AI/ML: Regulatory Perspective: Challenges and Considerations

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DISCLAIMER

This presentation reflects the views of the authors and should not be construed to represent FDA's views or policies

Everyone deserves confidence in their *next* dose of medicine.

Pharmaceutical quality assures the availability, safety, and efficacy of *every* dose.

FDA AI/ML Initiatives

- Develop guidances and policies for AI/ML use
- Engage in international collaboration on AI/ML regulatory principles
- Launch generative AI tools
- Host workshops and scientific discussions on emerging AI/ML technologies
- Provide funding to support extramural research on AI/ML

AI/ML Science and Research at OPQ

- Understand how AI/ML is being used to support product quality, particularly in drug manufacturing and complex product characterization
- Identify, assess, and manage potential risks associated with AI/ML use
- Support regulatory assessment of submissions that incorporate AI/ML related to product quality

Selected FDA Publications & Guidance

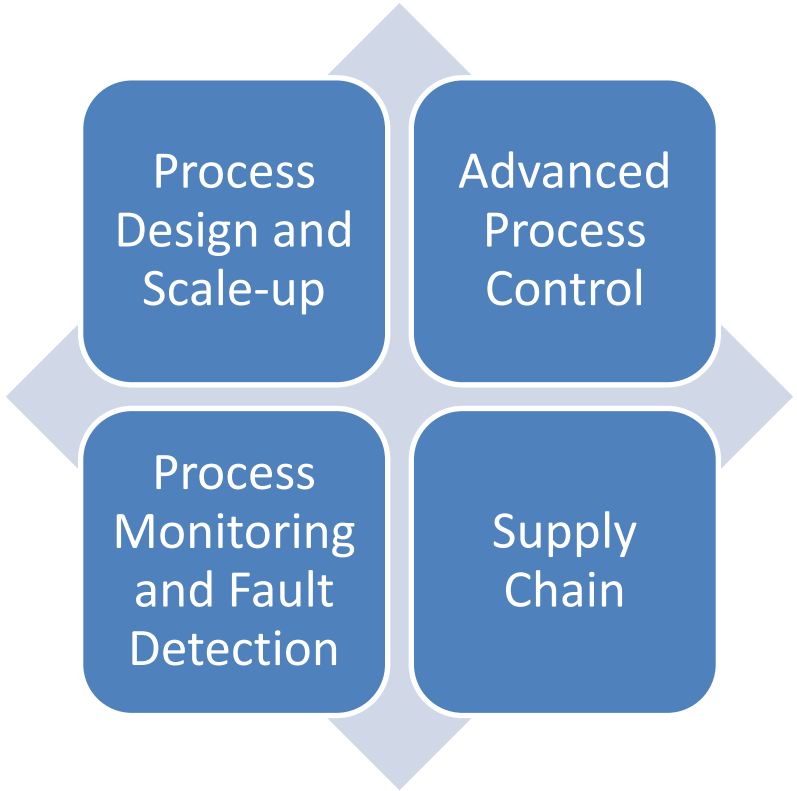
CDER Guidance Agenda
New and Revised Draft Guidances
Planned for Publication in Calendar Year 2026[1]
(February 2026)

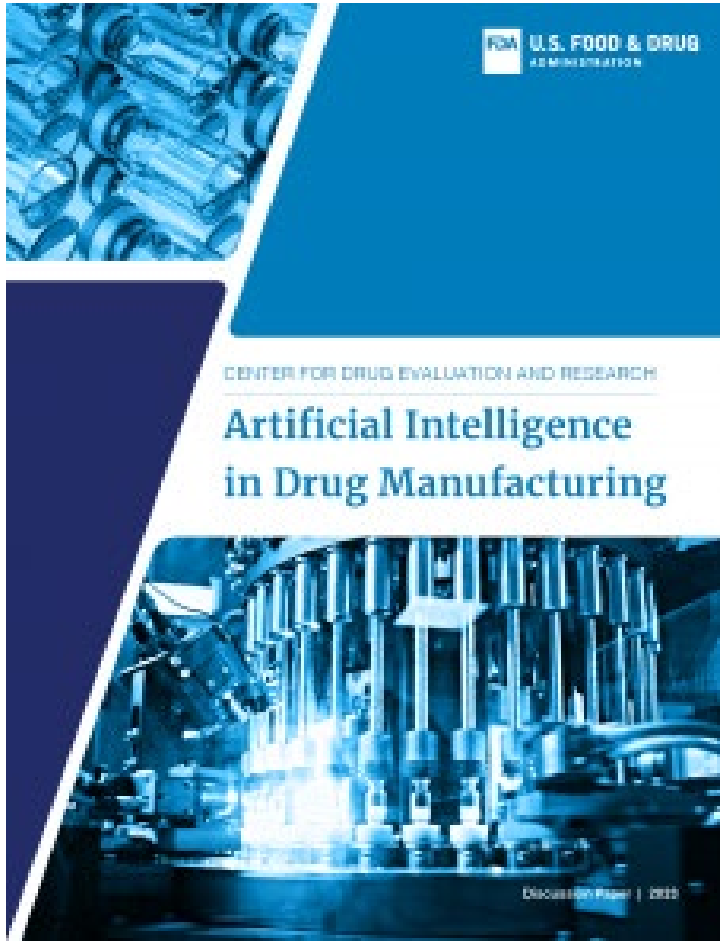
(See the Good Guidance Practices (GGPs) regulation on this Web page or 21 CFR 10.115 for details about the Guidance Agenda.)

CATEGORY – Pharmaceutical Quality/CMC

- AI and ML Quality Considerations in Pharmaceutical Manufacturing
- ANDAs: Stability Testing of Drug Substances and Products Q & A
- Container Closure Systems for Drugs, Including Biological Products
- Distributed Manufacturing – Recommendations for Application Content
- Guidelines for Establishing Impurity Limits for Antibiotics
- Postapproval Changes to Drug Substances; Revised Draft
- Quality Recommendations for BLA Applications
- Site Master Files
- Stability Considerations for Drug Substances and Drug Products in NDAs, ANDAs, and BLAs and Associated Labeling Statements for Drug Products
- Stability Recommendations for Additional Manufacturing Facilities in NDAs, ANDAs and BLAs, and Additional Drug Substance Sources in NDAs and ANDAs

AI Use Cases for Drug Manufacturing





Key Regulatory Challenges and Considerations

AI in the Pharmaceutical Quality System

Challenges:

- Integration with existing systems (quality control, process control, manufacturing execution)
- Compatibility issues with legacy systems
- Need for appropriately trained personnel
- Complex and lengthy integration process

Considerations:

- Use AI to augment (not replace) human oversight
- Implement human-in-the-loop for verification and correction
- Provide targeted insights to augmented workers
- Support decision-making across pharmaceutical operations
- Ensure correct implementation through appropriate personnel training

Key Regulatory Challenges and Considerations

Risk-Based AI/ML Model Credibility Assessment

Challenges:

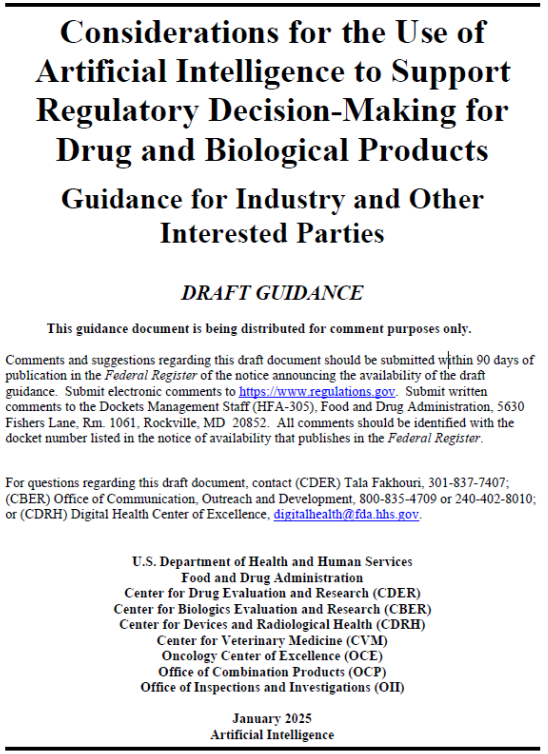
- Perception of AI/ML as "black box" models
- Need for publication of development and validation case studies
- Expectations for software quality assurance and verification

Considerations:

- Adopt standard and guidance for evaluating AI systems (e.g., ASME VV40 and FDA AI Draft Guidance)
- Publish case studies on AI/ML model development and validation
- Develop good AI/ML practices
- Develop trust in open-source code through guidelines

Considerations for Risk-Based Model Credibility Assessment

- A risk-based credibility assessment framework:
  - Step 1: Define the question of interest (QOI) that will be addressed by the AI model
  - Step 2: Define the Context of Use (COU) for the AI model
  - Step 3: Assess the AI model risk
  - Step 4: Develop a plan to establish the credibility of AI model within the COU
  - Step 5: Execute the plan
  - Step 6: Document the results of the credibility assessment plan and discuss deviations from the plan
  - Step 7: Determine the adequacy of the AI model for the COU



Considerations for the Use of Artificial Intelligence to Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry and Other Interested Parties

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Tala Fakhouri, 301-837-7407; (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010; or (CDRH) Digital Health Center of Excellence, digitalhealth@fda.hhs.gov.

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Artificial Intelligence

A Case Study

Advanced control of continuous pharmaceutical manufacturing processes: A case study on the application of artificial neural network for predictive control of a CDC line (2026) https://doi.org/10.1016/j.compchemeng.2026.109560

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Advanced control of continuous pharmaceutical manufacturing processes: A case study on the application of artificial neural network for predictive control of a CDC line

Jianan Zhao, Geng Tian *, Wei Yang, Das Jayanti, Abdollah Koolivand, Xiaoming Xu

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QOI and COU

QOI: Describes the specific question, decision, or concern that is being addressed by the AI model.
COU: Defines the specific role and scope of the AI model used to address a question of interest.

Example:
QOI: Is the API concentration in the final blend within the desired specification?

COU:
Role of the AI model:
A neural network predictive control (NNPC) model is used to predict a CDC line's outlet API concentration based on current and previous inputs and outputs, and to generate optimal control actions that adjust the inlet composition to maintain the outlet composition at target specifications.
Scope of the AI model:
The NNPC model will not be the sole determinant for blend uniformity. The NIR spectroscopy-based PAT method monitors blend uniformity for material diversion as primary control strategy

AI Model Risk Determination

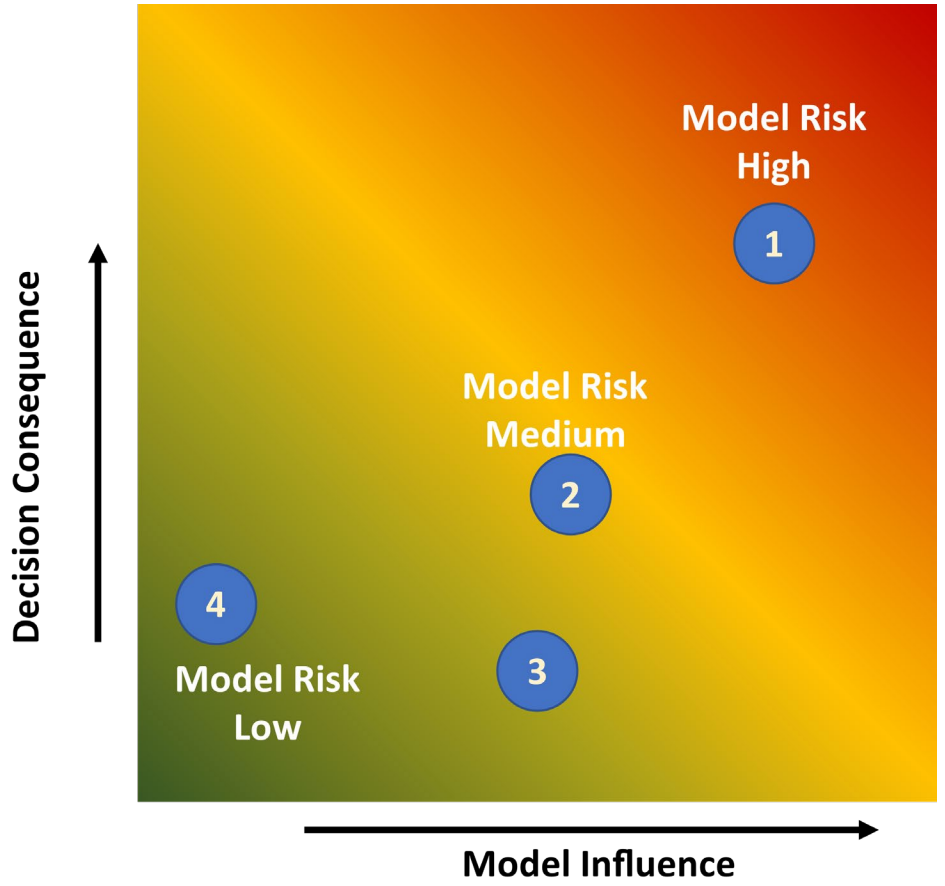
Model influence: the contribution of the evidence derived from the AI model relative to other contributing evidence used to inform the question of interest

Decision consequence: describes the significance of an adverse outcome resulting from an incorrect decision concerning the question of interest

Example:
Model influence: Medium because there are additional control steps for monitoring API content (e.g., NIR)

Decision consequence: High because blend uniformity is a critical quality attribute and non-conforming blend with respect to uniformity would have a high impact on product quality

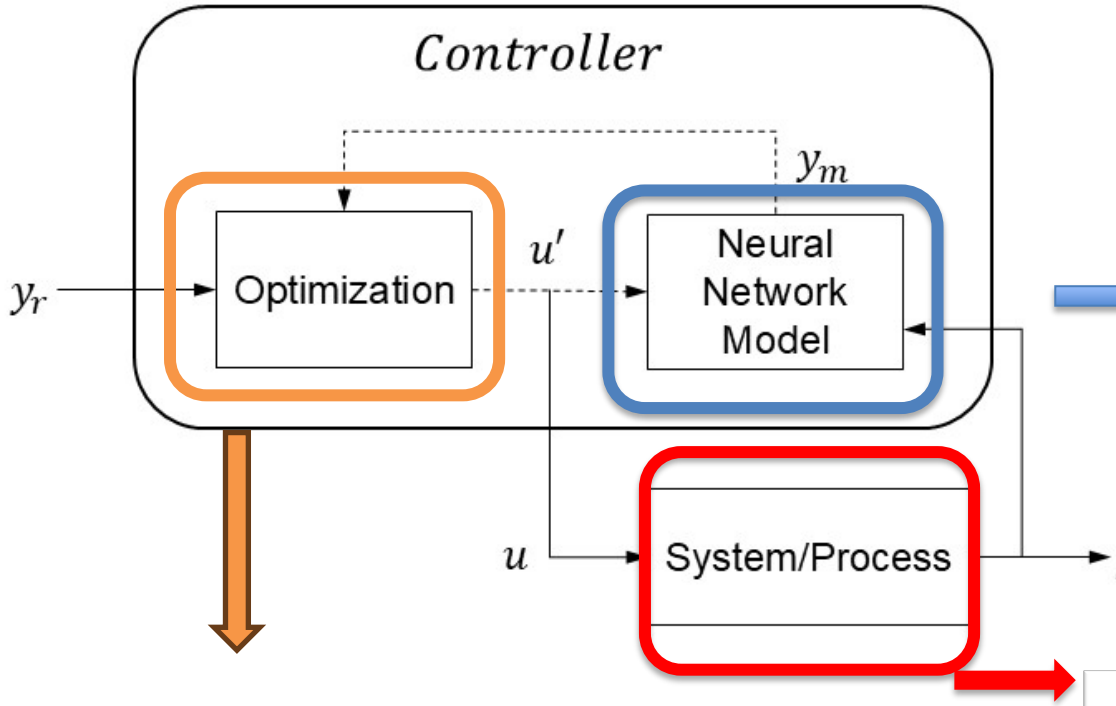
Model risk: Medium



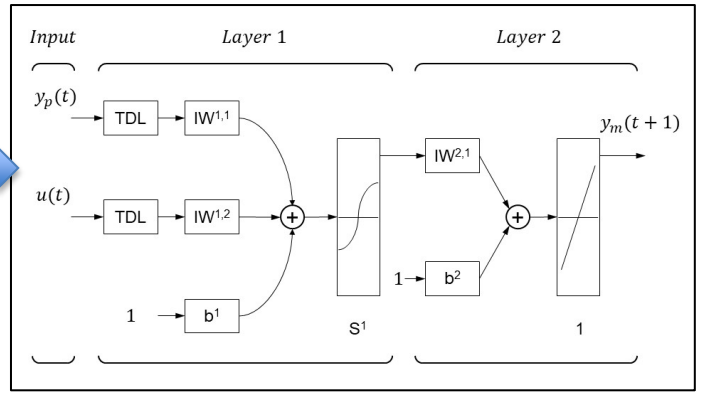
Develop a Plan to Establish AI Model Credibility within the COU (cont.)

Model architecture: two-layer feedforward neural network with model predictive control optimization, RTD-based digital CDC line

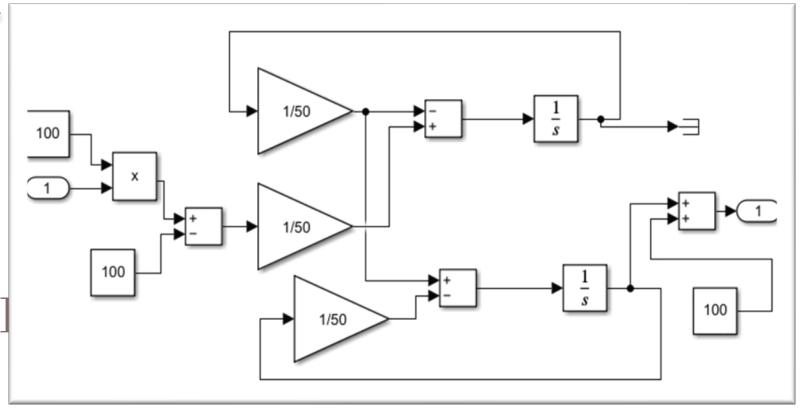
Model inp
and outpu
Input: API
concentra
at feeder
outlet
Output: Al
concentra
in the fina
blend



Neural network: number of neuron, activation function, weights, bias



RTD model: mean residence time, number of CSTRs in series



MPC: prediction horizon, control horizon, control weighting factor

$$J = \sum_{j=N_1}^{N_2} [y_r(t+j) - y_m(t+j)]^2 + \rho \sum_{j=1}^{N_u} [u'(t+j-1) - u'(t+j-2)]$$

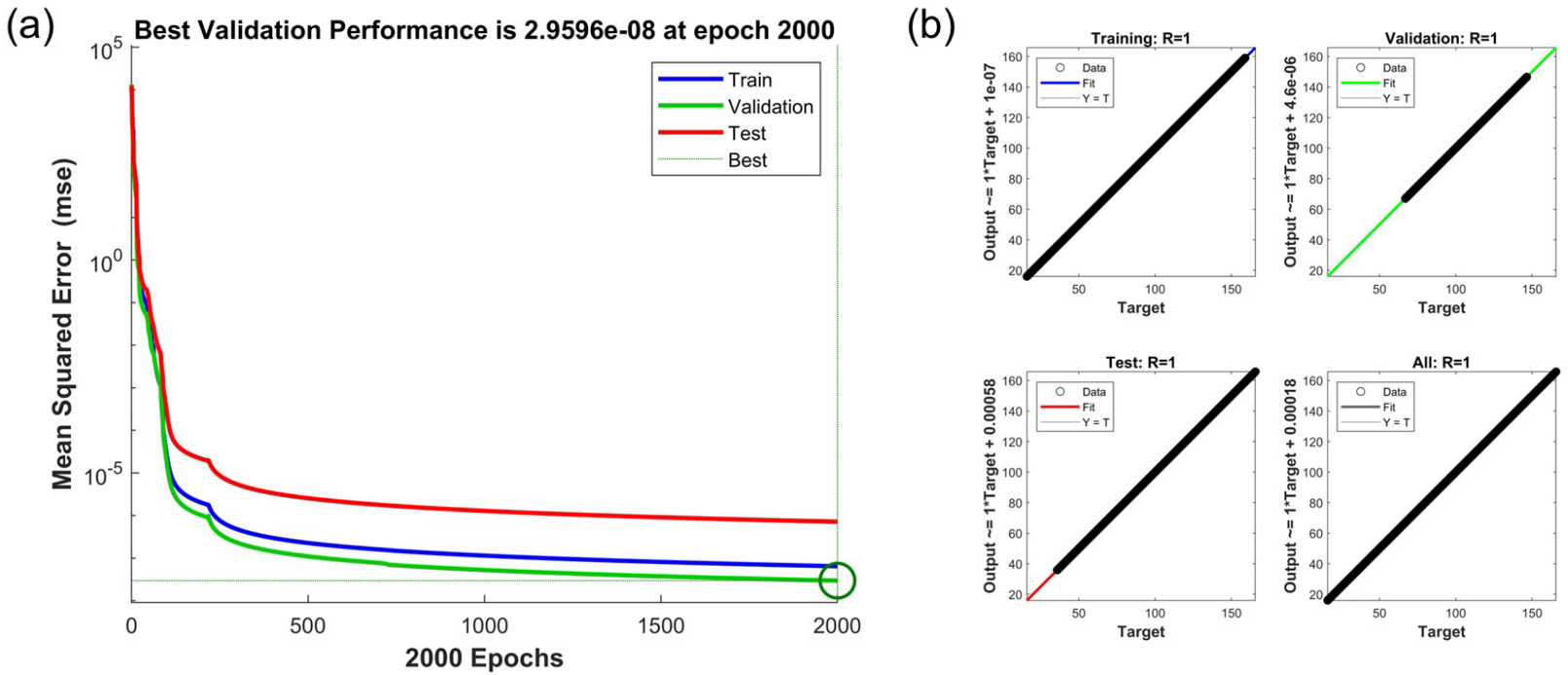
Develop a Plan to Establish AI Model Credibility within the COU (cont.)

Describe the model development process

Example:

Describe NN model training: Bayesian regularization algorithm to calculate weights and bias

$$F_{network} = MSE = \frac{1}{N}\sum_{t=1}^{N}(e_t)^2 = \beta\frac{1}{N}\sum_{t=1}^{N}\left[y_p(t) - y_m(t)\right]^2$$



Develop a Plan to Establish AI Model Credibility within the COU (cont.)

Describe the model development process

Example:

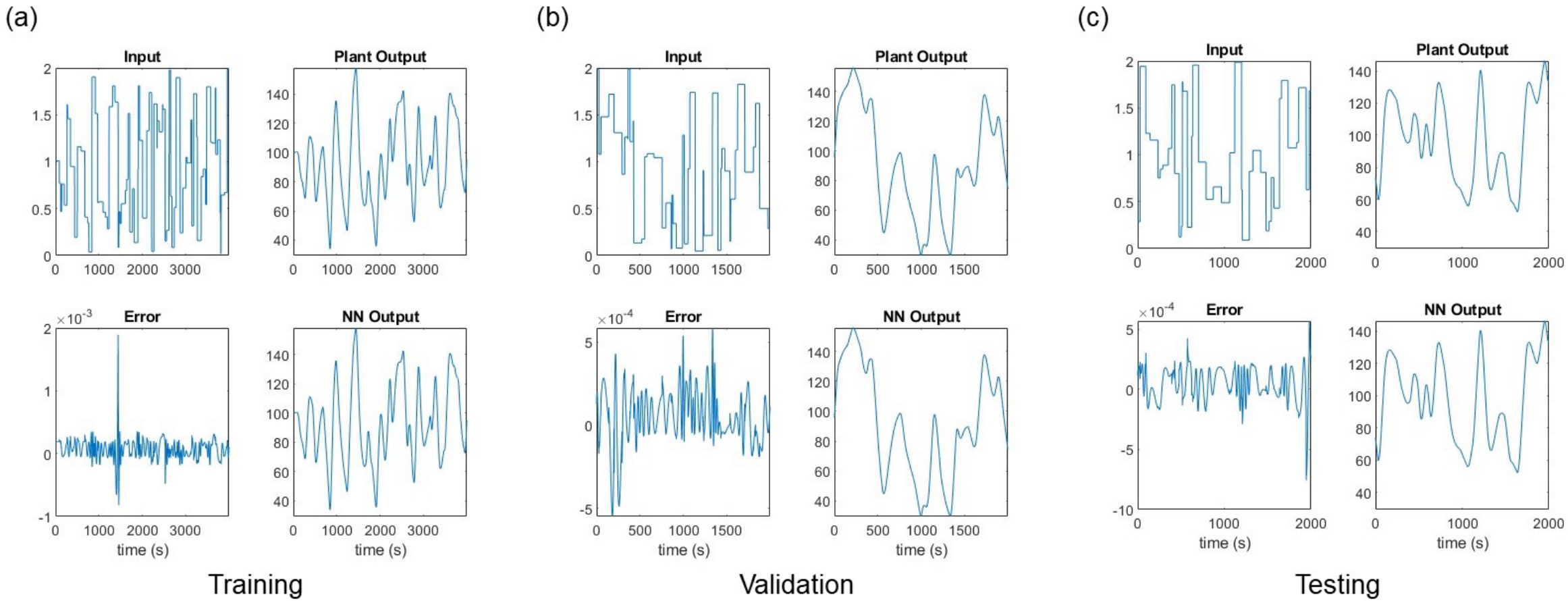
Describe NN model results

Data partitioning

Training – 70%

Validation – 15 %

Testing – 15%



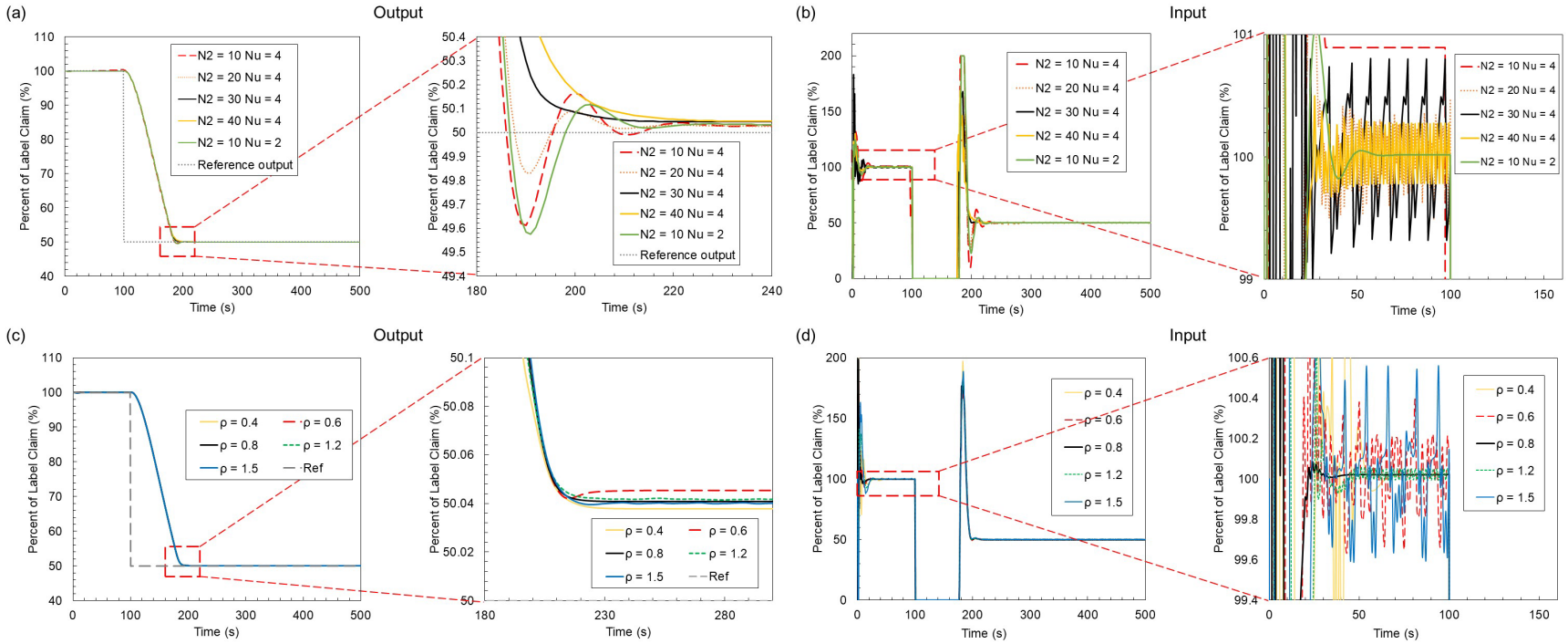
Develop a Plan to Establish AI Model Credibility within the COU (cont.)

Describe the model development process

Example:

Describe Model Predictive Control tuning: prediction horizon, control horizon, and control weighting factor

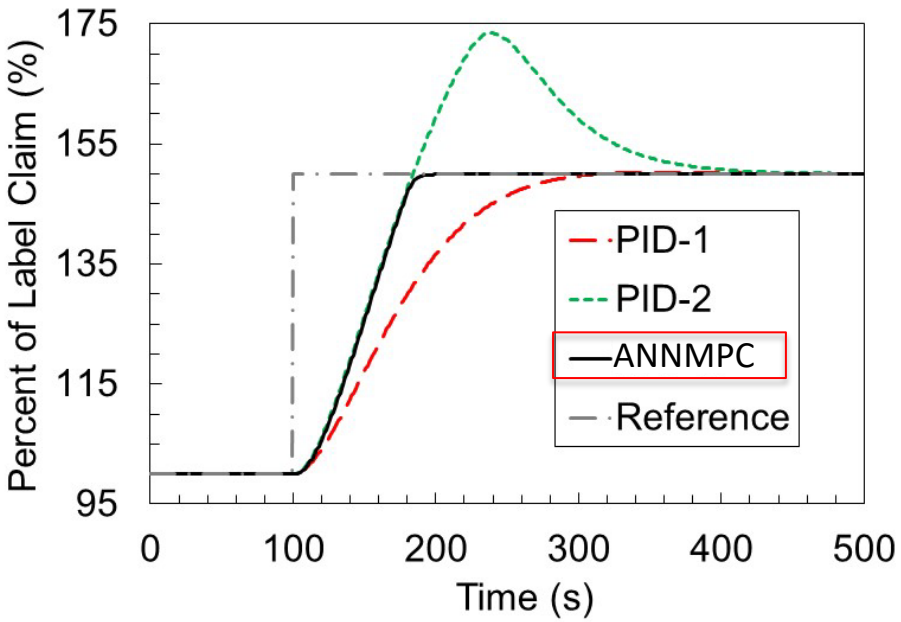
$$J = \sum_{j=N_1}^{N_2} [y_r(t+j) - y_m(t+j)]^2 + \rho \sum_{j=1}^{N_u} [u'(t+j-1) - u'(t+j-2)]^2$$



Develop a Plan to Establish AI Model Credibility within the COU (cont.)

Describe the model development process

Example:
Describe the NNPC model evaluation process



	δ (%)	τ_r (s)	τ_s (s)
C^*_{ref} = 50%			
PID-1	0	116.74	182.63
PID-2	46.90	58.41	287.85
ANNMPC	0	58.43	85.32

$$\delta = \frac{|\sigma_{max}|}{|C^*_{ref}|} \times 100\%$$

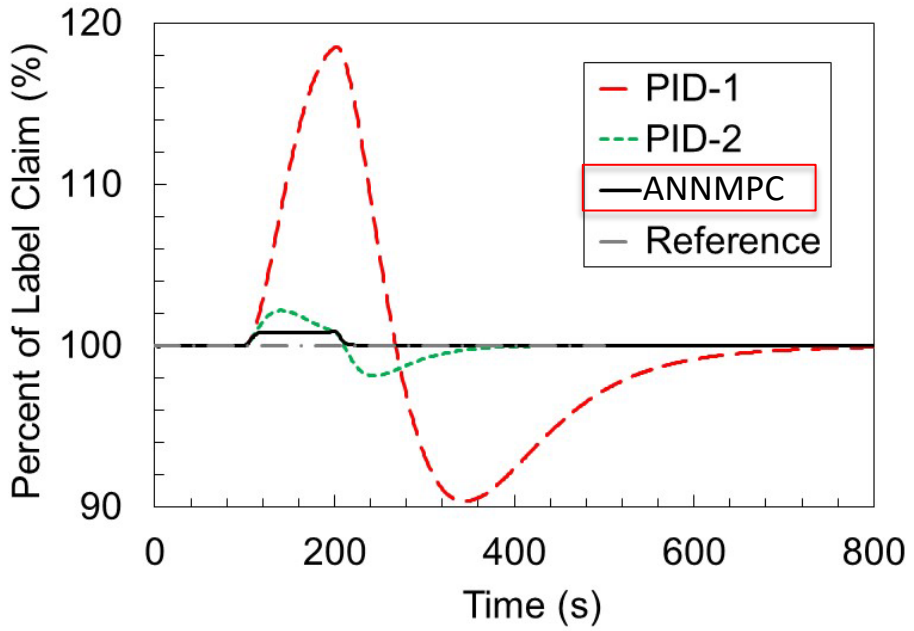
$$\tau_r = T\left(90\%\ C^*_{ref}\right) - T\left(10\% C^*_{ref}\right)$$

$$\tau_s = T\left(\frac{|C_{out-plant} - C^*_{ref}|}{C^*_{ref}} \leq 2\%\right) - T\left(C^*_{ref,0}\right)$$

Develop a Plan to Establish AI Model Credibility within the COU (cont.)

Describe the model and the model development process

Example:
Describe the NNPC model evaluation process



	ε (%)	τ_d (s)
D = 50%		
PID-1	37.1	485.8
PID-2	4.4	189.8
ANNMPC	1.56	0

$$\varepsilon = \frac{|\varepsilon_{max}|}{C_{ref}} \times 100\%$$

$$\tau_d = T\left(\frac{|C_{out-plant} - C_{ref}|}{C_{ref}} \leq 2\%\right) - T(D_0)$$

Concluding Thoughts

- Regulatory experience with AI/ML is evolving
- Apply a risk-based approach
- Adhere to standards and guidances
- Define a clear context of use
- Follow good model design and development practices
- Conduct risk-based performance assessment
- Implement data governance and documentation
- Maintain effective life cycle management

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