Industry Perspectives on Regulatory Frameworks for AI/ML in Drug Development

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abbvie

Contents

Case Study

A STAT INVESTIGATION

IBM pitched its Watson supercomputer as a revolution in cancer care. It's nowhere close

Background:

Leverage Memorial Sloan Kettering's Cancer Center program and make expertise available to patients all over the world and develop standardized optimal treatment recommendations.

Sources: https://www.statnews.com/2017/09/05/watson-ibm-cancer/, https://slate.com/technology/2022/01/ibm-watson-health-failure-artificial-intelligence.html

Case Study

A STAT INVESTIGATION

IBM pitched its Watson supercomputer as a revolution in cancer care. It's nowhere close

Key Challenges:

- In Denmark, oncologists agreed with Watson's recommendations in only 33% of cases.
- Trained by doctors at Memorial Sloan Kettering Cancer Center.
- Emphasis on American studies.
- Patients treated at Memorial Sloan Kettering tend to be more affluent.
- Disconnect: treatment practice, availability of medicines, and insurance coverage.
- Potential for race, gender, and class bias.
- Lack of explainability.

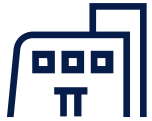
https://www.statnews.com/2017/09/05/watson-ibm-cancer/

AI/ML: What is it?

What it does

Extract structured data and insights from content.

Classify, predict, and **transform** data.



Generate content from learned patterns in data.

How it helps

Accelerate work through intelligent automation

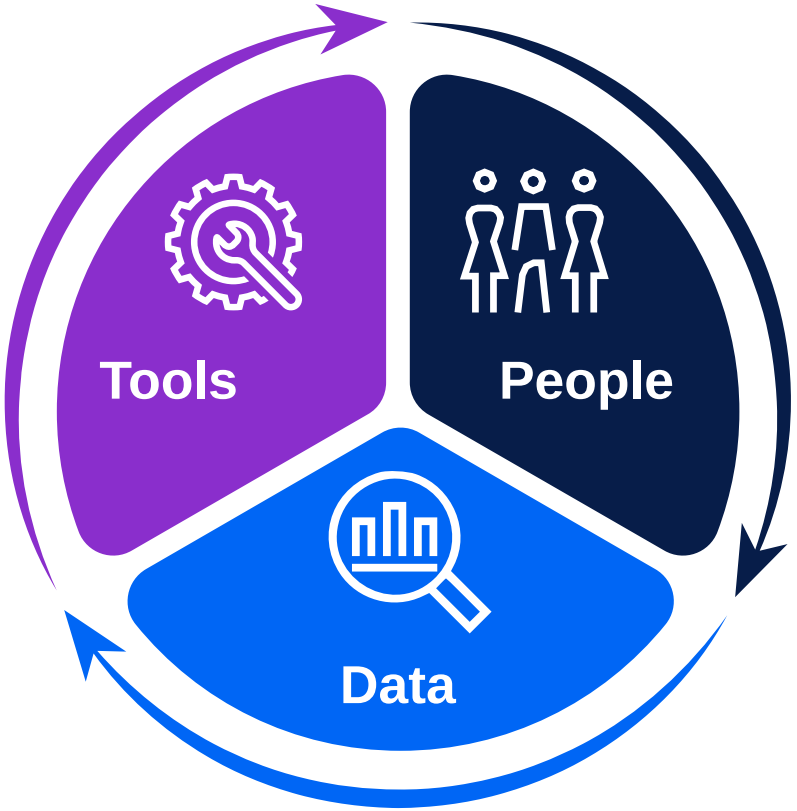
Scale work capacity through duplication and continuity.

Amplify and **hone** the quality and precision of work.

The Virtuous (AI) Cycle

“Enterprise AI”
Operational Value
Driving Efficiency

Business Operations



“Experience AI”
Experiential Value
Driving Insights

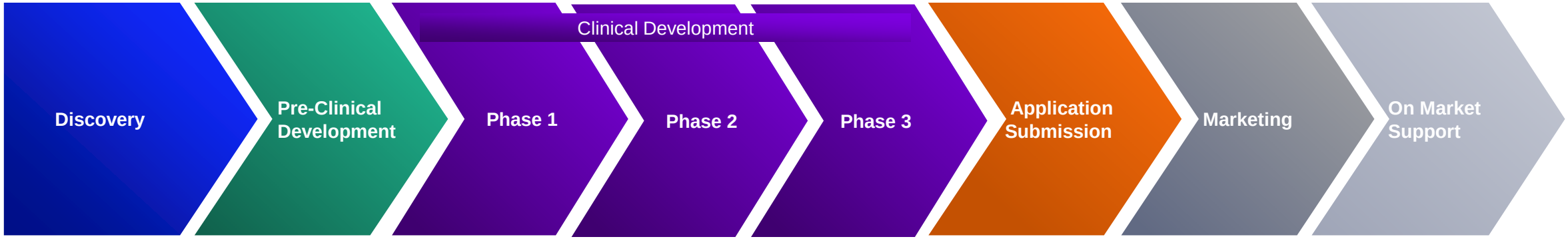
Clinicians, Healthcare Providers, Patients

“Expert AI”
Analytical Value
Driving Precision

Accelerating Drug Development

1. Which areas have the highest level of risk?
2. How can we extract the most value while balancing safety and risk?
3. What are the appropriate safety checks, governance, level of human involvement, and ethical considerations?

AI/ML Applications in the Drug Development Lifecycle



Drug target identification, screening, design, prioritization

Model informed drug development

Dose selection, optimization

Patient recruitment, selection, stratification, retention, site selection

Predictive models, digital twins

Decentralized clinical trials, Remote patient monitoring, novel digital endpoints

Regulatory Submission & Review

RWE generation, pharmacovigilance, patient support tools, diagnostics, precision medicine, clinical decision support software

Manufacturing and Supply Chain Management

AbbVie AI/ML Digital Health Technology Use Cases

Image Analysis

- Analyze skin diseases and conditions.
- Evaluate skin quality, texture, and facial lines.
- Range of motion for inflammatory arthritis.

Voice Analysis

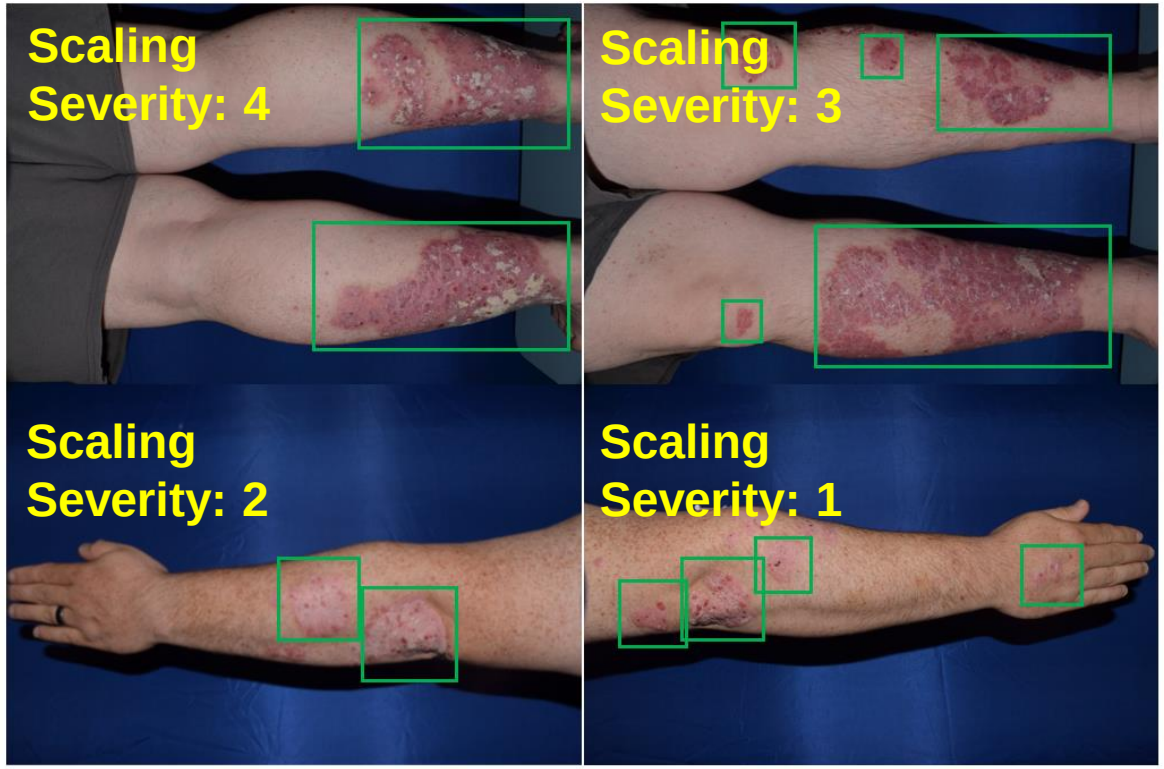
- Voice biomarker extraction for neurodegenerative disease.

Motion Analysis

- Detect and quantify scratch for skin conditions.
- Bradykinesia and other movement disorders for Parkinson’s disease.

Deep Learning (DL) Model for Psoriasis Area Severity Index (PASI)

- Psoriasis is a chronic inflammatory disease that causes painful skin damage and irritation. PASI score is a clinical assessment to measure disease severity.
- Evaluated historical clinical trial data of patients undergoing treatment for psoriasis.
- Training data set included tracking of an individual's disease changes from baseline over time.
- Individuals were sorted into training or testing datasets to prevent within-subject information leakage between training and test sets.

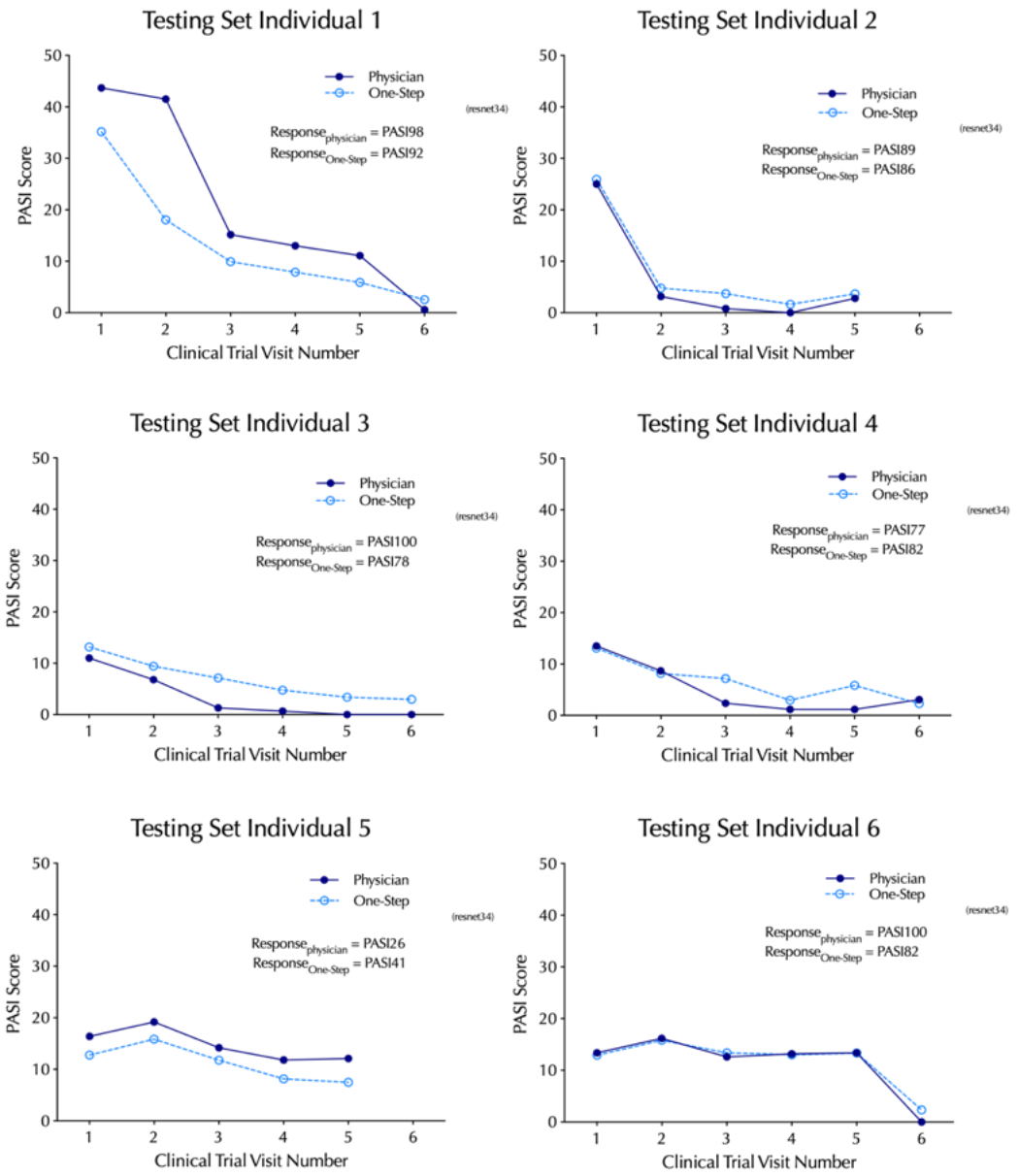


Examples of psoriasis area automated detection and severity scoring.

https://www.medrxiv.org/content/10.1101/2023.03.23.23287628v1

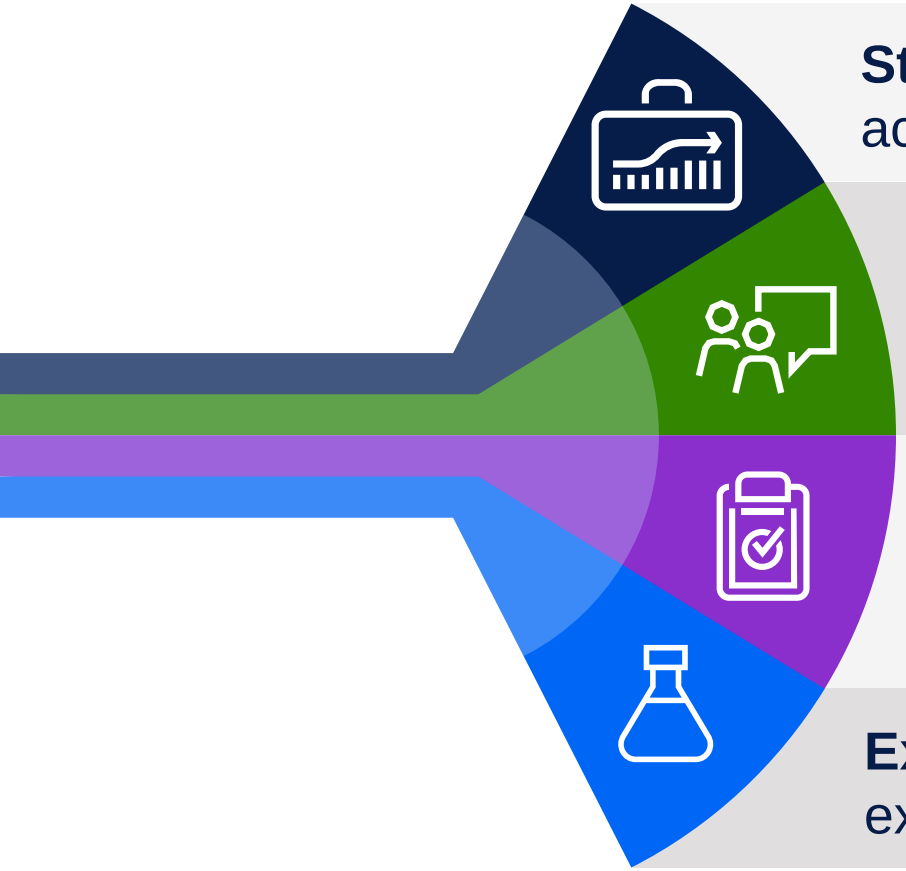
Deep Learning (DL) Model for Psoriasis Area Severity Index (PASI)

- Model performance tested against ground-truth physician PASI scores and demonstrated that PASI predictions closely tracked the trajectory of physician scores from severe to clear skin.
- DL model (‘One-Step PASI’) can be used to measure patient PASI scores while undergoing treatment.



Xing et al., A one-step deep learning framework for psoriasis area and severity prediction trained on interventional clinical trial images, Digital Biomarkers, 2024, Pre-print: https://www.medrxiv.org/content/10.1101/2023.03.23.23287628v1

Regulatory Considerations for AI/ML-enabled DHTs



Streamline & Leverage: How can AI/ML-enabled DHTs be leveraged across different clinical development programs?

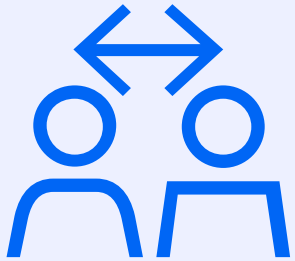
Third-Party Collaborations: How can Sponsors effectively manage third-party developers of AI/ML technologies?

Fit-For-Purpose: How do you define fit-for-purpose data sets?

Exploratory Research: Continued health authority support of exploratory endpoints to drive research and innovation.

Prognostic Models in Clinical Trials: ‘Digital Twins’

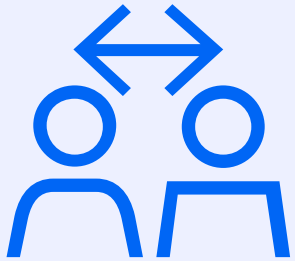
- **Ethical considerations** with clinical trial participants allocated to a non-treatment group, especially for long-term studies and trials investigating a degenerative disease.
- **Opportunity**:
  - Prognostic models of disease progression trained using observational study data and control arms of historical clinical trials.
  - Patient digital twin uses a clinical trial participant’s baseline data, and the prognostic model describes what may have happened to a participant if they had received a placebo.
  - Predicted placebo outcomes of participant’s digital twin has the potential to decrease sample size or increase statistical power by providing longitudinal information across placebo and treatment groups.



- **Streamline Development**
- **Decrease Sample Size**
- **Increase Statistical Power**

Prognostic Models in Clinical Trials: ‘Digital Twins’

- **Regulatory Challenges**:
  - Regulatory clarity on approaches to using patient digital twins and synthetic control methods in clinical trials.
  - Alignment on the terms and definitions for different types of digital twins in manufacturing processes, nonclinical, and clinical applications
  - Guidance on the appropriate use of digital twins in supporting benefit/risk assessments in drug development.



- **Streamline Development**
- **Decrease Sample Size**
- **Increase Statistical Power**

Exploring Potential AI Legislation

Risk-based and flexible approach to AI regulation. Current regulations successfully manage the development of safe, effective, and high-quality therapies and this ecosystem can adequately adapt to cover the use of AI.

Focus oversight of AI/ML technologies within FDA's existing authorities.

Support improvements to FDA's AI infrastructure, expertise, and capacity.

Adapt regulatory frameworks where needed: predetermined change controls, clinical decision support software, technology certification.

https://www.help.senate.gov/imo/media/doc/help_committee_gop_final_ai_white_paper1.pdf

White House AI Bill of Rights and Executive Order

White House Blueprint for an AI Bill of Rights

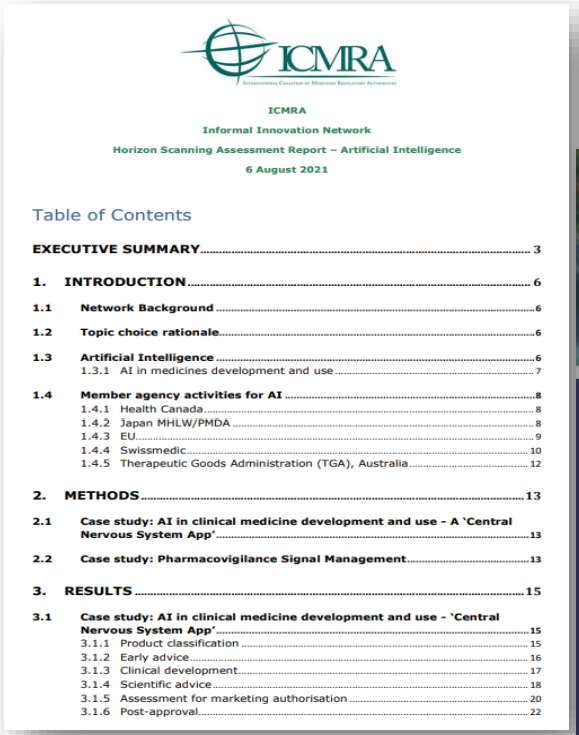
1. Safe and Effective Systems
2. Algorithmic Discrimination Protections
3. Data Privacy
4. Notice and Explanation
5. Human Alternatives, Consideration, and Fallback

Executive Order on the Safe, Secure, and Trustworthy Development and Use of Artificial Intelligence: Policy framework to manage potential risks of AI, and direct agency action to regulate the use of AI systems and tools.

- **Key provisions**: Develop a strategy for regulating the use of AI or AI-enabled tools in drug-development processes and define the objectives, goals, and high-level principles required for appropriate regulation throughout each phase of drug development.
- **Alignment**: AI Bill of Rights and EO largely aligns with FDA's public health mission and ongoing activities in AI guidance development.
- **Implementation:** Need for clarity of HHS and FDA implementation of EO provisions and engagement on broader EO efforts.
- **Potential impact of future legislation**

https://www.whitehouse.gov/ostp/ai-bill-of-rights/
https://www.whitehouse.gov/briefing-room/presidential-actions/2023/10/30/executive-order-on-the-safe-secure-and-trustworthy-development-and-use-of-artificial-intelligence/

Discussing Potential Regulatory Frameworks for AI in Drug Development



ICMRA

ICMRA
Informal Innovation Network
Horizon Scanning Assessment Report – Artificial Intelligence
6 August 2021

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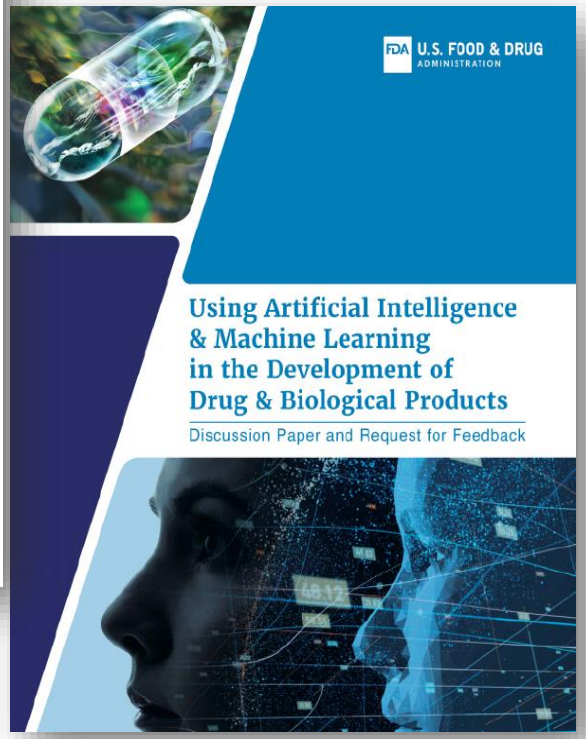


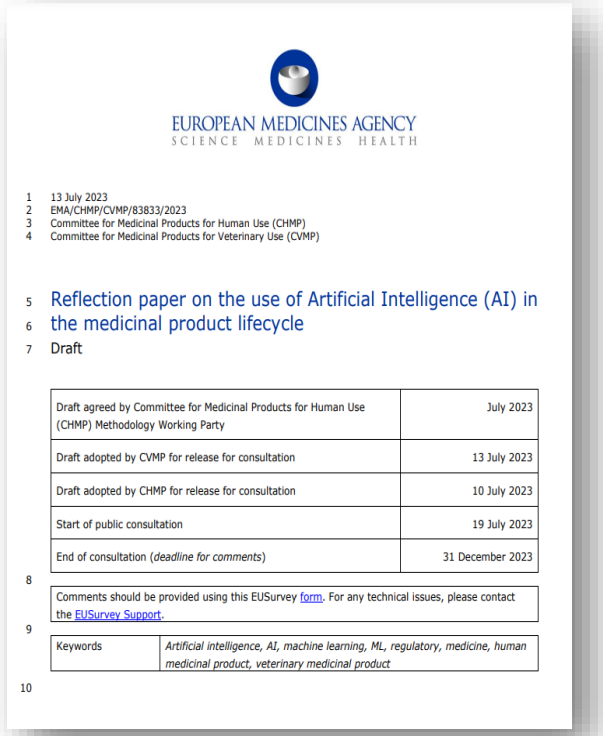
FDA U.S. FOOD & DRUG ADMINISTRATION

Using Artificial Intelligence & Machine Learning in the Development of Drug & Biological Products

Discussion Paper and Request for Feedback

Regulatory considerations on artificial intelligence for health

World Health Organization



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 July 2023
EMA/CHMP/CVMP/83833/2023
Committee for Medicinal Products for Human Use (CHMP)
Committee for Medicinal Products for Veterinary Use (CVMP)

Reflection paper on the use of Artificial Intelligence (AI) in the medicinal product lifecycle

Draft

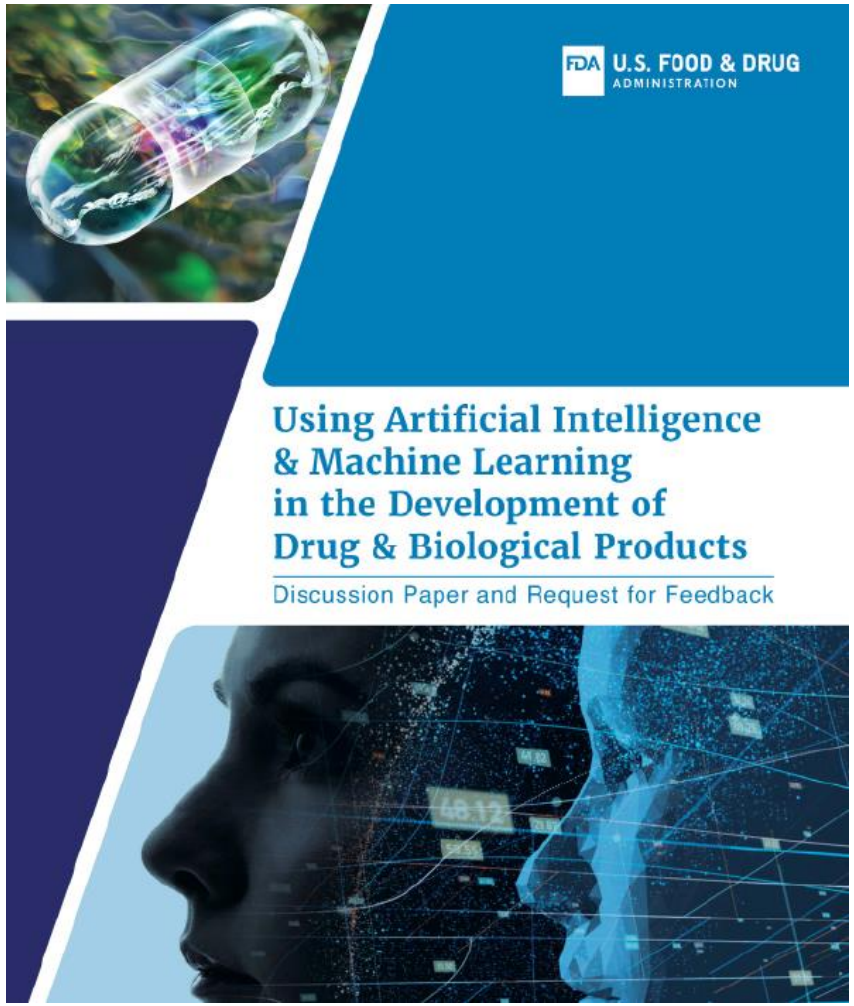
Draft agreed by Committee for Medicinal Products for Human Use (CHMP) Methodology Working Party	July 2023
Draft adopted by CVMP for release for consultation	13 July 2023
Draft adopted by CHMP for release for consultation	10 July 2023
Start of public consultation	19 July 2023
End of consultation (*deadline for comments*)	31 December 2023

Comments should be provided using this EUSurvey form. For any technical issues, please contact the EUSurvey Support.

Keywords	*Artificial intelligence, AI, machine learning, ML, regulatory, medicine, human medicinal product, veterinary medicinal product*

Sources: https://icmra.info/drupal/sites/default/files/2021-08/horizon_scanning_report_artificial_intelligence.pdf, https://www.fda.gov/media/167973/download https://iris.who.int/bitstream/handle/10665/373421/9789240078871-eng.pdf?sequence=1&isAllowed=y, https://www.ema.europa.eu/en/documents/scientific-guideline/draft-reflection-paper-use-artificial-intelligence-ai-medicinal-product-lifecycle_en.pdf

FDA Discussion Paper on AI



Requested public stakeholder feedback on the opportunities and challenges with utilizing AI/ML in the development of drugs, as well as in the development of medical devices intended to be used with drugs.

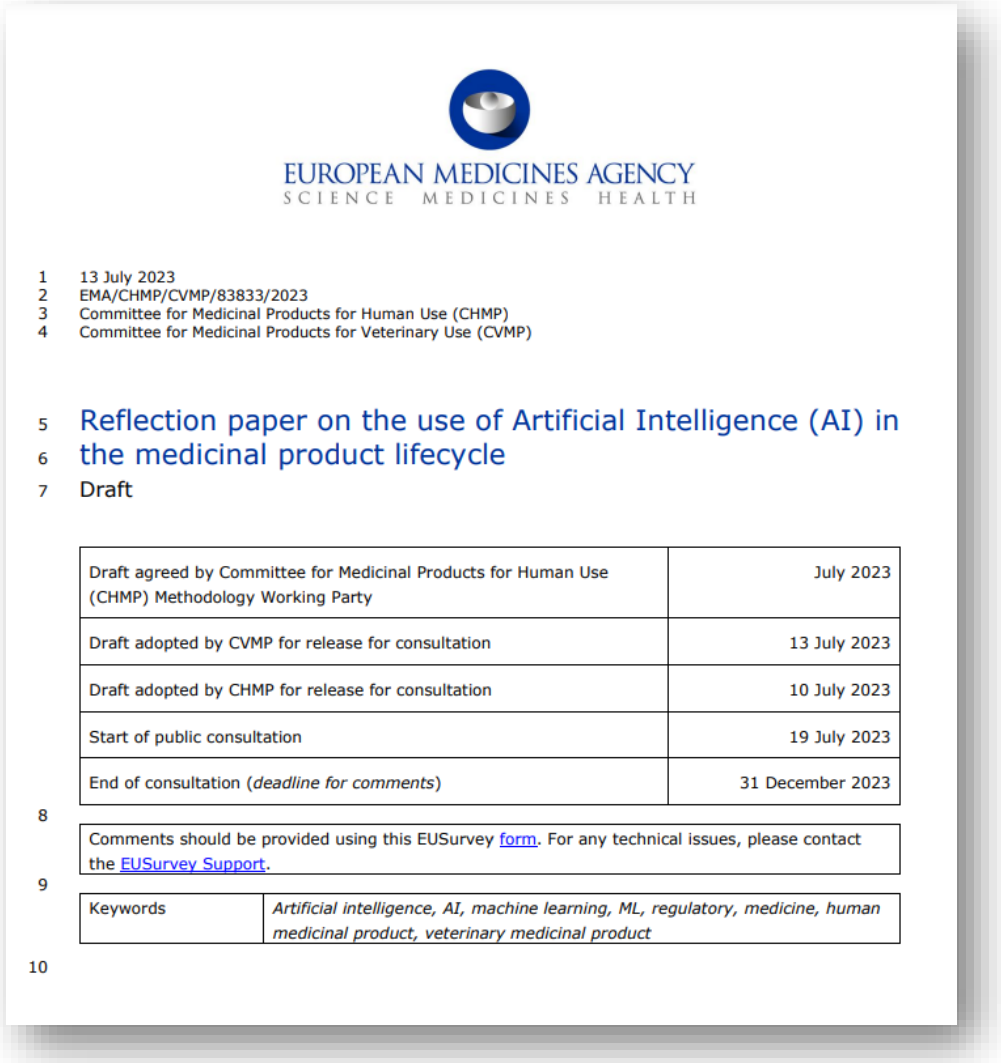
1. Landscape of current and potential uses of AI/ML: drug discovery, preclinical, clinical, postmarket, manufacturing.

2. Considerations for the use of AI/ML

3. Opportunities for public feedback and stakeholder engagement

https://www.fda.gov/media/167973/download

EMA Reflection Paper on AI



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Reflects on principles relevant to the application of AI/ML at any step of a medicines' lifecycle, from drug discovery to the post-authorization setting.

1. **Harnessing the potential of AI:** How to adapt existing regulatory frameworks, guidelines and best practices for data management, governance and statistical stringency.

2. **Providing early regulatory support:** Early regulatory feedback on qualification of innovative development methods and scientific advice.

3. **Mitigating new risks:** Non-transparent model architectures, data management, data leakage and model overfitting, unforeseen risks.

4. **Avoiding bias and promoting trustworthy AI:** Checks and balances through human agency and oversight.

https://www.ema.europa.eu/en/documents/scientific-guideline/draft-reflection-paper-use-artificial-intelligence-ai-medicinal-product-lifecycle_en.pdf

Key Themes: Potential Regulatory Frameworks for AI/ML

Patient Safety as guiding principle with a human-centric approach.

Health Authority Scope and oversight in drug development based on risk/benefit assessment and regulatory decision-making.

Harmonization and standardization of key terms and definitions. Alignment with legislation and other regulatory frameworks.

Classification of AI/ML technologies as medical device software and regulatory pathways needs to be clarified.

Flexible & Risk-Based. Clarity on determining risk based on context of use, drug benefit/risk assessment, and use in regulatory decision-making.

Intellectual Property, trade secret, and confidential commercial information needs to be protected and balanced with public and third-party disclosure obligations.

Transparency to different stakeholders needs to be clarified: health authorities, healthcare providers, end users, and patients. Expectations on level of detail and documentation.

Model Development & Monitoring: guidance and considerations on training, testing, validation, monitoring, and model versioning.

Digital Health Technologies & Medical Device Software

FDA Guidance: DHTs for Remote Data Acquisition in Clinical Investigations

- Outlines recommendations intended to facilitate the use of DHTs in clinical investigations as appropriate for the evaluation of medical products.
- Regulatory considerations for DHTs that meet the definition of a device.
- **Flexibilities**: verification and validation activities in lieu of design control requirements for medical devices.

FDA Guidance: Clinical Decision Support Software

- Clarifies FDA's oversight of clinical decision support (CDS) software intended for health care professionals based on four criteria.
- **Risk of automation bias** and time critical nature of certain health care tasks.

IMDRF Medical Device Software Guidance:

- "Software as a Medical Device": Possible Framework for Risk Categorization and Corresponding Considerations
- Draft Guidance: Medical Device Software: Considerations for Device and Risk Characterization
- **New considerations**: Users, use environment, target population, clinical workflow, level of automation, input source, timing, output type.

AI/ML-enabled Medical Devices

How can we leverage and clarify the use of certain medical device regulatory frameworks for innovative drug development?

IMDRF Machine Learning-enabled Medical Devices: Key Terms and Definitions: Establishes relevant terms and definitions across the total product life cycle for machine learning-enabled medical devices.

Predetermined Change Control Plans (PCCPs): Forward-thinking approach to implement certain modifications without necessitating additional marketing submissions.

Good Machine Learning Practice (GMLP) for Medical Device Development: Guiding Principles: 10 guiding principles to foster the development of GMLP to promote safe, effective, and high-quality medical devices that use AI/ML. **+ Active IMDRF GMLP WG.**

Technology Certification Scheme? "A Nationwide Network of Health AI Assurance Laboratories." To evaluate and monitor the performance of AI models in health care.

Shah NH, Halamka JD, Saria S, et al. A Nationwide Network of Health AI Assurance Laboratories. JAMA. 2024;331(3):245–249. doi:10.1001/jama.2023.26930
https://www.fda.gov/medical-devices/software-medical-device-samd/good-machine-learning-practice-medical-device-development-guiding-principles
https://www.imdrf.org/documents/machine-learning-enabled-medical-devices-key-terms-and-definitions
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/marketing-submission-recommendations-predetermined-change-control-plan-artificial

Potential Risks of AI: Misinformation

CNBC

HEALTH AND SCIENCE

Free ChatGPT may incorrectly answer drug questions, study says

PUBLISHED TUE, DEC 5 2023•12:01 AM EST | UPDATED TUE, DEC 5 2023•3:42 PM EST

"The preponderance and dissemination of medical misinformation is already having a significant negative impact on health outcomes, causing people to make plainly uninformed and adverse choices regarding their health."

– Dr. Robert M. Califf, FDA Commissioner

8 in 10

Americans seeks health-related information each year

73%

Find this information from online sources

Sources: https://www.cnbc.com/2023/12/05/free-chatgpt-may-incorrectly-answer-drug-questions-study-says.html , https://reaganudall.org/programs/improving-understanding-fda-and-fda-regulated-products https://www.fda.gov/news-events/speeches-fda-officials/speech-commissioner-robert-m-califf-house-medicine-06162023

AI & Patient Health Literacy

Patient Need: Accurate, up-to-date, and trustworthy sources of medical and scientific benefit-risk information.

Accelerating Access: These technologies need to be made accessible for historically marginalized communities.

Cultural Competence: Differences in language, culture, and customs.

Navigation: How will AI be leveraged to help navigate and distill an overwhelming amount of information for patients?

Sources of Information: LLMs like ChatGPT has the risk of replacing the voice of healthcare professionals and institutions.

Regulatory Precedence & Feedback

Important to have **transparency** on health authority acceptance, use, and authorization of AI/ML tools and medical devices.

Leverage qualification pathways (e.g. ISTAND, DDT) and early engagement opportunities for agency feedback (e.g. CPIM, MIDD, INTERACT).

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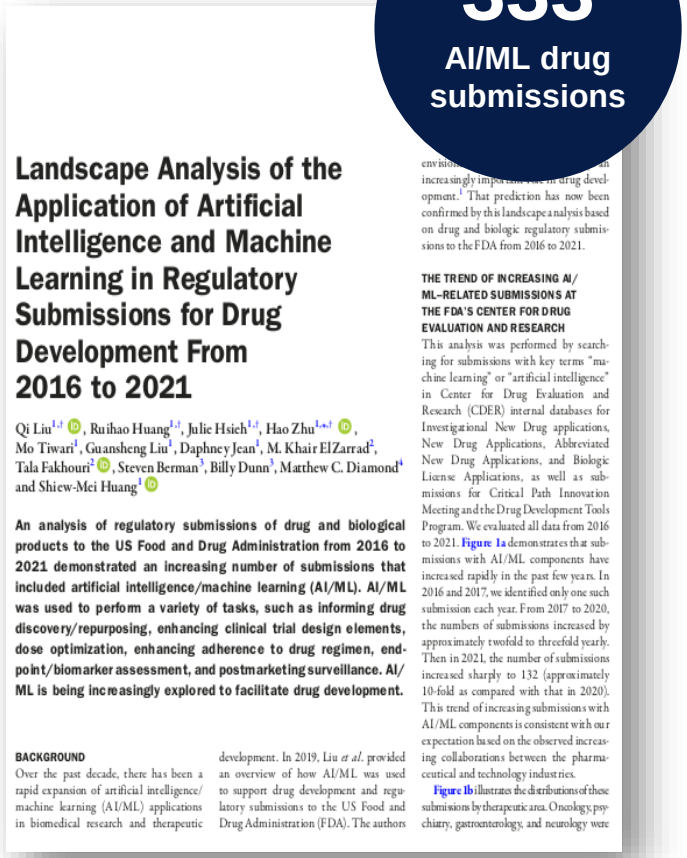
AI/ML drug submissions



Landscape Analysis of the Application of Artificial Intelligence and Machine Learning in Regulatory Submissions for Drug Development From 2016 to 2021

Qi Liu[1,†], Ruihao Huang[1,†], Julie Hsieh[1,†], Hao Zhu[1,*,†], Mo Tiwari[1], Guansheng Liu[1], Daphney Jean[1], M. Khair ElZarrad[2], Tala Fakhouri[2], Steven Berman[3], Billy Dunn[3], Matthew C. Diamond[4] and Shiew-Mei Huang[1]

An analysis of regulatory submissions of drug and biological products to the US Food and Drug Administration from 2016 to 2021 demonstrated an increasing number of submissions that included artificial intelligence/machine learning (AI/ML). AI/ML was used to perform a variety of tasks, such as informing drug discovery/repurposing, enhancing clinical trial design elements, dose optimization, enhancing adherence to drug regimen, end-point/biomarker assessment, and postmarketing surveillance. AI/ML is being increasingly explored to facilitate drug development.

BACKGROUND

Over the past decade, there has been a rapid expansion of artificial intelligence/machine learning (AI/ML) applications in biomedical research and therapeutic development. In 2019, Liu *et al.* provided an overview of how AI/ML was used to support drug development and regulatory submissions to the US Food and Drug Administration (FDA). The authors

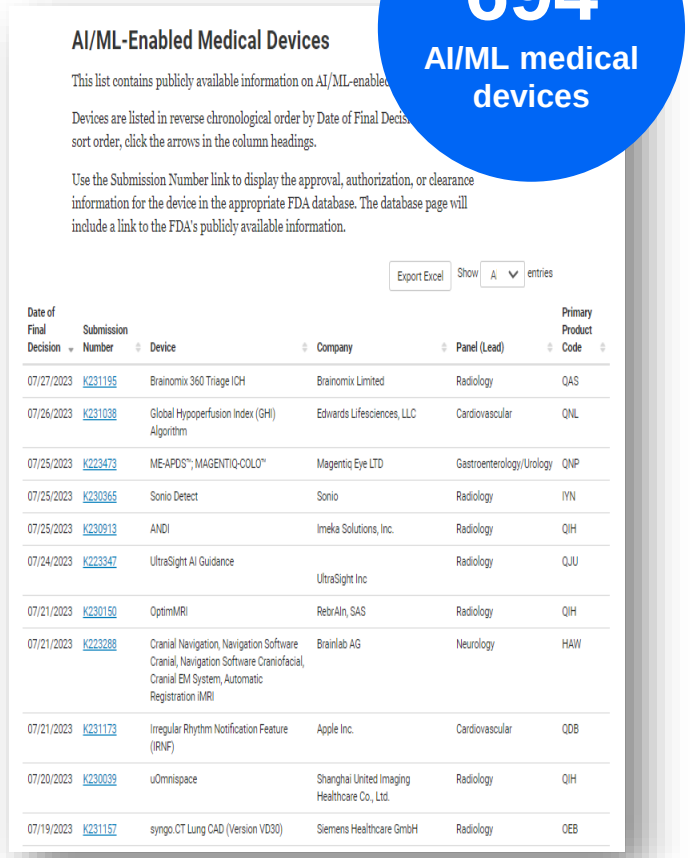
increasingly impact [illegible] in drug development.[1] That prediction has now been confirmed by this landscape analysis based on drug and biologic regulatory submissions to the FDA from 2016 to 2021.

THE TREND OF INCREASING AI/ML–RELATED SUBMISSIONS AT THE FDA'S CENTER FOR DRUG EVALUATION AND RESEARCH

This analysis was performed by searching for submissions with key terms "machine learning" or "artificial intelligence" in Center for Drug Evaluation and Research (CDER) internal databases for Investigational New Drug applications, New Drug Applications, Abbreviated New Drug Applications, and Biologic License Applications, as well as submissions for Critical Path Innovation Meeting and the Drug Development Tools Program. We evaluated all data from 2016 to 2021. Figure 1a demonstrates that submissions with AI/ML components have increased rapidly in the past few years. In 2016 and 2017, we identified only one such submission each year. From 2017 to 2020, the numbers of submissions increased by approximately twofold to threefold yearly. Then in 2021, the number of submissions increased sharply to 132 (approximately 10-fold as compared with that in 2020). This trend of increasing submissions with AI/ML components is consistent with our expectation based on the observed increasing collaborations between the pharmaceutical and technology industries.

Figure 1b illustrates the distributions of these submissions by therapeutic area. Oncology, psychiatry, gastroenterology, and neurology were

694
AI/ML medical devices



AI/ML-Enabled Medical Devices

This list contains publicly available information on AI/ML-enable[illegible]

Devices are listed in reverse chronological order by Date of Final Decis[illegible] sort order, click the arrows in the column headings.

Use the Submission Number link to display the approval, authorization, or clearance information for the device in the appropriate FDA database. The database page will include a link to the FDA's publicly available information.

Export Excel Show A entries

Date of Final Decision	Submission Number	Device	Company	Panel (Lead)	Primary Product Code
07/27/2023	K231195	Brainomix 360 Triage ICH	Brainomix Limited	Radiology	QAS
07/26/2023	K231038	Global Hypoperfusion Index (GHI) Algorithm	Edwards Lifesciences, LLC	Cardiovascular	QNL
07/25/2023	K223473	ME-APDS™; MAGENTIQ-COLO™	Magentiq Eye LTD	Gastroenterology/Urology	QNP
07/25/2023	K230365	Sonio Detect	Sonio	Radiology	IYN
07/25/2023	K230913	ANDI	Imeka Solutions, Inc.	Radiology	QIH
07/24/2023	K223347	UltraSight AI Guidance	UltraSight Inc	Radiology	QJU
07/21/2023	K230150	OptimMRI	RebrAIn, SAS	Radiology	QIH
07/21/2023	K223288	Cranial Navigation, Navigation Software Cranial, Navigation Software Craniofacial, Cranial EM System, Automatic Registration iMRI	Brainlab AG	Neurology	HAW
07/21/2023	K231173	Irregular Rhythm Notification Feature (IRNF)	Apple Inc.	Cardiovascular	QDB
07/20/2023	K230039	uOmnispace	Shanghai United Imaging Healthcare Co., Ltd.	Radiology	QIH
07/19/2023	K231157	syngo.CT Lung CAD (Version VD30)	Siemens Healthcare GmbH	Radiology	OEB

https://ascpt.onlinelibrary.wiley.com/doi/epdf/10.1002/cpt.2668, https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-aiml-enabled-medical-devices

Conclusion

- **Patient Safety** as guiding principle with a human-centric approach to AI/ML development.
- **Use AI/ML to drive greater precision, efficiency, and insights** in the drug development process to accelerate access to innovative therapies and treatments for patients.
- **Continued stakeholder engagement** and health authority transparency towards the development of flexible and risk-based regulatory frameworks.
- **Support health authority resourcing and capacity building:** AI infrastructure and technical expertise.

Acknowledgements

Huge Thank You!

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AbbVie Team Members:

- Digital Science : Michelle Crouthamel, Jie Shen, Dan Webster, Sandra Gross
- Siavash Mortezavi, Aesthetics Digital Science
- Business Technology Solutions: Philip Hajduk, Brian Martin, Saheeb Mohammed
- James Duhig, Patient Safety
- Regulatory Affairs: Christy Greenberg, Katie Chowdhury
- Korea Office: Mi Hyun Shin, Minseong Kim
- Regulatory Policy & Intelligence Team