FDA Issues Draft Guidance On the Use and Curation of Real-World Data in Registries

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On the Subject

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The US Food and Drug Administration has issued draft guidance outlining the agency’s recommendations for using real-world data from (and curating such data in) registries to support regulatory decision-making. Pharmaceutical manufacturers and other life-sciences industry stakeholders, as well as registry developers, should review the guidance and consider submitting comments before the February 28, 2022, deadline.

IN DEPTH
On November 30, 2021, the US Food and Drug Administration (FDA) announced the availability of its draft *Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products Guidance for Industry* (Draft Guidance). The Draft Guidance outlines the agency’s recommendations for using real-world data (RWD) from registries and curating RWD in registries to support regulatory decision making. Specifically, the Draft Guidance describes relevant considerations for evaluating the reliability and utility of data from registries in supporting clinical trials, observational studies, and approvals for new indications for drugs and biological products under certain circumstances.

Pharmaceutical manufacturers and other stakeholders from the life sciences industry, as well as entities that may develop or maintain registries, should consider the Draft Guidance for insights into how registries may be leveraged for regulatory decision making and consider submitting comments. FDA recommends that stakeholders submit any comments to the Draft Guidance by February 28, 2022.

**Background**

The 21st Century Cures Act (Cures Act) established section 505F of the Federal Food, Drug, and Cosmetic Act (FDCA), requiring FDA to establish a program to evaluate the potential use of real-world evidence (RWE) as well as a framework for the RWE Program. The Draft Guidance is the most recent guidance FDA has issued under the RWE Program. The RWE Program is an important element in FDA’s ongoing efforts to integrate more information regarding the patient experience with medical products into its regulatory decision making. The program recognizes that sources of RWD, including electronic health records (EHRs), medical claims, pharmacy and laboratory databases, and medical device outputs may contain valuable insights regarding patient and user experiences with regulated products. Stakeholders, including researchers, manufacturers, professional associations, disease advocacy organizations, contract research organizations (CROs) and technology companies, use data from these external sources to develop registries that collect standardized clinical and other data for a defined population, a particular disease or condition, or a particular product. The purposes of registries vary and may include, for example, monitoring of adverse events and outcomes for certain patient populations, satisfying FDA postmarket surveillance obligations, or supporting provider quality improvement and quality assessment activities.

The Draft Guidance sets out specific considerations for stakeholders regarding (i) a registry’s fitness for use in regulatory decision making, (ii) points to consider when linking a registry to another data source (e.g., EHRs or technologies such as wearables and biosensors), and (iii) specific considerations for regulatory review of registry data to support approvals. These considerations are also informative for developers who may be interested in providing registry data to sponsors or their CROs.

**Fitness for Use in Regulatory Decision Making**

The suitability of registry data may vary based on myriad factors, such as how the population is enrolled, general data quality, and how a registry is created and
maintained (e.g., entirely retrospective or prospective, or a hybrid). Consistent with prior guidance that it has issued under the RWE Program, FDA recommends that sponsors consider the **relevance** and **reliability** of data before using it as RWD for regulatory decision-making purposes.

**Relevance**

To assess relevance, sponsors should confirm that registry data includes key data elements for the intended use (e.g., patient characteristics, exposures, outcomes) and a sufficient number of representative patients. Additionally, FDA suggests that objective endpoints (e.g., death or hospitalization) captured in a registry are often more useful in the regulatory context than subjective endpoints (e.g., pain), as subjective endpoints are difficult to meaningfully quantify.

The Draft Guidance notes that the method for selecting the individuals whose data will be included in a registry may impact the relevance of the data for a sponsor’s regulatory purposes. For example, the characteristics of an individual who (i) meets the inclusion and exclusion criteria for a registry that was established for a purpose distinct from the sponsor’s regulatory purposes, or (ii) is more likely to remain enrolled in a registry after agreeing to participate, may influence the nature of the registry data. Sponsors and registry developers alike should consider the impact of these factors on the relevance of registry data that they are considering using to support regulatory purposes.

**Reliability**

To demonstrate the reliability of registry data, sponsors should implement processes and procedures to help assure the quality of the registry data and oversee the registry’s operation.

FDA stated it will consider the following factors to assess whether registry data is reliable:

- Data accrual (*i.e.*, how the data were collected)

- Whether processes and personnel in place at the time of data collection provide assurance that data integrity is upheld and errors are minimized

- Whether there are privacy controls to preserve confidentiality and security, and

- Whether any patient-reported outcomes (PROs) are appropriately captured, taking into consideration the recommendations in FDA’s December 2009 guidance, *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Changes*

FDA recommends that sponsors establish and train registry staff on procedures and policies and engage in resource planning. The Draft Guidance suggests several areas for specific policies and procedures, such as the establishment of a data dictionary (which should establish data elements, ranges and allowable values, and source-data references); rules for validating queries; a process for data collection, curation, management and storage; compliance with 21 C.F.R. Part 11; and methods
to capture and account for human error (e.g., coding, interpretation and transformation errors). Sponsors should review established policies and procedures on a regular basis to ensure data consistency, and they should perform routine descriptive statistical analyses to detect any missing or inconsistent data.

For registries maintained as electronic databases, FDA recommends specific safeguards, including:

- Maintaining a version control system.
- Employing a process to ensure data are not unintentionally altered when transferred.
- Updating old technology and integrating data maintained in outdated programs or software.
- Accounting for clinical changes over time (e.g., criteria for disease diagnosis; cancer staging).
- Explaining auditing rules and the errors identified based on audit finding.
- Employing a system for correcting errors.

A registry also must comply with applicable human subject protection requirements and privacy and data-security laws. Sponsors and registry developers should be particularly mindful of whether the establishment and maintenance of a registry would fall within the scope of FDA’s good clinical practice regulations, which apply to “clinical investigations.” Even if a registry itself does not fall within the scope of such FDA regulations, a registry developer may wish to consider whether to nonetheless structure the registry to comply with such regulations due to the contemplated recipients of registry data and their likely use cases. Therefore, as sponsors or registry developers are developing a registry they should consult with institutional review boards or independent ethics committees to help assure reliability of the registry data.

### Linking Registries to Other Data Sources

One registry may not necessarily provide the entirety of the data that a sponsor requires for a particular regulatory purpose. Fortunately, the proliferation of tokenization software and other technologies that enable, without the disclosure of identifiers, the linking of disparate data sets regarding common individuals has made it easier to obtain a more comprehensive picture of a data subject.

The Draft Guidance provides specific considerations when sponsors seek to link data from multiple sources (e.g., from medical claims, EHRs, digital health technologies (such as wearables) or other registries). FDA encourages using common data elements to promote standardized, consistent and universal data collection among registries for better results when linking registry data.

**Appropriateness of Linking Registries to Other Data Sources**
Linking data may be useful if a particular registry does not capture all of the necessary data elements to sufficiently address a sponsor’s question. However, sponsors should consider:

- Whether linkage is appropriate for the proposed research question.
- Whether linking databases can be accomplished accurately, and whether the potentially linked data can be appropriately matched to patients in the registry.
- Whether the variables of interest are defined consistently across datasets.
- Whether the data is complete and accurate, such that it meets registry objectives.

**Data Integrity Considerations**

Sponsors should also consider the potential impact on data integrity of linking data sources, and have ready solutions for common issues such as redundant data, inconsistencies across data sets, and privacy and data security. FDA recommends that sponsors establish a procedure to address adequacy of patient-level linkages (i.e., that the same patient is being matched) and compliance with various jurisdictional requirements when seeking to link patient-level data. Further, sponsors should assess the compatibility and interoperability of data systems (including when there are software updates), that any automated electronic transmission of data elements is consistent and repeatable, and that the linking process accurately, consistently and comprehensively captures the relevant data. Sponsors should be able to make available to FDA during sponsor inspections any documentation of the process used to validate the transfer of data.

**FDA Submissions**

FDA recommends that sponsors meet with the agency to review their proposed plan to incorporate a registry before conducting an interventional or non-interventional study. The meeting can be used to address issues concerning data integrity, confirmation of data validation, and issues concerning linkage and related protocols (if applicable) and outcomes. In preparation for the meeting, sponsors should also prepare protocols and submit a plan for statistical analysis to FDA for review and comment.

Sponsors should ensure that patient-level data complies with applicable legal and regulatory requirements and that the sponsor can make applicable attestations to FDA. This is particularly relevant when using data from a third-party registry. If a third party owns or otherwise licenses the applicable registry data to the sponsor, the sponsor should ensure its agreement with the third party requires the third party to share patient-level data with FDA as part of the application process and otherwise cooperate with any inspections or reviews of the registry or registry data by FDA.

**Takeaways**
While randomized, controlled trials remain the gold standard to support clinical decision-making, the way in which stakeholders generate, analyze and use data in the regulatory landscape is evolving. Registries have the potential to allow for expanded studies and more efficient regulatory decision making when used with the proper safeguards. Sponsors, registry developers and other stakeholders involved in the use or generation of RWD and RWE to support regulatory decision making should consider submitting comments to the Draft Guidance (Docket No. FDA-2021-D-1146). FDA recommends that the public submit comments by February 28, 2022, to ensure the agency considers them before it begins work on the final version of the guidance.

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