	56%	33%	67%	75%	84%	40%
FIR1	61%	40%	71%	70%	82%	0%
FIR2	**57%**	**27%**	**69%**	**88%**	**92%**	**67%**

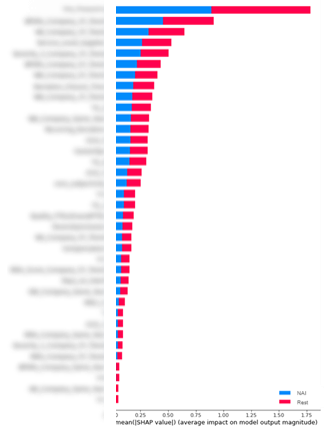
Results in multiclass and binary classification settings showed better accuracy with FIR2, since the model has more data available. Additionally, due to our aim, the sequentially binary classification is more suitable and reveals better accuracy compared to the multiclass.

Therefore, we continued with a sequentially binary classification with FIR2 as target variable.

Overview on the feature selection in iteration 4
Features Overview Overall Model



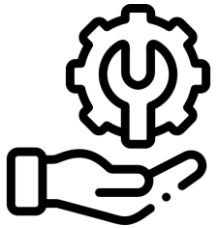
	Number of Features 37(70)*
Outcome Metrics	5 (9)
Maturity Indicators	7 (16)
Compliance History	16 (28)
External Signals	9 (17)



- Compliance history is the dimension with the majority of features in this iterations. Site perspective is the feature with the greater contribution;
- However, for better model accuracy, a balanced mix between the four dimensions is required

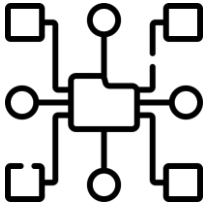
We could extend our research to a second year

We aim to propose additions to the site surveillance strategy



Technically

Including addtional influential factors with critcality levels to existing site selection algorithm.



Organizationally

How to include the additional influential factors and what are the implications to the site selection process.

… leveraging findings from year-one and generating new insights

1 Findings from year-one

The basis for year two extension. Identified important relations between compliance history, maturity, outcome performance, and external signals.

2 Criticality Levels for selected Metrics

Derivation of criticality levels, upper or lower limits, to flag risks. Provides information about the influential degree and boundary conditions of parameters.

3 Site Excellence Ranking Logic

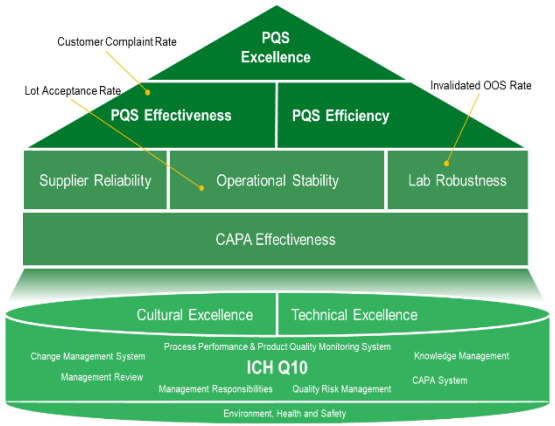
Derivation of a site ranking logic and measurement scale. Categorization might have an impact on surveillance strategy.

4 Qualitative Validation

Interviews with regulators (FDA & PICS) as well as with **the industry**

Our new Excellence Score considered several perspectives

PPSM



Sand Cone Model

Steps to QMM

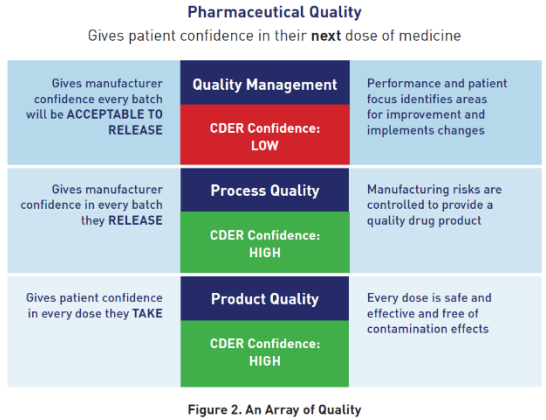


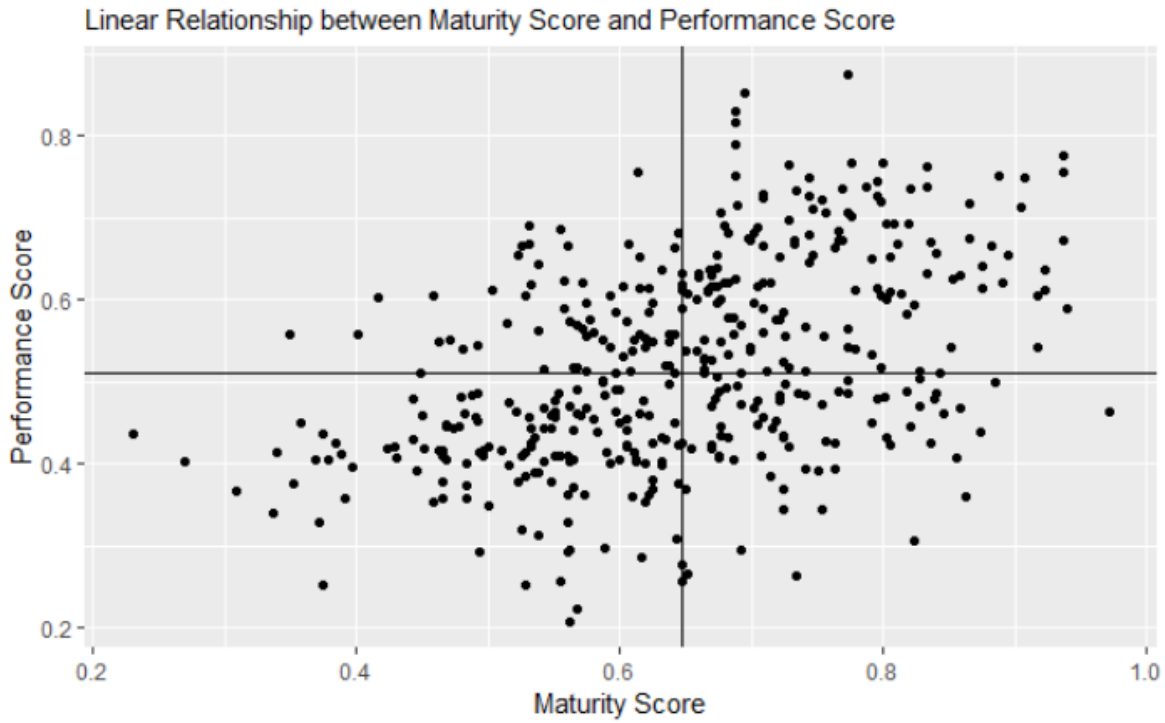
Figure 2. An Array of Quality

FDA (2022). Quality management maturity: essential for stable U.S. supply chain of quality pharmaceuticals

Ferdows & de Meyer (1990). Lasting improvements in manufacturing performance: in search of a new theory. Journal of Operations Management

Friedli et al. (2019). FDA quality metrics initiative – third year report.

The excellence score must consider both performance and maturity scores simultaneously, since the analysis reveals the existence of synergies



Our analysis shows a positive linear relationship between maturity and performance. The Excellence Score must reflect this relationship and especially the 4 quadrants depicted in the graph, by providing a higher weighting to maturity instead of performance since this provides the basis for a sustainable performance outcome.

Our concept of the Excellence Score must respect multiple criteria to guarantee a correct scoring and resulting ranking logic

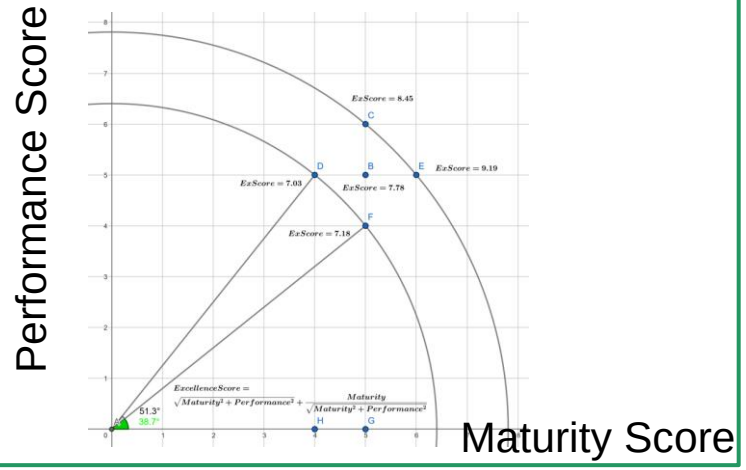
Criteria

EXCELLENCE SCORE

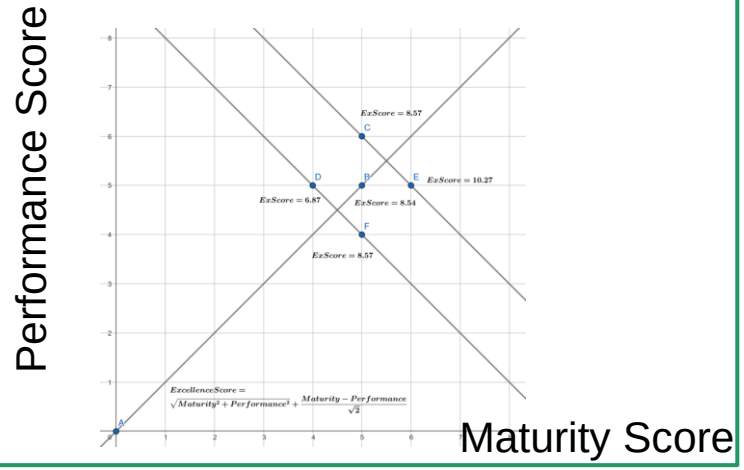
1) For equal performance score a higher maturity score must lead to a higher Excellence Score;
2) For equal maturity score a higher performance score must lead to a higher Excellence Score;
3) If the average value of performance and maturity score is the same for two establishment, the one with the higher maturity score must have a higher Excellence Score;

Options

A) Angle-based Correction



B) Orthogonal-based Correction



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The FDA is thinking about fostering superior quality management – Quality Management Maturity (QMM)

Pharmaceutical producers should sustain superior quality with QMM and continuous improvement

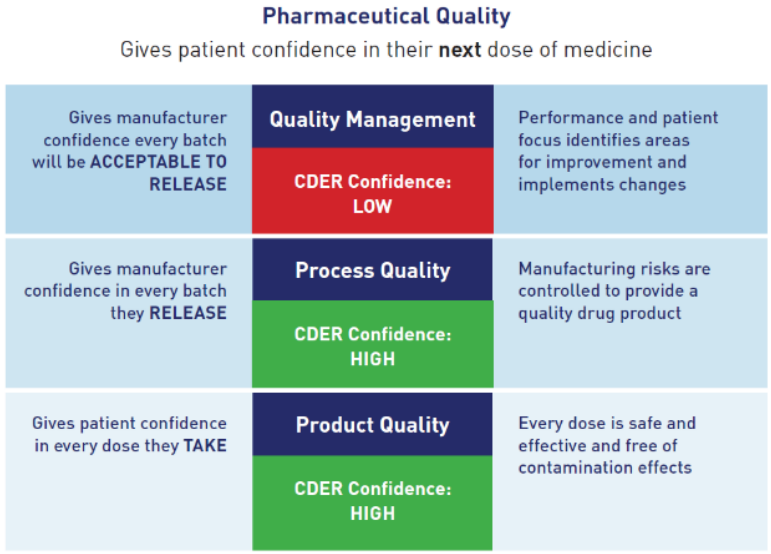


Figure 2. An Array of Quality

…benefits of the program are very promising, however, there are still some open questions

- Increase supply chain resilience and robustness
- Mitigate drug product shortages
- Reward high quality maturity facilities

Source: FDA (2022), Maguire et a., (2023)

What is the current status quo on improving quality practices?

Advanced quality management practices positively correlated with PQS effectiveness, and facilities with greater PQS effectiveness are more likely to have implemented advanced QM practices (Friedli et al, 2019, VanDuyse et al., 2021)

Greater level of operational stability (i.e. stable and reliable processes/equipment) and robust quality practices positively impact delivery performance (Cua et al., 2001; Fellows et al., 2022)

Operational stability must be guaranteed (normally in the form of SOPs), however, firms should not fall into complacency due to having SOPs in place as well as company inertia due to fix procedures (Nelson and Winter, 1982; van de Ven, 1986)

However, adherence to quality practices decays over the time (Gray et al., 2015) and is hard to maintain (Ocasio, 1997). In case of missing renewal of quality practices, the level of process entropy increases, decreasing the adherence to SOPs (Anand et al, 2012)

How can continuous improvement be supported in a highly regulated environment?

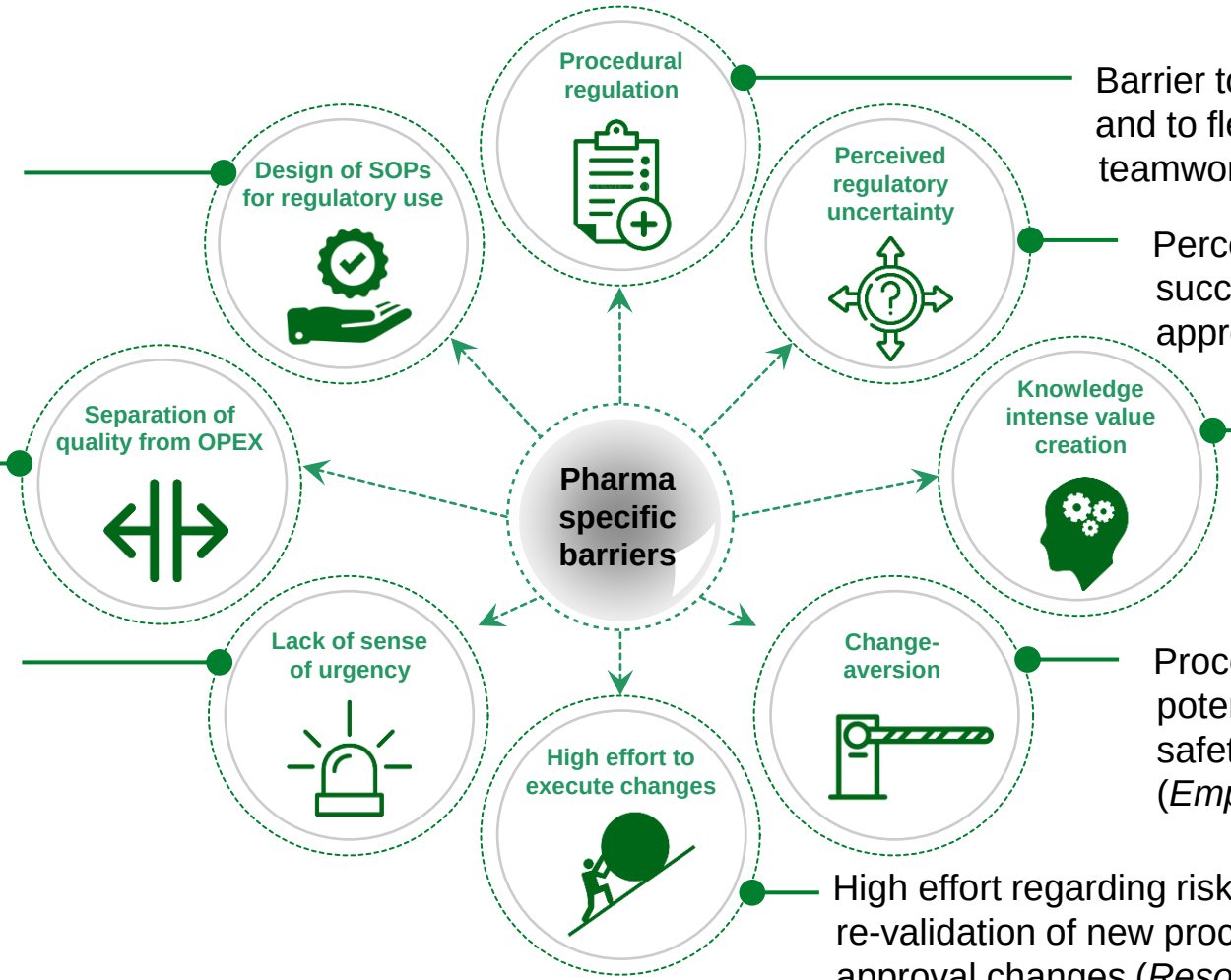
We identified eight pharma-specific barriers to continuous improvement

Barriers

Separation of SOPs and concepts of standardized work, resulting in increased task complexity and higher cognitive load for operators (*Conflicts*[1])

Oversight function of quality organization, resulting in a strict separation of responsibilities between quality and production (*Employee & Culture*[1])

Limited the sense of urgency for operational improvement, due to pharmaceutical business model (*Employee & Culture*[1])



Barrier to change and to flexible cross-functional teamwork (*Conflicts*[1])

Perceived uncertainty regarding success, effort, and timeline for post-approval changes (*Knowledge*[1])

Pronounced silo thinking due to value creation process and high degree of task specialization (*Knowledge*[1])

Process changes are perceived as potential risks to quality, patient safety and regulatory compliance (*Employee & Culture*[1])

High effort regarding risk management, documentation, re-validation of new processes and procedures for post-approval changes (*Resource*[1])

Source: Macuvele (2022)

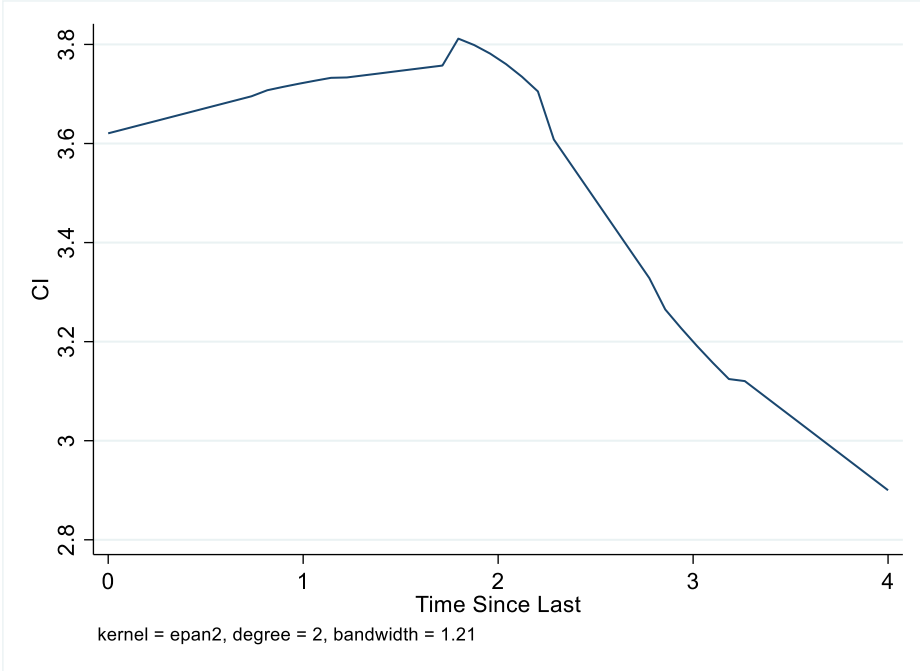
[1] Zhang et al. (2017) (excerpt)

In our recent research, we showed that regulatory inspections have a positive impact on a CI mindset

We investigated the interdependence between a CI mindset and quality practices in FDA regulated facilities

- We examine how quality practices impact the Ci mindset in pharmaceutical manufacturing establishment in the context of regulatory oversight and inspection;
- We find that although practitioners perceive regulatory burden as barrier to CI, a CI mindset can exist in a highly regulated industry and regulatory inspections even positively influence the impact of quality practices on the CI mindset;
- However, the positive effect of inspections decays over time (see graph). Therefore, plant inspection is a fundament tool for guaranteeing drug product quality, programs such QMM might help to encourage more sustainable quality management practices

Combination of linear and quadratic effect of time since last Inspection



Source: Bernasconi et al., (forthcoming)

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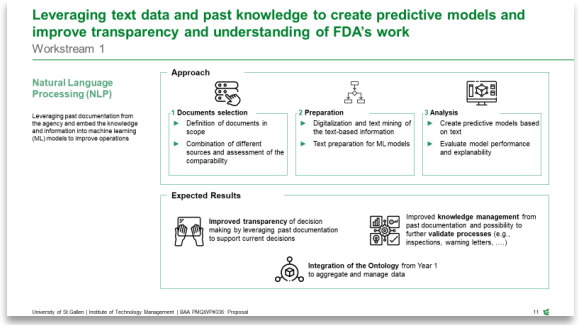
We have been awarded a new 2-years BAA with the FDA (2023-2025)

Drive Predictive Continuous Improvement (CI) Acceleration – Towards Performance Based Regulation Regulations and Oversight

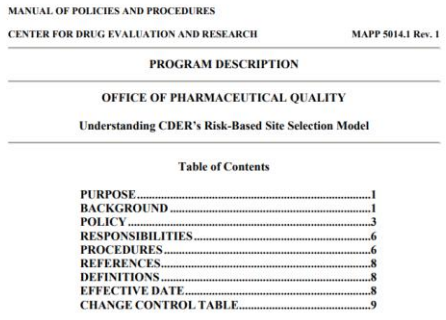
FDA Knowledge Management System



Work Stream Expected Results

- Improved transparency of decision-making process
- Improved knowledge management
- Further process validation
- Integration into the ontology from Y1 RiskSurve Project

Site Selection Model Review


MANUAL OF POLICIES AND PROCEDURES

CENTER FOR DRUG EVALUATION AND RESEARCH MAPP 5014.1 Rev. 1

PROGRAM DESCRIPTION

OFFICE OF PHARMACEUTICAL QUALITY

Understanding CDER's Risk-Based Site Selection Model

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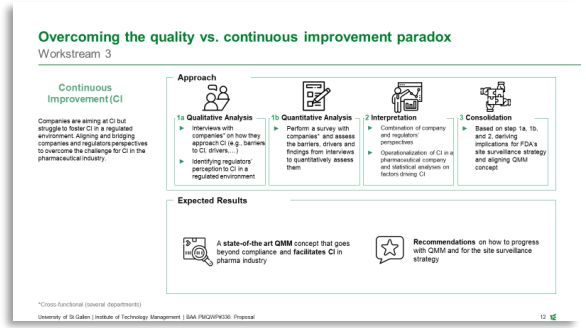
Work Stream Expected Results

- Strengths and Weaknesses of current approach
- Evaluation of possible additional metrics and aggregation logics
- Update recommendations

Continuous Improvement



Work Stream Expected Results

- QMM facilitates continuous improvement in pharma industry
- Recommendation on how to overcome CI hurdles
- Refinement of predictive models
- Considerations of the integration of QMM into site surveillance strategy

University of St.Gallen
Institute of Technology Management

Contact Details

Please do not hesitate to contact us if you have any questions

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