Artificial Intelligence

Continued reliable use (not only) in Pharmacovigilance

Disclaimer

- Any views, thoughts, and opinions expressed herein are solely those of the author and do not reflect the views, opinions, policies, or position of any other entity.
- No legal advice should be construed from the information given herein.
- Except for two images for illustration purposes only no part of this presentation has been created using AI technology.

- Thank you Martin Henzl, PhD, Dr. Giorgio Pesci, Deepa Thoopurani Giridhar, Robert (Bob) McDowall, PhD, Dr. Marc Zittartz for your valuable input on draft versions of this presentation. It kept me grounded and broadened my perspective. Any remaining errors are solely mine.

- Created by:
  Pharma Process System Consult
  Christian Schmitz-Moormann
  Mobile: +49 176 8107 9930
  Email: c@schmimo.de

Overview

- Automation and AI
- Data in AI
- AI and Ethics
- Validating AI
- Outlook
- Discussion

Automation and AI

Automation and AI Promises

Automation using Artificial Intelligence will

- Reduce cost
- Reduce cycle times
- Increase consistency
- Improve quality and accuracy
- Simplify Intake
- Provide no-touch processing
- Identify signal trend patterns across existing boundaries
- Gain unprecedented insights into risk and benefit
- …

AI Application Areas in PV

- ICSR process
  - More than 50 decision points where AI-based services seem warranted
- Signal detection
  - Support the identification, confirmation and refuting of potential signals
  - Aid with better clustering of data for the discovery of previously unnoticed associations
- Report aggregation
- Natural language processing
  - Translations in support of local entities
  - Support generation of narratives

AI is Just one Flavor of Automation

- Deterministic
  - Code-based
    - Software specifically developed
  - Rule-based
    - Generic software with rules specifically developed
- Stochastic
  - AI-based
    - Generic software with algorithms being trained usually leveraging **vast amounts of quality data** and through **reinforcement techniques**

AI Key Challenges: Learning and Evolution

- Abstract Concepts
  - AI cannot (yet!) understand abstract concepts
- Bias
  - If data used for training is skewed, decisions will be skewed
- Data Scope
  - If data used for training is too narrow or too broad, decisions may become erratic or have low confidence levels

➔ Data remains at the center of everything

„Even the developers of an AI frequently cannot explain how decisions come about.“
(Prof. Thomas Metzinger, Philosophy, Mainz University)

Data in AI

Role of Data in AI

- Data is to AI what fuel is to a car – it powers the entire system
  - The more relevant and comprehensive the data, the better the AI model can learn and adapt
- **High quality** data
  - Improves accuracy and reliability of the models
  - Reduces the presence of bias and errors in the models
- **High quantity** of data provides more examples for the models to learn from
- **Diversity** in data is crucial for the robustness of the models
- Data must be collected ethically, cleaned, prepared, validated, and stored securely, being mindful of the potential for bias, discrimination, and misuse, to ensure responsible AI development, regulatory compliance and maintaining user trust
- Datasets must be **updated** to remain effective and allow models to stay relevant and accurate

Role of Metadata And Private Data in AI

To process data correctly and enable more accurate and meaningful insights

- Metadata provides essential context about the data being processed
  - Also supports maintaining compliance
- Private Data provides specific facts to the models
  - Various approaches to make private data available, e.g., as prompt

AI and Ethics

Ethics of AI

Transparency	Fairness	Privacy	Robustness	Reliability
Explainable output	Bias detection and nondiscrimination	Data protection	Withstand intentional and unintentional interference	Explicit and well-defined uses
Use of open standards	Diversity in development teams	Data minimization	Oversee policy decisions during development and audit and review improvements	Verify safety, security and effectiveness of capabilities across entire lifecycle
Ensure regulatory and legal compliance	Authentic results		Human oversight and intervention according to clear guidelines	As sources change, output must remain stable or improve

EMA's draft "Reflection paper on the use of artificial intelligence in the lifecycle of medicines" is open for commenting until 31-Dec-2024 and Guiding principles on the use of large language models in regulatory science and for medicines regulatory activities was published on 29-Aug-2024.

Also see: https://unesco.org/en/artificial-intelligence/recommendation-ethics: A human rights approach to AI

AI Risk Management Framework (example guidance: NIST)

Artificial Intelligence Risk Management Framework (AI RMF 1.0) (published Jan. 2023)

4 Core Elements:

- Govern
  - Establishes foundational roles and oversight mechanisms to ensure accountability and transparency
- Map
  - Identifies and understands the context, potential impact, and scope of AI applications
- Measure
  - Evaluates AI systems' performance, including accuracy, reliability, and potential biases
- Manage
  - Implements strategies to mitigate identified risks, ensuring AI systems operate within accepted boundaries

EU AI Act (Regulation (EU) 2024/1689)

- Broad definition of AI. (Art. 3) – Decisive factor: Designed for autonomous operation?
- Certain AI practices prohibited
- 4 key stakeholders: providers, deployers, importers, distributors
- Obligations of end-users not discussed
- AI use in medical devices (under (EU) 2017/745) and in-vitro medical devices (under (EU) 2017/746) is high-risk. Implications in Art. 9 through Art. 15
- List of practical examples of high-risk and non-high-risk use cases no later than 02-Feb-2026
- Complements existing regulation

Is a safety database (with AI components) a safety-critical system?

Validating AI

AI Validation

- Verification (system built right), Validation (right system built)
- Understand the difference between an AI-based static system and an AI-based dynamic system
- Validation of AI is like assessing a human candidate for expert qualification rather than executing a well-defined harness, and having to keep an eye on it throughout

Can these positions be reconciled?

In the context of AI development, the role of Software verification and validation is more vital than ever.
(The Engineering Design of Systems: Models and Methods, 2nd ed., Buede & Miller, 2024)

LLMs make it possible to bypass the need to train AI models or algorithms on what to look out for and/or what something means…
(Beyond GenAI: The Training-Free Discovery Potential of LLMs in a Drug Safety and Regulatory Context, Pharmtech.com, Ramani & Valigari, published 1-Jul-2024, accessed 27-Aug-2024)

Validation (Model)

- Model requirements and specification
- Separated Data Sets for Training, Parametrization, and Testing
  - Limit data for parametrization and testing
  - Ensure data similarity across sets
  - Cross-validation using alternative models
    - k-fold cross-validation for smaller datasets
- Repeated (continuous) simulations and statistical evaluation

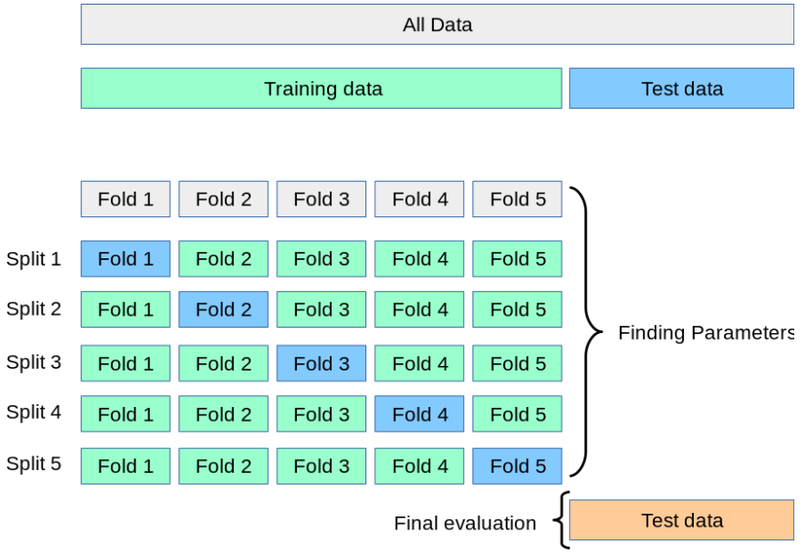
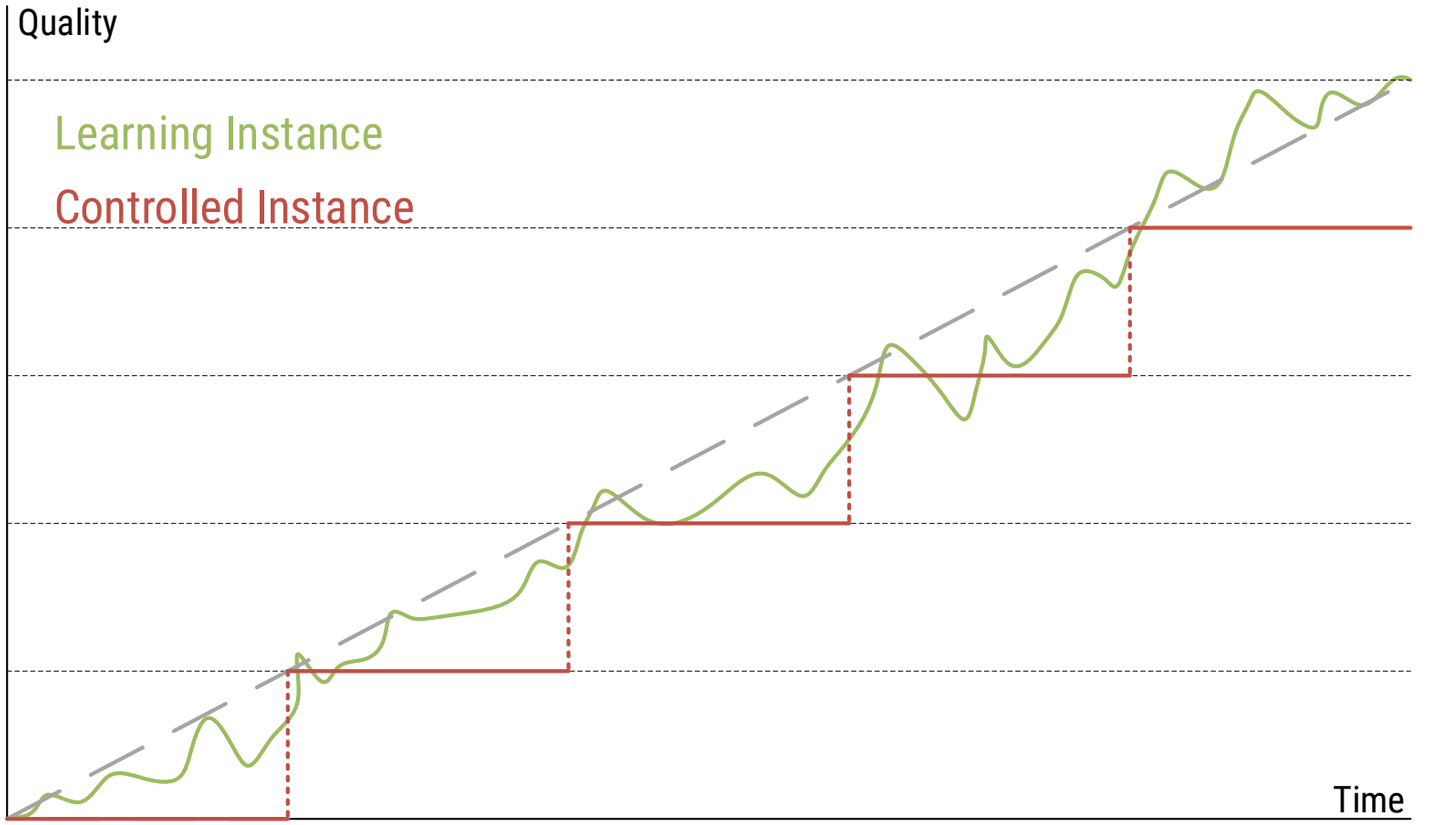


Image from the Sklearn user guide. BDS license

- US FDA AI/ML Discussion Paper on Drug Development nods to AI use in pharmacovigilance and the FDA Sentinel Initiative
- US FDA AI/ML Discussion Paper (SaMD) looks at dynamic (learning) AI systems and refers to FDA's Total Product Lifecycle (TPLC) Regulatory Approach and Predetermined Change Control Plans (PCCP)
- First proposal for AI validation strategy by ISPE DACH AI validation groups based on system autonomy and control design with 6 categories for AI validation

Possible Change Path for Controlled Learning AI

- Two „production“ instances
- Controlled instance generates official output
- Learning instance determines next change control and verifies continued data quality based on predetermined, monitored KPI



Outlook

Outlook

- Use of AI has transitioned into mainstream tools and evolves at record pace
- AI should be seen as a non-tiring co-worker, but in the foreseeable future well-defined human oversight will be indispensible
- Validation of learning AI-based tools is still a developing topic
- Applying standard CAPA processes to deviations/errors identified in AI-generated output proves challenging, mostly due to complex root-cause identification
- Depending on the goals to be achieved, AI may be just right, not there yet, or overkill
- The current shake-up in approaches to „do it right“ opens the PV tool market for new participants delivering on the promises mentioned initially, with or without AI

Discussion

Further Reading

- Mockute, R., Desai, S., Perera, S. et al. Pharm Med (2019) 33: 109. https://doi.org/10.1007/s40290-019-00269-0
- Schmider, J., Kumar, K., LaForest., C. et al. Clin. Pharm.&Ther. (2019) 105/4: 954-961. Innovation in Pharmacovigilance: Use of Artificial Intelligence in Adverse Event Case Processing
- Ball, R., Dal Pan, G., „Artificial Intelligence“ for Pharmacovigilance: Ready for Prime Time? Drug. Saf. 2022;45(5): 429-438 https://doi.org/10.1007/s40264-022-01157-4
- Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD) https://www.fda.gov/media/122535/download
- Cho, A., Kim, G.C., Karpekov, A., Helbling, A., Wang, J., Lee, S., Hoover, B., Chau, P., Transformer Explainer, https://poloclub.github.io/transformer-explainer, accessed 01-Sep-2024
- Erdmann, N., Blumenthal, R., Baumann, I., Kaufmann, M., AI Maturity Model for GxP Application: A foundation for AI validation, Pharmac. Eng., March/April 2022, https://ispe.org/pharmaceutical-engineering/march-april-2022/ai-maturity-model-gxp-application-foundation-ai, accessed 01-Sep-2024
- Mintanciyan, A., Budihandojo, R., English, J., HCCP, Lopez, O., Matos, J.E., McDowall, R., PhD, Artificial Intelligence Governance in GxP Environments, Pharmac. Eng., July/August 2024, https://ispe.org/pharmaceutical-engineering/july-august-2024/artificial-intelligence-governance-gxp-environments, accessed 09-Sep-2024
- Weber, W., Zwingmann, T., Augmented Analytics, June 2024: 1st ed., O‘Reilly Media, ISBN: 9781098151720
- Iantosca, M.l Nagy, H., Sandri, W., Document Object Model Graph RAG, https://img1.wsimg.com/blobby/go/8d83b4d9-fe3b-41c3-ba74-a645effc4bf2/downloads/The%20DOM%20GraphRAG%20Project.pdf?ver=1726416712048, accessed 16-Sep-2024