Navigating Regulatory Landscape for AI /ML Implementation in Life Science and Healthcare

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8-12-2023

PROGRESS

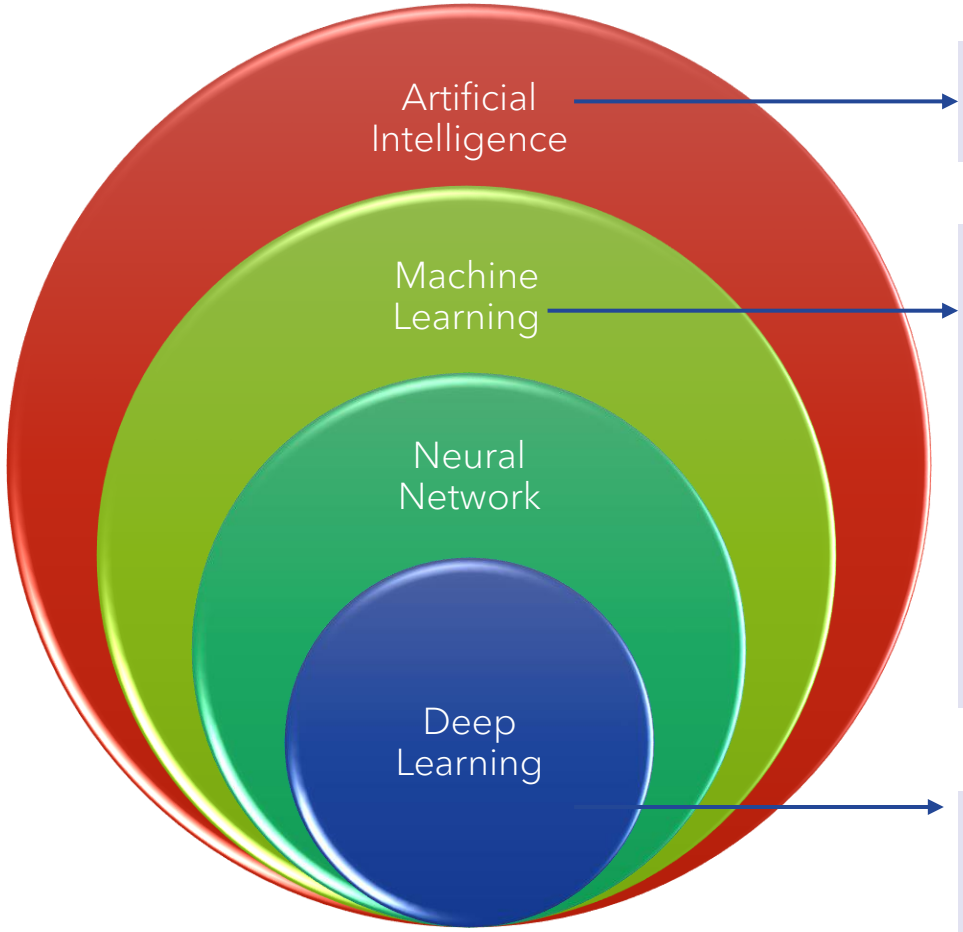
Agenda

1. Introduction of AI/ML throughout product lifecycle
2. Current Regulatory landscape of AI/ML
3. Validation Risk management of AI and ML Models
4. Challenges and Solutions for Trustworthy AI

Introduction to AI/ML throughout product lifecycle

PROGRESS

Understanding Artificial Intelligence, Machine Learning and Deep Learning



Artificial Intelligence: AI enables the machine to think and mimic human actions

Machine learning :ML is a Statistical tool to explore data

Supervised Learning: Classification/Labelling e.g. Fraud detection, Image recognition
Regression : Market and weather forecasting

Unsupervised Learning :Clustering : Target Marketing, Customer segmentation

Reinforcement Learning: Eg: Predictive text, text summarization, question answering, robotic navigation, real time answering

Deep Learning : Multilevel neural network architecture thinks like a human brain

- Generative Adversarial network (GAN)
- Convolutional neural network (RNN)
- Recurrent neural network(CNN)

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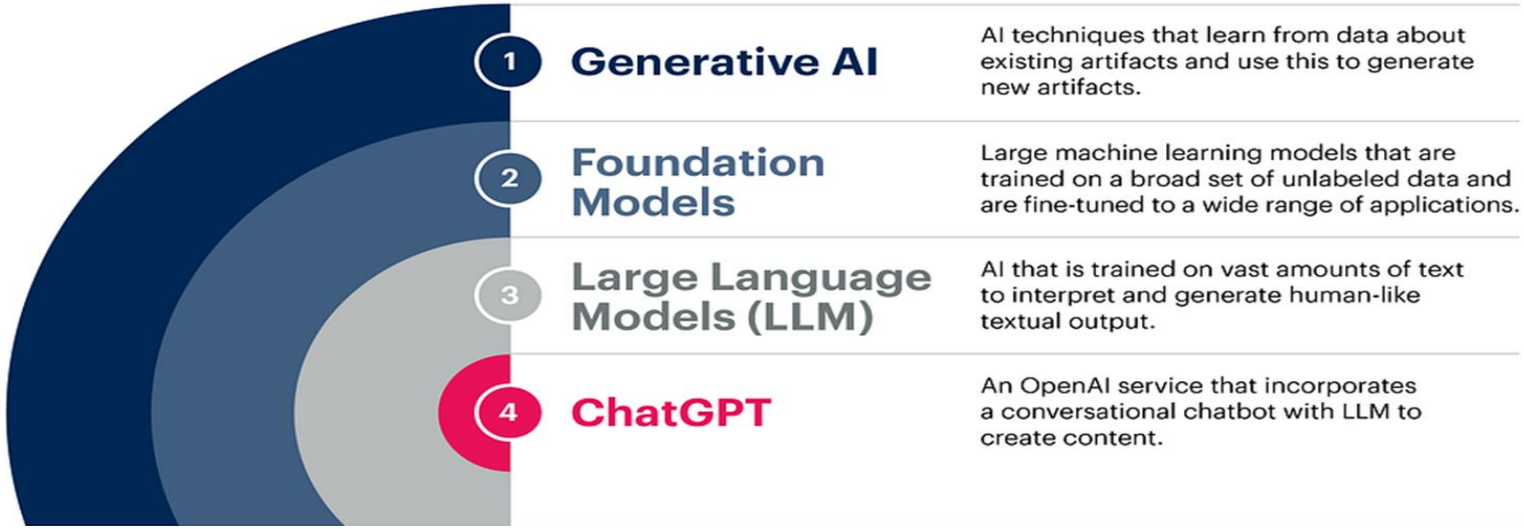
About Generative AI, Foundation Model and Large Language Model



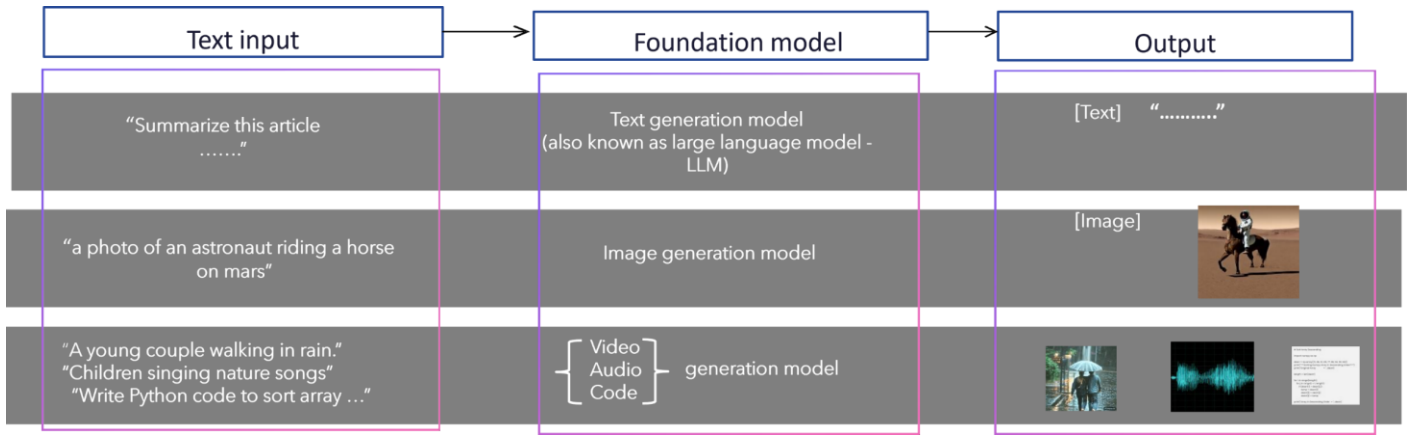
Reference: Gartner@2023

E.g.: Midjourney
Stable diffusion(text to image)

E.g. BERT for NLP, Chat GP3.5

E.g: Google PaLM,
Meta LLaMA, RLHF

Generative Pre-trained Transformer : GPT 3.5, 4



SIGN IN / UP

The Register

AI + ML

98

Lawyers who cited fake cases hallucinated by ChatGPT must pay

Judge sanctions attorneys for failed reality check

Thomas Claburn

Thu 22 Jun 2023 22:49 UTC

Attorneys who filed court documents citing cases completely invented by OpenAI's ChatGPT have been formally slapped down by a New York judge.

Judge Kevin Castel on Thursday issued an opinion and order on sanctions [PDF] that found Peter LoDuca, Steven A. Schwartz, and the law firm of Levidow, Levidow & Oberman P.C. had "abandoned their responsibilities when they submitted non-existent judicial opinions with fake quotes and citations created by the artificial intelligence tool ChatGPT, then continued to stand by the fake opinions after judicial orders called their existence into question."

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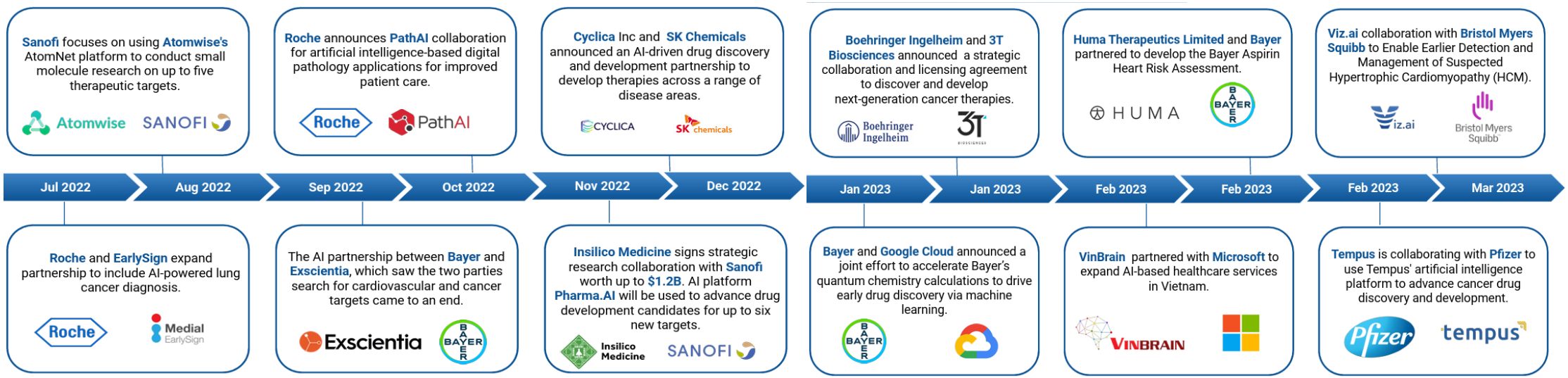
AI technology providers and pharma collaboration since last year



Reference : Deep pharma intelligence report May 2023

Pharma AI Readiness Index

Ranking is based on a scoring model using CB Insights datasets.

Rank	Bank	Score ▼	Talent	Execution	Innovation
1	Roche	77.48	★★★★☆	★★★☆☆	★★★★★
2	BAYER	70.16	★★★☆☆	★★☆☆☆	★★★★★
3	Johnson & Johnson	67.43	★★★★☆	★★★☆☆	★★★☆☆
4	NOVARTIS	61.37	★★★★☆	★★★☆☆	★★☆☆☆
5	sanofi	59.14	★★★★☆	★★★☆☆	★★★☆☆
6	AstraZeneca	58.12	★★★★☆	★★★☆☆	★★☆☆☆
7	AMGEN	57.66	★★★★☆	★★★☆☆	★★☆☆☆
8	Pfizer	52.10	★★★★☆	★★☆☆☆	★★☆☆☆
9	GSK	51.79	★★★★☆	★★☆☆☆	★☆☆☆☆
10	Bristol Myers Squibb	49.74	★★★☆☆	★★☆☆☆	★★☆☆☆

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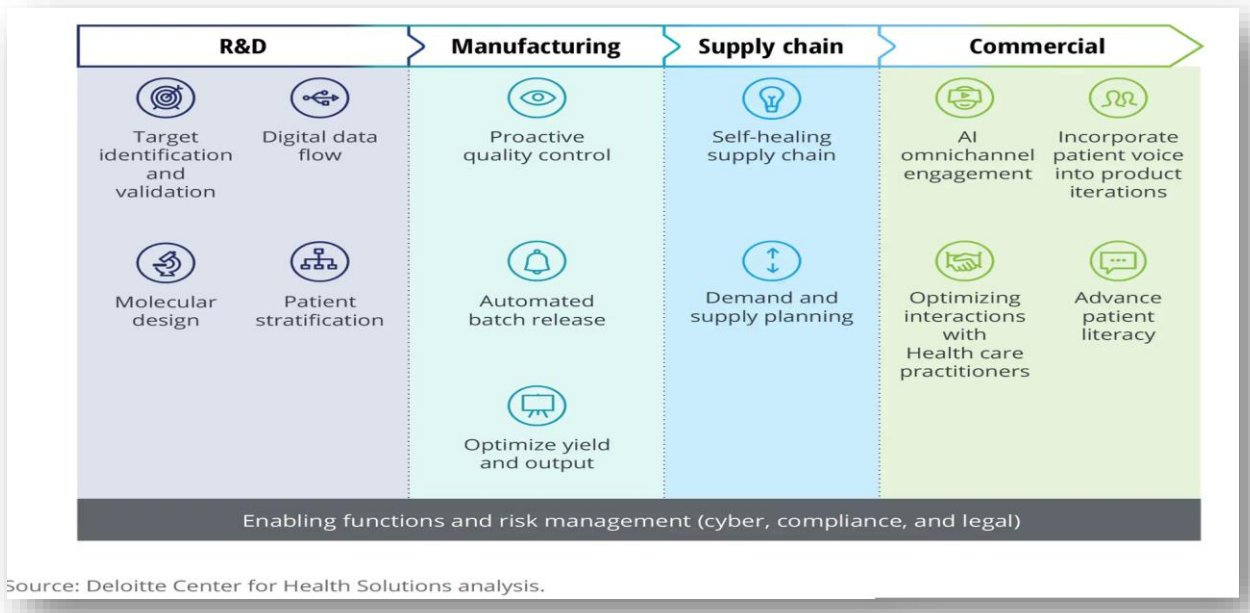
Application of Artificial Intelligence across pharma value chain



- F Findability
- L Lineage
- A Accessibility
- I Interoperability
- R Reusability

Data Governance Strategy

Research and Discovery

- Pathogenesis
- Target Identification
- Molecular Structure prediction
- Biomarker identification
- Compound identification
- Pharmacokinetics prediction

Clinical development

- Trail Design,Site selection
- Recruitment optimization
- RWD Clinical trial monitoring
- Predictive Toxicity and Risk Monitoring

Manufacturing and QMS:

- Process yield optimization
- Investigations,RCA
- Proactive Quality Intelligence
- Fault detection : AI in AVI
- Continuous Process verification
- Predictive Stability
- Digital Twin

Post Market surveillance:

- Identification of safety trends
- Utilization as a part of care
- PV safety and effectiveness using AI

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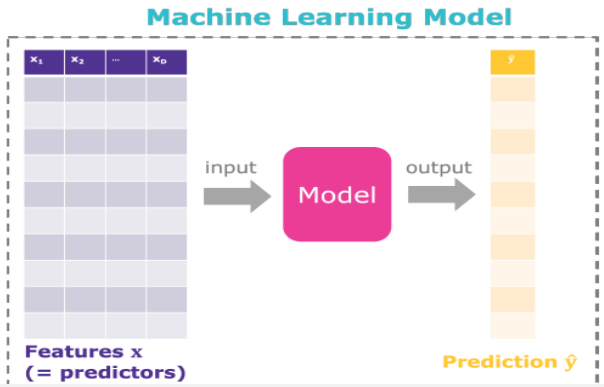
AI/ML for Investigations and Root cause Analysis: QMS

Challenges in QMS Investigations root cause analysis

- Time-consuming searches for similar deviations.
- No insights for investigation and CAPA's.
- Difficulty to manually interpreting large unstructured data sets.



RCA Machine learning: predict target based on features
Example : Model Interpretability: GBDTs(Gradient boost Decision tree)

Deviation Detected

Deviation Opened in QMS system

Investigation And System data Entry

Deviation Complete

IA :Investigation agent identifies similar event based on event description define appropriate RCA using ML

IA (Investigation Agent) IDP, Data Extraction, Labelling Vectorization (ML –Supervised)

CAPA suggested by the IA algorithm based on success factors *(ML-unsupervised)*

IA-Algorithm is dynamic and constantly adapting to identify new smart CAPA

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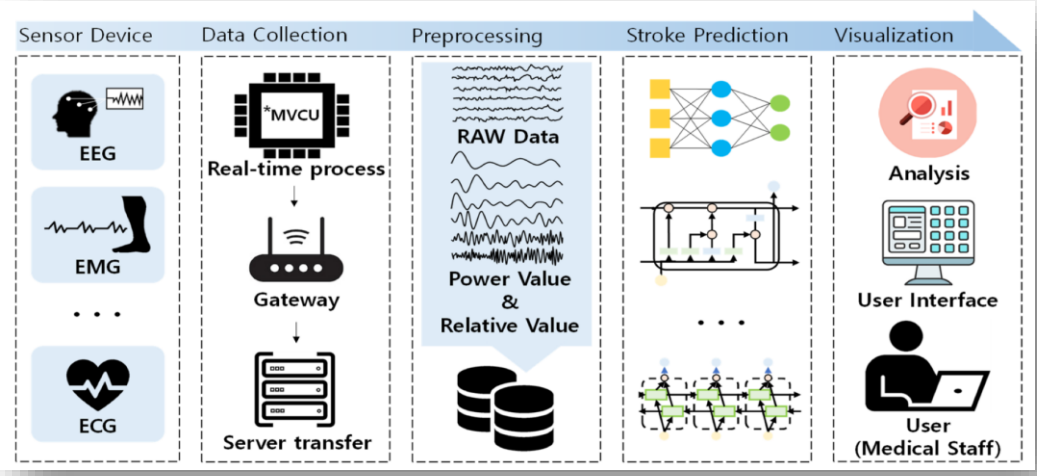
Holistic AI/ML in medicine and SaMD (Software as Medical device)

Reference : Medtech Europe, Socio economic Impact Report 2023



Application of todays AI /ML based biosensors

- Enhance disease detection and diagnosis
- Predicting outcome e.g **Stroke view app**
- Novel disease Characterization

Traditional ML Models for SaMD (Software as medical device)

- Vector machine
- Random forest

Regulatory outlook

- US FDA has approved several AI/ML-based SaMD. Since from Yr 2016 29 approval granted.
- FDA mentioned that SaMD algorithms that are "**locked" prior to marketing, where algorithm changes likely require FDA premarket review.**

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Current Regulatory Landscape of AI/ML

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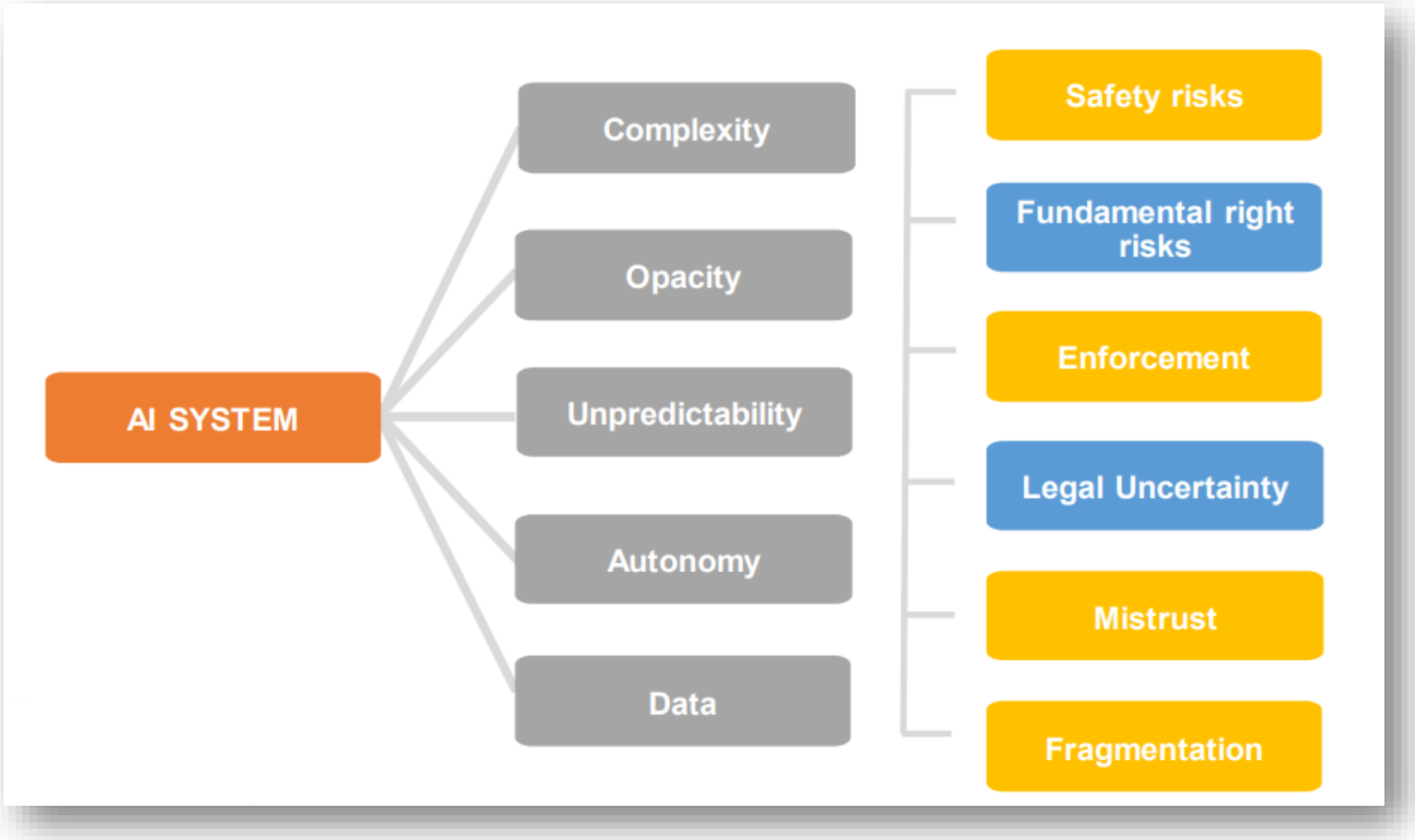
Need for Legislation and Regulation

Why do we need to regulate AI use cases?



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Current Regulatory Guidance on AI

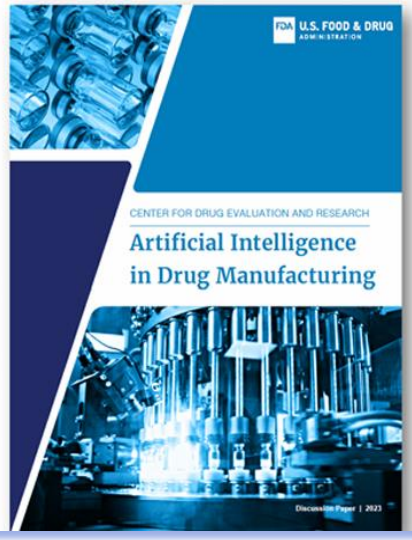
Guidance

- ASME V&V 40-2018
- GAMP 5v2 Appendix D11, Good Machine Learning Practices (GMLP)
- ISO_IEC_38507_2022(en) - Governance of IT - AI implications
- ISO_IEC_TS_4213_2022(en) - Assessment of ML classifier performance
- ISO/IEC TR 24028:2020, Information technology – artificial intelligence – overview of trustworthiness in artificial intelligence
- FAQ by Danish Medicine:https://laegemiddelstyrelsen.dk/en/devices/new-tech-new-technological-possibilities-and-medical-devices/faq-on-ai-in-medical-devices/pdf
- SFDA guidance of AI in Medical Device as well:
- https://www.sfda.gov.sa/sites/default/files/2023-01/MDS-G010ML.pdf
- Dutch Innovation Funnel AI https://www.datavoorgezondheid.nl/documenten/publicaties/2021/07/15/innovation-funnel-for-valuable-ai-in-healthcare
- MHRA Software and Artificial Intelligence (AI) as a Medical Device ;Updated 25 October 2023

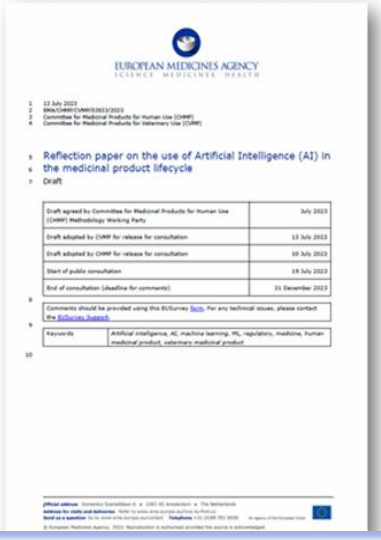
FDA / CDRH
AI/ML-Based Software as a Medical Device (SaMD)
(Action plan, 2021'01)

FDA & Health Canada & MHRA
Good Machine Learning Practice for Medical Device Development
(Guiding Principles, 2021'10)

FDA / CDER
AI in Drug Manufacturing
(Discussion paper, 2023'02)



EMA
Reflection Paper on the use of AI in the medicinal product lifecycle (draft, 2023'07)



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Difference between EMA reflection and FDA discussion paper on AI

EMA Reflection Paper

- Covers the use of AI/ML on medicines' lifecycle, from drug discovery to the post-authorization setting.
- Safety and Efficacy Considerations: Emphasizes safety, efficacy, throughout the product lifecycle
- Data Quality and Integrity: Highlights in clinical settings.
- Technical aspects: Data acquisition, augmentation, overfitting data leakage, interpretability and explainability.
- Recommends transparent AI models quality review procedures, and careful handling of issues like overfitting; addresses ethical and privacy concerns
- Advocates for a risk-based approach.
- Reliability : Raised Concerned about AI systems prone to hallucination and emphasizes the need for reliable outputs
- Key concerns : Patient safety, reliability of development data, guidelines for data reliability, transparency.

FDA Discussion Paper

- Focus on the use of AI/ML in pharmaceutical manufacturing process design advance process quality control, compliance.
- Safety and Efficacy Considerations: Focuses on the quality, consistency, and compliance of manufactured drugs
- Data Quality and Integrity: Highlight in manufacturing processes
- Life cycle approach: data collection,curation, model development, testing, deployment, monitoring, updation, and retirement.
- Stresses transparency in manufacturing and process data.
- Risk based approach :Not explicitly mentioned
- Reliability : Addresses appropriate performance assessment metrics and the importance of regulatory interactions during development.
- Key concerns : Governance, accountability, transparency, data quality, reliability.

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EU Legislative and Regulatory Landscape and WHO Guidance on AI

Consider: EU AI Legislative and Regulatory Landscape

The use of AI in medicines development must be considered in the context of the broader EU policy landscape

Horizontal Legislation

- AI Act (draft)
- AI Liability Directive (draft) / PLD (to be revised)
- General Data Protection Regulation (GDPR)
- Data Act
- Data Governance Act (DGA)
- Cybersecurity Directive / NIS2

Vertical Legislation

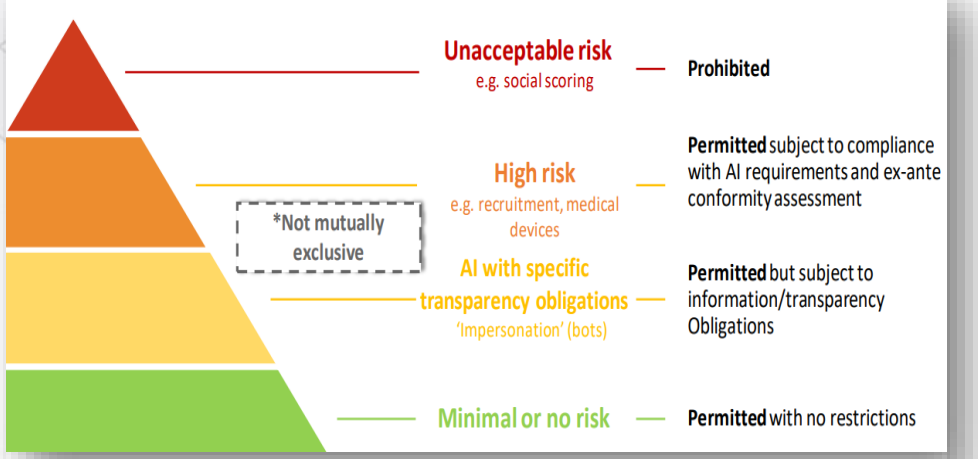
- MDR and IVDR
- CTR
- EHDS (draft)

Soft law e.g. guidance

- EMA Reflection paper on AI (and possible future guidances)

Standards and Terminologies

EU/US Cooperation within TTC



WHO: Regulatory considerations on artificial intelligence for health (October 2023)

- Documentation and transparency
- Risk Management and AI systems lifecycle
- Intended use, analytical and clinical validation
- Data quality
- Privacy and data protection
- Engagement and collaboration

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Validation Risk management of AI and ML Models

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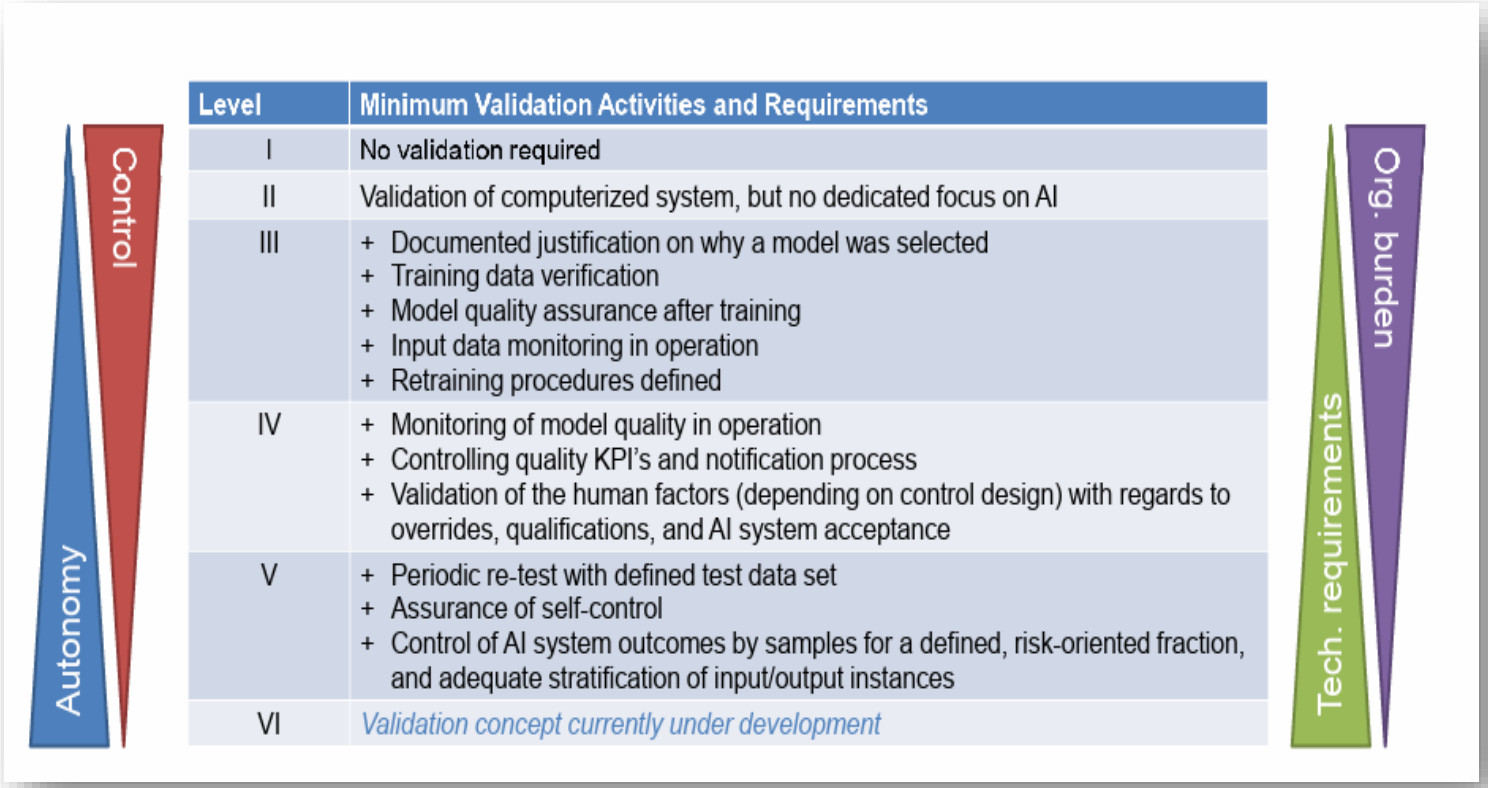
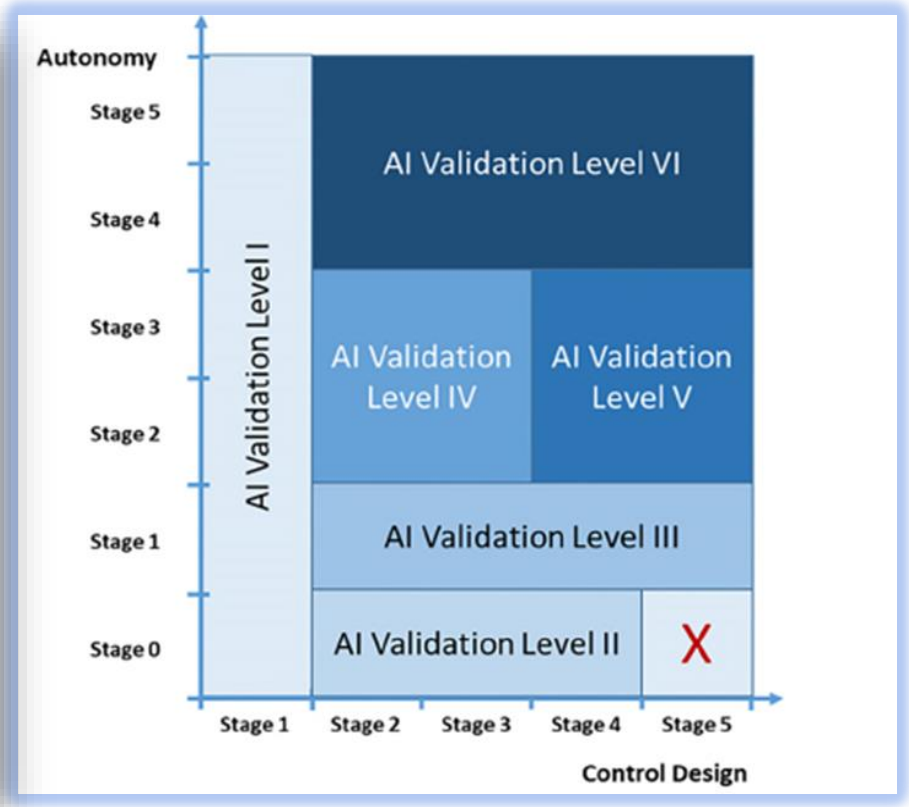
Understanding the AI Maturity Models for Validation



Level	Minimum Validation Activities and Requirements
I	No validation required
II	Validation of computerized system, but no dedicated focus on AI
III	+ Documented justification on why a model was selected + Training data verification + Model quality assurance after training + Input data monitoring in operation + Retraining procedures defined
IV	+ Monitoring of model quality in operation + Controlling quality KPI's and notification process + Validation of the human factors (depending on control design) with regards to overrides, qualifications, and AI system acceptance
V	+ Periodic re-test with defined test data set + Assurance of self-control + Control of AI system outcomes by samples for a defined, risk-oriented fraction, and adequate stratification of input/output instances
VI	*Validation concept currently under development*



Reference :AI Maturity Model for GxP Application: A Foundation for AI Validation (PE Mar/Apr 2022)

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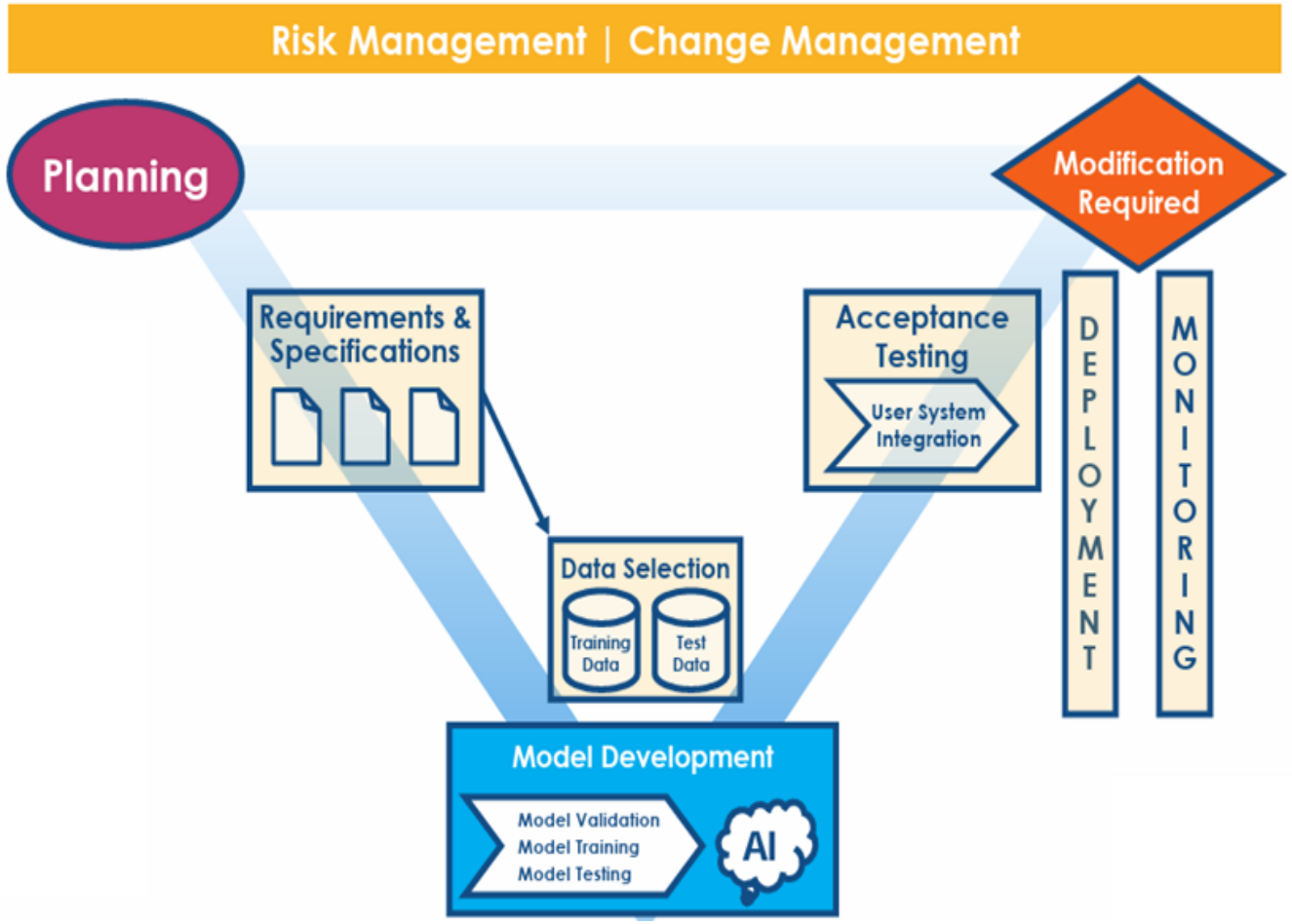
Validation of Machine models

- Validation Planning
- Requirements and specifications
- Data Selection
  - Training Data
  - Test Data
- Model Development
  - Model Validation
  - Model Training
  - Model Testing
- Acceptance Testing (System Integration)
- Modification
  - Deployment
  - Monitoring



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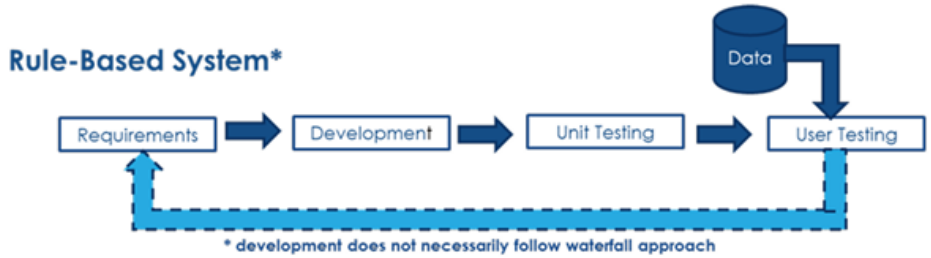
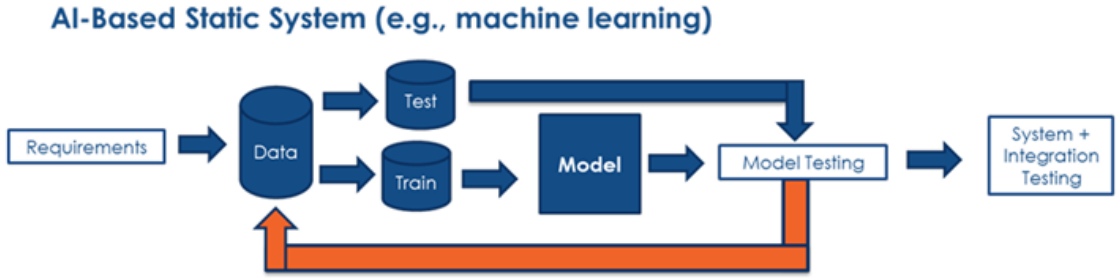
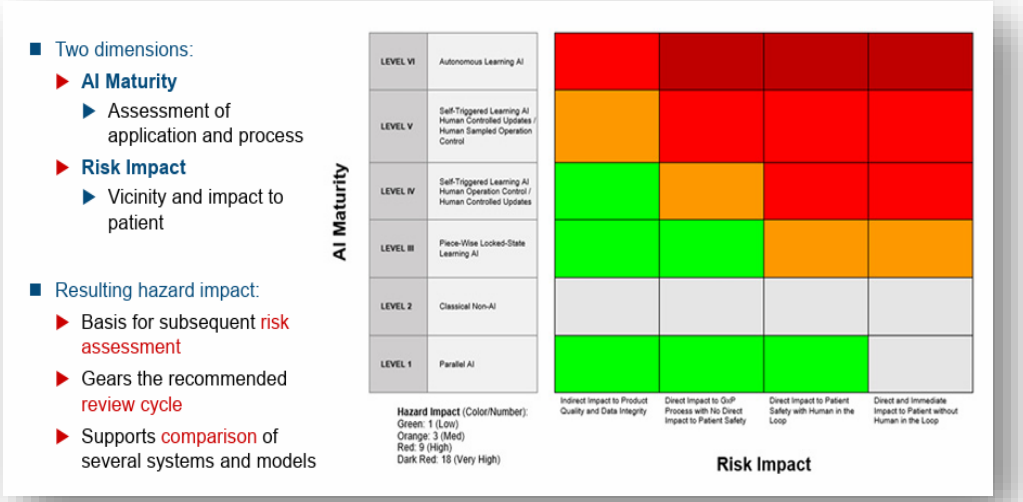
Validation of Machine models

- The requirements (i.e., rules or logic) are not known for AI-based systems, making the outcome less transparent than with rule-based systems.
- Always consider Static ML models require periodic performance reviews and re-training.
- Validating against "gold standards." Comparing AI/ML predictions against established gold standards or conventional methods provides a basis for measuring accuracy and safety
- Risk Management and Change management
- Identify using risk map heat plan. Risk controls/mitigation measures reduce risks along selected quality dimensions.
- Model modification and changes are verified against model metrics score.







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Challenges and Solutions for Trustworthy AI

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Validation Challenges and Solutions

Challenges	Solutions
Data Quality and Bias **Hallucinations**	• Rigorous data collection and preprocessing • Use diverse and representative datasets • De bais fairness, Data augumenation,filtering • RLHF,RAG(retrieval-augmented generation) (RAG), reasoning and iterative querying.
Interpretability And Exaplainibility	• Implement explainable AI techniques for understanding model behavior • Develop user-friendly interfaces and visualization tools. Encourage transparency and openness in model architectures
Adversarial Attacks	• Employ robustness testing and adversarial training • Continuously monitor for unusual behavior and stay informed on defense strategies
Generalization and Overfitting	• Apply cross-validation, dropout, and regularization • Continuously evaluate model performance on unseen data. Utilize domain adaptation techniques

Challenges	Solutions
Ethical and Legal Concerns	• Collaborate with legal experts for compliance . • Develop factual AI ethics guidelines. • Clearly define responsibilities for AI system outcomes
Scalability And Security	• Conduct stress testing and performance optimization. • For security Implement robust authentication and access controls
Data Robustness	• Implement techniques like data augmentation and domain adaptation. • Continuously monitor data distribution and adapt models accordingly
Regulatory Compliance	• Stay informed about changing regulations and work with regulatory bodies
Continuous Monitoring and Validation	• Develop strategies for model retraining, version control, and drift detection. Set up monitoring and alert systems for detecting deviations

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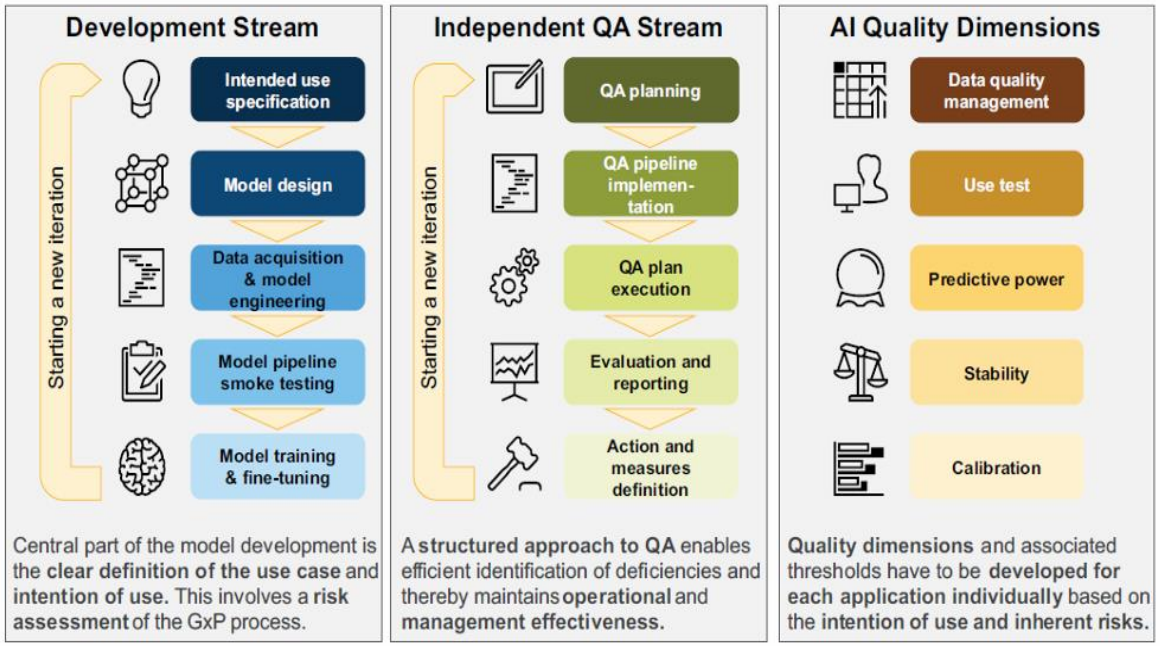
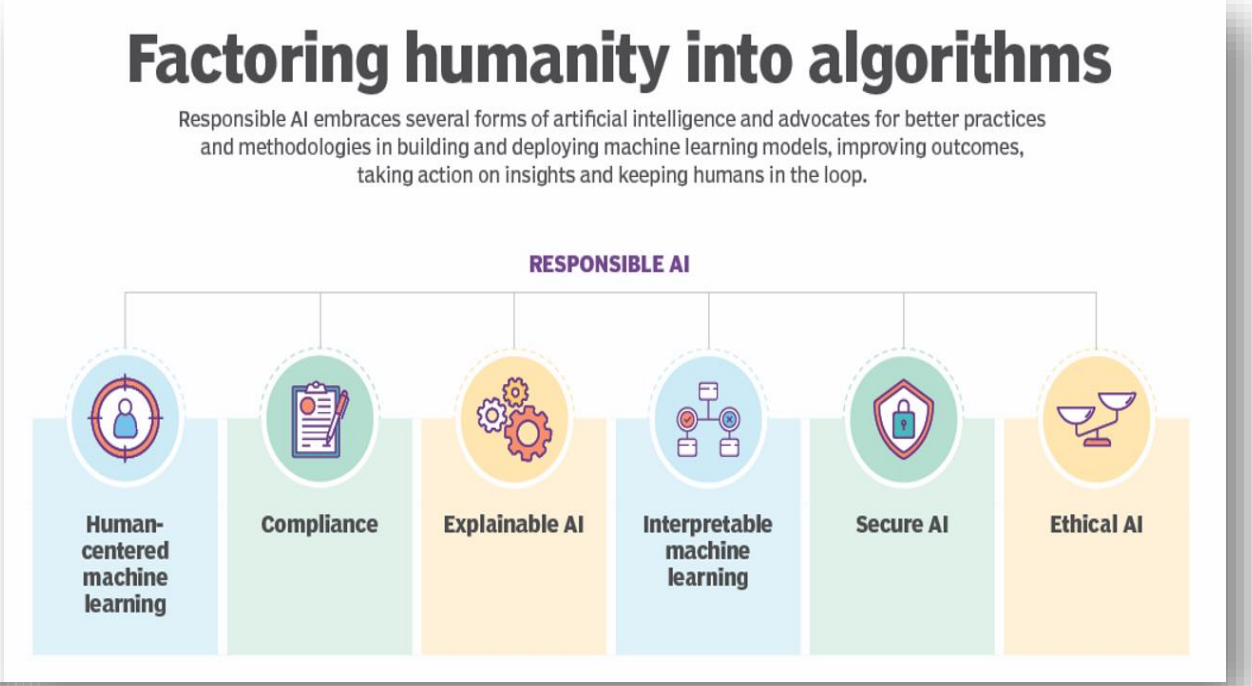
Road to trustworthy and Responsible AI

- An assessment list for trustworthy AI(ALTAI) presented by a high-level expert group established by the European Commission is encouraged.
- The report should include: Human agency oversight, Tech robustness and safety, Privacy and data governance, Transparency, accountability, societal and environmental well-being, diversity, and non-discrimination fairness.





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Conclusion

- Field of AI /ML shows **great potential for enhancing all phases of the product lifecycle.**
- **Validating against "gold standards."** Comparing AI/ML predictions against established gold standards or conventional methods provides a basis for measuring accuracy and safety.
- Availability of **relevant /reliable data, data privacy is key**. Points like **transparency, bias, and explainability of algorithms need to be evaluated** while designing these models.
- Regulatory Authorities are trying to bring **guidance and governance** in discussion with stakeholders who need **consistent definitions and International harmonization.**
- **Intellectual property** concerns. Despite the crucial role transparency with respect to AI and ML algorithms could play in facilitating drug development, concerns about freely **sharing proprietary algorithms or data** continue to hinder transparency efforts.
- **Human centric approach** should guide all development and deployment AI/ML models. Integration of bias to the model **promoting trustworthy AI.**

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Questions?

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