Pharmaceutical Quality System Effectiveness

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Learning Objectives

- Learn how OQS utilizes FARs and BPDRs to inform the assessment of a Pharmaceutical Quality System
- Learn how OQS utilizes FAR data in conjunction with predictive analytics to reduce uncertainty

Background

- ICH guidance for industry Q12 *Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* provides a framework to facilitate the management of postapproval CMC changes in a more predictable and efficient manner.
- ICH Q12 includes regulatory tools and enablers that should enhance industry's ability to manage postapproval changes effectively with less need for extensive regulatory oversight.
  - This approach can incentivize continual improvement by providing an opportunity for greater flexibility in making postapproval changes.
- An **effective Pharmaceutical Quality System** (as described in ICH Q10) is necessary to support the use of the tools

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
- Establishment inspection history documented in EIRs, exhibits, firm responses, regulatory actions
- Product quality defect reports:
  - Field Alert Reports
  - Biological Product Deviation Reports
  - MedWatch Reports
- Future state:
  - Quality Metrics
  - Quality Management Maturity

FAR/BPDR Considerations for a PQS Assessment

- Was the FAR/BPDR product quality issue effectively escalated internally for submission to FDA in a timely manner per the regulations?
- Does the FAR/BPDR include a structured approach to enable an effective investigation and root cause determination?
- Does the FAR/BPDR have a proposed CAPA methodology which should result in product and process improvements and enhanced understanding?
- Does the FAR/BPDR proposed CAPA focus on continual improvement and product and process understanding?
- Does the FAR/BPDR include effectiveness checks for the proposed CAPA?
- Are there multiple FAR/BPDR that appear to represent an adverse quality trend for a specific drug product or across multiple drug products?
- Are there multiple FAR/BPDR with trends associated with CAPA? Recurring issues may indicate poor root cause analysis and/or effectiveness?
- Are there multiple FAR/BPDR where the failure occurs in the same System (Quality, Packaging & Labeling, Materials, Production, Facility & Equipment, Laboratory controls)?

Qualitative Assessment – Elements Assessed

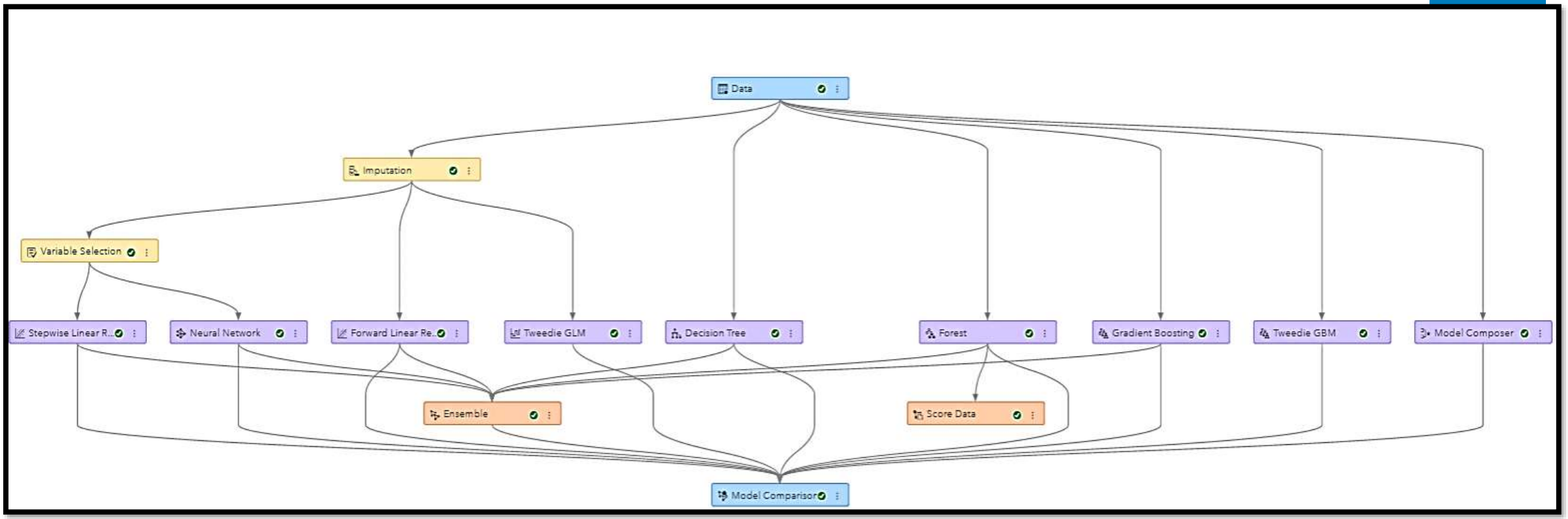
- Management commitment
- Quality policy
- Quality planning
- Resource management
- Internal communication
- Management review
- Management of outsourced activities and purchased materials
- Process performance and product quality monitoring system
- CAPA systems
- Change management
- Continuous improvement

Quantitative Assessment

- Machine learning models predicted PQS effectiveness metrics using Field Alert Reports (FAR) 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 FAR for each fiscal year.	To compare the time a site takes to close FAR against other pharmaceutical sites for application products.
Repeat Deviations	The percentage of FAR 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 FAR 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.

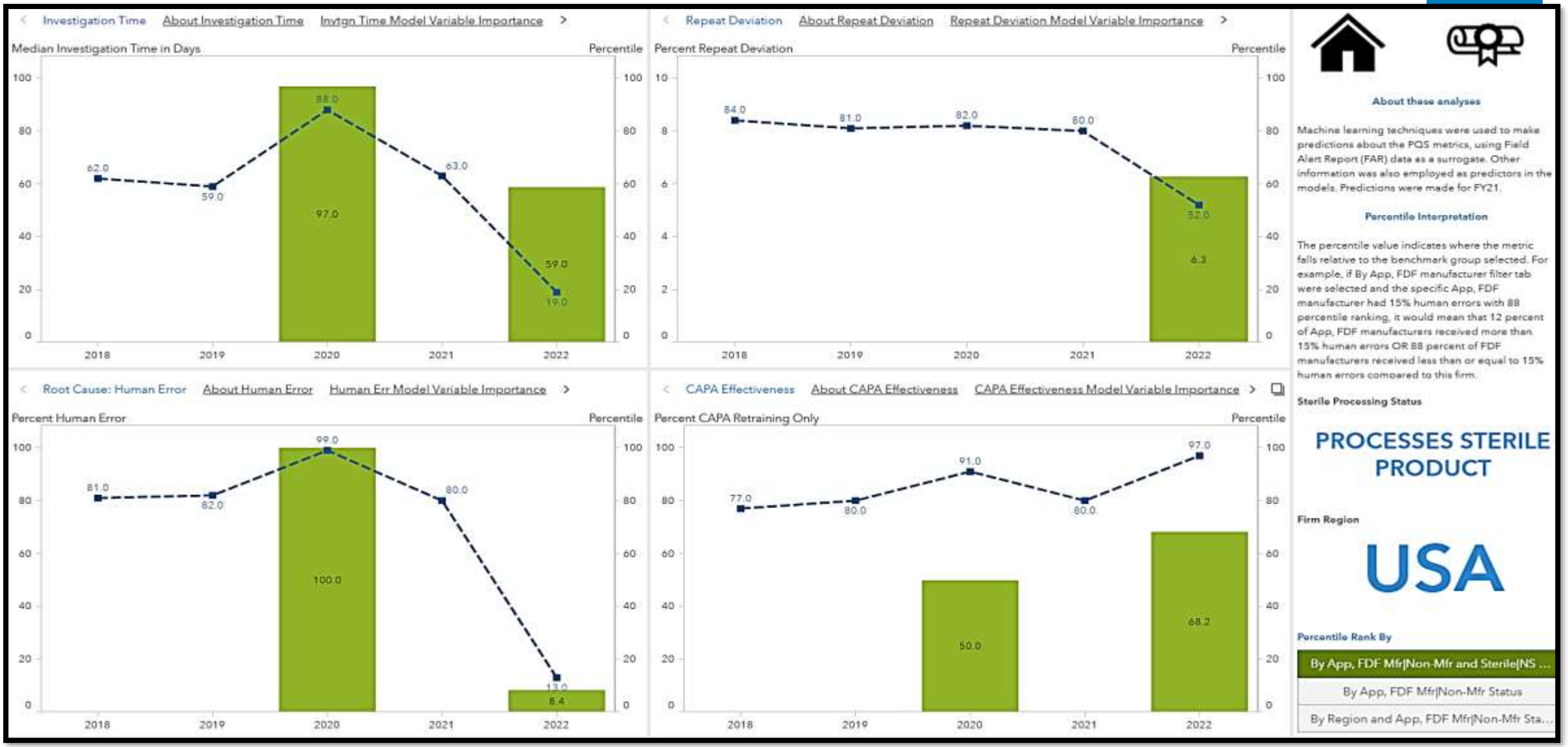
Modeling Pipeline and Performance Metrics



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

Predictive Scoring and Benchmarking Illustration



Implementation and Next Steps

- Address current gaps 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.
    - Oct 2022 update to Compliance Program was revised to add elements of ICH Q9, Q10, and Q12
  - Application of Machine Learning/Predictive Analytics are used to provide some estimates.
  - Utilize certain vehicles (e.g., IRs during assessment timeline, etc.) 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 Established Conditions (EC) into comprehensive quality surveillance decisions.
- OQS assessment is intended to support EC decisions for original submissions and supplements.

Summary

- FARs and BPDRs are an important factor when assessing the effectiveness of a PQS
- FARs and BPDRs are a rich source of information that can be leveraged to reduce uncertainty

Challenge Question

- Which ICH Guidance describes a comprehensive model for an effective pharmaceutical quality system (PQS)?
  - A: ICH Q9
  - B: ICH Q10
  - C: ICH Q11
  - D: ICH Q12

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