Public consultation on EMA Regulatory Science to 2025

Fields marked with * are mandatory.

*Name

*Email

Introduction

The purpose of this public consultation is to seek views from EMA's stakeholders, partners and the general public on EMA's proposed strategy on Regulatory Science to 2025 and whether it meets stakeholders' needs. By highlighting where stakeholders see the need as greatest, you have the opportunity to jointly shape a vision for regulatory science that will in turn feed into the wider EU network strategy in the period 2020-25.

The views being sought on the proposed strategy refer both to the extent and nature of the broader strategic goals and core recommendations. We also seek your views on whether the specific underlying actions proposed are the most appropriate to achieve these goals.

The questionnaire will remain open until June 30, 2019. In case of any queries, please contact: RegulatoryScience2025@ema.europa.eu.

Completing the questionnaire

This questionnaire should be completed once you have read the draft strategy document. The survey is divided into two areas: proposals for human regulatory science and proposals for veterinary regulatory science. You are invited to complete the section which is most relevant to your area of interest or both areas as you prefer.

We thank you for taking the time to provide your input; your responses will help to shape and prioritise our future actions in the field of regulatory science.

Data Protection

By participating in this survey, your submission will be assessed by EMA. EMA collects and stores your personal data for the purpose of this survey and, in the interest of transparency, your submission will be made publicly available.
For more information about the processing of personal data by EMA, please read the privacy statement.

Questionnaire

Question 1: What stakeholder, partner or group do you represent:
- ○ Individual member of the public
- ○ Patient or Consumer Organisation
- ○ Healthcare professional organisation
- ○ Learned society
- ○ Farming and animal owner organisation
- ○ Academic researcher
- ○ Healthcare professional
- ○ Veterinarian
- ○ European research infrastructure
- ○ Research funder
- ○ Other scientific organisation
- ○ EU Regulatory partner / EU Institution
- ○ Health technology assessment body
- ○ Payer
- ○ Pharmaceutical industry
- ○ Non-EU regulator / Non-EU regulatory body
- ● Other

Please specify: Press/media/NGO/Not-for profit organisation/other scientific organisations/policy maker, etc.

Health care technology company

Name of organisation (if applicable):

Aetion, Inc.

Question 2: Which part of the proposed strategy document are you commenting upon:

- ◉ Human
- ○ Veterinary
- ○ Both

Question 3 (human): What are your overall views about the strategy proposed in EMA's Regulatory Science to 2025?

Please note you will be asked to comment on the core recommendations and underlying actions in the subsequent questions.

Dear Prof. Guido Rasi:

Thank you for publishing "EMA Regulatory Science to 2020." We at Aetion, Inc. agree that as science and technology evolve in the future, maintaining agility to adapt to the changing conditions has the power to propel the kind of change necessary to ensure patients have timely access to the most effective medications.

Integrating transparent, auditable, reproducible, and scientifically valid real-world evidence (RWE) into regulatory decision-making will facilitate more efficient drug development, enhance our understanding of product safety and efficacy, and contribute to the critical transition to value-based care. RWE generated using principled methods of database epidemiology addresses data accuracy, data availability, and controlling for confounding factors, which enables the production of clinically meaningful results in RWE analyses. (1) Having transparent and scientifically-valid evidence of therapies that work for patients in the real-world setting will better enable patients, providers, payers, and regulators to make more informed decisions about the most medically appropriate and cost-effective treatments for patients.

Aetion's flagship product, the Aetion Evidence Platform, was originally created by two Harvard academic pharmaco-epidemiologists to address a widely recognized need: scalable and transparent real-world data (RWD) analyses at the highest level of scientific rigor and governance to identify the safety and efficacy of clinical interventions. We are inspired by the European Medicine Agency (EMA)'s reflective and thorough process of mapping and selecting challenges and opportunities in medicines development. Aetion's efforts are highly complementary to the goals you recently articulated, including ensuring "the sound assessment of ground-breaking, more complex therapies." (2) We are committed to fostering use of RWE in regulatory decision-making when such evidence meets EMA's standards for product safety and efficacy.

Aetion welcomes and appreciates the opportunity to comment on "EMA Regulatory Science to 2020." EMA's five-year strategy outlines important considerations for medicines development through enabling patients, providers, payers, and regulators to make more informed decisions about the most medically appropriate and cost-effective treatments for patients. Per question five of the questionnaire, we at Aetion believe the three core recommendations (in order of importance) that will deliver the most significant change in the regulatory system over the next five years are:

18. Promote use of high-quality real-world data (RWD) in decision-making
10. Develop the regulatory framework for emerging clinical data generation
12. Invest in special populations initiatives

We provide our rationale and guidance below on these recommendations as well as four other recommendations:
16. Bridge from evaluation to access through collaboration with payers
19. Develop network competence and specialist collaborations to engage with big data
27. Support the development and implementation of a repurposing framework
29. Leverage collaborations between academia and network scientists to address rapidly emerging regulatory science research questions

Aetion thanks the EMA for the opportunity to comment on "EMA Regulatory Science to 2025." We appreciate the agency's interest in using RWE to inform and improve safety and efficacy, and its focus on approaches that can improve the regulatory process to the benefit of patients. Transparent, auditable, and reproducible RWE—generated using principled database epidemiology—can facilitate more efficient drug development, enhance our understanding of product safety and efficacy, and drive desired outcomes and value (for both the system and patients).

Aetion looks forward to our continued collaboration with the agency to help facilitate the successful implementation and use of RWE in regulatory decision-making. Please contact Carolyn Magill at carolyn. magill@aetion.com with any questions regarding these comments or other issues related to RWE policy and development.

Sincerely,
Carolyn Magill, Chief Executive Officer, Aetion
Jeremy Rassen, Sc.D., President and Chief Science Officer, Aetion

Endnotes:
1. Schneeweiss S, Avorn J. A review of uses of health care utilization databases for epidemiologic research on therapeutics." JCE 2005;58(4):323-37. Retrieved from https://doi.org/10.1016/j.jclinepi.2004.10.012
2. Ridley, D. "EMA Is Exploring How Real-World Data Can Benefit Europe's OTC Market, Says Agency Head Rasi." Informa Pharma Intelligence HBW Insight 2019 April 1.

Question 4 (human): Do you consider the strategic goals appropriate?

Strategic goal 1: Catalysing the integration of science and technology in medicines development (h)

- ⦿ Yes
- ◯ No

Strategic goal 2: Driving collaborative evidence generation – improving the scientific quality of evaluations (h)

- ⦿ Yes
- ◯ No

Strategic goal 3: Advancing patient-centred access to medicines in partnership with healthcare systems (h)

○ Yes
○ No

Strategic goal 4: Addressing emerging health threats and availability/therapeutic challenges (h)

○ Yes
○ No

Strategic goal 5: Enabling and leveraging research and innovation in regulatory science (h)

○ Yes
○ No

Question 5 (human): Please identify the top three core recommendations (in order of importance) that you believe will deliver the most significant change in the regulatory system over the next five years and why.

First choice(h)

18. Promote use of high-quality real world data (RWD) in decision-making

1st choice (h): please comment on your choice, the underlying actions proposed and identify any additional actions you think might be needed to effect these changes.

Rationale for #18: Promote use of high-quality real-world data (RWD) in decision-making

Our comments center on Aetion's:

I. Principles for working with real-world data; (3)
II. Principles for real-world evidence; (4) and,
III. Applications of real-world evidence.

Aetion's comments reflect our strong commitment to continued work with EMA to contribute to the successful development and implementation of the agency's RWE program that will facilitate decision-making on research and development and market access to innovative methods of treatment to benefit patients.

I. Principles for working with real-world data
Aetion believes four principles governing RWD are critical to the generation of scientifically-valid and accurate RWE. Adoption of each of these principles within a harmonized EU-wide regulatory framework would ensure that when RWD are used to generate RWE, the RWD must be "fit for purpose," must have clear provenance, must be handled transparently and responsibly, and must contain the full amount of information originally captured.

II. Principles for real-world evidence
Aetion believes certain principles governing RWE are critical for having regulatory-level confidence in the results produced from such analyses. Adoption of each of these five principles within a harmonized EU-wide regulatory framework will increase confidence that RWE used to support regulatory decision-making employ principled methods of database epidemiology and are transparent, auditable, and reproducible—all

foundations of good science.

III. Applications of real-world evidence
Fully transparent, reproducible, and scientifically-valid RWE can provide an improved and more comprehensive understanding of how therapies work in various patient populations in real-world settings. That view gives providers, product developers, payers, and regulators the opportunity to understand performance in broad populations that represent real-world variation in co-morbidities, co-medications, clinical practice, adherence, and other factors frequently not observed in clinical trials.

RWE has the potential to be most applicable and of most use to regulators, payers, product developers, providers, and ultimately patients when the resulting analyses ask clinically meaningful questions and produce clinically meaningful results. Clinical meaning does not necessarily manifest in a particular p-value or effect-size threshold, but rather it manifests through thorough evaluation of the study considerations, incorporating an assessment of factors noted above, such as appropriateness, fitness for purpose, approach, and implementation. Clinical meaning also comes from the selection of relevant outcomes; whereas RCTs can be limited to assessment of biomarkers (e.g., bone mineral density), RWD analyses can address endpoints that are most meaningful to providers and patients (e.g., bone fractures).

Certain types of RWD analyses within a European regulatory RWE framework have the potential to generate clinically meaningful results, (32-33) and to reflect the key principles for RWD and RWE outlined above. These RWD analyses include:
-Measuring the efficacy and safety in real-world populations, including subgroups: RWE can be used to assess the safety and efficacy of a medication among all treated patients and within clinically-meaningful subgroups.
-Identifying subgroups in which risk-benefit profiles are likely to be most favorable: RWE can be used to assess the background risk of safety and efficacy outcomes among clinically relevant subgroups and can facilitate clinical decision-making.
-Identifying gaps in treatment and adherence issues: RWE can be used to evaluate real-world adherence patterns and identify issues with non-persistence and non-adherence which may reduce the efficacy of a medication.
-Generating evidence to support coverage decisions: RWE can be used to support payer coverage decisions and to design formularies appropriate for populations that may be underrepresented in certain clinical trials (e.g., older adults, individuals with multiple chronic illnesses).

The RWE that is created can benefit patients, providers, payers, product developers, and regulators in a variety of ways, as described in the associated letter. As the science and technology evolve in the future, RWE analyses have the potential to uncover even more clinically meaningful results to support regulatory decision-making.

Please refer to the associated letter for our complete rationale, guidance, and endnotes.

Second choice (h)

10. Develop the regulatory framework for emerging digital clinical data generation

2nd choice (h): please comment on your choice, the underlying actions proposed and identify any additional actions you think might be needed to effect these changes.

Rationale for #10: Develop the regulatory framework for emerging clinical data generation

Novel sources of RWD hold tremendous promise. For example, better data on physical fitness and socio-behavioral factors could improve risk stratification and confounding control; earlier and more comprehensive detection of adverse events could help with pharmacovigilance; and better data on social activity and treatment experiences could assist in contextualizing and evaluating quality-of-life measures.

These novel sources of data could involve almost any technology that routinely collects personal data, including machine learning techniques that extract semantic knowledge and identify complex patterns from raw data. Examples include but are not limited to: (36)
-Wearable devices: Devices such as fitness monitors and smartwatches can provide data on daily exercise activity, heart rate, blood pressure, and sleep quality, and can identify episodes of disease at the time of occurrence, such as atrial fibrillation and epilepsy.
-Location data: Location data from smartphones, cars, and other sources could potentially be used to assess a broad range of inputs, such as a patient's physical mobility, socioeconomic conditions, or environmental exposures, or to determine when a patient is hospitalized or has had other health care encounters.
-Social media, patient forums, and internet search queries: Online discussions and search queries can illuminate patient symptoms, diagnoses, treatment experiences, and adverse events, thereby assisting pharmacovigilance. (37-39) In addition, these approaches could be used to detect infectious disease outbreaks and to estimate disease incidence.
-Voice assistants: As voice assistants such as Alexa help patients manage their health care, these devices can provide data on a diverse range of topics, such as drug prescriptions, medical appointment scheduling, and medical information shared with care providers.

The foremost consideration is protecting patient privacy, particularly as personal data collection and linkage across multiple data sources become ever more pervasive, and as linkage, by adding more specific data to a record, can render data items identifiable. The improvement and use of validated, automated de-identification systems will be key in minimizing privacy risks and ensuring regulatory compliance. (40) Furthermore, patients must be informed about how their data are collected, and must have control over when their data are used for research. (41)

While these new sources of RWD may hold significant promise, they are also accompanied by a number of challenges, including: (42)
-Data integration: Novel sources of data are most powerful when they can be linked to other health records, such as claims and EHR data. Standardized applications can help facilitate this integration while ensuring regulatory compliance.
-Development and validation of machine learning techniques: Although significant progress has been made in machine learning technologies, further development is needed. Machine learning models must be validated and maintained over time, especially when used in rapidly evolving information environments such as social media, where changes in communication styles may render models less relevant over time and the presence of incentivized social media influencers may make it difficult to separate noise from signal. (43-45)
-Generalizability: Data sourced from wearable devices and similar technologies may contain differential representations of patient groups compared to the general population. For example, patients who use wearable devices and social media may differ based on socioeconomic status, culture, language, health, and other factors. As a result, models and conclusions developed from this type of data may not be generalizable to the wider population, and there are obvious downsides of excluding disadvantaged populations from realizing the benefits of these research efforts.
-Study design challenges: As with any observational data, the effects of missing data, selection bias, and other epidemiological issues must be understood and addressed in order to produce valid results. For example, can and should periods of missing wearable data be imputed? Is a patient who stops using a wearable device systematically different from one who continues to use it? How can we perform suitable risk adjustment in comparative studies when incorporating alternative sources of RWD?

These are just a few examples of issues that will need to be addressed when working with new sources of RWD, and we do not yet fully understand all of the challenges that they will bring. As we are just at the beginning of working with these new data sources, we must establish and standardize methods for protecting privacy while also realizing the full potential of these new data sources to improve patient health.

Endnotes: Please refer to the associated letter.

Third choice (h)

12. Invest in special populations initiatives

3rd choice (h): please comment on your choice, the underlying actions proposed and identify any additional actions you think might be needed to effect these changes.

Rationale for #12: Invest in special populations initiatives

We at Aetion agree that EMA should invest in approaches that serve special populations. Adequate representation of certain patient groups in clinical trials remains a concern. Groups such as children, pregnant women, and older adults are significantly underrepresented in clinical research even though research demonstrates variation in disease pattern, clinical presentation, and therapeutic response among these different groups. According to researchers, in contemporary heart failure trials, "older patients and women are consistently underrepresented. Race/ethnicity data are reported in less than half of the trials." (1)

We also know that early users of a newly approved treatment typically have an existing diagnosis and failed an earlier therapy or suffer from intolerable side effects. Furthermore, according to researchers at Duke University, over one-third of metastatic renal cell carcinoma patients would not have met eligibility criteria for the landmark Phase III trials of new, targeted therapies—based on their age and severity of disease—that led to approval of the treatment they received. (2) Real-world data open the door to:
-Identifying subgroups in which risk-benefit profiles are likely to be most favorable in actual clinical practice: RWE can be used to assess the background risk of safety and efficacy outcomes among relevant subgroups and facilitate clinical decision-making;
-Providing an external control arm or confirming a response rate in a single-arm trial for patient (sub-) populations in urgent need; and,
-Using specialized analytics that take individual-level randomized controlled trial data and demonstrate the treatment's efficacy in underrepresented groups. (3-4)

Endnotes:
1. Oh SS, et al. Diversity in Clinical and Biomedical Research: A Promise Yet to Be Fulfilled. PLoS Med 12 (12):e1001918. Retrieved at https://doi.org/10.1371/journal.pmed.1001918
2. Tahhan AS, et al. Enrollment of Older Patients, Women, and Racial and Ethnic Minorities in Contemporary Heart Failure Clinical Trials. JAMA Cardiol 2018;3(10):1011-19. doi:10.1001/jamacardio. 2018.2559
3. Mitchell AP, et al. Clinical trial subjects compared to "real world" patients: Generalizability of renal cell carcinoma trials. Journal of Clinical Oncology 2014; 32:15_suppl, 6510. Retrieved at https://ascopubs.org/doi /abs/10.1200/jco.2014.32.15_suppl.6510
4. Wang S, et al. Prediction of rates of thromboembolic and major bleeding outcomes with dabigatran or warfarin among patients with atrial fibrillation: new initiator cohort study. BMJ 2016;353:i2607. http://dx.doi. org/10.1136/bmj.i2607

Question 6 (human): Are there any significant elements missing in this strategy. Please elaborate which ones (h)

Question 7 (human): The following is to allow more detailed feedback on prioritisation, which will also help shape the future application of resources. Your further input is therefore highly appreciated. Please choose for each row the option which most closely reflects your opinion. For areas outside your interest or experience, please leave blank.

Should you wish to comment on any of the core recommendations (and their underlying actions) there is an option to do so.

Strategic goal 1: Catalysing the integration of science and technology in medicines development (h)

	Very important	Important	Moderately important	Less important	Not important
1. Support developments in precision medicine, biomarkers and 'omics'	○	○	◉	○	○
2. Support translation of Advanced Therapy Medicinal Products cell, genes and tissue-based products into patient treatments	○	○	◉	○	○
3. Promote and invest in the Priority Medicines scheme (PRIME)	○	◉	○	○	○
4. Facilitate the implementation of novel manufacturing technologies	○	○	○	◉	○

5. Create an integrated evaluation pathway for the assessment of medical devices, in vitro diagnostics and borderline products	○	○	◉	○	○
6. Develop understanding of and regulatory response to nanotechnology and new materials' utilisation in pharmaceuticals	○	○	○	◉	○
7. Diversify and integrate the provision of regulatory advice along the development continuum	○	◉	○	○	○

Please feel free to comment on any of the above core recommendations or their underlying actions. **Kindly indicate the number of the recommendation** you are commenting on:

Strategic goal 2: Driving collaborative evidence generation – improving the scientific quality of evaluations (h)

	Very important	Important	Moderately important	Less important	Not important
8. Leverage novel non-clinical models and 3Rs	○	○	○	●	○
9. Foster innovation in clinical trials	○	○	●	○	○
10. Develop the regulatory framework for emerging digital clinical data generation	○	●	○	○	○
11. Expand benefit-risk assessment and communication	○	○	●	○	○
12. Invest in special populations initiatives	○	●	○	○	○
13. Optimise capabilities in modelling and simulation and extrapolation	○	○	●	○	○
14. Exploit digital technology and artificial intelligence in decision-making	○	○	○	●	○

Please feel free to comment on any of the above core recommendations or their underlying actions. **Kindly indicate the number of the recommendation you are commenting on**:

Strategic goal 3: Advancing patient-centred access to medicines in partnership with healthcare systems (h)

	Very important	Important	Moderately important	Less important	Not important
15. Contribute to HTAs' preparedness and downstream decision-making for innovative medicines	○	○	◉	○	○
16. Bridge from evaluation to access through collaboration with Payers	○	◉	○	○	○
17. Reinforce patient relevance in evidence generation	○	○	○	◉	○
18. Promote use of high-quality real world data (RWD) in decision-making	◉	○	○	○	○
19. Develop network competence and specialist collaborations to engage with big data	○	◉	○	○	○
20. Deliver real-time electronic Product Information (ePI)	○	○	○	◉	○

21. Promote the availability and uptake of biosimilars in healthcare systems	◎	◎	◎	◉	◎
22. Further develop external communications to promote trust and confidence in the EU regulatory system	◎	◎	◎	◉	◎

Please feel free to comment on any of the above core recommendations or their underlying actions. **Kindly indicate the number of the recommendation you are commenting on**:

Rationale for #16: Bridge from evaluation to access through collaboration with payers

We at Aetion agree that "access to medicine does not depend solely on regulatory decisions." Health technology assessment (HTA) is also of critical importance. RWE can support the bridge between drug assessment and drug coverage if there is early and frequent stakeholder involvement—among regulators, payers, and manufacturers—in a safe harbor environment to define the unmet needs a clinical trial and/or RWE study may address. In a recent survey with regulators, payers, and biopharma leaders, requested areas for increased collaboration on evidence requirements included data (e.g., biomarkers, patient-reported outcomes), endpoints (e.g., primary, secondary, surrogate), comparators, and study design (e.g., subgroup analyses). (1)

In summary, we advise the following actions:
-Identify opportunities to avoid duplicative efforts between EMA and its HTA/payer partners; and,
-Create a mechanism for early and frequent stakeholder involvement—between regulators, payers, and the manufacturer—in a safe harbor environment to determine unmet medical need and the information needed in a clinical trial and/or RWE study.

As you may know, in late 2019, Health Canada and its HTA partners such as the Canadian Agency for Drugs and Technologies in Health (CADTH), will issue a joint document to "optimize and formalize the use of RWE across the drug life cycle." (2) We are tracking and monitoring Health Canada's progress on this topic and we believe there is a great opportunity for Health Canada and its HTA partners, particularly because the two largest provinces in Canada—Ontario and British Columbia—have comprehensive claims data.

We encourage EMA—in collaboration with payers, industry, and experts in the generation and use of RWE—to provide proper guidance to industry.

Rationale for #19: Develop network competence and specialist collaborations to engage with big data
We at Aetion agree that there is great value in collaborating with the FDA, Health Canada, and other national competent authorities to ensure multilateral insights on big data initiatives and RWE. The FDA, for example, has ongoing demonstration projects on data relevancy, quality, and linkage that will contribute to its guidance formation. The RCT DUPLICATE researchers and FDA's Associate Director of Real-World Evidence Analytics, as an example, created an instructive schema. (3-4)

Other important data initiatives include those by professional societies and registry holders (e.g., Thrombosis Research Institute's GARFIELD-VTE), patient advocacy organizations (e.g., NORD), data holders (e.g., CPRD, SNDS/SNIIRAM, iOMEDICO, Techniker Krankenkasse), academic centers (in the EU, U.S., and

Canada), and by organizations in and involving China and Japan. Please also refer to our response to core recommendation 18, specifically:
-"Principles for working with real-world data;" and,
-Section five of "Principles for real-world evidence."

We underscore that use of a validated RWE software platform contributes to the reliability, transparency, and reproducibility of RWE.

Endpoints:
1. EMA Regulatory Science to 2025. EMA 2019. Retrieved at https://www.ema.europa.eu/en/documents /regulatory-procedural-guideline/ema-regulatory-science-2025-strategic-reflection_en.pdf
2. Optimizing the Use of Real World Evidence to Inform Regulatory Decision-Making. Health Canada 2019. Retrieved at https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products /announcements/optimizing-real-world-evidence-regulatory-decisions.html
3. The RCT DUPLICATE series of demonstration projects includes "Effectiveness Research with Real World Data to Support FDA's Regulatory Decision Making: A Real World Evidence Demonstration Project" and "Predicting Findings of Ongoing Phase 4 RCTs with Real World Data Analyses: An Assessment to Support FDA's Regulatory Decision Making." The former aims to replicate the results of 30 published Phase III and Phase IV RCTs to see whether use of RWE would have led to the same regulatory decisions. The results will demonstrate whether RWE could be used to supplement or, in certain circumstances, even replace clinical trials for drug development and regulatory approval. In the latter, the researchers are conducting RWD analyses to predict the results of seven ongoing Phase IV RCTs.
4. Franklin JM, et al. Evaluating the Use of Nonrandomized Real-world Data Analyses for Regulatory Decision Making. CPT 2019;105(4):869. https://doi.org/10.1002/cpt.1351

Strategic goal 4: Addressing emerging health threats and availability/therapeutic challenges (h)

	Very important	Important	Moderately important	Less important	Not important
23. Implement EMA's health threats plan, ring-fence resources and refine preparedness approaches	○	○	○	◉	○
24. Continue to support development of new antimicrobials and their alternatives	○	○	○	◉	○
25. Promote global cooperation to anticipate and address supply challenges	○	○	○	◉	○
26. Support innovative approaches to the					

development and post-authorisation monitoring of vaccines	○	○	○	●	○
27. Support the development and implementation of a repurposing framework	●	○	○	○	○

Please feel free to comment on any of the above core recommendations or their underlying actions. **Kindly indicate the number of the recommendation you are commenting on**:

Rationale for #27: Support the development and implementation of a repurposing framework

"It's in the realm of public health to see if we can effectively repurpose drugs," said U.S. FDA's Joohee Sul, M.D., (1) as doing so accelerates drug development, lowers costs, and improves outcomes for new patient populations—by using drugs and clinical data that already exist.

RWE use cases
RWE can enhance the validity of the screening process. To identify new indications for approved or investigational agents, researchers start by screening approved drugs and investigational agents for new drug-outcome relationships. To confirm or refute a causal association, researchers can use a RCT or a RWE study. If a researcher is using a RWE study, it must be transparent, scientifically valid, and reproducible. It is critical that the RWE study is designed carefully for confounding control, using effective bias reduction techniques such as high-dimensional propensity score (hdPS) adjustment to increase validity and speed. Automation of such methods can enable efficient implementation of highly valid studies. A RWE study by Brigham & Women's Hospital (BWH) is a good example of using RWE to identify new indications. In the study, researchers screened more than 700 approved drugs with interactome network analyses and used the Aetion Evidence Platform to efficiently and reliably confirm or refute signals with real-world data analyses. (2) The study—led by Joseph Loscalzo, M.D., Ph.D., BWH's chairman of the Department of Medicine and professor of medicine at Harvard—validated two network-based predictions: carbamazepine was associated with an increased risk of coronary artery disease (CAD), and hydroxychloroquine was associated with a decreased risk of CAD. The work used two large health care databases with longitudinal data on more than 220 million patients; it employed propensity score matching techniques.

RWE can support application of an existing agent for a label extension. Similar to the use case above, a researcher needs to start with hypotheses, perhaps informed by clinical practice or by prior RCT results. It is important to use the same standards as with the use case noted above, including EMA's evidentiary standards for approvals. For example, in a RWE study by BWH on telmisartan, with the drug's primary indication for hypertension and its secondary indication for cardiovascular (CV) risk reduction in patients unable to take ACE inhibitors, researchers tested, with RWD, the CV reduction for telmisartan and obtained substantially similar results to the RCT. (3) The effort took 12 weeks, using RWD and a real-world evidence platform, (4) vs. a seven-year, 32,000-patient trial (which amounts to potential savings of hundreds of millions of dollars in estimated direct costs). Most important, the RWE study demonstrated CV risk reduction in patients unable to take ACE inhibitors. In another RWE study, a manufacturer used RWE to show that compared with sitagliptin, the initiation of empagliflozin was associated with a decreased risk of hospitalization for heart failure among patients with type 2 diabetes. (5)

Endnotes:
1. The Harvard-MIT CRS Regulatory Science Symposium. April 2, 2019.

2. Cheng F, et al. Network-based approach to prediction and population-based validation of in silico drug repurposing. Nature Communications 2018;9(2691):1-12. DOI: 10.1038/s41467-018-05116-5

3. Fralick M, et al. Use of Health Care Databases to Support Supplemental Indications of Approved Medications. JAMA Intern Med 2018;178(1):55–63. Doi: 10.1001/jamainternmed.2017.3919

4. All analyses were performed using the Aetion Evidence PlatformTM with R.

5. Patorno E, et al. Empagliflozin and the Risk of Heart Failure Hospitalization in Routine Clinical Care. Circulation 2019;139(25):2822-30. Retrieved at https://doi.org/10.1161/CIRCULATIONAHA.118.039177

Strategic goal 5: Enabling and leveraging research and innovation in regulatory science (h)

	Very important	Important	Moderately important	Less important	Not important
28. Develop network-led partnerships with academia to undertake fundamental research in strategic areas of regulatory science	○	●	○	○	○
29. Leverage collaborations between academia and network scientists to address rapidly emerging regulatory science research questions	○	●	○	○	○
30. Identify and enable access to the best expertise across Europe and internationally	○	○	○	●	○
31. Disseminate and share knowledge, expertise and innovation across the regulatory network and to its stakeholders	○	○	○	●	○

Please feel free to comment on any of the above core recommendations or their underlying actions. **Kindly indicate the number of the recommendation you are commenting on**:

Rationale for #29. Leverage collaborations between academia and network scientists to address rapidly emerging regulatory science research questions

We at Aetion agree that EMA should use collaborations with academia and network scientists to address rapidly emerging regulatory science research questions. In the generation and use of RWE, academics systematically push the limits to improve the inference possible from RWE studies through methods

development, training, and applied analytic work on the efficacy and safety of medications—often in collaboration with regulators, government agencies, or other stakeholders in the health care system.

Consider the topic of validity, where academics and regulators are actively collaborating, before the validity of a RWD analysis can be assessed, full transparency in the study design and implementation is necessary. A joint task force between ISPE and ISPOR, which largely is composed of representatives from academia and EMA, defined the transparency needs for regulators when reviewing RWD analyses. A landmark project conducted by academic investigators with guidance from EMA, the FDA, and the Pharmaceuticals & Medical Devices Agency of Japan, is another good example of a cross-institution collaboration for the advancement of regulatory science. The study, Reproducible Evidence: Practices to Enhance and Achieve Transparency (REPEAT), is systematically evaluating the reporting and transparency of 250 published database studies and is attempting to replicate 150 published studies. (1) This open science initiative—coordinated with similar activities in other fields of science—will establish the current state of transparency to develop specific recommendations that will allow regulators to fully understand the study design and implementation and to assess the validity of the RWD analysis.

RCT DUPLICATE, a large-scale ensemble of projects mentioned earlier, is addressing emerging regulatory science research questions and is only possible with funding and guidance from the FDA. The agency is critically involved in developing a shared learning process to determine when RWE is or is not fit for decision-making and how it can be used as an accelerant to drug approval. To that end, we are pleased with the progress of our ongoing work on RCT DUPLICATE, together with the agency and with colleagues from Harvard Medical School, and as part of the FDA's broader RWE Program. For example, in August 2018, RCT DUPLICATE's co-lead Jessica Franklin, PhD, and study lead Elisabetta Patorno, M.D., DrPH, registered the first pilot study of the seven RWE studies aimed to predict ongoing RCTs. The RWE study, powered by the Aetion Evidence Platform, and the postmarketing study, CAROLINA: CARdiovascular Outcome Trial of LINAgliptin Versus Glimepiride, showed substantially similar results. Both the RWE study and the RCT demonstrate non-inferiority regarding cardiovascular risk and superiority of linagliptin regarding severe hypoglycemia. (2-3)

A RWE analytics platform can enable easy collaboration among stakeholders, such as federated queries that touch both industry and academia, or it can provide regulators with a study for review and collaboration. A RWE analytics platform, with an intuitive interface and comprehensive archival, can enable a deep dive on findings. These studies can range from simple descriptives to sophisticated comparative analyses.

We are also pleased to read your proposal to train early-career researchers in regulatory science. There is already an under supply of well-trained people in the generation and use of RWE. It is only through intentional funding and placements—as well as academics who train current and aspiring leaders in the field—that we can keep pace with the workforce demand.

Endnotes:
1. Information on REPEAT is at https://www.repeatinitiative.org/.
2. Boehringer Ingelheim's protocol is at https://clinicaltrials.gov/ct2/show/NCT01243424.
3. Patorno E, et al. Using real-world data to predict findings of an ongoing phase IV cardiovascular outcome trial–Cardiovascular safety of linagliptin vs. glimepiride. Diabetes Care 2019;42(7). Retrieved at https://doi.org/10.2337/dc19-0069

Thank you very much for completing the survey. We value your opinion and encourage you to inform others who you know would be interested.

Useful links

EMA website: Public consultation page (https://www.ema.europa.eu/en/regulatory-science-strategy-2025)

Background Documents

EMA Regulatory Science to 2025.pdf

Contact

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