Assessing the Effectiveness of a Pharmaceutical Quality System: Office of Quality Surveillance Perspective

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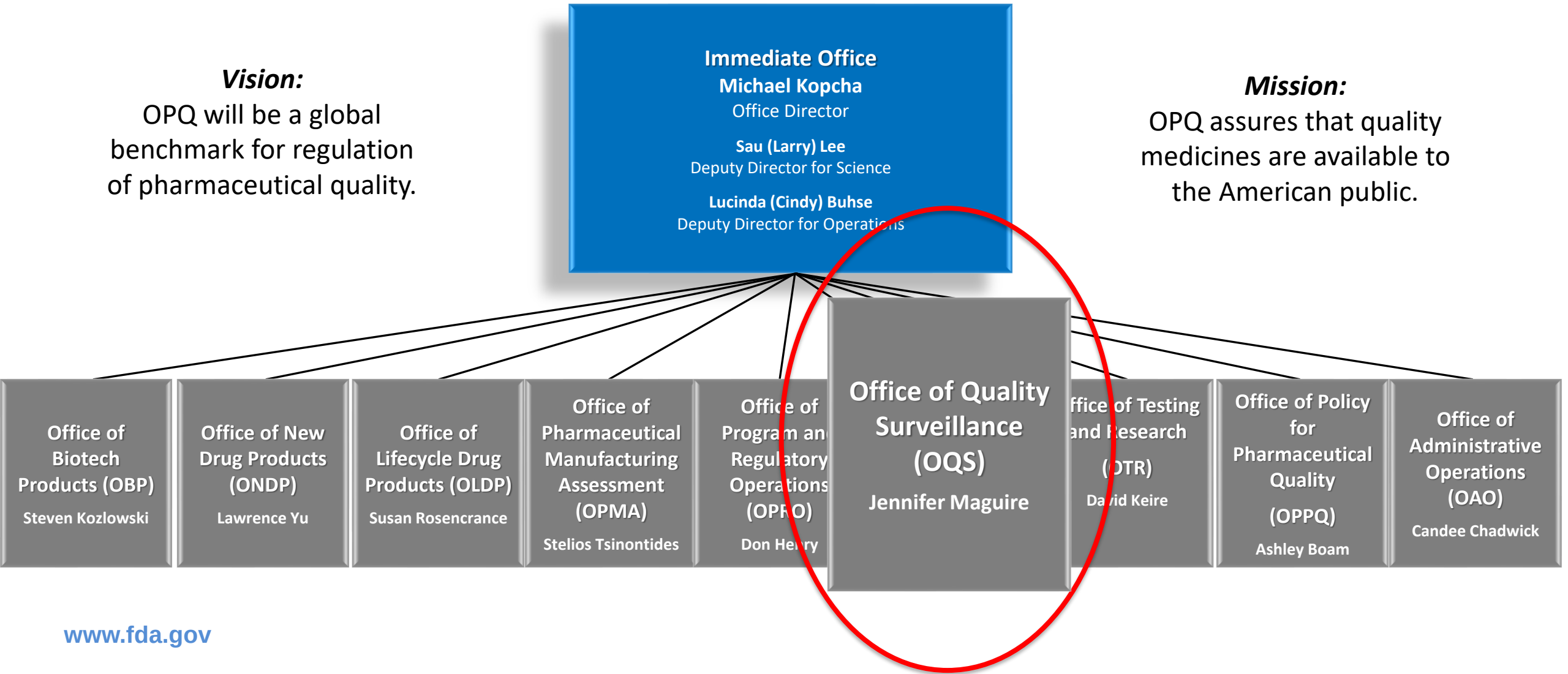
Presentation Outline

- Introduction to OPQ Office of Quality Surveillance (OQS)
- Knowledge Management Overview
- Assessing the Pharmaceutical Quality System
  - Framework – ICH Q10
  - Inputs
  - Qualitative Assessment
  - Quantitative Assessment
  - Implementation

Office of Pharmaceutical Quality (OPQ)

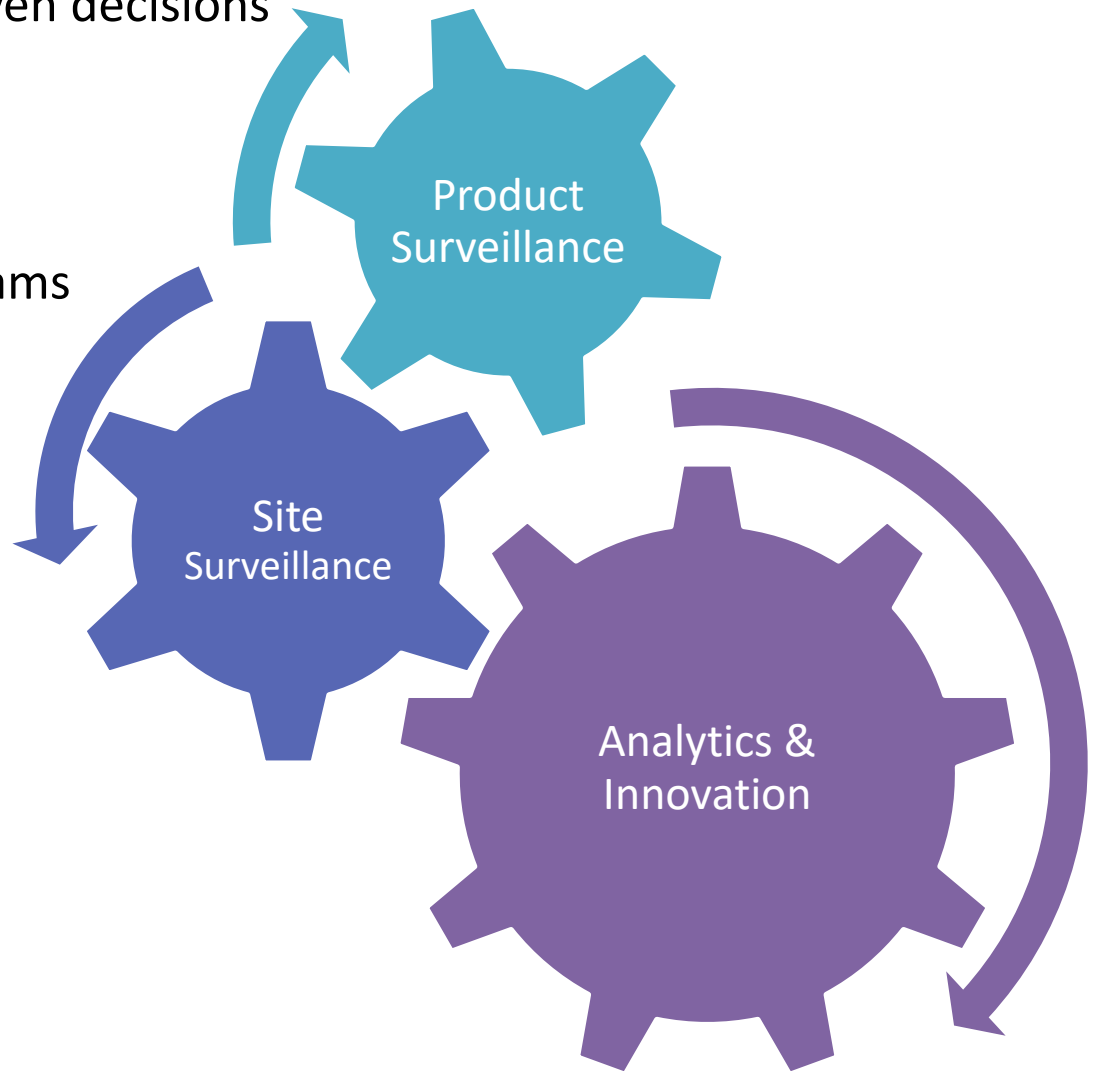
Vision:
OPQ will be a global benchmark for regulation of pharmaceutical quality.

Mission:
OPQ assures that quality medicines are available to the American public.



Office of Quality Surveillance (OQS)

- Monitors quality and manages information about CDER-regulated sites and products
- Uses intelligence collected and analytics to make data-driven decisions that can reduce risk to patients
  - Prioritization of sites for CGMP inspections
  - Human drug surveillance sampling and testing programs
  - Site engagement
  - Quantitate the state of quality
  - Pharmaceutical Quality System assessments
- Proactively identify potential quality signals and trends before serious quality problems occur
- Continuously improve surveillance strategies by applying new methods or techniques



Knowledge Management (KM) Overview

- Knowledge Management (KM)
  - Systematic approach to acquiring, analyzing, storing, and disseminating information related to products, manufacturing processes, and components (ICH Q10)
- Key Features of KM Systems usually include:
  - Aggregation of content from both internal and external sources
  - Classification/Categorization of content
  - Search/Views/Dashboards
- Effective knowledge management enables:
  - Comprehensive lifecycle oversight
  - Reduction in uncertainty
  - Risk-based decision making
  - Effective Pharmaceutical Quality System

Pharmaceutical Quality System Effectiveness: Framework, Inputs, and Assessment

Framework

- Overall PQS Assessment Framework
  - Qualitative: Assessment of data and information related to the facility to ensure adequate oversight of product quality (e.g. Establishment Inspection Reports, exhibits, product quality defect reports, etc.) utilizing the ICH Q10 framework
    - Systems-based approach across the network of products managed at the facility.
    - Holistic assessment of quality system effectiveness based on numerous inputs.
  - Quantitative: Assessment of historical data to make predictions for certain PQS effectiveness metrics related to an establishment (e.g. CAPA effectiveness, investigation times, Human Error, Root cause, Repeat Deviation, and time to initiate recall)

Qualitative Assessment – Inputs

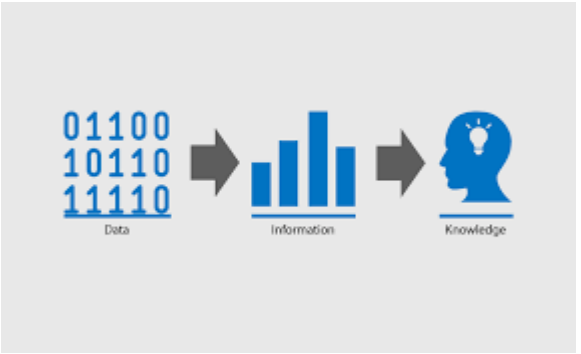
- Annual Reports and annual product reviews (opportunity for request)
- CMC change history
- Establishment inspection history documented in EIRs, exhibits, firm responses, regulatory actions
  - Does management advocate for continual improvement?
  - Are systems in place to communicate quality issues?
  - How is customer experience monitored?
  - Does management routinely review conclusions of periodic assessments and drive continual improvement initiatives?
  - Is a program in place using standardized techniques to identify root cause?
  - Are effectiveness checks routinely performed? Etc.

Qualitative Assessment – Inputs

- Quality defect data available through FARs, BPDRs, MW, Complaints, Informants, Recalls
  - Are there trends or clusters identified?
  - Are there patterns with root cause identification or CAPA outcomes?
  - Is there significant variability in investigation times and time between events?
  - Has the firm routinely submitted follow-up/final FARs?
- Future state:
  - Quality Metrics
  - Quality Management Maturity
  - Maturity elements covered under NIPP Inspection Protocols
  - Assessments will inform flexibility given for ECs

Qualitative Assessment – Elements Assessed

- Management commitment
- Quality policy
- Quality planning
- Resource management
- Internal communication
- Management review
- Management of outsourced activities and purchased materials
- Process performance and product quality monitoring system
- CAPA systems
- Change management
- Continuous improvement



Qualitative Assessment – Example Outputs

- CAPA Systems:
  - *"The EIRs from the April 2019 and May 2019 EIs documented recurrent observations associated with the inadequate CAPA procedure and/or inadequate CAPAs implemented in response to the investigations. Specifically, the April 2019 EI documented that the QA unit failed to conduct a thorough assessment and establish adequate and timely CAPAs to address a complaint trend associated with the autoinjector delivery system. There is no evidence from the review of EIRs that the corrective actions implemented by the firm to address this deficiency were evaluated for adequacy and effectiveness"*

- Quality Policy:
  - "Could not be assessed; information is not available in the reviewed documentation"

Qualitative Assessment – Example Outputs

- Investigations / Root cause:
  - *"The EIR from the May 2017 inspection documented instances of deficient written procedures describing handling of complaints to determine the need for an investigation of any unexplained discrepancy trends"*

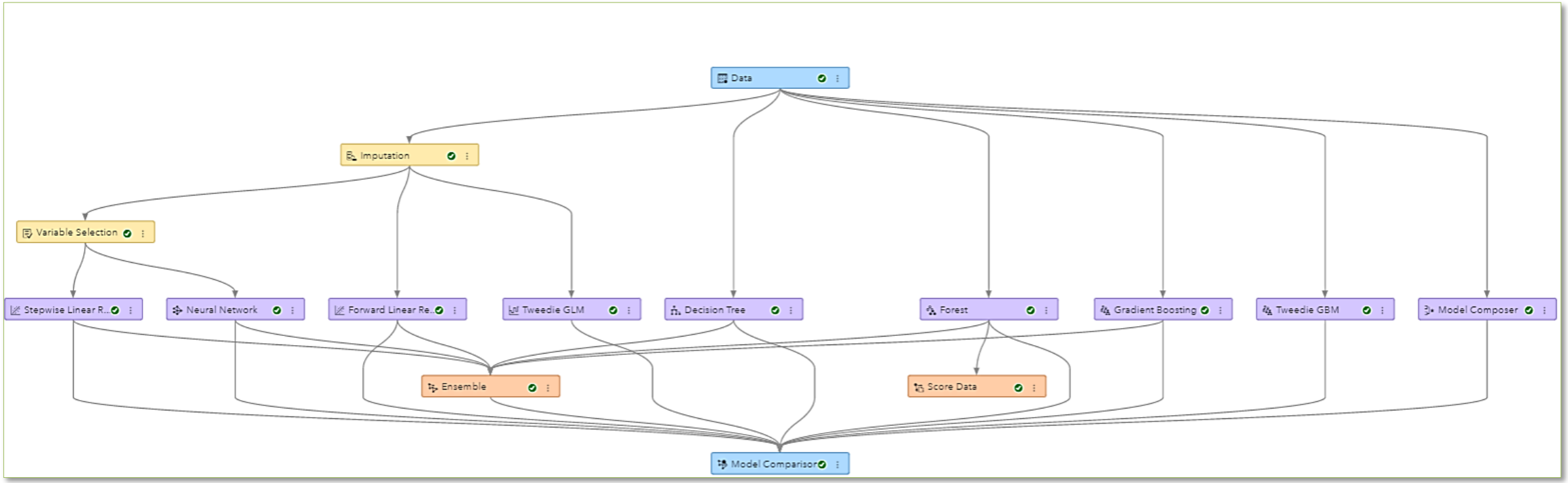
- Process Performance and Product Quality Monitoring System:
  - *"The EIRs provide evidence that the firm's management uses data obtained from internal audits, complaints, investigations to implement quality improvements"*

Quantitative Assessment

- Machine learning models were utilized to make predictions about certain PQS effectiveness metrics using Field Alert Report data as a surrogate.
- Other data (e.g., establishment demographics, recent inspections, citations, etc.) are routinely updated and incorporated as potential predictors.
- Models are currently run on a Fiscal Year basis for predictions and trending.
- OQS has ongoing research to identify alternative outcomes and potential predictors

PQS Metric	Definition	Use
Investigation Time	Median time, in days, that a facility takes to close reported FARs for each fiscal year	To compare the time a site takes to close FARs against other pharmaceutical sites for application products
Root cause found	The proportion of FARs for which a facility was able to identify the root cause	Facilitate comparison against similar pharmaceutical sites for thoroughness in conducting RCA and use of standardized practices
Repeat deviations	The percentage of FARs with the same root cause and dosage form reported by a facility for each fiscal year	Indicator of how effective PQS is at preventing repeat problems
CAPA Effectiveness	The proportion of FARs having CAPA SOP changed/Retraining as the only outcome	Reflects maturity of CAPA effectiveness; low results may indicate robust CAPA implementation
Human Error	The proportion of root causes associated with human error	Reflects maturity of investigations and program effectiveness

Modeling Pipeline and Performance Metrics

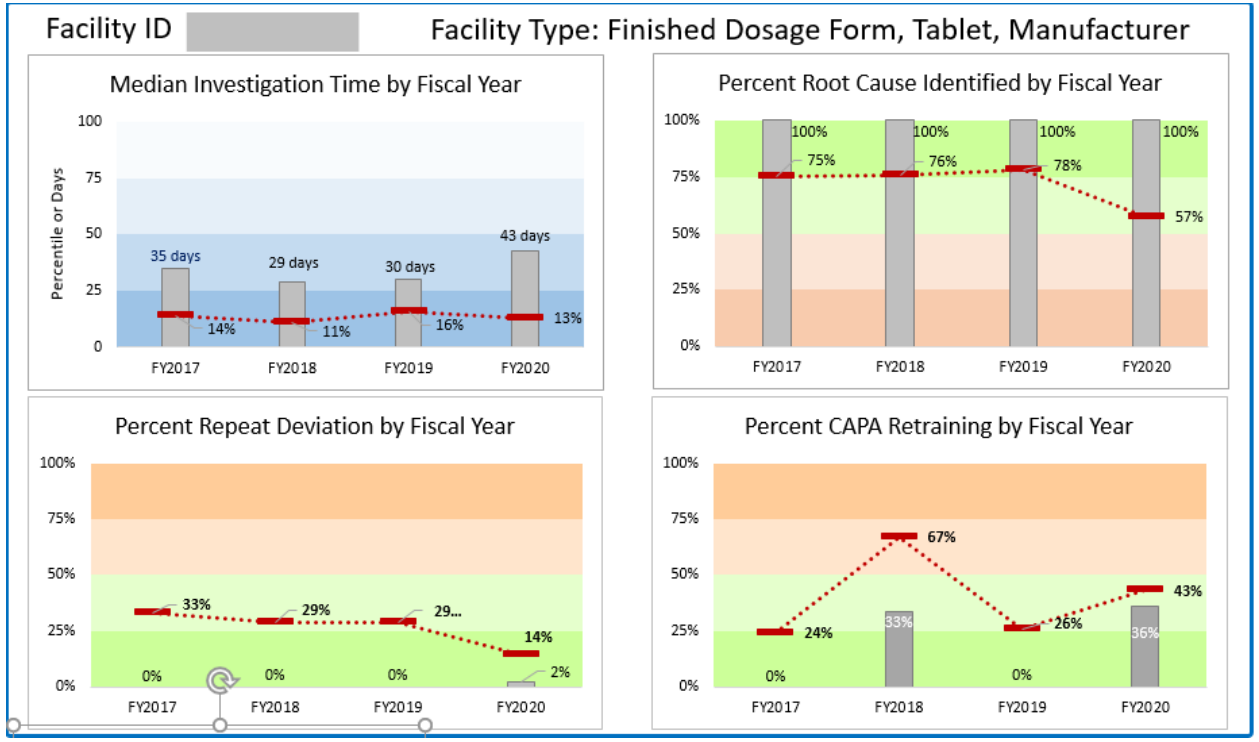


Model Comparison

Champion	Name	Algorithm Name	Average Squared Error	Root Average Squared Error	Root Mean Absolute Error
✓	Forest	Forest	412.8282	20.3182	3.6738
	Ensemble	Ensemble	439.9762	20.9756	3.9515
	Tweedie GBM	Gradient Boosting	462.9994	21.5174	3.5926
	Decision Tree	Decision Tree	523.2492	22.8746	4.3078
	Neural Network	Neural Network	550.0602	23.4534	4.2105
	Gradient Boosting	Gradient Boosting	595.3753	24.4003	3.8590
	Tweedie GLM	GLM	679.8125	26.0732	4.6266
	Stepwise Linear Regression	Linear Regression	701.9705	26.4947	4.5912
	Model Composer	Model Composer	707.4086	26.5972	4.7172
	Forward Linear Regression	Linear Regression	795.6261	28.2068	4.5478

Quantitative Assessment – Example output

- Historical trending for each PQS metric
- Prediction for upcoming FY
- Benchmarking against similar establishments



Implementation and Next Steps

- Address current gap in available data to complete a full assessment of PQS effectiveness
  - Current processes (e.g., inspections, post-market reporting, etc.) do not routinely capture all Q10 elements
  - Application of Machine Learning/Predictive Analytics are used to provide some estimates
  - Utilize certain vehicles (e.g., IRs during assessment timeline, FD&C Act 704(a)(4) requests) to obtain data, records, and information needed to properly assess the effectiveness of the PQS
- Archiving assessments to ensure adequate knowledge management is critical
  - Ensures effective communication to field investigators
  - Integrating information related to approved ECs into comprehensive quality surveillance decisions
- OQS assessment is intended to support EC decisions for original submissions and supplements

No one can do this alone

Let’s work together to improve global pharmaceutical quality to improve the lives of patients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