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Artificial intelligence and real-world data for drug and food safety – A regulatory science perspective

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ABSTRACT

In 2013, the Global Coalition for Regulatory Science Research (GCRSR) was established with members from over ten countries (www.gcrsr.net). One of the main objectives of GCRSR is to facilitate communication among global regulators on the rise of new technologies with regulatory applications through the annual conference Global Summit on Regulatory Science (GSRS). The 11th annual GSRS conference (GSRS21) focused on "Regulatory Sciences for Food/Drug Safety with Real-World Data (RWD) and Artificial Intelligence (AI)." The conference discussed current advancements in both AI and RWD approaches with a specific emphasis on how they impact regulatory sciences and how regulatory agencies across the globe are pursuing the adaptation and oversight of these technologies. There were presentations from Brazil, Canada, India, Italy, Japan, Germany, Switzerland, Singapore, the United Kingdom, and the United States. These presentations highlighted how various agencies are moving forward with these technologies by either improving the agencies' operation and/or preparing regulatory mechanisms to approve the products containing these innovations. To increase the content and discussion,

Abbreviations: GCRSR, Global Coaliation for Regulatory Science Research; GSRS, Global Summit for Regulatory Science; AI, Artificial Inteligence; RWD, Real-World Data; ML, Machine Learning; NCTR, National Center for Toxicological Research.

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the GSRS21 hosted two debate sessions on the question of "Is Regulatory Science Ready for AI?" and a workshop to showcase the analytical data tools that global regulatory agencies have been using and/or plan to apply to regulatory science. Several key topics were highlighted and discussed during the conference, such as the capabilities of AI and RWD to assist regulatory science policies for drug and food safety, the readiness of AI and data science to provide solutions for regulatory science. Discussions highlighted the need for a constant effort to evaluate emerging technologies for fit-for-purpose regulatory applications. The annual GSRS conferences offer a unique platform to facilitate discussion and collaboration across regulatory agencies, modernizing regulatory approaches, and harmonizing efforts.

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1. Introduction

Recent decades have seen a significant advancement in the innovation of fundamental research, particularly with emerging technologies, including artificial intelligence (AI) and the application of real-world data (RWD) (Gunasekeran et al., 2021; Holzinger et al., 2019 Chen et al., 2021). Regulatory science research aims to develop, refine, and translate these innovations and advancements into their potential applications in regulatory decision-making (Hamburg 2011). Regulatory science is applied globally and therefore its continued evolution requires worldwide collaborations and harmonization. For a technology to be successfully translated into regulatory application in a global setting, it is critical to understand these technologies in the context of international regulatory requirements. Consequently, effective communication among global regulatory agencies is essential. In 2013, the Global Coalition for Regulatory Science Research (GCRSR) was established with members from over ten countries (www.gcrsr.net). One of the main objectives of GCRSR is to facilitate communication among global regulators and to advance the application of new technologies in the regulatory space through the annual conference, the Global Summit on Regulatory Science (GSRS) (Slikker Jr et al. 2012, 2018; Miller et al., 2013; Howard et al., 2014; Tong et al., 2015; Healy et al., 2016; Lambert et al., 2017; Thakkar et al., 2020; Allan et al. 2020; Anklam et al., 2022). While the GSRS annual conference is organized by the GCRSR members, the attendees and presenters have involved both government, industry, and academia. The GSRS participants have an opportunity to discuss innovations and regulatory considerations by interacting with presenters from various regulatory agencies, industries, and academia across the globe.

The GSRS conferences have been held annually in various countries and have focused on a broad range of topics in the area of emerging technologies (Slikker Jr et al. 2012, 2018; Anklam et al., 2022), including bioinformatics (Tong et al., 2015; Thakkar et al., 2020; Miller et al., 2013; Healy et al., 2016) and nanotechnologies (Allan et al. 2020; Lambert et al., 2017; Howard et al., 2014). For example, GSRS20 was focused on emerging technologies, including the future application of AI (Anklam et al., 2022). The latest conference, GSRS21, significantly focused on both AI and RWD, with a broader perspective and direction on evaluating recent advances and their ability to modernize regulatory function, improve efficiency, and facilitate global agency collaboration and coordination (https://gcrsr.net/2021-gsrs/) (Fig. 1). This 3-day virtual conference was organized jointly by FDA/NCTR and GCRSR and held Oct 4–6, 2021, with day 1 devoted to digital health and safety and day 2 to AI and Machine Learning (ML). To facilitate discussion, the GSRS21 also hosted two debate sessions based on the question "Is Regulatory Science Ready for AI?" as well as a workshop to showcase the data analytics tools that global regulatory agencies have been using and/or plan to apply to their regulatory space. The conference drew a large audience (>800 participants) with speakers from 10 different countries.

Continued progress in AI and RWD provide enormous opportunities for regulatory application with two significant aspects, improving the agencies' operation and preparing regulatory mechanisms to review and approve products utilizing these innovations. This is especially important to drug development which usually spans many years and comes with a huge cost, where AI and RWD have demonstrated the ability to improve drug safety and review. In terms of food, RWD has shown potential to provide opportunities for development in the real-world setting and improve food safety. With the understanding that AI can efficiently analyze a large amount of data and provide predictive analytics to foresee future outcomes, the GSRS21 conference provides a platform to discuss these innovations with a specific emphasis on regulatory need. Specifically, four topics were extensively discussed which are summarized in the subsequent sections; these are (1) Can AI and RWD be applied to drug and food safety assessments? (2) Is regulatory science ready for AI? (3) Are data science tools readily applicable to regulatory applications? and (4) Where should regulatory science research go from here?

2. Can AI and RWD assist regulatory science in drug and food safety?

The review processes for food safety, pattern recognition, and foodborne outbreaks primarily relies on a manual analysis of images, spectrometric data, genomic data, chemical compositions, and identification of contaminants. These manual processes are time-consuming, labor-intensive, and expertise driven. AI and machine learning (ML) could significantly shorten review time and reduce variations typically introduced by humans. Several agencies, including the US-FDA and the Canadian Food Inspection Agency, have ongoing programs for developing genomics techniques for food safety and traceability (Franz et al. 2016; Kovac et al., 2017; Carrillo et al., 2019), where both AI and RWD methodologies have been evaluated and developed. This has been a longstanding effort by several agencies, some of which were extensively discussed in previous GSRS conferences (Tong et al., 2015). For example, the GCRSR bioinformatics working group has established a special technical team to evaluate the potential impact of microbial genomics and whole genome sequencing (WGS) on food safety and outbreak detection in order to develop international standards for the analysis and reporting of next-generation sequencing data in regulatory applications (Lambert et al., 2017). Because WGS and other digital technologies can evaluate massive amounts of data in a short amount of time, it is crucial to establish a regulatory framework to define the boundary of application and context-of-use in order to realize the full potential of these approaches.

During the GSRS21, the U.S. FDA's New Era of Smarter Food Safety initiative was discussed. In the recent release *Blueprint for New Era of Smarter Food Safety*, there was a discussion outlining the steps the US-FDA planned to take over the next decade to create a more digital, traceable, and safer human and animal food system (https://www.fda.

gov/food/new-era-smarter-food-safety). There is a substantial challenge in developing digital data collection and rapid analysis systems for food safety. For example, blockchain technology may be pivotal in food safety outbreak responses. Within this initiative, the US-FDA issued a final foundational rule on food traceability as the first step to harmonizing key data elements and critical tracking events needed for enhanced traceability of contaminated foods. AI/ML tools could support this rule and provide more efficient tracing systems in the near future as a part of the goals of US-FDA's New Era of Smarter Food Safety.

In addition to the importance of RWD and AI approach in food safety, both have also been demonstrated that augmenting that knowledge to existing information aids in improving our understanding of efficacy determinations as well as drug safety and toxicity assessments. These technologies enable scientists to make sense of the massive amounts of data for this regulatory application. For example, the Swiss Federal Statistical Office comprehensively collects administrative hospital data of all inpatient stays at any hospital in Switzerland. Swissmedic, the Swiss authority responsible for the authorization and supervision of therapeutic products, discussed the utility of using serious adverse drug reactions (ADRs) related to hospital admissions as RWD that could be useful in developing automated pharmacovigilance signal detection. However, to effectively incorporate data science into regulatory applications agencies could consider adoption of open data science principles such as FAIR principles (Findable, Accessible, Interoperable, and Reusable data) while maintaining all the data security related considerations. Regulatory agencies may also consider having an option for the regulatory data sharing. For example, The Brazilian Health Regulatory Agency – ANVISA – is making 29 databases available on health surveillance products and services (Carvalho-Soares et al., 2021). Regulatory bodies of multiple countries making regulatory data freely available, would not only promote transparency, but also provide valuable insights into regulatory questions. For example, the FDA established the Data Dashboard to facilitate new and more accurate regulatory science research and thus improving science-based regulatory decision-making.

Crowdsourcing is another vital mechanism to achieve consensus on data science methods to support their regulatory application (Mishima et al., 2018; Barber et al., 2015). For example, the National Institute of Health Science (NIHS) of Japan initiated a crowdsourcing program to assess the utility of QSAR models for Ames mutagenicity prediction (Honma et al., 2019; Liu et al., 2021). In this program, a large number of chemicals with known mutagenicity was first released to all the participants to construct predictive models. Once these models were completed and "frozen", the program released a test set of chemicals whose mutagenicity data were blinded (i.e., the participating scientists didn't know the mutagenicity potential of the agents in the test set). Lastly, each QSAR model from all the participants were evaluated based on their performance on the test set. This program highlighted the key features that need to be considered with regulatory application of this type of model.

3. Is Regulatory Science Ready for AI?

We're all aware of the promise of AI, but do we have the right scientific knowledge and assessment practices within the regulatory community to cope with the challenges that is inherent with AI? In contrast with the previous GSRS conferences, the GSRS21 hosted two debate sessions using a virtual format on the question of "Is Regulatory Science Ready for AI?" The debate session started with one debater who gave a short presentation to describe a position on the matter, and then the second debater delivered a rebuttal.

The first debate session limited the scope of the debate to the preclinical domain specifically for drug discovery and development, where AI plays an increasing role. Specific examples were given of target identification using AI-powered language models (Liu et al., 2021; Zhao et al., 2020) and other AI methodologies (Henstock 2021). Regulatory agencies have also developed the framework and guidelines to facilitate the application of AI in drug safety assessment and development. For example, the US-FDA established a qualification program called Innovative Science and Technology Approaches for New Drugs (ISTAND) (Food and and Drug Administration, 2021). The program is intended to provide a pathway for novel approaches to be integrated into drug

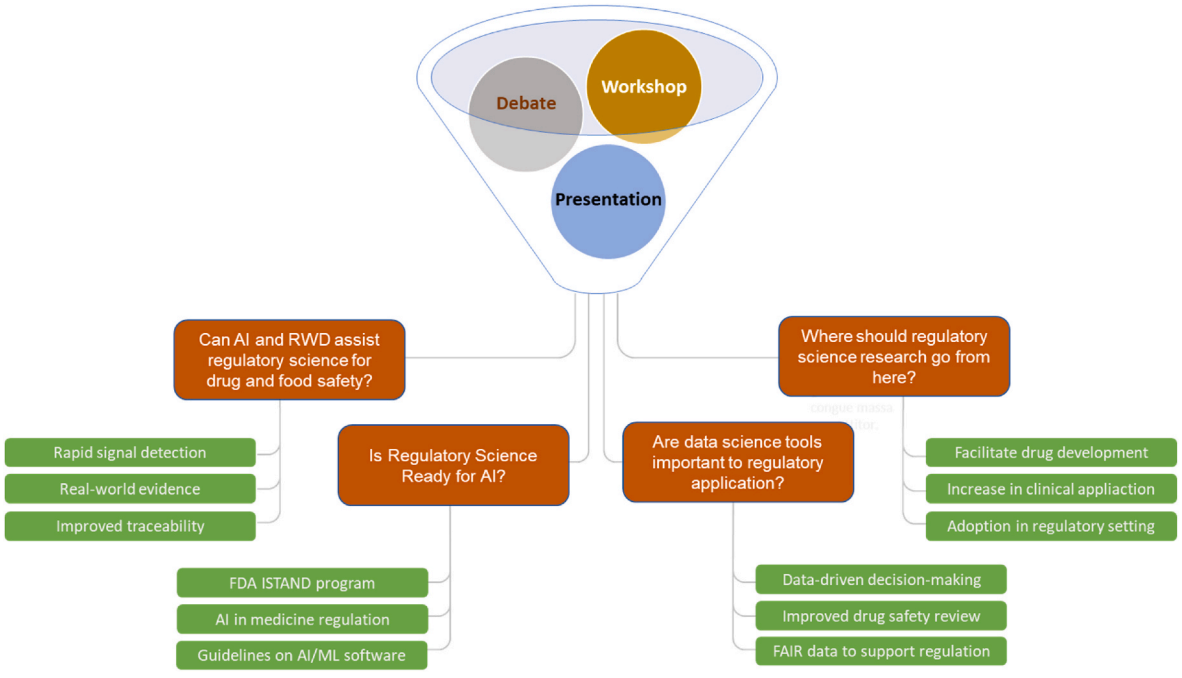

Fig. 1. GSRS21 adopted three different formats to discuss the four different topics. Innovative research ideas and developments in AI and RWD were presented through a series of presentations. In addition, a workshop presented and/or demonstrated the tools that are being currently used in various regulatory agencies around the world and a debate session on the role of regulatory science to improve the readiness of AI for the regulatory environment. The overall discussion shed light upon providing the status of AI applications in regulatory sciences along with the discussion on how these technologies evolved and its future direction.

development and regulatory decision-making. The program is focused explicitly on nonanimal-based methodologies and technologies including AI/ML that "use human biology to predict human outcomes in order to help reduce and replace animal testing as part of drug development."('Physicians Committee Policy Work Pushes FDA to Launch Pilot Program to Evaluate and Accept Nonanimal Approaches in Drug Development' 2020; 'FDA Launches Program to Approve Human Biology-Based Methods for Use in Drug Development' 2020). This process starts with a Letter of Intent (LOI), followed by a Qualification Plan (QP), and finalized with a Full Qualification Package (FQP) (Food and Drug Administration, 2020). Once a tool is qualified, it could be available for use in any drug development program and even be included in the drug approval process (i.e., IND, NDA, BLA applications, etc.) without the need for FDA to reconsider and reconfirm its suitability (Food and Drug Administration, 2021; Food and Drug Administration, 2017; Food and Drug Administration, 2021).

The second debate was centered on clinical applications of AI. In the past five years, many studies have demonstrated the promising performance of AI in diagnosis and prognosis in specific cases, such as task-specific applications when dealing with clinical images such as radiological images (Bi et al., 2019). While most agree that AI plays an increasing role in our lives, important questions have been debated on including (1) which AI technology available today that are ready for clinical application, to what extent, and in which contexts? (2) How can we ensure that safe and effective AI technologies are available to patients? and (3) what is important for patient so that they can understand and trust these technologies? There is no question that these scientific achievements are very promising, but are the patients comfortable with AL playing a significant role in their medical care? How can these technologies augment the role of the physician and other health care providers? The physician is certified to provide medical care, but what are the best methods to evaluate these products, and how to empower providers, patients and caregivers to use AI-enabled technologies (Jussupow et al., 2021; Durán, 2021)? It is important to consider to what extant patients may or may not be fully ready to use AI-enable technologies for different applications; and it is also important to consider the applications of AI in regulatory science.

Regulatory agencies like US-FDA are taking a very active role in facilitating AI's clinical applications. For example, US FDA has posted a list of more than 500 regulatory authorizations of AI/ML-enabled medical devices across many different medical disciplines. These include an AI software for detecting small but potentially cancerous lesions in the lungs (Acs et al. 2020; Hosny et al., 2018). The US-FDA also has cleared the marketing of the GI Genius, the first device that uses ML to assist clinicians in detecting lesions (such as polyps or suspected tumors) in the colon, in real-time during a colonoscopy (Strümke et al., 2021; Spadaccini et al., 2022). More recently, US-FDA cleared the marketing of a device called Paige Prostate, the first software that uses AI to aid in prostate cancer diagnosis based on the prostate biopsy image (Perincheri et al., 2021). As noted further below, US, FDA has sought extensive stakeholder input for its innovative approach to the regulation of AI/ML enabled medical devices, including for its journey 2021 Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD) Action Plan (Vokinger et al. 2021).

In contrast to AI/ML models, mechanistic-based models (i.e., agent-based models) do not rely on the software to "learn" a behavior from large data sets. Instead, they rely on established knowledge (biological, medical, immunological). These other models can predict the outcome of an "*in silico* experiment" or an "*in silico* trial" to assist clinical decision-making or drug discovery (Pappalardo et al., 2019). In this context, Universal Immune System Simulator (UISS) (Russo et al., 2022) is a simulation framework to model the immune system. The UISS model is used in several funded projects to model knowledge on immunological aspects of different pathologies and support *in silico* trials, with particular attention to those regulatory aspects that may not be addressed. In an EU-funded project, UISS will be submitted to (European Medicines Agency) EMA for qualification advice when used in tuberculosis context. One of the aims of the *In Silico* World project is to provide a precise and suitable regulatory pathway to assist developers that would like to pursue regulatory applicability and to ultimately develop a recognized harmonized standard in accordance with EMA requirements to support regulatory activities for *in silico* trials.

While we can identify successful examples of AI's application in medicine, the discussion raised additional questions. For example, how can regulatory science development ensure the evaluation and surveillance methodologies are well suited to AI technologies and can support regulatory decision-making? Is regulatory science ready to endorse the use of AI across all applications or only a few areas? Regulatory science could play a critical role in developing a regulatory structure and framework for evaluation of AI application, including promoting trustworthiness and reliability in these technologies.

4. Are data science tools important to regulatory applications?

A unique component of this conference was the workshop on "Data analytical tools for drug and food review by global regulatory agencies." The workshop was designed to showcase the global regulatory agencies' data analytics tools, possibly fostering future collaborations. The workshop hosted a live presentation and demonstrations of data analytics tools by US-FDA, EMA, and Swissmedic. These tools have been developed (or are being developed) to facilitate regulatory application in their respective agencies by addressing specific needs, such as systematic review, data fitness, data searching, extraction, harmonization, and validation of extracted data.

The vast majority of data used in regulatory decision-making are presented in text document, where AI could be of significance to facilitate the review process. Globally, regulatory agencies have not only reviewed vast quantities of submitted application, papers, and/or literature data, but have also generated a plethora of documents during the product-review process. It is typical that these types of records are unstructured text and often do not follow the use of standard vocabulary. AI has advanced the field, providing some fashion of automation to significantly reduce the current manual reading process in assessing the safety and efficacy of drug and food products (Wang et al., 2021; Liu et al., 2021). For example, Adverse drug reactions (ADRs) are of great concern. It is one of the top 10 leading causes of hospitalization and death worldwide (Patel et al., 2007). Therefore, many government agencies have developed and implemented frameworks to detect ADRs early. To help reviewers identify reported ADR-related published literature, Swissmedic is developing the AI-based search engine (LiSA) to automatically determine the relevant safety signals in published biomedical literature (Martenot et al., 2022). The intent is to identify relevant ADRs from various literature sources about a specific topic and also determine the relevance of this shortlisted literature and learn from the feedback provided about the quality and relevance of the search (Martenot et al., 2022). The relevance of the shortlisted search is established by causality assessment and determining the seriousness of ADRs. The development of this tool will help the reviewer quickly identify ADRs from the relevant biomedical literature (Martenot et al., 2022).

As EU efforts are underway to develop harmonized electronic product information, the US-FDA also developed the FDALabel system that provides a full-text search of the drug product labeling via a web-based application (Fang et al., 2020). FDALabel used FDA's SPL (Structured Product Labeling) for human and animal prescription and nonprescription drugs and biological product information. Currently, it contains >140,000 labeling data and is updated regularly. FDALabel is a powerful web-based database tool that allows flexible and customizable searches of human prescription drug, biological, and over-the-counter (OTC) labeling documents (Fang et al., 2016). This web-based tool can perform a combination of text search, product names, drug application types, pharmacologic classes search etc., which are repeatable and

reproducible. FDALabel is integrated with Medical Dictionary for Regulatory Activities (MedDRA) standards, allowing automation and advanced searches across various drug labeling sections (Fang et al., 2016) for ADR studies. FDALabel recently demonstrated its successful use in identifying pharmacogenomics information by identifying the relationship between drug response and genetic biomarkers from individuals/populations to facilitate precision medicine studies. FDALabel was developed by providing scientifically validated information that assists health care professionals in prescribing and dispensing medicine and benefits patients and consumers as they learn about safe product usage. Like FDALabel, efforts from EMA demonstrated the development of similar approaches (Getova and Getov 2022).

EMA presented the electronic product information (ePI) system for EU medicines. In the EU, a medicine's product information includes the summary of product characteristics, labeling and the package leaflet. It is a crucial source of regulated and scientifically validated information that assists health care professionals. ePI is presented in a semi-structured format developed using the EU Common Standard. ePI is centrally authorized (through EMA) and nationally certified (through Member State authorities), enabling the electronic handling of product information and allowing dissemination via the web and various e-platforms, as well as print. A proof-of-concept prototype was discussed during the workshop. This published prototype was created using the draft standard to generate example Fast Healthcare Interoperability Resources (FHIR)-based documents associated with products in the Substance, Product, Organizational, and Referential (SPOR) program (EMA's data management services for ISO IDMP compliant master data). ePIs exist in Word documents in 25 different languages, are open access with flexible implementation, and have interoperability with other EU eHealth initiatives.

During the workshop, US-FDA's Center for Food Safety and Applied Nutrition (CFSAN) extensively discussed the development of tools and knowledge bases for food safety, including FoodTrak that provides CFSAN with US food label and product sales data, FARM (Food Application and Regulation Management) provides the submission and literature data, STARI (Scientific Terminology and Regulatory Information) provides regulation-related information, and WILEE (Warp Intelligent Learning Engine) includes horizon scanning, data analytics, and data lake functions. Combined with the institutional knowledge captured by CERES (Chemical Evaluation and Risk Estimation System), interoperability of these tools through common data (substance names, substance synonyms and substance IDs) provides the capability to unleash the power of big data in regulatory decision-making. Specifically.

- WILEE is an advanced data-driven, risked based decision-making tool being developed by the Office of Food Additive Safety (OFAS) in CFSAN. It leverages AI technologies to integrate, process, and analyze a large variety of data sources to provide horizon-scanning capabilities. Once fully implemented, these capabilities will enable OFAS to maintain a proactive posture and have the capacity to "forecast" industry trends. The intention is to stay ahead of the development cycle, prepare for a potentially large influx of submissions, and prioritize actions based on risk or stakeholder perceived risk regarding substances under the Office's regulatory purview. This project utilizes the power of big data to identify food safety trends. WILEE has multiple modules that enable post-market surveillance, signal detection, and knowledge discovery. The development is underway in various phases. The first phase in development of WILEE is dedicated to creating a centralized data resource for OFAS/CFSAN with an architecture that enables advanced analytics and on-demand data analysis.
- FoodTrak provides a more comprehensive, efficient, and accurate solution for monitoring the US food supply by integrating post-market label and nutrition data from packaged and restaurant food as well as dietary supplement data. The platform will help support CFSAN's mission by developing dashboards and user interface functionality that overlay cleaned, standardized, and structured data. Goals for the platform include centralizing access to data, optimizing linking of data sources, driving functionality of data integration between CFSAN and FDA data systems, reducing analysis time by enabling turn-key analyses and more efficient use of data, and improving accuracy of analysis output because of improved data quality and data standardization. Once completed, the tool will help identify novel hidden trends and data connections and execute multiple important analyses, such as determining if foods have been reformulated and understanding the changing dynamic of the food supply.
- FARM is an electronic document repository and workflow management system which supports the premarket and post-market safety review of food additives, color additives, food contact substances, and generally recognized as safe (GRAS) substances and business processes through Appian workflows developed for tracking the status of these pre-and post-market review processes. This system can perform advanced searches and display the results in a user-friendly dashboard. It can also generate structured reports based on the data tracked in the business workflows.
- STARI is a multi-hierarchical ontology of chemical, biological, technical, and regulatory data of interest to CFSAN programs. The user-friendly search and display interface not only provides data housed in STARI but provides linkages back to other OFAS/CFSAN system including FARM and CERES. Additional linkages to other CFSAN systems are envisioned in the future including linkages to WILEE and FoodTrak allowing quick access to a more global view of regulatory, chemical, and toxicological data of substances under the regulatory purview of OFAS/CFSAN.
- CERES, OFAS's institutional knowledge-based system, is a chemical structure-based institutional knowledgebase with a simple user interface that allows the user to search for and display chemical and toxicological data that has been captured from OFAS's scientific evaluations of food additives, color additives, food contact substances, and GRAS substances. The system also links these substances to their administrative records in FARM, so users have quick access to scientific reviews as well as original data archived in food additive and color additive petitions, food contact notifications, and GRAS notifications. Because CERES is chemical structure-based, it allows the user to conduct structure similarity searches to identify relevant information on related substances. Of note, CERES is currently being expanded to include the TRAM (Toxicity Reports and Analysis Management) system, which provides a simple user front-end that allows access to a number of tools including FARM, CERES, STARI, a compound registration and curation tool, a toxicity data harvesting tool to collect legacy toxicity data from older submissions housed in FARM, and the MyMemo tool.
- The MyMemo tool is a web-based tool that allows the user to select standardized letter or memorandum templates and build their letter or memorandum within the web-based tool. Because of the standardized format of the MyMemo templates and linkages between TRAM and other OFAS systems, OFAS is able to programmatically extract important institutional knowledge from these documents and populate other systems such as FARM, Appian, and CERES to ensure these systems are easily updated.

5. Where should regulatory science research go from here?

As stated in a recent Nature article titled *Rise of Robot Radiologists*, "AI won't replace radiologists, but radiologists who use AI will replace radiologists who don't" (Reardon 2019). This statement highlights the role of AI-enabled technologies in augmenting the work of human clinicians and it reflects where regulatory science can play a role in advancing AI and RWD to support regulatory decision-making. One of the most significant benefits of AI/ML resides in its ability to learn from real-world use to improve its performance (Food and Drug

Administration, 2019). A US-FDA/Center for Devices and Radiological Health (CDRH) presentation described how medical device manufacturers are using AI to innovate their products to assist health care providers and improve patient care (Helm et al., 2020). In light of the unique considerations for these technologies, and to meet the needs of a broad set of stakeholders, US FDA has taken a collaborative and innovative approach to the development of a regulatory framework for AI-enabled medical devices to ensure these devices are safe and effective. This has included the issuance of a discussion paper and request for feedback from the public in April 2019, convening numerous public workshops and meetings including a patient engagement advisory committee (PEAC) meeting focused on patient trust in AI/ML technologies [https://www.fda.gov/media/143266/download], publishing an internationally harmonized set of Guiding Principles for Good Machine Learning Practice (GMLP) [https://www.fda.gov/medical-devices/software-medical-device-samd/good-machine-learning-practice-medical-device-development-guiding-principles], and in January 2021 issuing its AI medical device software action plans (Food and Drug Administration, 2021). The goals of the Action Plan include fostering a patient-centered approach, strengthen US-FDA's role in harmonizing Good Machine Learning Practices (GMLP), supporting regulatory science efforts including those focused on bias and health equity, updating the proposed AI/ML framework, and advancing the use of RWD to understand product performance.

For any application of an emerging technology, it is important for a risk assessment to be carefully performed. An European Food Safety Authority (EFSA) presentation demonstrated that AI could achieve this operating in conjunction with human interventions and currently improving regulatory sciences (Anklam et al., 2022). A human-centric approach — where the core accountability of the risk assessment planning is human while the execution is more computer driven — is more realistic, allowing human and AI to work in tandem (Akerlind et al., 2022). As executed by EFSA and as a more general model for regulatory science, this risk assessment involves a structured process where selected scientists are asked to provide scientific recommendations to inform managerial decisions. Automation of the process through AI is mainly designed to move the workload from the human experts to machines (IZSTO et al., 2017) (Cappè et al., 2019). However, AI-powered models are still far from demonstrating human-like causal reasoning, imagination, top-down reasoning, or general intelligence that could be applied broadly and effectively. Therefore, human intervention is important to address with general intelligence, such as the risk assessment process, where the human-centric approach is designed to augment AI models. These models could be applied to narrow, well-defined areas of risk assessment where AI guardrails could be deployed by incorporating rule-based algorithms that serve as a substitute for human judgment.

Clearly, evaluation of the potential for AI readiness requires research initiatives from multiple stakeholders, as the research and regulatory bodies go hand in hand. The Burroughs Wellcome Fund (BWF) offers two programs that promote innovation in this area. One is the Innovations in Regulatory Science Award (IRSA). The IRSA provides investigators with substantial funding over five years to develop innovative and implementable solutions to regulatory questions. Research proposals must indicate the direct implications for regulatory policy. In addition, BWF is launching a one-time initiative called Technology Innovation for Equitable Clinical Outcomes (TIECO). TIECO addresses the prevalence of bias in healthcare tools, both physical (medical devices) and computational (diagnostic algorithms), leading to severe health outcomes for individuals for whom the system is not designed. Some examples include pulse oximeters for individual with darker-skin pigmentation, hip implants for women (physical bias), kidney function estimation and lung spirometers, the use of race as in input (computational bias). The example mentioned above are supported by BWF and through that support fuels the innovation pipeline to create an environment that facilitates testing of AI applications. It should be emphasized that data bias could lead to AI bias, potentially resulting in tremendous social impact and regulatory consequences.

EMA is also putting considerable emphasis on the advancement of regulatory science through the use of AI and ML (Hines et al., 2019). Several cross-agency coordination groups on AI were formed to promote oversight and harmonization, mapping expertise across the agencies, and defining more explicit roles and responsibilities. Discussions are also ongoing within EMA as part of AI technical group initiatives for knowledge sharing, researching and developing recommendations and best practices to support innovation in data science and AI (Hines et al., 2020). The Digital Business Transformation Task Force serves as a hub for innovation, experimentation, and collaboration throughout the phases of digital business transformation, from strategic planning and design, testing and piloting to full implementation. EMA provides various AI-driven services like Process (re-) engineering for digital mapping of business processes or re-engineering processes to exploit digital technologies, automation, and AI. The initiative also supports identifying new digital solutions and selecting proof-of-concept ideas. Under this initiative, EMA continually searches for promising novel digital solutions on the market and explores how these could be exploited for EMA business value, such as increasing organizational efficiencies. EMA houses the Analytics Center of Excellence (ACE). ACE explores how analytics - including AI, ML and Robotics – can be used to build pragmatic solutions to existing EMA business needs with the primary objective of gaining efficiency. EMA also supports the efforts for Healthcare Data Analytics. A key component is understanding how AI, ML and new digital technologies can be leveraged to structure and expose messy data and achieve more profound insights into healthcare data.

The recent global pandemic and our response to it demonstrates the important role science plays in mitigating the effects of a crisis. Data-driven scientific and policy decisions play pivotal roles in response to a health crisis and drive decisions to best protect lives. AI and big data analytics played crucial roles in guiding the Joint Research Center's (JRC) response to COVID-19 from many different angles, particularly by providing epidemiological models and research data on outbreak dynamics. The pandemic has nurtured and enhanced interest in AI's application in the health care sector. Reliance on big data, ML, and other AI-related techniques expedited vaccine development by speeding up the research pipeline and the supply chain. The EU has emphasized its support of big data and AI, supporting the increase of automation in analytics and the production line to increase treatment availability and illness prevention (Egilman et al., 2021). To help understand the landscape, JRC analyzed the global technology landscape for AI in healthcare and identified 2000 players worldwide that were actively applying AI to the healthcare sector.

AI can play a role in regulatory science, which has already been demonstrated in multiple instances where AI approaches have enabled us to solve problems with over the-shelf products and/or with already available algorithms. However, for an AI system to perform well, superior datasets must be available. Quality data is comprised of a large volume of good quality semantically structured data. Therefore, data governance is a necessary global step in addition to boosting shared data repositories. The biggest challenge the research community faces is the current fragmentation of data in many repositories with multiple formats and definitions. Another challenge is that, in some cases, the data codes are not uniform. Each data source has a coding system, and different ways of assigning codes to medicines are employed without national or international standardization (Leal et al., 2021). Therefore, bringing these data together presents a substantial regulatory challenge. For example, the JRC put forward its strategy to create a single market for data (Van Roy et al., 2021). A single market would allow data to flow freely within the EU and across sectors to benefit businesses, researchers, and public administration. Importantly, to be ready for AI approaches, there have been multiple policy-driven initiatives. The EU has also put forward several regulatory framework proposals on AI to

provide adequate risk assessment and mitigation systems, including high-quality datasets ready to feed the AI pipeline with high robustness, security and accuracy, also ensuring appropriate human oversight is implemented to minimize the risk. Moving forward a similar approach could be globally implemented to greatly enhance the data available for utilization by AI to further improve application in regulatory science.

6. Summary

To understand the role both AI and RWD play in the global regulatory science environment, GSRS21 took a multifaced three-dimensional approach to facilitate the discussion (Fig. 1). The first approach identified innovative research ideas and developments presented through a series of talks focused on new developments at the cross-section of AI/ML and regulatory sciences as related to food and drug safety. The second approach showed and/or demonstrated the tools currently being used in various regulatory agencies worldwide. The third approach evaluated different standard points on the same topic by debating and defining regulatory science's role in improving AI readiness for the regulatory environment. GSRS21 highlights include the opening remarks by the US-FDA Acting Commissioner and presentations by government-agency senior leadership from the US and EU. In addition, scientists representing ten countries worldwide made platform presentations. A unique feature of the conference was the live debate on the topic of "Is Regulatory Science Ready for AI?" A special workshop also showcased data-science tools currently in regulatory use by US-FDA, EMA, and Swissmedic.

Examples were presented for new analytical tools playing significant functions in the global regulatory agencies. Some of these tools are already an integral part of the regulatory process. It has been evident that RWD can be used as real-world evidence to improve our ability to assess food and drug safety and thus improve public health. We have also seen tremendous regulatory engagement in facilitating AI to improve an agency's operation and develop the regulatory structure to regulate products containing AI. The conference was concluded with the question of where regulatory science research should go. Emerging technologies need to be constantly evaluated to actively facilitate the use of these new tools in regulatory settings. New methods in regulatory applications across the globe are continuously becoming available and GSRS is a unique platform to facilitate the discussion and collaboration across regulatory agencies to improve oversight and hasten approvals for such applications that improve public health.

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No data was used for the research described in the article.

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