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

Reference: Docket No. FDA-2023-D-4395 for “Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices”; Draft Guidance for Industry

Dear Madam or Sir,

PDA appreciates the opportunity to provide feedback to the FDA as the agency provides clarification on its process of evaluating real-world data (RWD) to determine whether they are of sufficient quality for generating real-world evidence (RWE) that can be used in FDA regulatory decision-making for medical devices. In our attached comments, PDA offers specific comments and feedback that we believe will be helpful in the further development of this important guidance.

PDA is a non-profit international professional association of more than 10,000 individual members scientists having an interest in fields of pharmaceutical, biological, device manufacturing, and quality. Our comments have been prepared by a committee of PDA members with expertise in the areas covered in the Public Docket on behalf of PDA’s Science Advisory Board.

If you have any questions, please do not hesitate to contact me via email at wright@pda.org.

Sincerely,

Glenn E. Wright
President and CEO

cc. Josh Eaton,PDA; Carrie Horton,PDA; Jessie Lindner,PDA; Danielle Bretz,PDA

PDA (Parenteral Drug Association®) Comments to FDA's Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices: Draft Guidance

General Comments Section:

Comment
PDA acknowledges and agrees with the draft guidance content addressing data relevance and reliability in section V., and the overall recommendation in lines 357-358 that *"sponsors should ensure that RWD were collected using good data management practices."* However, we observe that the guidance does not include data governance, which is generally considered a critical function to enabling data as an asset, as in this case to support Real World Evidence. Further, the applicability of good data management and data quality reaches broadly across data use cases within the purview of The Agency, for example, Quality Management Maturity, AI/ML, and data integrity compliance with CGMP. Including data governance as a suggested discipline will guide users to adopt rules/standards, responsibilities, control strategies, and improvement mechanisms essential for enabling agile data management and data quality. Data governance also assures compliance by design by centralizing accountability and oversight for the implementation of policies and procedures to meet regulations and requirements for privacy, security, transparency, etc. If possible, The Agency may consider referencing an established framework to further support industry. For example, in the recent FDA Discussion Paper, "Using Artificial Intelligence & Machine Learning in the Development of Drug & Biological Products," FDA suggests adopting the Government Accountability Office (GAO) framework, "Artificial Intelligence: An Accountability Framework for Federal Agencies and Other Entities," as a model to enable human-led AI governance. We note that the GAO is also leading initiatives for the implementation and assessment of data governance frameworks within other industries.
PDA proposes The Agency include a glossary that defines key terms either in a general way or within the specific context of this guidance and RWE or direct the user to where these definitions may already be defined. For example, numerous terms are included in reference to data management and data quality such as "missingness", "accrual", and "data quality." These terms may vary across disciplines and within the data management landscape.

Section I: INTRODUCTION (lines 16-60)

Line number(s) of the relevant text (e.g., 2-8)	Current Text	Comment	Proposed Change	Rationale for Change
47-48	"FDA recognizes and anticipates that the Agency and industry may need up to 60 days to perform activities to operationalize the recommendations within the final guidance."	PDA recommends a duration longer than 60 days be allotted for the operationalization of the recommendations in this guidance.	"FDA recognizes and anticipates that the Agency and industry **needs a minimum of 90 days with a maximum of 6 months, with the option to request additional time** to perform activities to operationalize the recommendations within the final guidance."	Due to the required coordination and approval across multiple departments to review the ongoing trial models and statistical significance and robustness of the data, additional time is needed to successfully complete this process.

Section III: SCOPE (154-186)

Line number(s) of the relevant text (e.g., 2-8)	Current Text	Comment	Proposed Change	Rationale for Change
168	"This draft guidance does not address the use of non-clinical data, adverse event reports, secondary use of clinical study data, or systematic literature reviews."	PDA suggests providing rationale for why the items listed in line 168 would be considered "out of scope" for this document. For example, is guidance for the use of these examples for real world data/real world evidence found elsewhere? If this guidance is not found elsewhere, we would suggest including that guidance in this document.		These sources provide relevant and reliable real world data for product safety and efficacy and improvement. Additionally, in this portion of the document, these items are listed as "out of scope" while later in the document in line 1038, these items are used as reference examples in the text.
155	"This draft guidance is applicable for the use of RWE to support regulatory submissions for medical devices."	PDA would encourage The Agency to clarify expectations for combination products approved by the Center for Biologics Evaluation and Research (CBER)/Center for Drug Evaluation and Research (CDER).		No guidance on RWD/RWE gives a pathway forward for using RWD/RWE for the device constituent of combination products approved as a drug product.

Regulatory Context in Which Use of RWE May be Appropriate

A. General Considerations for the use of RWE (191-260)

Line number(s) of the relevant text (e.g., 2-8)	Current Text	Comment	Proposed Change	Rationale for Change
198-199	"FDA recognizes that RWE can be generated from a variety of RWD sources that are primarily intended for another purpose."	PDA recommends that The Agency address HIPAA concerns at this juncture of the document.	"FDA recognizes that RWE can be generated from a variety of RWD sources that are primarily intended for another purpose. **Attention should be given to applicable global privacy regulations such as HIPAA and GDPR."**	This is addressed later in document, but PDA feels this should be moved to the first instance of RWD/RWE sources being used in the guidance document.
209-220	"Data sources that may be considered RWD sources include the following: • Registries • EHRs • Administrative claims data; • Patient-generated data created, reported, or gathered by patients including in-home use settings (e.g., data from digital health technologies (DHTs) such as wearables); • Device-generated data (e.g., implantable devices,	PDA suggests providing clarification if summary data would be sufficient when source data is not available to the sponsor.	"Data sources that may be considered RWD sources include the following: • Registries • EHRs • Administrative claims data; • Patient-generated data created, reported, or gathered by patients including in-home use settings (e.g., data from digital health technologies (DHTs) such as wearables); • Device-generated data (e.g., implantable devices,	Proprietary data and registries might only allow for queries without a sponsor having full access to the data.

	physiological monitoring devices); • Public health surveillance data (e.g., COVID-19 case surveillance); • Clinically annotated biobanks; and • Medical device data repositories (e.g., imaging, electrocardiography databases)."		physiological monitoring devices); • Public health surveillance data (e.g., COVID-19 case surveillance); • Clinically annotated biobanks; and • Medical device data repositories (e.g., imaging, electrocardiography databases). **Note: Source data might not always be available. Inference from summarized data may be made when source data is not available provided that there are considerations for the method of summarization, the number of original source values comprising the data set, and evaluation of any statistical treatment of that data, if any."**	
209 – 220	"Data sources that may be considered RWD sources include the following: • Registries • EHRs	PDA suggests providing clarification if the listed items are the only forms of RWD sources the Agency will accept.	"Data sources that may be considered RWD sources include, **but are not limited to**, the following: • Registries	This will enable the utilization of other potential data sources.

	• Administrative claims data; • Patient-generated data created, reported, or gathered by patients including in-home use settings (e.g., data from digital health technologies (DHTs) such as wearables); • Device-generated data (e.g., implantable devices, physiological monitoring devices); • Public health surveillance data (e.g., COVID-19 case surveillance); • Clinically annotated biobanks; and • Medical device data repositories (e.g., imaging, electrocardiography databases)."		• EHRs • Administrative claims data; • Patient-generated data created, reported, or gathered by patients including in-home use settings (e.g., data from digital health technologies (DHTs) such as wearables); • Device-generated data (e.g., implantable devices, physiological monitoring devices); • Public health surveillance data (e.g., COVID-19 case surveillance); • Clinically annotated biobanks; and • Medical device data repositories (e.g., imaging, electrocardiography databases)."	

V. Assessing Data Relevance and Reliability

A. Relevance (377-382)

Line number(s) of the relevant text (e.g., 2-8)	Current Text	Comment	Proposed Change (text to be introduced)	Rationale for Change
363 -367	"Studies using RWD should also be carefully designed to mitigate potential bias, and a study protocol and analysis plan should be created prior to analyzing RWD, regardless of whether the RWD are extant or if they are to be collected in the future. An existing RWD source may have some inherent sources of bias that could limit the relevance or reliability for drawing causal inferences between medical device exposures and outcomes."	PDA suggests that these studies align with good data governance practices.	"Studies using RWD should also be carefully designed to mitigate potential bias, and a study protocol and analysis plan should be created prior to analyzing RWD, regardless of whether the RWD are extant or if they are to be collected in the future. An existing RWD source may have some inherent sources of bias that could limit the relevance or reliability for drawing causal inferences between medical device exposures and outcomes. **In such instances, where RWD is still considered to be relevant, mitigation strategies should be considered to identify and address potential sources of bias, and this is in keeping with data governance."**	At times, the only data available is limited and has inherent bias. To ensure data reliability, this data needs to be assessed and evaluated to account for inherent bias so that data is acceptable. This addition also ties into our proposal to add data governance found in the General Comments section of this document.

V. Assessing Data Relevance and Reliability

A. Relevance

(1) Data Availability (384- 416)

Line number(s) of the relevant text (e.g., 2-8)	Current Text	Comment	Proposed Change	Rationale for Change
414-416	"If the RWD source is insufficient on its own, the sponsor should determine whether supplemental data sources are available and sufficient to provide any missing information necessary to address the study question."	PDA encourages the provision of guidance from The Agency regarding effective methodology in vetting supplemental data sources and in combining data from more than one source in order to supplement missing information from RWD sources.		The provision of Agency guidance on how to supplement missing information would aid the industry in their adherence to the recommendations in this document.

V. Assessing Data Relevance and Reliability

B. Reliability

(1) Data Accrual (466-512)

Line number(s) of the relevant text (e.g., 2-8)	Current Text	Comment	Proposed Change	Rationale for Change

505	• "Data Cleaning and cross-referencing procedures;"	PDA has proposed the inclusion of, or reference to, a glossary of terms to assure clarity on the meaning of terms such as "cleaning." In addition, we propose to replace "data cleaning" with the term "data refinement" to address additional activities that may be needed such as data transformation or enrichment.	• "Data **Refinement** and cross-referencing procedures;"	Data refinement is a broader term that includes additional activities that may be needed to ensure the quality of the data.

V. Assessing Data Relevance and Reliability

B. Reliability

(2) Data Quality and Integrity (514-630)Line number(s) of the relevant text (e.g., 2-8)	**Current Text**	**Comment**	**Proposed Change**	**Rationale for Change**
551	"Study sample size should be adequate to address study question."	PDA would encourage The Agency to clarify this statement to reduce misinterpretation from a statistical point of view.	"Study sample size should be adequate to address study question. **Rationale for sample size should be provided."**	Regarding extant data, it is extremely difficult to have an "adequate" sample size, especially in the case of exploratory analysis and

				hypothesis setting. Although, you cannot change the power and sample size of existing studies, the sponsor may want to use the conclusions as supportive information.
579-580	"Sponsors should ensure any automated electronic transmission of data fields to a repository (e.g., registry or data warehouse) occurs in a consistent and reproducible fashion."	PDA suggests the addition of the term "secure" in this sentence.	"Sponsors should ensure any automated electronic transmission of data fields to a repository (e.g., registry or data warehouse) occurs in a **secure**, consistent, and reproducible fashion."	Transmission of data must be protected from manipulation (intentional or otherwise) and error. Good data security practices should be followed.
565-567	" • If extant RWD are used, adequate statistical power to detect a clinically meaningful difference should be determined based on the available sample size and should account for any sampling of participants from the data source. ▪ If there is inadequate statistical power based on the available sample size, sponsors should consider the use of multiple existing RWD sources to increase sample size.	PDA recommends The Agency provide clarification on if they will require any special statistical adjustments for interim analysis. (e.g., alpha spending)	" • If extant RWD are used, adequate statistical power to detect a clinically meaningful difference should be determined based on the available sample size and should account for any sampling of participants from the data source. ▪ If there is inadequate statistical power based on the available sample size, sponsors should consider the use of multiple existing RWD	Typical statistical practice requires an alpha spending strategy. It is unclear if this is required in these situations.

	▪ If the sample size could be expected to increase in the near future (e.g., device is new to market), sponsors should consider conducting "interim" analysis with extant data, monitoring uptake, and conducting final analysis when sufficient sample size is available."		sources to increase sample size. ▪ If the sample size could be expected to increase in the near future (e.g., device is new to market), sponsors should consider conducting "interim" analysis with extant data, monitoring uptake, and conducting final analysis when sufficient sample size is available. **No statistical adjustment for alpha will be required after an interim analysis."**	
607-610	"When the RWD source is not owned by the sponsor, the sponsor should attempt to obtain participant-level data for each participant. If not available, the sponsor should define the entity(ies) which do have access/permission for data entry, quality assurance, storage, aggregation or other linkage, and assessment of	This limits the data that can be used, especially public registries which are not available to regulators. Sponsor should seek to understand and document the data standards/registry standards in use by the entity in addition to elements already listed (e.g., QA, linkages etc.).	"When the RWD source is not owned by the sponsor, the sponsor should attempt to obtain participant-level data for each participant. If not available, the sponsor should define the entity(ies) which do have access/permission for data entry, quality assurance, storage, aggregation or other linkage, and assessment of	Often data is proprietary and not available to 3rd party sources such as the FDA. The use of globally recognized standards will add confidence to the overall data reliability.

	traceability from data entry to dataset, as applicable. Sponsors should consider the level of access which could be shared with FDA and the potential for third parties to provide participant-level data directly to FDA. The availability of data should be described in the regulatory submission for FDA review."		traceability from data entry to dataset, as applicable. Sponsors should consider the level of access which could be shared with FDA and the potential for third parties to provide participant-level data directly to FDA. **Sponsors may request that data owners/suppliers provide access to patient level data directly to FDA while protecting proprietary aspects of the data from the sponsor (similar to LOAs). However, the inability for direct access to patient level data either to the sponsor or to FDA should not automatically preclude the data from use. Accessibility should be assessed in context with known governance and control of the source data (i.e., "masked data") from the data owner/supplier.** The availability of data should be described in the regulatory submission for FDA review."	

VI. Considerations for Methodologies for Collection and Analysis of RWD to Generate RWE

B. Defining study design elements

(3) Appropriate integration of data elements within study design and analysis (848- 878)

Line number(s) of the relevant text (e.g., 2-8)	Current Text	Comment	Proposed Change	Rationale for Change
863-865	"Other variables may also exhibit heterogeneity in risk of the outcome (i.e., modifiers or "interaction" terms) and stratified analyses for these variables may also be appropriate."	This is hard to avoid with observational data. This is inherently a risk.	"Other variables may also exhibit heterogeneity in risk of the outcome (i.e., modifiers or "interaction" terms) and stratified analyses for these variables may also be appropriate. **Stratified analysis using observational data may represent a risk that, if present, will need to be mitigated (e.g., when cell sizes are too small)."**	The nature of observational data does not always permit statistically valid stratified analysis (e.g., cell sizes too small).