Review

Dynamic Regulatory Assessment: evolving the European Regulatory Framework for the Benefit of Patients and Public Health—an EFPIA View

Esteban Herrero-Martinez, PhD[1]; Nasir Hussain, PhD[2]; Nadege Le Roux, PhD[3]; Judith MacDonald, BSc[4]; Mark Mayer, PharmD, MBA[5]; Rodrigo Palacios, MBA[6]; and Thomas C. Kühler, PhD[7]

[1]AbbVie Ltd, Maidenhead, United Kingdom; [2]Gilead Sciences, Uxbridge, United Kingdom; [3]Celgene, a Bristol Myers Squibb company, Boudry, Switzerland; [4]Pfizer Research and Development Ltd, Tadworth, United Kingdom; [5]Eli Lilly and Company, Indianapolis, IN, USA; [6]F. Hoffmann–La Roche, Basel, Switzerland; and [7]Global Regulatory Affairs, Sanofi R&D, Chilly Mazarin, France

ABSTRACT

The European Union regulatory framework supports development, review, authorization, and maintenance of medicines to benefit public health; however, many elements are 2 decades old and undergoing review. Scrutiny was triggered by the coronavirus disease 2019 pandemic, the need to support future innovative medicines, the digital transformation of data exchange, and the need to address efficiency and capacity limitations. There are also ongoing evolutions in regulatory science for medicines (eg, cell and gene therapies), medical device combinations, and software, as well as the need to fully leverage contemporary information technology (IT). Important initiatives to address these challenges include the European Medicines Agency (EMA) Regulatory Science Strategy,[1] the EU Regulatory Network Strategy,[2] and the Big Data Steering Group,[3] alongside European Commission–led initiatives such as the Pharmaceutical Strategy.[4] Dynamic regulatory assessment (DRA) is a concept that seeks to integrate these various elements to re-imagine regulatory review interactions across the product life cycle. DRA calls for iterative regulatory dialogue, data submission, and evidence assessment, enabled by contemporary IT. DRA will facilitate iterative interaction and data assessment as it accumulates over a product's life cycle, bringing significant efficiencies for all product types. The DRA concept primarily evolved through dialogue within working groups of the European Federation of Pharmaceutical Industries and Associations. This article describes the long-term vision of the European Federation of Pharmaceutical Industries and Associations and outlines important strategic elements of progress, including: aligning on a multi-stakeholder vision for DRA in the European Union and across regions; leveraging learnings from ongoing initiatives; and advancing IT, governance, and standards considerations. Ultimately, DRA should consider outcomes that deliver optimal benefits for patients in the European Union and worldwide. (*Clin Ther.* 2022;44:132–138.)

Key words: data assessment, discrete data packets, dynamic regulatory assessment, iterative regulatory dialogue.

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INTRODUCTION

The European Union (EU) legal framework for medicinal products for human use (including Directive 2001/83 and Regulation 746/2004)[5] was enacted to support the development, review, authorization, and maintenance of medicinal products in the EU. The framework is currently undergoing significant scrutiny as part of the strategies released by EU regulators,[2] as well as the European Commission's Pharmaceutical Strategy.[4] In parallel, the pharmaceutical sector is experiencing a significant digital transformation. This provides an opportunity to propel the EU regulatory framework to the next level, able to deal with the latest scientific developments, with efficient yet robust operation under both normal conditions and health emergencies.[6]

Dynamic regulatory assessment (DRA) is the term for a regulatory science concept developed by the European Federation of Pharmaceutical Industries and Associations (EFPIA). The term "dynamic" expresses an ongoing or iterative level of interaction and assessment of data, and "assessment" describes dialogue and regulatory evaluation of data and evidence as they accumulate throughout a product's life cycle. When fully implemented, DRA will benefit patients and public health by supporting progressive data submission and assessment for efficient and effective regulatory decision-making, underpinned by a contemporary information technology (IT) infrastructure (including cloud-based systems and advanced analytics). In the present article, contemporary IT includes (but is not limited to) cloud-based systems augmented by advanced analytics.

The coronavirus disease 2019 (COVID-19) vaccines and treatments developed during the pandemic revealed the benefits of a more dynamic approach, strengthened the EU network and global collaboration, enhanced research and development (R&D) support, and expedited assessments, including rolling reviews.[7,8] This information should be leveraged and transposed to also apply for treatments of other life-threatening diseases as a first step. In time, however, the DRA concept (described in the following sections), or elements of it, may enable more efficient processes across the life cycle for all product types, including innovative medicines, biosimilars, drug devices, and generic drugs.

Full implementation of the DRA concept into the EU regulatory framework is viewed as a long-term objective. Top-level multi-stakeholder alignment on a long-term vision for DRA in the EU, and beyond, is essential to guide the advancement of the best possible regulatory framework that will be fit for purposes for the coming decades and conducive to increasingly global medicine development approaches. The EU also needs a multi-stakeholder vision to ensure that it maintains long-term global competitiveness in enabling innovation and to allow it to actively engage in this transformative regulatory science debate, which is gaining increasing traction and pace locally and globally.[9,10]

Multiple international initiatives such as the Real-Time Oncology Review of the US Food and Drug Administration,[11–13] the Innovative Licensing and Access Pathway of the United Kingdom,[14] and the formation of a not-for-profit company, Accumulus Synergy,[15] also articulate the value of a DRA-type approach. Recently, the US Food and Drug Administration announced the Split Real-Time Application Review, which expands the Real-Time Oncology Review to non-oncology products.[16]

DISCUSSION

Full implementation of the DRA concept in the EU will take several years to accomplish and will require adjustments to policies and practices, spanning multiple parts of the regulatory framework. An aligned vision of the desired future state will help navigate between now and then, however.

THE DRA VISION

Regulatory application dossiers are snapshots of available information on safety, efficacy, and quality data at the time of submission. However, data continue to be generated and gathered throughout the entire life cycle, and knowledge increases as medicines are used in clinical practice and further studied. Current health authority processes, which have evolved over many years based on paper documents, create some innate barriers to dynamic information sharing and assessment. In addition, increasing amounts of data are being captured across multiple platforms and of diverse origins to better characterize diseases, their treatments, and how they perform in the real world.[17] In DRA, data for regulatory decision-making will be uploaded to a common (cloud-based) platform once it has been quality assured and reviewed. Access to the data will then be securely provided, with individual reviewers

having access to the data necessary to perform their assessment activities based on their role in the review procedure. Consistent with the current EU regulatory system, we propose to work primarily in English, but the system should be able to support multiple EU languages when needed (eg, for labels/ indications). This approach creates a flexible mechanism for progressive provision of data for assessment by the regulators as the data become available. It is important to note that the required technology for DRA, such as cloud-based systems, is not new and is increasingly considered the norm for data processing, analysis, and storage in other sectors.[18] It is also a given that all technological components of the DRA system must meet or exceed requirements based on all laws and regulations regarding data security and privacy for all sponsor and health authority jurisdictions, including the EU General Data Protection Regulation.[19]

As discussions progress under the various strategies mentioned earlier, additional considerations are being identified that may enable DRA, including the following: further enhancing EMA and EU Regulatory Network decision-making processes, from EMA and National Competent Authority collaboration, to better knowledge management and improved regulatory decision-making; realizing the potential of electronic patient information; and optimizing the regulatory assessment pathways for integral drug and device combinations and companion diagnostics by the EMA and Notified Bodies.

DRA should, over the longer term, offer benefits across a product's life cycle. The approach may vary, however, based on the type of product, data generated, stage in the cycle, and other considerations.

DRA: PICTORIAL OVERVIEW

DRA could also potentially provide a means of supporting international collaboration between different regulatory jurisdictions beyond the EU as long as inter-operability can be assured (figure 1). The pharmaceutical sector should be ambitious regarding this aspect, noting the significant successes already achieved elsewhere (eg, finance, aviation). The EU was the original pioneer for collaboration, and the current network depends on this approach. Work-sharing/collaboration mechanisms are now operating in other regions in schemes such as ACCESS[20] and Orbis.[21] These are good examples of global collaboration in regulatory assessment as the concept of regulatory reliance continues to gain traction around the world.[22,23] As with other aspects of the DRA concept, this will develop over time, but a clear long-term aim, facilitated by an EU view on DRA, will help all stakeholders. Early steps may include using a cloud-based platform for work sharing similar to that of another region or initiative, piloting in specific settings, or focusing on regulators that have similar approaches to the EU. Longer term elements include engagement in conversations on international harmonization of data standards (eg, as done for the Common Technical Document), alignment on data protection, and capacity building outside the EU.

STRATEGIC ELEMENTS TO ACHIEVE THE VISION

DRA will be a far-reaching and complex multi-year undertaking, and it is not possible to describe every step in detail at this point in time. Instead, we have highlighted in the following sections key strategic elements that we believe are important to bridge between now and the full realization of the long-term DRA vision.

Development of a Multi-Stakeholder Vision for DRA in the EU

This article outlines an EU industry vision for DRA at a period of significant reflection prompted by the COVID-19 pandemic and opportunity to review the regulatory framework. Now is the time to establish a multi-stakeholder vision, including the European Commission, the EMA, Member State health authorities, patients, industry, and other interested parties, to help guide the EU regulatory system forward. Broad stakeholder involvement in co-creating this vision is needed for DRA to deliver maximal value in the future.

Leverage Ongoing Discussions and Initiatives

Strategic input into ongoing discussions and initiatives is essential to advance key elements of DRA. In the shorter term, policy discussions of significant relevance include:

- Scientific dialogue: short-term changes to regulator interactions that support development (eg, scientific advice), which could improve the current landscape based on certain principles,

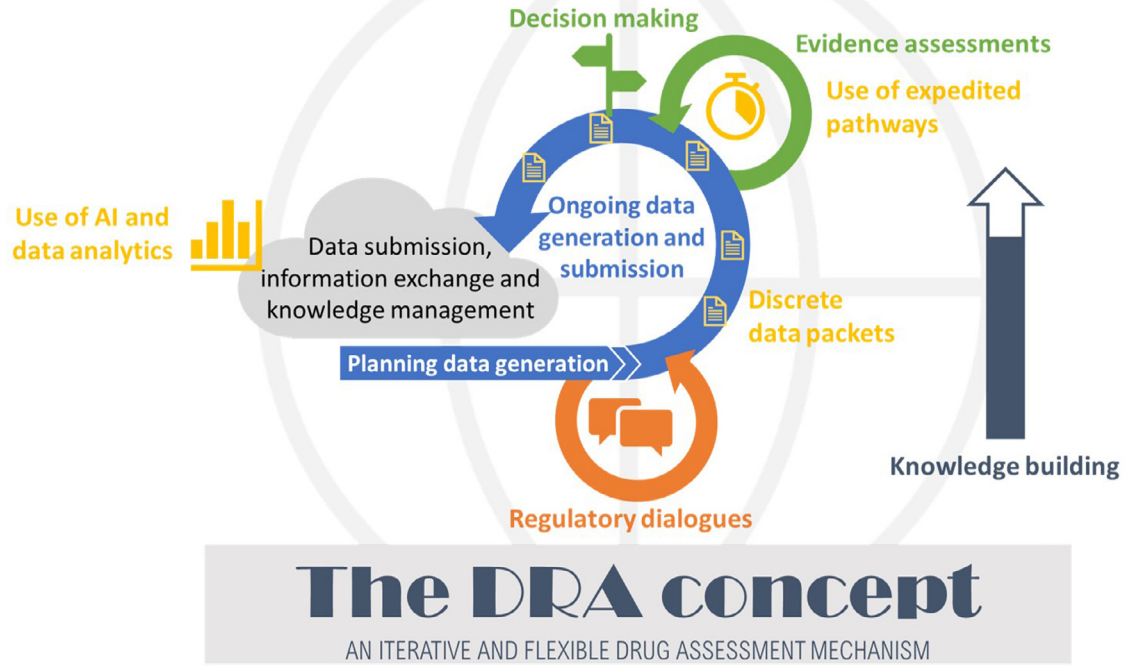

Figure 1. Starting counter-clockwise from the bottom left (6 o'clock), early, iterative multi-stakeholder discussions will facilitate generation of discrete data packets (documents or data, 3 o'clock) for regulatory assessment (1 o'clock) supporting regulatory decision-making (12 o'clock). Advanced analytics (9 o'clock) could be applied to augment or even automate human postmarketing surveillance efforts. Over time, regulatory assessment(s) (perhaps expedited) will be performed as dynamic regulatory assessment (DRA) continues through the product's life cycle. Information technology facilitates information sharing and assessment, analysis (from multiple data sources), and institutional memory of regulatory actions (grayish cloud at 9 o'clock). The system will be cyber secured to protect patient and company confidential information. AI = artificial intelligence.

including improved orientation, agility, and multi-stakeholder engagement.[24] Longer term improvements will better integrate R&D product dialogue along the medicine life cycle and leverage contemporary IT capabilities for data exchange, decision support, and institutional memory.

- Expedited regulatory pathways (ERPs): In the EU, ERPs currently include PRIME,[25] Accelerated Assessment,[26] and Conditional Marketing Authorisations.[27,28] he EFPIA is undertaking a strategic reflection on their functioning as part of the association's response to the EU Pharmaceutical Strategy. This could inform policy change and create an opportunity to pilot some DRA concepts in ERPs, connecting iterative dialogue, iterative submission (dynamic review, including learnings from rolling review), and accelerated assessment to speed assessment timelines.
- Discrete data packets: The EFPIA defines discrete data packets as dossier/data elements that can be submitted and reviewed when quality assured, ahead of a complete regulatory submission, although multi-stakeholder discussion and an eventual EU view are needed. Elements of the concept can be piloted now (eg, as components of the electronic Common Technical Document dossier) to guide how this approach could evolve in the mid-term postlegislative

review and to provide principles for a long-term vision.
- Dynamic assessment: Developing sustainable processes based on the learnings from the more dynamic approach used during the COVID-19 review of vaccines and treatments, including increased collaboration within and outside the EU and rolling reviews of data.

Advancing the aforementioned DRA-enabling initiatives, among multiple others, should inform subsequent discussions. Although assessing what has worked less well will be informative, we should also look forward, guided by the long-term vision for DRA, to truly take advantage of the current opportunities for nonlegislative and potential legislative change in the EU.

IT and Its Governance and Standards

We should explore consistent and robust use of proven technologies to support regulatory processes and identification of unique business processes that need to be addressed in the EU. One example is R&D support, including scientific advice. Another element could be supporting work sharing across the EU network, creating a single point for data exchange and assessment.

It is noteworthy that robust IT governance is an essential concept that underpins the evolution of the EU regulatory framework and successful implementation of DRA. Proceeding according to the principles outlined in the following sections is important for successful DRA implementation.

1. A robustly governed and dynamic EU regulatory IT strategy, with multi-stakeholder engagement to ensure solutions deliver value to users. Individual projects and business users must work jointly from the start, avoiding creation of duplicate tools and/or systems to support the same or similar processes in different geographic or functional jurisdictions. A clear connection to an overall business strategy[1] is needed, linking individual projects to successful delivery of the strategy. We must also drive (as much as possible) consistent adoption and implementation of tools and processes across the EU regulatory network. Finally, this must be underpinned by a sustainable IT infrastructure resourcing model that allows consistent progress toward the overall vision, not just legislatively mandated elements.
2. An overarching EU data strategy: consideration of data is needed across the EU regulatory network, not individually per project. For this reason, an overarching information architecture and data model needs to be developed and international engagement on data standards prioritized. Important steps toward this goal have been taken through, for instance, the EU Big Data Task Force and the DARWIN EU (Data Analytics and Real World Interrogation Network) initiatives.[29]
3. Software development is not a core regulator competence, often taking place per-project, per regulator, and risking potential downstream interoperability challenges. More long-term partnerships and investments, consistency, and strategic alignment are needed. Engaging in long-term partnerships with proven software vendors will improve quality and consistency as well as reduce cost. Development of software is needed to test case studies to advance the DRA concept from theory to practice.

CONCLUSIONS

We consider that DRA will eventually support all stakeholders in the EU Regulatory System and have described considerations for a long-term vision and key strategic elements to achieve it. The review of the pharmaceutical acquis, as part of the EU Pharmaceutical Strategy, and actions taken to advance other strategies from EU regulators constitute a pivotal moment. The ensuing policy proposals will be an opportunity for stakeholders to improve the regulatory framework for the benefit of patients and public health in the EU and globally, recognizing that the maintenance of a vibrant EU R&D ecosystem and pharmaceutical sector is an essential component.

We trust that the presentation of a long-term EFPIA vision for DRA, our request for multi-stakeholder alignment, and proposals of key strategic elements will be the beginning of an important dialogue and better alignment of views as the EU embarks on some of the most significant policy change in decades. Our patients and EU citizens deserve no less.

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All authors designed the commentary and wrote the whole manuscript. The views expressed in this research paper are the independent views of the authors and should not be understood or quoted as being made on behalf of or reflecting the position of their respective companies.

DISCLOSURES

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Address correspondence to: Thomas C. Kühler, Global Regulatory Affairs, Sanofi R&D, 1 avenue Brossolette, Chilly Mazarin 91385, France. E-mails: esteban.herreromartinez@abbvie.com.