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June 12, 2023

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA–2023-N-1052 Data and Technology Strategic Plan

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to submit comments regarding the request for information and comments on the Agency's **Data and Technology Strategic Plan**.

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO's members develop medical products and technologies to treat patients afflicted with serious diseases, to delay the onset of these diseases, or to prevent them in the first place.

BIO applauds the Agency's efforts to embark on a data and technology modernization strategy, consistent with Prescription Drug User Fee Act (PDUFA) VII commitments and FY23 Omnibus Bill requirements. BIO encourages FDA to think strategically and would welcome opportunities to provide feedback as FDA's strategy evolves.

General Comments

1. BIO recommends de-emphasizing the importance of upgrading the Electronic Submissions Gateway (ESG) to the cloud and focus on more dynamic and modern data exchange mechanisms with a goal of working towards a "real-time" submission. Ideally, the ESG would be replaced by real-time cloud-based submissions that can support advanced and decentralized manufacturing technologies by facilitating connections across multiple, disparate sites, potentially without increasing inspection burden.

2. BIO recognizes that technological transformation of the information technology (IT) infrastructure for regulatory submission exchange will consist of an iterative process. On a global scale, regulators may introduce certain process changes on different timelines. Accordingly, multiple versions of the electronic common technical document (eCTD) may need to coexist to meet global regulatory requirements, but where possible, efforts should be made to avoid introducing or exacerbating further divergence in submission content and format. While eCTD 4.0 and many of its features (data tagging, keyword search) may not be relevant in a future-oriented cloud-based submission platform that

leverages structured data, these features may confer near-term advantages for some regions. Additionally, by requiring a PDF format, eCTD 4.0 enforces a document-based paradigm that may not be applicable or effective in a data-driven environment. While the benefits of eCTD 4.0 are clear in a global context, in the US, BIO recommends that FDA considers a more transformative solution than what eCTD 4.0 is positioned to offer.

3. The Fast Healthcare Interoperability Resources (FHIR) application to CMC has been well-communicated by the Agency. However, the FDA is also working on other projects for converting labeling and other domains to FHIR (including real-world data). BIO recommends that the Data and Technology Strategic Plan outline how these efforts converge and support each other in a cloud-based submission environment.

4. BIO requests more information on how the Global Substance Registration System (GSRS) could be used to support submissions, as the GSRS contains very detailed identifying information. It is unclear if, in a future state, one can omit information from filings if it is submitted to GSRS. In addition, it is unclear if the GSRS can be used as a starting point for the IDMP implementation in the regulatory filing. In addition, as FDA recently published an IDMP Implementation and Use Guidance for Industry, where it stated that further guidance and/or technical specifications will be provided, as needed for global implementation of the IDMP standards, BIO requests clarity on how these standards and identifiers would be implemented in the product lifecycle (Investigational and Authorized medicinal products).

5. BIO strongly recommends that in the frame of FDA's IDMP approach to "facilitate the international exchange of medicine product data", a clear alignment of the controlled referential list used across regions (e.g., SPL versus SPOR) would be achieved, with the potential use of a single portal with relevant mappings of terms.

6. BIO requests that the Agency disclose any plans to leverage the use of generative artificial intelligence (AI) and natural language processing (NLP technologies) in reviewing applications.

7. BIO recommends that industry (and perhaps FDA as well) would benefit from a cohesive mapping of how all technologies and initiatives fit together — there is perceived divergence across and within the Centers regarding priorities and outcomes. Additionally, industry would benefit from a revised mapping to similar initiatives at other global health authorities and related global standards. BIO also recommends that there would be benefits to cross-Agency/cross-Center enterprise strategy for addressing data and technology initiatives across Centers.

8. The Data and Technology Strategic Plan provides information on the manufacturing process, data management, and exchange. To expand the scope of the plan beyond manufacturing, BIO recommends including analytic opportunities, such as stability modeling.

SPECIFIC COMMENTS IN RESPONSE TO FDA'S GUIDING QUESTIONS

1. **What are up to three outcomes the FDA Data and Technology Strategic Plan can help you achieve, e.g., speed to market?**

    - BIO believes that the FDA Data and Technology Strategic Plan will enable interoperability within a cloud-based ecosystem supporting a rapid and efficient exchange of information for a more dynamic review paradigm. Further, BIO asserts that modernized technology can increase transparency and transform collaboration between sponsors and the FDA.

    - BIO believes that structured and standardized data will drive global harmonization, reduce the time to global product registration, may allow sponsors to submit only a single application across regulatory authorities, and improve the life-cycle management burden sponsors face in managing numerous unstructured and non-standardized filing details (data elements, established conditions, registered details). Taken together, these will allow for increased throughput and resource savings.

    - BIO believes that FDA's plan will improve the industry's ability to benefit from an ever-increasing rate of innovation in the areas of data, modeling, machine learning, and AI, by significantly reducing the burden associated with the current non-Agile computer systems validation framework, moving to a risk-based approach, with an emphasis on, but not limited to, Software as a Service (SaaS) offerings. Advanced technologies such as AI/ML/NLP can accelerate clinical trial data analysis and help identify adverse events quickly, thereby accelerating approval processes and reducing manual analysis.

2. **What are up to three challenges you are facing while trying to achieve these outcomes?**

    - BIO suggests that one challenge is collaboration and communication between sponsors, the FDA, and other health authorities. For example, the realization of cloud-based systems, new methods for discovering, sharing and accessing data, and advanced collaboration tools for submissions and their review, is sometimes at odds with existing data management laws, regulations, policies and practices.

      BIO recommends that alignment is needed between Global Health Authority initiatives, such as FDA's PQ/CMC and EMA's SPOR ISO/IDMP, and a needed sponsor initiative (i.e., HL7s DX-PQ) to structure and standardize sponsor content and data to enable efficient upload into Health Authority systems such as KASA.

- The time to implement initiatives from global health authorities is often longer than the advancement of new technology, standards, etc. For example, eCTD v4.0 is not yet implemented with a standard that HL7 may not support much longer. Furthermore, the lack of standards and open-source reference implementations built using Agile development approaches that can adapt and respond to an evolving technology landscape and stakeholder requirements is also a challenge. Management of these standards should ideally occur through international harmonization (e.g., ICH). BIO recommends that clear timelines and a roadmap to ensure enablement of initiatives is critical. Further, timelines help drive internal initiatives at companies that support these efforts.

- BIO suggests that another challenge may relate to digitization, namely the ability to have information (e.g., specifications) as data and not embedded in documents, and the investment required to maintaining a system that can manage such information throughout the lifecycle of the product. Additionally, as digital health technologies increase. a challenge will be determining whether FDA will expect, and the technical infrastructure be able to handle, multiple terabytes of raw sensor data with a corresponding algorithm to FDA cloud site in order for data scientists and statisticians to confirm validity of information included in the submission.

3. **What data and technical capabilities could FDA strengthen to help support its public health mission?**

- **Improved data management & standardization, move to data-driven submission**: continue to develop, standardized, and adopt data formats and definitions for regulatory submissions to ensure data is consistent, high-quality, and interoperable across different systems, enabling better data sharing and analysis and expedited decision making. This includes accelerating the entry into an interoperable Cloud-based Data Exchange ecosystem. This will also force sponsors to advance their data management capabilities to maintain compliance driving overall interoperability of the health care ecosystem.
- **Advanced Analytics**: invest in machine learning, natural language processing / generation (NLP/NLG), and predictive analytics. This will help the FDA analyze and interpret complex data sets more quickly and accurately, identify emerging safety issues, and make more informed and faster regulatory decisions. The FDA should be at the forefront of AI applications, including but not limited to demonstrating thought-leadership and deep expertise in the use of large language models.
- **Real-Time Surveillance**: by leveraging data from a variety of sources (e.g., EHR/EMR, devices, social media), the FDA could detect and respond more quickly to emerging safety issues, improve post-market surveillance, and enhance public health outcomes.
- **Cloud Infrastructure / Cloud-Based Submissions**: transforming from on-premise technology to modern cloud-based infrastructure is fundamental to the FDA's mission. Cloud platforms provide benefits such as scalability, accessibility, faster

times to market, tool stacks and cost savings that can drive outcomes, e.g., better data management, faster reviews (leveraging advanced analytics tools), and improved collaboration with stakeholders.

- **Cybersecurity**: the move to cloud is an opportunity for the FDA to continue to strengthen its data protection capabilities while at the same time leveraging modern identity management and governance tools and zero trust architectural principles to enable advanced collaboration and data discovery and sharing. The development of cloud native applications that can take full advantage of robust cloud threat detection, data loss prevention, and advanced cryptographic tools and methods will further assure the public and collaboration partners that their data is safe with the FDA.
- **Harmonization:** developing a strategic alignment across Centers (CDER, CBER, CDRH). For example, a harmonized regulatory cloud approach which could be exploring/leveraging precisionFDA and other regulatory cloud initiatives within the Agency.

4. **What opportunities or risks do you foresee for the FDA Data and Technology Strategic Plan?**

- **Opportunities:**
    - Working with other global health authorities to streamline and simplify processes and reviews.
    - Explore interactive channels for questions and answers rather than only relying on formal correspondence, to provide quicker response times.
    - Exchanging data instead of documents.
    - Moving towards cloud technology and structured data is an opportunity that can bring review consistency and efficiency. To achieve success across industry and FDA, ensure a buildable cloud platform that can be rolled out in phases with clear expectations and time to ensure readiness.
    - There is an opportunity for the FDA to partner more directly and effectively with a large ecosystem of start-up companies that are leading the way in the creation of value through the use of data, modeling, machine learning, and artificial intelligence.
    - There is an opportunity for greater external stakeholder engagement not only between Industry and FDA, but including technology companies in the life sciences domain, health care providers and patients. The DMAP, TMAP, EMAP, LMAP and CMAP cover the spectrum of strategic opportunities. That said, the risk is if the process by which the strategic, tactical, and operational plans are developed and implemented require resource/expertise beyond FDA's scope and capabilities, or that the speed of innovation far exceeds the Agency's ability to apply it to the regulatory initiatives. Initiatives such as the Advancing Regulatory Science at FDA report on more engagement through technology transfer, public-private partnerships, and intra/extramural grant programs would mitigate this risk and ensure a broad range of expertise and resources are engaged.

- **Risks:**
    - The policies and regulations implemented by FDA are different from other health authorities and it slows down world-wide patient access to medicines. Being at the forefront and helping influence global change will really help achieve this public health goal.
    - There is a risk that sponsors will be unable to effectively and efficiently structure and standardize content and data in line with FDA initiatives (PQ/CMC) for efficient upload into FDA systems (KASA) resulting in an increased manual and labor-intensive burden for sponsors.
    - FedRamp and security risks, especially when interoperating with proprietary information in a collaborative cross-region setting.
    - Time is also a risk. The pharmaceutical sector is one of the last industries to leverage these available technologies. Progressing too slowly in their adoption will impede the acceptance, utility, and benefit of making this transition.
    - It will be difficult to get the necessary knowledgeable resources to make sufficient progress.

5. What changes or trends in your industry could impact the FDA Data and Technology Strategic Plan?

- ICH and EMA initiatives around structured data; it is a challenge to meet the expectations of so many guidances as they are evolving independently of each other, and industry is trying to guess to be prepared for all possibilities
- A reluctance to change could impact the ability to leverage 21st-century technologies implementation. Therefore, thoughtful change management will be critical for success.
- A focus on data and technology at the expense of sufficient attention to the necessary workforce transformation at the FDA (and industry) could lead to a negative result. A workforce with appropriate skills and expertise will be critical to implementing and sustaining the significant changes an ambitious plan would affect.
- Artificial intelligence and machine learning (ChatGPT type of applications in the scientific/regulatory domain). Language models that support analytics that make the regulatory assessment process more automated and efficient.
- Adoption of Cloud-based and Data-Driven Submissions:
    - Use of AI and Machine Learning: the move to leverage AI/ML by sponsors to analyze data sets, support Regulatory intelligence, automate processes, etc. will require the FDA adopt similar capabilities to support the review and analysis of data generated by these technologies.
    - Increased use of Real-World Evidence/Data: sponsors are increasing the use of RWE/RWD to support regulatory submissions. There is an opportunity for FDA to implement infrastructure and adapt guidance and policies to support the use of RWE/RWD in decision making.
    - Investment in Digital Health: sponsors are increasingly investing in digital health technologies, such as wearables, sensors, and mobile health apps,

software as a medical device, etc. There is an opportunity for FDA to implement infrastructure and adapt guidance and policies to support the use of digital health technologies which may allow for faster signal or safety monitoring.
    - Diversity in clinical trials and need to include patients from more markets.
    - Increased variability in the data/technology capabilities across industry players.
    - Non-traditional players bringing innovation technologies to the space (e.g., Accumulus).

6. **How might FDA best communicate and engage stakeholders in developing and implementing the strategy?**
    - As success will depend upon both sponsor and FDA capabilities, BIO recommends that developing and implementing data and technology standards should be done in close collaboration through consortia (e.g., ICH, ICMRA) or cross-pollinated organizations.
    - BIO recommends that the FDA continues holding public meetings (e.g., the 2022 FDA Digital Transformation Symposium) or other annual or semi-annual forums. Future meetings should include sponsors, vendors, start-ups, and other regulatory agencies to ensure effective cross-dissemination of information and cross-pollination of ideas.
    - BIO recommends that FDA staff attend industry conferences (e.g., ISPE) to communicate the plan to a much broader audience than the data/technology subject matter experts that would typically interact with health authorities.
    - The Modernization Action Plans and the Advancing Regulatory Science at FDA report, outline multiple opportunities for engagement beyond the more traditional channels of FR Notices and public comment periods, conferences, trade association engagement, etc. BIO suggests that more offerings per the FDA Small Business and Industry Assistance (SBIA) program/resources would be ideal as a further means of communication in additional to traditional public meetings.
    - BIO recommends that FDA allow stakeholders to participate in user testing, and FDA incorporate that feedback within development phase.

Sincerely,

/s/
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Biotechnology Innovation Organization