



Chinese Pharmaceutical Association
Institute of Materia Medica, Chinese Academy of Medical Sciences

Acta Pharmaceutica Sinica B

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REVIEW

The applications and advances of artificial intelligence in drug regulation: A global perspective

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Received 12 June 2024; received in revised form 6 September 2024; accepted 11 September 2024

KEY WORDS

Artificial intelligence;
Machine learning;
Regulatory science;
Safety surveillance;
Pharmacovigilance;
Regulation;
Emerging technology

Abstract Artificial intelligence (AI) has emerged as a transformative force in healthcare, with applications spanning diagnostics to drug development. However, its integration into drug regulation remains nascent, with varying degrees of adoption and implementation across different regulatory bodies worldwide. This review aims to provide a comprehensive overview of the current state of AI in drug regulation, encapsulating AI-related policies, initiatives, and its practical application in regulatory agencies globally. It further discusses the challenges and future prospects of AI in this field. The findings reveal that numerous agencies have launched action plans and initiatives to incorporate AI, aiming to streamline regulatory processes and enhance data-driven regulatory decision-making. Moreover, AI's deployment in safety surveillance, workflow optimization, and regulatory science research is expanding, highlighting its increasing impact on drug regulation. Nonetheless, key challenges persist, such as data quality and reliability, technical limitations, talent shortage and the absence of standards. The review concludes that interdisciplinary collaboration is crucial to harness AI's full potential in drug regulation and overcoming its current limitations. In the future, AI may become a pivotal catalyst in drug regulation, promising a new era of enhanced scrutiny, efficiency, and innovation that will benefit public health on a global scale.

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Peer review under the responsibility of Chinese Pharmaceutical Association and Institute of Materia Medica, Chinese Academy of Medical Sciences.

<https://doi.org/10.1016/j.apsb.2024.11.006>

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1. Introduction

In recent years, artificial intelligence (AI) has significantly impacted people's daily lives, as its application scope extends to various domains including image recognition, speech recognition, predictions, self-driving cars, and urban management¹. Particularly in healthcare, AI has been widely applied in clinical practice, where it can be used to diagnose diseases, develop treatment strategies, and assist clinicians with decision-making². Notably, the advancement of innovative research has yielded substantial data resources related to healthcare, and AI, through techniques like machine learning (ML), and deep learning (DL), has shown significant capabilities in analyzing this "big data"³, thus playing a pivotal role in advancing healthcare and biomedical research⁴. However, while AI's impact on healthcare is increasingly recognized, its application in drug regulation has yet to reach its full potential.

Drug regulation is a complex and critical component of healthcare systems, tasked with ensuring the safety, efficacy, and quality of medications⁵. Over the past decade, with the advancement and development of biomedical technology, a variety of new technologies and medical products are constantly being developed. However, drug research and development (R&D) remains a time-consuming and costly process, with efficiency declining around 80-fold since 1950, beset by various factors such as high failure rates and uncertainty^{6,7}. Another factor influencing drug R&D efficiency may be regulators, because they play an important role in fostering the development and approval of new drugs⁸. Pharmaceutical companies generate abundant volumes of data and content, which are integrated into electronic or paper documentation for regulatory submissions. Generally, the time for gaining regulatory approval spans several months to several years, as the drug authority must receive, review and respond to these submissions⁹. However, the current review process of drug applications may delay the availability of novel therapeutics to patients, as it still requires significant manual and repetitive labor¹⁰.

In addition, the emergence of new technologies—such as omics, precision medicine, microphysiological systems, and bioimaging—coupled with the rise in new therapeutic products and drug regulatory submissions, presents considerable challenges for drug regulatory agencies¹¹. To address these challenges and efficiently transform scientific innovations into medical products, regulatory agencies need to adapt flexibly and stay abreast of technological development¹². As a representative emerging technology, AI offers a promising solution to overcome these challenges and will play a crucial role in regulatory science¹¹.

The application of AI technology will not only help drug regulators keep pace with the latest industry trends, but also simplify the complexity of drug regulatory affairs, thereby forming a more scientific and efficient regulatory system¹³. Currently, regulatory agencies around the world, including those in the United States, the European Union, and China, are proactively exploring the use of AI technology to enhance work efficiency, accelerate drug review and approval processes, and expedite the market launch of drugs. Despite various regulatory agencies have

realized the great potential of AI in the field of drug regulation, its application still lags behind its established use in drug R&D and remains in the early stages of exploration. This paper reviews and analyzes AI-related policies and initiatives of major international regulatory agencies, and presents an in-depth view of the current state and future prospects of AI application in drug regulation, with the aim of providing valuable insights for the global development of drug regulatory science. Finally, the challenges and prospects of AI in drug regulation are fully discussed.

2. Overview of AI and its application in the pharmaceutical field

2.1. Definition and classification of AI

AI is a branch of computer science, statistics, and engineering^{14,15}. Artificial intelligence refers to the ability of computers to execute tasks associated with human intelligence by simulating the structure and functioning of the human brain, including thinking, discovering, and learning from previous experiences^{13,16}. Typical AI algorithms include ML and DL. ML, a subset of AI, refers to the study and use of computer algorithms that automatically improve predictions or decisions through experience and interactions with training data¹⁷. This encompasses methods such as decision trees, random forests, K-nearest neighbors, and deep neural networks¹⁸. As a subset of ML, DL mimics the cognitive behaviors associated with the approach that the human brain would take in learning and solving data-intensive problems, which primarily differs from ML in terms of the data volume required and model complexity¹⁷. DL is generally more suited for handling large datasets and employs more complex models, such as deep neural networks (DNNs), convolutional neural networks (CNNs), and recurrent neural networks (RNNs)¹⁶. The correlations between AI, ML, and DL and the landmark events related to AI are illustrated in Fig. 1.

2.2. A brief history of AI

Initially, the development of AI began in the 1950s, Alan Turing proposed the "Turing Test" as a criterion for judging whether a machine possesses intelligence¹⁹. Briefly, the history of AI can be broadly divided into four stages (Table 1^{20–24}). During the conceptual formation stage (1940s–1960s), AI was officially born in 1956²⁰. During the expert system (1960s–1980s) phase, the focus transformed from general intelligence to human experts²⁵. A typical example is the MYCIN system, which was successfully deployed in medical diagnosis and treatment using a rule-based approach²². During the ML stage (1980s–2000s), the backpropagation algorithm proposed by Paul Werbos in 1988 was critical for training DNNs, enabling effective training of multilayer neural networks²³. During the DL stage (2006–present), deep belief networks (DBNs) laid the foundation for the widespread application of DL. A typical example was the AlphaGo program, which defeated the Go World Champion Lee Sedol, representing a noteworthy advancement of DL in complex decision-making and gaming scenarios²⁶. Presently,

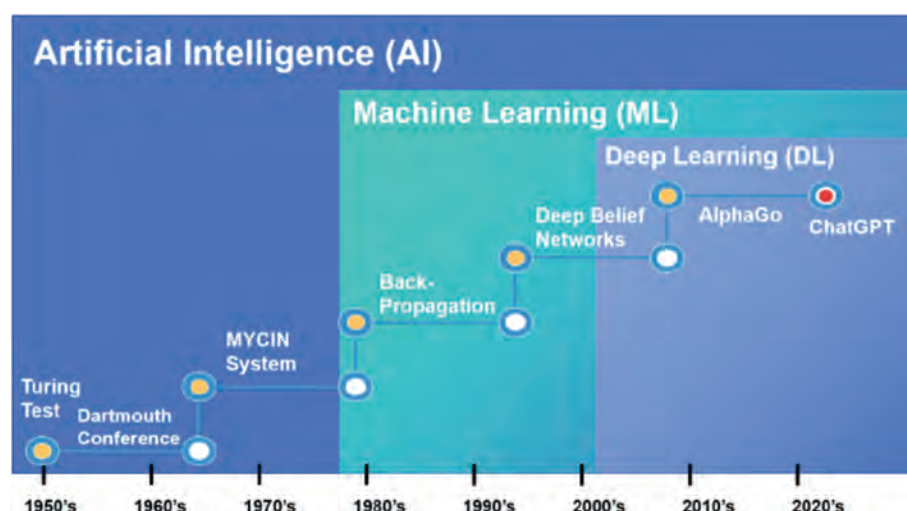


Figure 1 Relationship between AI, ML, DL, and major AI milestones.

the ChatGPT chatbot developed by OpenAI is a generative large-scale language model that has attracted global attention worldwide for its potential to revolutionize our approaches to work, life, and education.

2.3. Application of AI in the pharmaceutical field

After a long period of data accumulation, massive amounts of biomedical data have been collected²⁷. Due to the growing amount of biomedical data, massive increases in computing power, and the revival of AI algorithms, AI technology has been extensively applied in various domains of the healthcare industry²⁵. These include drug development, medical imaging, diagnostic assistance, and gene therapy. In particular, drug development accounts for the largest share of the global medical AI market²⁸. Examples of AI-assisted drug development are becoming increasingly common in drug registration applications, with over 100 applications utilizing AI/ML technologies submitted to the U.S. Food and Drug Administration (FDA)²⁹. Fig. 2 illustrates the widespread application of AI technologies, including ML and DL algorithms, in various aspects of new drug development. These fields encompass drug screening³⁰, drug discovery and molecular design¹⁶, determination of the optimal dosage³¹, quantitative structure–activity relationship (QSAR)

modeling³², drug repurposing^{33,34}, clinical trial design³⁵, pharmacovigilance³⁶, and regulatory science^{11,17,37}.

Drug R&D is a long-cycle, high-cost, high-risk endeavor that takes approximately 10–15 years and costs 1–2 billion dollars from early-stage discovery to clinical market launch, but 90% of clinical drugs suffer from R&D failure³⁸. Accordingly, many researchers have employed AI/ML to optimize the drug development process, improve the success rate of drug R&D, find new therapeutic uses for existing drugs, and transform traditional drug production models. For example, ML and DL have been employed to optimize the drug development process by replacing extensive experiments procedures and rapidly analyzing drug structures and efficacy using big data in pharmaceuticals^{39,40}. AI/ML technology is integrated with model-induced drug discovery (MIDD) to optimize the value of information and data, and enhance the prediction accuracy of the efficacy and safety of candidate drugs³¹. Some researchers deploy graph neural networks and heterogeneous data to repurpose existing drugs to find new indications³³. AI technology is rapidly changing the landscape of the pharmaceutical industry and provides hitherto unseen potential for promoting the intelligent transformation of traditional drug development and production models⁴¹. In short, the implementation of AI enables industries to shorten the drug R&D cycle, reduce development costs, and improve the success rate⁴².

Table 1 A brief history of AI.

Time	Stage	Description	Ref.
1940s–1960s	AI conceptual formation	In 1956, the concept of AI, was first introduced at the Dartmouth Conference, signifying the birth of AI as a field.	20,21
1960s–1980s	Expert system	Expert systems became the focus of AI research and were capable of simulating the decision-making processes of human experts to solve problems in specific fields.	22
1980s–2000s	Formation period of ML and neural networks	In 1988, the backpropagation algorithm proposed by Paul Werbos was critical to training DNNs, enabling effective training of multilayer neural networks.	23
2006–Present	The rapid development stage of DL	In 2006, Geoffrey Hinton et al. proposed the DBNs, which overcame long-standing bottlenecks in the development of neural networks and brought an unprecedented breakthrough to ML.	24

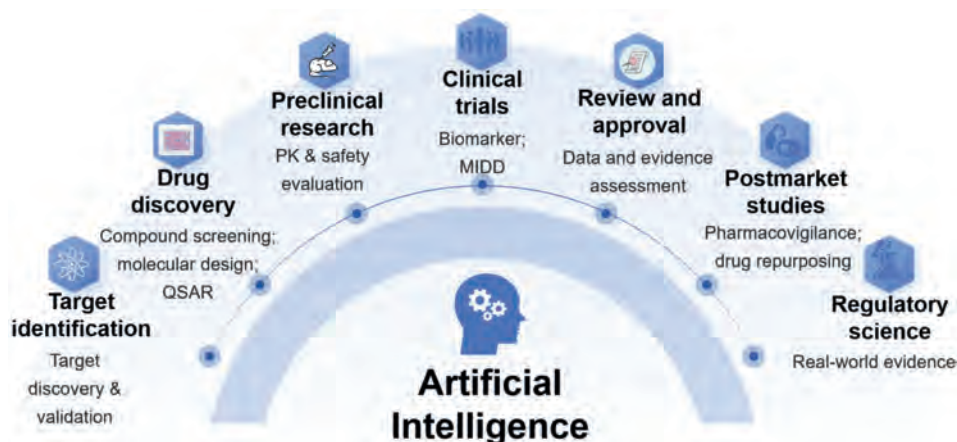


Figure 2 Role of AI technology in drug research, development, and regulation.

3. The application of AI in drug regulation

With the rapid development of cutting-edge medical technologies such as cell and gene therapies, combination products, and the increasing reliance on new data sources such as real-world data (RWD), the regulatory complexity and barriers faced by regulatory agencies across multiple global jurisdictions are intensifying. Concurrently, with the advent of Industry 4.0, emerging technologies such as the Internet of Things, AI, robotics, and advanced computing are poised to fundamentally change the landscape of manufacturing, creating autonomous and self-organizing production systems that operate independently of human involvement^{43,44}. These unprecedented trends undoubtedly pose significant impacts and challenges to regulatory agencies. To address the regulatory challenges posed by new technologies, new business models, and new risks, regulatory agencies worldwide have formulated and launched several action plans in recent years. These plans aim to support and promote the development, application, and innovation of AI and other new technologies in drug regulation.

3.1. Policies and initiatives

3.1.1. FDA

With the reauthorization of the Prescription Drug User Fee Act (PDUFA), the Biosimilar User Fee Act (BsUFA), and the Generic Drug User Fee Amendments (GDUFA), the FDA has received increased funding support. However, it also faces the burden and challenges of a high volume of regulatory drug applications and shorter review timelines, which necessitate continuous improvement in its review capacity and efficiency⁴³. Consequently, the FDA has issued a series of action plans and initiatives (Table 2) to advance the modernization of data, technology, and the internet, as well as the modernization of the FDA as an enterprise, aiming to enhance review efficiency and accuracy to meet clinical needs as quickly as possible.

In May 2008, the FDA launched the Sentinel Initiative with the goal of creating a national electronic system known as the Sentinel System⁴⁵. This system is designed to monitor FDA-regulated medical products and complement existing postmarket safety surveillance capabilities, such as the FDA Adverse Event Reporting System (FAERS). In October 2017, the Center for Biologics Evaluation and Research (CBER) developed the

Biologics Effectiveness and Safety System (BEST) as part of the Sentinel Initiative. BEST aims to efficiently utilize electronic health records (EHRs) by leveraging high-quality data, advanced analytics, and innovative methodologies such as NLP technology to automatically report AEs, thereby enhancing the monitoring capabilities for AEs of biologics regulated by CBER⁴⁶.

In September 2019, the FDA introduced the Technology Modernization Action Plan (TMAP), outlining its strategy for updating computer hardware, software, data, and analytics. The plan aims to establish a robust foundation for enhancing regulatory efficiency by optimizing resource allocation, such as by integrating AI and other technologies to facilitate data usage in regulatory decision-making⁴⁷. TMAP solidifies the groundwork for the modernization of the FDA's technological infrastructure, signifying a long-term strategic plan for the agency in data management and application. In November 2020, the FDA initiated a pilot program called Innovative Science and Technology Approaches for New Drugs (ISTAND)⁴⁸. This program aims to provide a pathway for novel approaches to be integrated into drug development and regulatory decision-making, specifically focusing on nonanimal-based methodologies and technologies. For instance, AI/ML, organ-on-chip, and other *in silico* methods can replace or reduce animal testing⁴⁹. Alternatively, AI-based algorithms can be utilized to assess patients, develop new end-points, or assist in study design to expedite the accessibility of effective new therapies to patients⁴⁸.

The development and application of innovative technologies have yielded an ever-growing volume of data, serving as the cornerstone for scientific evidence-based regulatory decision-making. Therefore, there is a mounting need for regulatory bodies to possess modern professional knowledge, methods, and technologies to handle and scrutinize this data effectively. However, the FDA's current data systems are primarily geared towards unstructured, non-digital, document-based information paradigms (electronic documents such as PDFs)⁵⁰. Thus, data modernization has become the next essential step for the FDA to comprehensively innovate its technology and data methods. In March 2021, the FDA proposed the Data Modernization Action Plan (DMAP), clarifying the framework and initiatives for data strategy, particularly focusing on updated methods, information technology (IT), and data usage processes to accelerate the accessibility of better therapeutic products⁵¹. The driver projects of the DMAP aim to promote the transformation of the entire agency by employing

predictive models and cutting-edge technologies such as AI⁵². In March 2022, on the occasion of the first anniversary of DMAP's implementation and nearly three years since TMAP's launch, the FDA released the Modernization in Action 2022. This report reviews the achievements of TMAP and DMAP in streamlining workflows, reducing data maintenance and cybersecurity costs, and improving service delivery efficiency⁵³.

To enhance the work efficiency of FDA staff and optimize the use of vast amounts of data, the FDA needs to enhance not only its technology and data but also its business processes. In May 2022, the FDA introduced the Enterprise Modernization Action Plan (EMAP) to improve operational efficiency and enhance data utilization by optimizing common and essential business processes⁵⁴. Cybersecurity involves all aspects of the FDA's responsibilities, with a focus on defense efforts to safeguard critical data that support regulatory decisions. Accordingly, in November 2022, the FDA released the Cybersecurity Modernization Action Plan (CMAP) to utilize AI and ML technologies to improve network detection and response capabilities, addressing global cyber threats, vulnerabilities, and risks to the FDA's IT infrastructure and sensitive data⁵⁵. In September 2023, the FDA published the FDA Information Technology Strategy for Fiscal Years 2024–2027. This strategy aims to promote the modernization of key systems and data sharing, emphasize data-driven decision-making using emerging technologies such as AI, proactively identify opportunities and risks related to AI, and improve the safety and efficacy of products⁵⁶.

3.1.2. EMA and other drug regulatory agencies in Europe

The European Medicines Agency (EMA) also emphasizes the application of AI in drug regulation to advance regulatory science, improve regulatory efficiency, and promote scientific decision-making⁵⁷.

In response to the challenges posed by innovative technologies in drug regulation, several working groups have been established to support the work of AI in aiding regulation. The drug regulatory agencies of EU member states and the EMA together constitute the European Medicines Regulatory Network (EMRN), which is responsible for coordinating pharmaceutical regulatory affairs across the EU. As a representative of the EMRN, the EMA is responsible for consolidating scientific advice and maintaining close cooperation with the Heads of Medicines Agencies (HMA)⁵⁸. Additionally, the International Coalition of Medicines Regulatory Authorities (ICMRA) has set up an Informal Network for Innovation, led by the EMA, to respond to the increasing challenges posed by innovative technologies on drug regulatory frameworks⁵⁹. The HMA and EMA have jointly established the Big Data Steering Group (BDSG) to promote the EMA's regulatory support for the development of innovative treatments by integrating big data into regulatory system evaluation and decision-making⁶⁰. Furthermore, the EMA has established the Analytics Centre of Excellence (ACE) to explore how to utilize new analytical technologies such as AI, ML, and robotics to construct practical solutions that meet the EMA's business needs, including optimizing business processes, automatically identifying personal data in documents, and knowledge management, thereby improving work efficiency³⁷.

The EMA and several other national regulatory agencies in the European Union (EU) have issued multiple action plans and strategic initiatives to promote the application and research of AI in regulation (Table 2). In March 2020, the EMA launched its Regulatory Science to 2025-Strategic reflection, outlining five

core strategic objectives for regulatory science. This strategy emphasized the transformative impact of big data and AI in regulatory decision-making, particularly in the goal of “*Driving collaborative evidence generation—improving the scientific quality of evaluations*”⁶¹. In December 2020, the HMA/EMA published the “EMA Network Strategy to 2025” to support initiatives related to the “Regulatory Science Strategy to 2025,” which identified six strategic focus areas including data analysis, digital tools and digital transformation. By promoting the establishment of AI regulatory systems, it aims to enhance dynamic regulation, policy learning, and improve the automation level of the regulatory network through AI and digital technologies, deepening the understanding of clinical trial data, patient health records, and drug monitoring data^{62,63}. In May 2022, the HMA/EMA released the “Clusters of Excellence Discussion Paper,” which created six Clusters of Excellence (CoE) modules—data access, legal issues, capacity building, infrastructure, method development, and AI—aiming to integrate data analysis into the daily work of the EMRN⁶⁴. In November 2023, the HMA/EMA BDSG issued the first “Multi-annual AI workplan 2023–2028,” aiming to establish an AI-based regulatory system to enhance insights into data and strengthen support for public health decision-making⁶⁵. In January 2024, the EMA and HMA jointly published the “Big Data Workplan 2023–2025,” which proposed to enhance the EMRN's analytical capabilities based on RWD and AI. The plan also recommends establishing a network of analytics centers linked to regulatory agencies, developing AI analysis and large language models, and strengthening the network's ability to validate AI algorithms⁶⁶.

In Europe, in addition to the EMA, other drug regulatory agencies are also actively promoting the regulatory application of AI. The Federal Institute for Drugs and Medical Devices (BfArM) in Germany is strengthening the construction of AI computing infrastructure to support applications in review and licensing, health data laboratories, and scientific research. These applications include using artificial neural networks for drug epidemiology analysis or employing AI-assisted text mining for signal monitoring. Similarly, the Paul Ehrlich Institute in Germany is directing its research efforts towards two pivotal projects: the RENUBIA project, which aims to elucidate the decision-making principles underlying ML models; and the KIMERBA project, which applies NLP algorithms to extract and integrate the information required for regulation⁶⁴. Furthermore, Swissmedic has launched the digital initiative “Swissmedic 4.0” to deeply explore the possibilities of digital transformation as a priority. For example, AI can be applied to process applications or prepare and compile assessment reports, with the aim of delegating standardized and repetitive processes to machines, thereby allowing experts to concentrate on knowledge-intensive work⁵⁹.

3.1.3. NMPA

China's authorities also realized the urgent need to fully leverage IT to enhance foresight, targeting, and timeliness of regulation, and to implement risk management throughout the entire lifecycle of drugs and modernize drug regulation. In recent years, to direct and prepare for AI approaches, multiple policy-driven initiatives and policy guidelines have been issued by China's drug regulatory authorities.

In December 2018, the National Medical Products Administration (NMPA) of China published a document titled “Progressing with the Times and Composing a New Chapter in Drug Regulation—A Review of 40 Years of Drug Regulation Work

Table 2 FDA, EMA and NMPA regulatory science initiatives related to AI.

Agency	Time	Action plan	Description
FDA	2019.9	Technology Modernization Action Plan (TMAP)	To establish a robust foundation for enhancing regulatory efficiency by optimizing resource allocation, such as integrating AI and other technologies to facilitate data usage in regulatory decision-making
	2020.11	Innovative Science and Technology Approaches for New Drugs (ISTAND)	To provide a pathway for novel approaches to be integrated into drug development and regulatory decision-making, specifically focusing on nonanimal-based methodologies and technologies
	2021.3	Data Modernization Action Plan (DMAP)	To promote the transformation of the entire agency
	2022.3	Modernization in Action 2022	To review the achievements of TMAP and DMAP in streamlining workflows, reducing data maintenance and cybersecurity costs, and improving service delivery efficiency
	2022.5	Enterprise Modernization Action Plan (EMAP)	To improve operational efficiency and enhance data utilization
	2022.11	Cybersecurity Modernization Action Plan (CMAP)	To improve network detection and response capabilities, addressing global cyber threats, vulnerabilities, and risks to the FDA's IT infrastructure and sensitive data
	2023.9	FDA Information Technology Strategy for Fiscal Years 2024–2027	To promote the modernization of key systems and data sharing
EMA	2020.3	EMA Regulatory Science to 2025—Strategic reflection	To emphasize the transformative impact of big data and AI in regulatory decision-making
	2020.12	EMA Network Strategy to 2025	To enhance dynamic regulation and policy learning and improve the automation level of the regulatory network through AI and digital technologies
	2022.5	Clusters of Excellence Discussion Paper	One of the six Clusters of Excellence (CoE) modules is AI, aiming at integrating data analysis into the daily work of the EMRN
	2023.11	Multi-annual AI workplan 2023–2028	To establish an AI-based regulatory system to enhance insights into data and strengthen support for public health decision-making
	2024.1	Big Data Workplan 2023–2025	To enhance the EMRN's analytical capabilities based on RWD and AI
NMPA	2019.4	Chinese Drug Regulatory Science Action Plan	To accelerate the modernization of the drug governance system and capabilities
	2019.5	Action Plan for Accelerating Smart Drug Regulation	To expedite the transformation and upgrade of the regulatory system by promoting the application of new technologies such as big data, AI, and blockchain in smart drug regulation
	2021.12	14th Five-Year Development Plan for the Pharmaceutical Industry	To explore the application of new-generation information technology such as AI, cloud computing, and big data
	2021.12	14th Five-Year National Drug Safety and High-Quality Development Plan	Using big data and AI technology to achieve data sharing, risk early warning, and identification to enhance the efficiency of drug safety regulation
	2022.4	14th Five-Year Plan for Drug Regulatory Cybersecurity and Informatization Construction	To strengthen risk management capacity and explore the application of big data and AI technologies to improve the national ADR monitoring system

Since the Reform and Opening Up". This document emphasized the pivotal role of regulatory science in enhancing regulatory standards, and the NMPA is committed to promoting the construction of a smart regulatory system supported by big data, cloud computing, and AI to ensure public drug safety and improve regulatory efficiency⁶⁷. In April 2019, the NMPA launched the "Chinese Drug Regulatory Science Action Plan," with one of the key tasks being the introduction of new systems, tools, standards, and methods for drug review and regulation. This initiative aims to address the prominent issues affecting and constraining drug innovation, quality, and efficiency and to accelerate the modernization of the drug governance system and capabilities⁶⁸. In May of the same year, the NMPA issued the "Action Plan for

Accelerating Smart Drug Regulation". The goal was to expedite the transformation and upgrade of the regulatory system by promoting the application of new technologies such as big data, AI, and blockchain in smart drug regulation. Furthermore, the NMPA emphasized cooperation with enterprises and third-party organizations to jointly build regulatory data analysis laboratories, construct an informatized system for drug regulation, and enhance the effectiveness of drug regulation⁶⁹.

In April 2021, the General Office of the State Council issued the "Implementation Opinions on Comprehensively Strengthening the Capacity Building of Drug Regulation" ([2021] No. 16), emphasizing the importance of informatization in drug regulation to establish a scientific, efficient, and authoritative drug regulatory

system⁷⁰. In December of the same year, the NMPA and eight other departments jointly released the “14th Five-Year Development Plan for the Pharmaceutical Industry,” highlighting the importance of “innovation leadership”. This plan encouraged the exploration of the application of new-generation information technologies such as AI, cloud computing, and big data in the field of pharmaceutical R&D to improve the efficiency of new drug development and promote the continuous development and innovation of China’s pharmaceutical industry⁷¹. Moreover, the NMPA and seven other departments jointly issued the “14th Five-Year National Drug Safety and High-Quality Development Plan,” which clarified the task of strengthening technical support capacity construction and proposed the use of big data and AI technology to achieve data sharing, early risk warning, and identification to enhance the efficiency of drug safety regulation⁷².

The issuance of the aforementioned strategic plans has raised higher requirements for drug review and approval efficiency, as well as for drug safety risk management capabilities. To this end, the NMPA released the “14th Five-Year Plan for Drug Regulatory Cybersecurity and Informatization Construction” in April 2022, with one of the key tasks being to strengthen risk management capacity and explore the application of big data and AI technologies to improve the national adverse drug reactions (ADRs) monitoring system. Another key task is to enhance the integration and innovation capacity of technology and business. To meet the innovative regulatory needs of full lifecycle, digitalization, mobility, and dynamic regulation, regulators should actively explore the application of big data, AI, blockchain, the Internet of Things, and privacy computing in scenarios such as drug review and approval, regulatory inspection, and full-chain traceability⁷³. In July 2020, the NMPA issued the “Opinions on Further Strengthening the Construction of the Drug Adverse Reaction Monitoring and Evaluation System and Capacity Building”. This opinion proposed the goal of advancing the construction of a high-performance national ADR monitoring sentinel system for postmarket drug safety monitoring and evaluation, by integrating professional social resources, innovating monitoring and evaluation models. For example, by relying on the “National Drug Regulatory Cloud,” the plan calls for the implementation of International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E2B(R3) data standards and the application of big data, AI, and other technologies in data sharing, early risk warning and identification⁷⁴.

3.1.4. ICH

In the field of drug regulation, the ICH has also emphasized the application of AI technology in various policy documents and guidelines. In May 2021, the ICH published the “Outcome of public consultation on ICH Reflection Paper on Patient-Focused Drug Development (PFDD),” which mentioned the potential use of AI, ML, and wearable devices to collect data, thereby improving patient compliance and safety in drug development⁷⁵. In October of the same year, the ICH released the document titled “Future Opportunities & Modernization of ICH Quality Guidelines: Implementation of the ICH Quality Vision from the ICH Quality Reflection Paper.” It highlighted that advancements in new therapeutic approaches, AI, and modeling technologies will lead to an increase in data volume and complexity. It proposed improving knowledge management through data clouds and structured data formats to accelerate and synchronize regulatory processes⁷⁶. In March and November 2022, the ICH issued the “Considerations with Respect to Future MIDD Related

Guidelines”⁷⁷ and the “Targeted Revisions of the ICH Stability Guideline Series (Guidelines ICH Q1A-F, ICH Q5C)”⁷⁸, both of which identified AI/ML as areas of future focus for ICH and suggested using AI modeling to improve the understanding of products. Additionally, the ICH continues to explore the application of big data, AI, and other technologies for ADR monitoring (ICH E2B(R3)) and improving the quality of CTD documents (ICH M4Q)⁷⁹. These documents reflect the ICH’s emphasis on the application of AI technology in drug development and regulation, as well as its ongoing efforts to enhance regulatory efficiency and product quality.

3.1.5. PMDA

Unlike regulatory agencies such as the FDA and EMA, the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan has not yet established a unified reform plan for AI in drug regulation. Instead, it encourages researchers to apply for research projects independently by providing research grants⁸⁰. The Ministry of Health, Labour and Welfare (MHLW) in Japan offers several scientific research funding programs, including topics closely related to AI and drug regulation, such as “Clinical Research and Other Information and Communication Technology Infrastructure Construction and Artificial Intelligence Practice Research Projects” under the “Administrative Policy Research” field and “Pharmaceutical and Medical Device Regulatory Science Policy Research” under the “Comprehensive Research on Health and Safety Security” field⁸¹. Although AI/ML is widely used in clinical applications at medical institutions, there is currently a lack of mature cases of AI being used to develop drug regulatory systems, according to the “MHLW Science Research Achievements Database”⁸².

3.2. AI applications in drug regulation

To improve process efficiency and gain deeper insights from data, different regulatory agencies around the world have explored and practiced the adoption of AI in multiple aspects of drug regulation. Below, the major applications and advances of AI in drug regulation are described, including safety surveillance, workflow optimization, regulatory science research, and international exchange (Fig. 3).

3.2.1. Safety surveillance

In the post-approval phase, postmarket safety reporting of adverse events (AEs) associated with drug utilization is part of postmarket safety monitoring or safety surveillance activities, which are integral to broader scope pharmacovigilance (PV)^{15,83}. The World Health Organization (WHO) defines pharmacovigilance as “science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine/vaccine related problem”⁸⁴. The responsibility of drug regulatory agencies includes collecting, receiving, identifying, evaluating, and processing AEs from all over the world^{15,85}. This may pose a great challenge for drug regulatory agencies to monitor the safety of the medical products regulated by them. For example, the US FDA receives more than 2 million postmarket reports each year^{36,86}. AI technology has great potential in assisting regulatory bodies in processing AE reports. Consequently, different drug regulatory agencies worldwide have made much effort to enhance the efficiency and scientific value of processing drug safety reports by applying AI.

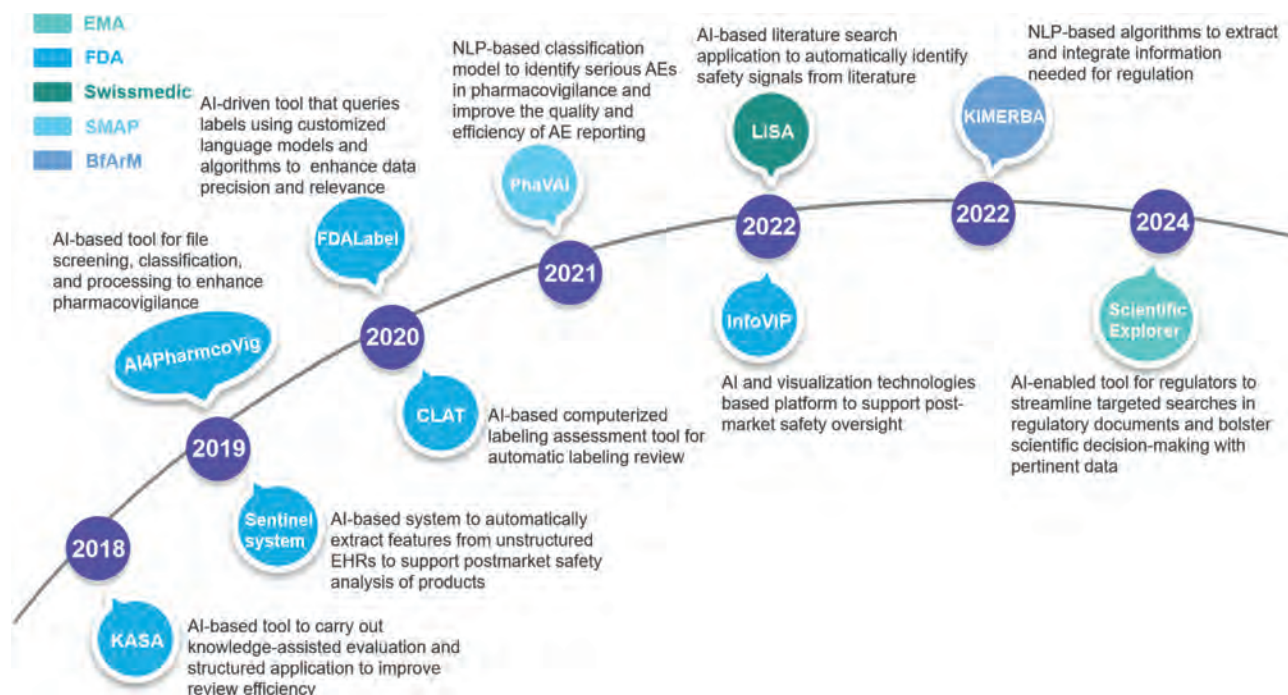


Figure 3 Exploration and applications of AI in drug regulation by different agencies.

As the number of Individual Case Safety Reports (ICSRs) continues to grow, the Center for Drug Evaluation and Research (CDER) of the FDA is harnessing the power of AI to strengthen the processing and evaluation of ICSR submitted to the FAERS³⁶. For example, the office of surveillance and epidemiology (OSE) of CDER has developed and evaluated ML models to automate the classification of AE reports in the FAERS by using supervised machine learning and text engineering methods⁸⁷. This study suggests that these classification models have the potential to augment the PV workflow by streamlining the review process and focusing expert evaluation on more informative cases. Another crucial tool for safety surveillance is the Sentinel System, which was fully operationalized in 2016 following a phased development and implementation process. It has been incorporated into the FDA's PV and surveillance toolbox, enabling proactive tracking of adverse events (AEs) associated with regulated products⁸⁸. In September 2019, the FDA announced in the Sentinel System Five-Year Strategy 2019–2023 that its investment would focus on innovations emerging from new data science disciplines, such as NLP and ML, to automatically extract features from unstructured EHRs to support postmarket safety analysis of products^{89,90}. In addition, Wang et al.⁹¹ from the National Center for Toxicological Research (NCTR), a division of the FDA, proposed a novel transformer-based causal inference model, InferBERT. This model integrates the A Lite Bidirectional Encoder Representations from Transformers (ALBERT) and Judea Pearl's Do-calculus to infer causality for PV using FAERS case report data. In 2019, CDER's OSE developed the Information Visualization Platform (InfoViP), a safety monitoring tool that combines AI/ML (NLP) and advanced visualization⁹². InfoViP can categorize ICSR based on the level of information quality, detect duplicate ICSR, and visualize the clinical event timeline to assist in analyzing reported AEs. InfoViP not only supports OSE safety reviewers in examining data or content to uncover deeper insights but also enables the generation of predictive analytics or recommendations, thereby enhancing postmarket safety surveillance^{86,87}.

The ICMRA has identified and prioritized three challenging topics through a horizon scanning approach: 3D printing, gene editing, and AI. In August 2021, the ICMRA published an assessment report on AI, focusing on the area of PV, where certain regulators and companies are trialing AI to process PV data from literature and signals⁵⁹. For example, Swissmedic has sponsored a program to develop an AI-based literature search engine called LiSA, which can automatically identify ADRs and assess the relevance of selected literature from various sources. The development of this tool will help reviewers quickly identify relevant safety signals for better monitoring and investigation of clinical product safety⁹³. The Swedish Medical Products Agency (SMPA), in cooperation with Lund University and Stockholm University, started the PhaVAI project in October 2021, expanding from quantitative pharmacology modeling to include all data science applications, such as ML. The project attempts to use NLP triage models to identify serious AEs from full-text event descriptions, to improve the quality and efficiency of the SMPA's processing of AE reports⁶⁴. These projects demonstrate that AI methods can effectively contribute to the identification and monitoring of AEs in clinical trials.

In the field of PV, another challenge is the step of coding medicinal products described in AE reports, which is a time-consuming step in case processing activities. Thus, Lucie Gatepaille's team from the WHO Collaborating Centre for International Drug Monitoring in Uppsala, Sweden, has developed the AI-based drug coding engine WHODrug Koda, which significantly enhances the efficiency of automated coding of drugs in AE reports⁹⁴.

3.2.2. Workflow optimization

The FDA's Office of Pharmaceutical Quality (OPQ) developed the Knowledge-aided Assessment and Structured Application (KASA) tool in 2018 to address the increasing volume of Abbreviated New Drug Applications (ANDAs)¹⁰. Unlike the text-based eCTD, KASA is based on structured assessment templates and risk-level-based algorithms, significantly improving review

efficiency, objectivity, and consistency⁴³. Initially, KASA was mainly used for ANDAs of solid oral dosage forms, by 2020, OPQ had further developed and tested new structured interfaces for drug substance information and ANDAs of liquid dosage forms⁹⁵. Currently, the application of KASA has been extended to registration applications for new drugs and biologics¹⁰.

Labeling data has been collected by the FDA for decades and serves as an important resource for regulatory science research and decision-making. However, the vast number of labeling documents makes it challenging to retrieve and utilize this data⁹⁶. To this end, the FDA developed the Computerized Labeling Assessment Tool (CLAT) in 2020, which employs AI technology to automatically review labels and identify elements such as prescription information, package boxes, and container labels^{97,98}. Additionally, since 2012, the FDA has developed the FDALabel database, a web-based application enabling a full-text search of drug labels⁹⁹. This web-based tool allows various search combinations, including text, product name, and drug application type, to effectively capture key information pertinent to drug safety and efficacy^{96,99,100}. Furthermore, in 2020, the FDA began developing an AI-based component to allow querying of labeling documents using customized and fine-tuned public language models and algorithms, aiming to enhance the specificity and relevance of retrieved labeling data for drug repurposing studies¹⁰⁰. In addition, the team from NCTR also developed RxBERT, an AI-based language model optimized for analyzing U.S. drug labeling documents, which enhances the processing and analysis of these documents to support drug safety reviews and regulatory decisions¹⁰¹.

Regarding the application scenarios of AI in the drug regulatory field, the HMA-EMA BDSG suggested that AI could be used for internal regulatory processes, such as employing NLP to process text—categorizing eCTD submissions into review templates for assessors, or performing a quantitative review of image data submitted to support clinical claims from drug manufacturers¹⁰². Furthermore, Joaquim Berenguer Jornet and Florence Butlen-Ducuing (both from the EMA) presented the AI and digitalization activities of the EMA at the joint HMA/EMA workshop on AI in medicine regulation in April 2021⁶³. These activities involve using AI for workflow optimization, with a focus on text analysis, document processing, and the analysis of text and image leveraging NLP to extract content, structure information, classify and cluster content from documents, automating document categorization and assigning them to reviewers. Moreover, OCR technology is utilized to interpret images and charts, facilitating comprehensive content analysis and all necessary information extraction¹⁰³. The EMRN will roll out an AI enabled tool “Scientific Explorer” for EU regulators in 2024, which will facilitate easy, focused and precise searches within regulatory procedure documents submitted to regulators, and support scientific decision-making by providing access to relevant scientific information⁶⁰. Additionally, in the “EMA’s Regulatory Science Strategy to 2025—Mid-point achievements to end 2022” released in March 2023, the ACE has implemented several pilot projects: a tool to automate registration of applications submitted to the EMA, a speech to text chatbot “ASK-EMA” for talent acquisition, and “PEDAR” for personal data identification¹⁰⁴.

3.2.3. Regulatory science research

Regulatory science is the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of regulated products¹⁷. Currently, the FDA has carried out multiple regulatory science projects by applying AI

technology. For example, the FDA’s Office of Minority Health & Health Equity (OMHHE) employs AI and RWD to study racial and ethnic disparities in intensive care for patients with heart failure. Additionally, projects funded by the FDA’s Perinatal Health Center for Excellence have used 3D printing and ML to study predictive toxicological models of drug placental permeability¹⁰⁵. Female subjects are often overlooked in clinical trials, and pregnant women are frequently excluded. To fill this gap, the FDA’s Office of Women’s Health (OWH) has sponsored multiple regulatory science research projects, encompassing AI-driven cancer risk prediction in patients with endometrial dysplasia following hormonal therapy and the creation of AI models simulating pregnant women to forecast drug and vaccine impacts. These studies are pivotal for increasing women’s participation in medical research and providing more precise and extensive scientific evidence to inform medical decision-making¹⁰⁶. The NCTR has launched the AI4TOX program, which aims to apply advanced AI methods to develop new tools supporting FDA regulatory science and strengthening the safety review of FDA-regulated products. This program consists of four initiatives: AnimalGAN for predicting animal toxicology data for untested chemicals through learning models, SafetAI for developing novel deep learning methods for toxicological endpoints, BERTox for developing the most advanced AI-powered NLP to facilitate analysis of FDA documents and public literature, and PathologAI for developing an effective and accurate framework for analysis of histopathological data¹⁰⁷. Additionally, the team from NCTR developed a deep learning model named DeepDILI for predicting drug-induced liver injury (DILI) within the regulatory science framework, aiming to enhance drug safety evaluations^{17,108}.

Although the PMDA has not yet implemented an action plan for the use of AI in regulation, the National Institute of Health Sciences (NIHS) in Japan has already established a chemical mutagenicity prediction model using QSAR and AI to improve some traditional technologies commonly used for risk assessment³².

3.2.4. International exchange

The FDA places great emphasis on the research and application of AI in drug regulation, with several officials presenting their insights on AI-supported regulation at numerous scientific forums and conferences. For instance, in September 2020, the former FDA Commissioner, Dr. Stephen Hahn mentioned in his speech to the Global Coalition for Regulatory Science Research (GCRSR) that AI/ML has the potential power to employ large amounts of information and gather postmarket data on how certain regulated products are being used or misused as in the case of opioids¹⁰⁹. One of the key regulatory science topics discussed at the FDA Science Forum in May 2021 was the efficient utilization of big data and AI tools¹¹⁰. At the 11th Global Summit on Regulatory Science (GSRS) in October 2021, Acting Commissioner Janet Woodcock highlighted that AI and RWD provide significant opportunities for the FDA’s regulatory work. AI/RWD has the potential to enhance the FDA’s understanding of drug safety and efficacy profiles, modernize regulation, improve efficiency, and promote collaboration and coordination among global agencies¹¹¹. In September 2023, the GSRS focused on the topic of emerging technologies and their application in the safety regulation of food and drugs. The current FDA Commissioner, Robert M. Califf, emphasized the significant support provided by AI for FDA staff in improving work efficiency and decision-making, and shared several cases of AI/ML applications in regulation¹⁰⁵. For instance, the NCTR supports CDER’s AI needs through the IND Smart

Template System and an AI model for drug safety review. NCTR's "AI4PharmcoVig" research employs AI models for document screening, classification, and processing to enhance pharmacovigilance¹⁰⁵. At the NCTR's 50th-anniversary celebration in September 2021, the NCTR director William Slikker, Jr., and chief scientist RADM Denise Hinton expressed their views that AI would have a significant impact on future regulation and NCTR was committed to AI-related research to support the FDA's strategic initiatives in AI¹¹².

At the joint HMA/EMA workshop on AI in medicine regulation in April 2021, stakeholders shared research progress and practical applications of AI in the field of drug regulation and proposed action recommendations for the construction of AI regulation. For example, Dr. Lucie Gatepaille from the Uppsala Monitoring Centre presented research progress on the development of innovative pharmacovigilance methods employing statistical and predictive models, ML, and NLP. This includes the utilization of clustering methods to identify clinically consistent report sets and the development of new data-driven approaches for drug and disease information⁶³. These research achievements have contributed to improving the efficiency and accuracy of pharmacovigilance.

4. Challenges of AI applications in drug regulation

Despite numerous examples have demonstrated the vast potential of AI technology in regulatory science, there are still many remaining challenges due to the uniqueness and complexity of drug regulation. These challenges include data quality and reliability, technical limitations, talent shortages, and a lack of standards.

4.1. Data quality and reliability

As science-based and information-driven regulatory agencies, data plays an extremely important role in drug regulation. Drug development is a massive undertaking, involving multiple stages, such as target validation, drug discovery, preclinical evaluation, clinical evaluation and formulation development, with each stage generating a large amount of data and documentation. Before a drug is approved for launch, its efficacy, safety, and quality control must undergo rigorous evaluation and monitoring, and all of the data and documentation will be compiled for regulatory submission. The data produced by different types of drugs and from different sources present challenges such as significant differences in data types, uneven quality, and data fragmentation with multiple formats and definitions. This may also lead to the robustness of AI model. For example, the Brazilian health regulatory agency faced the problem of non-uniform coding from different data sources when conducting drug utilization studies¹¹³. Globally, the vast majority of data submitted to regulatory agencies by pharmaceutical companies are presented in the form of text documents³⁷. Regulatory agencies have not only reviewed numerous registration applications, papers, and literature data, but also generated a substantial amount of documentation during the product-review process, which is typically unstructured text^{11,37}. The successful application of AI algorithms requires high-quality data as a foundation, necessitating a large dataset of high-quality, semantically structured data for training AI algorithms. Therefore, integrating data from different sources and of varying quality levels poses a significant regulatory challenge. Additionally, the data accumulated and compiled in regulatory filing dossiers might

be company sensitive, posing a challenge for data sharing even within regulatory bodies. Moreover, how to apply AI technology to process large volumes of complex data represents another challenge that needs further exploration and research. Therefore, regulatory agencies should prepare high-quality and accurate sufficient balanced data firstly for better application of AI¹¹⁴.

4.2. Technical limitations

AI technologies such as ML, DL, and NLP encompass a variety of algorithms and models, presenting a challenge in selecting the appropriate algorithm for developing AI-based regulation applications. Another important factor that needs to be considered in regulatory applications is adaptability, which means the adaptive behavior of a model as it is retrained on unseen data¹⁷. The more complex the algorithm is, the lower its interpretability, posing a significant challenge to regulatory networks in understanding the reasons behind AI decisions. Many ML algorithms produce models that are "black boxes," making the descriptions of the models are not easily interpretable by humans. Before successfully applying AI to assist in regulatory decision-making, the "black box" issue of ML algorithm models needs to be resolved to reduce bias and improve the interpretability of decisions, thereby validating the quality and credibility of the models⁶⁴. The transparency of the algorithms themselves and their intended purposes, as well as the risks of AI failure, will have broader implications for their application in drug development and ultimately for patient health. Moreover, the advantage of ML algorithms is their self-learning capability, which can also introduce bias and prejudice through the iterative updating process. Therefore, when applying AI to assist in regulation, it is essential to thoroughly verify the reliability, repeatability, interpretability, and traceability of the models to facilitate their successful development and application.

4.3. Talent shortage

The advancement of any discipline and technology is inseparable from the support of skilled professionals. Drug regulation is a multidisciplinary field, and an agency's ability to engage in AI-related communications largely depends on whether it has personnel who have received adequate training or guidance or possess professional knowledge. However, there is a shortage of high-end interdisciplinary talent who can bridge data, computer science, and pharmaceuticals, which also limits the application of AI technology in drug regulation¹¹⁵. For example, the progress and integration of biomedical informatics, analytics, AI, and ML, may change the extent and pace of PV, which indicates that PV professionals may need to be trained in entirely new skill sets⁸³. Given that AI in drug regulation remains in its infancy stage, there is an urgent need to establish a stable interdisciplinary team of experts, including professionals in IT, data science, regulation, and pharmaceuticals.

4.4. Lack of standards

Currently, there are no standards for AI-related data exchange or the application of AI in regulatory activities, which may hinder communication between parties interested in exchanging AI-related information and slow down the full utilization of AI's potential⁶⁴. In February 2021, the Danish Medicines Agency (DMA) proposed 16 key considerations for static AI/ML

algorithms and supervised learning in GxP application scenarios, focusing mainly on four aspects—datasets, bias and variance, confusion matrices and metrics, and result interpretation—to ensure that the application of AI/ML in regulation is more precise and effective¹¹⁶. For the validation and optimization of AI drug regulatory systems, international associations related to drug regulation are recommended to refer to the key considerations proposed by the DMA and the “Good Automated Manufacturing Practice (GAMP)” compiled by the International Society for Pharmaceutical Engineering (ISPE), to issue similar official validation guidelines or establish corresponding gold standards.

5. Conclusions and prospects

As science rapidly evolves, drug regulators must keep pace with the times and stay at the forefront of science, equipping themselves with sufficient technical knowledge and capabilities to effectively address new challenges. The essence of scientific progress demands that regulatory agencies continuously innovate and refine their regulatory processes to better adapt to new situations and higher standards. In this process, AI has played a critical role. The AI tools mentioned in this paper all have optimized regulatory workflows to different degrees, improved regulatory efficiency and accuracy, reduced the workload of drug regulators, accelerated patients’ access to therapeutic products, and thereby better protected public health.

Although the application of AI in drug regulation is fraught with challenges, its prospects remain broad as technology continues to advance and policies are refined. Compared with other industries, the application and research of AI in drug regulation are still in the early stage, with multiple aspects where AI can assist in regulatory decision-making. For instance, drug regulatory agencies can leverage AI technologies such as knowledge management, combined with the prior knowledge of reviewers, to provide relevant consultations to patients, healthcare professionals, and drug developers, thereby accelerating the acquisition of knowledge related to drug regulation. Additionally, AI can be fully utilized to conduct regulatory scientific research. This includes assessing drug safety in specific populations, establishing regulatory standards for future new technology treatment products, and analyzing RWD, to facilitate the rapid transformation and application of novel therapeutics.

To better promote the deployment and application of AI in drug regulation, concerted efforts and close collaboration from academia, industry, and regulatory authorities are essential. Strengthening international cooperation and exchange, and refining pertinent regulations and policies will promote the robust development of AI technology in this domain, thereby enhancing the effectiveness of drug regulation.

Acknowledgments

We would like to thank Huanhuan Cui, Rong Chen and Shuangmin Ji for their insightful suggestions.

Author contributions

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Writing — review & editing. Yimin Cui: Writing — review & editing, Supervision, Conceptualization.

Conflicts of interest

The authors declare no conflicts of interest.

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