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OFFICE OF THE VICE PRESIDENT – RESEARCH AND INNOVATION

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Submitted through: www.regulations.gov *(if applicable)*

March 9, 2022

Lauren K. Roth
Associate Commissioner for Policy
Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Building, 4th Floor
Silver Spring, MD 20993-0002

RE: Docket No. FDA-2021-D-1214: Considerations for the Use of Real-World Data and Real-World Evidence To Support Regulatory Decision-Making for Drug and Biological Products; Draft Guidance for Industry; Availability (December 9, 2021)

Dear Ms. Roth:

I write on behalf of the University of California (UC) system with regard to the draft guidance for industry entitled "Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products" published on December 9, 2021.

The UC system – comprised of ten campuses, six academic health centers, and three affiliated U.S. Department of Energy national laboratories – stands at the forefront of cutting-edge research and technology development. As a system, UC receives approximately $6 billion annually of extramural awards to support research conducted throughout all UC locations. The UC system strives to conduct research with the highest ethical standards and utmost precautions to protect human subjects.

The UC system appreciates the clear guidance regarding FDA's expectations for clinical studies using real-world data (RWD) submitted to FDA for approval of a new indication for a drug already approved under section 505(c) of the FD&C Act or to satisfy post-approval study requirements. We understand that this guidance focuses primarily on clinical studies that are non-interventional but additional clarification is needed regarding Institutional Review Board (IRB) review. As such, we write to suggest clarifications to the guidance document regarding 1) certain non-interventional studies that may not trigger 21 CFR parts 50 and 56, and 2) when 21 CFR 50 and 56 are triggered, options to seek a determination of exemption from IRB review. Further information is provided below.

1. Clarification Regarding 21 CFR 50 and 56 in Non-Interventional, Non-Interactive Studies

The UC system appreciates the risk-based distinction FDA makes in its guidance between studies that only use RWD for "the analysis of data reflecting the use of a marketed drug in routine medical practice" [1] from studies that add "ancillary protocol-specified activities or procedures (e.g., questionnaires, laboratory tests, imaging studies)" [2] to the collection of RWD. The FDA notes that both types of studies are not clinical investigations under 21 CFR 312 and an IND is not required. However, the FDA also notes the need for subject protections under 21 CFR 50 and 56 for both these studies.

UC believes that there is value in separating out risk considerations between the two types of studies indicated in this guidance, particularly for IRB review. For studies that include ancillary activities and procedures with the collection of RWD, subject protections under 21 CFR 50 and 56 may be triggered. However, we suggest that studies using RWD alone would benefit from an explicit statement that such studies **do not** trigger subject protections under 21 CFR 50 and 56.

To facilitate decision-making by sponsors and institutions, and to avoid unnecessary barriers to use of RWD, we suggest that FDA add a table such as the following. This table includes references to the Common Rule, as even if 21 CFR 50 and 56 are not triggered, institutions providing data to sponsors may still need to consider the applicability of the Common Rule, depending on factors such as federal funding or institutional policy applying Common Rule requirements regardless of funding source. Note that this table also suggests an approach of considering some post-approval studies as public health activities under both the Common Rule and HIPAA. *It would be useful to the regulated community for the FDA and the Office for Human Research Protections (OHRP) to explore this option.*

	Approval of a new indication for a drug already approved under section 505(c) of the FD&C Act	**Satisfy post-approval study requirements**
Non-Interventional <u>but</u> Interactive (includes ancillary protocol-specified activities or procedures)	• Triggers 21 CFR 50 and 56 • May qualify for Common Rule exemption determinations	• Triggers 21 CFR 50 and 56 • May qualify for Common Rule exemption determinations • May be public health activity under Common Rule 46.102(l)(2)
Non-Interventional <u>and</u> Non-Interactive	• Does not trigger 21 CFR 50 and 56 • Sites should consider whether Common Rule or	• Does not trigger 21 CFR 50 and 56 • Public health activity under Common Rule 46.102(l)(2)

[1] Lines 117-118
[2] Lines 119-120

(no ancillary protocol-specified activities or procedures)	equivalent institutional policies apply	• Public health activity under HIPAA 45 CFR 164.512(b)(1)(iii)

UC's recommended approach would harmonize FDA rules with human subject protections under 45 CFR 46 as required by the 21st Century Cures Act.[3] In addition, utilizing this approach gains efficiencies by reducing unnecessary IRB review in some cases. Sponsors simply collecting and using RWD, with sites merely providing RWD, often would not trigger 45 CFR 46 requirements, either because provision of coded data does not involve "human subjects" as defined under 45 CFR 46.102(e)(1) or would not "engage" a site in human subjects research under OHRP guidance.[4]

To facilitate site decision-making, FDA should consider enhancing this draft guidance with a reminder about, if not an outright endorsement of, OHRP's guidance on Coded Private Information or Biospecimens Used in Research. This tiered risk approach would streamline IRB review and reduce confusion among lead sponsors, physicians and/or site IRBs. It would also clarify that local IRB review is not needed in all circumstances, especially when such IRB review would not meaningfully add to protection of human subjects.

2. Clarification Regarding Exemption Determinations

We appreciate the FDA is clear in its guidance to "accelerate medical product development and bring innovations faster and more efficiently to the patients who need them." For studies that might trigger subject protections under 21 CFR 50 and 56, there is a further opportunity to harmonize FDA requirements with 45 CFR 46 specific to exemption determination. We recommend that FDA take the two following steps in this guidance document to harmonize its approach to 45 CFR 46, which will allow for an appropriate level of human subject protections.

First, on lines 202-205 of the draft guidance, the FDA provides that: "When a non-interventional study includes additional protocol-specified activities and procedures, study monitoring should also ensure that applicable human subject protections are met and data integrity is maintained[15]." This information ends with a footnote stating that: "15. See, e.g., 21 CFR 56.111, which includes as a criterion for IRB approval of research that the research plan, where appropriate, makes adequate provision for monitoring data collected to ensure the safety of subjects."

UC suggests that the FDA revise lines 202-205 and clarify the associated footnote 15 to be consistent with the approach provided above and consistent with lines 117-125 and lines 207-211 of the guidance document. Specifically, some studies covered by this guidance document would likely qualify for exemption under 45 CFR 46.104 (for example, a study involving a questionnaire and collection of RWD).

[3] See also the 2012 recommendations from the HHS Secretary's Advisory Committee on Human Research Protections
[4] See OHRP 2009 Guidance on Determining When Institutions are Engaged in Research

As such, UC strongly recommends that the FDA revise its guidance to provide the following clarification:

> When a non-interventional study includes additional protocol-specified activities and procedures, study monitoring should also ensure that applicable human subject protections are met and data integrity is maintained[15]. Depending on institutional requirements and the nature of procedures, this might involve a determination of exemption from IRB review. More information on exemption determinations can be found in the below.

Second, UC recommends that FDA further harmonize its approach of rules related to human subject protections by allowing institutions to utilize certain exemption determinations available under 45 CFR 46.104 but not currently available under 21 CFR 56.104. Drawing from a similar approach FDA took in its guidance on "IRB Waiver or Alteration of Informed Consent for Clinical Investigations Involving No More Than Minimal Risk to Human Subjects," we suggest that FDA provide information about allowable exemption determinations for research that utilizes RWD to support an FDA marketing application. For example, the following information could be added:

> *5. Allowable IRB Exemption Determinations for Non-Interventional Studies that Include Ancillary Protocol-Specified Activities or Procedures*
> In light of the Cures Act amendment to the FD&C Act described in the introduction, FDA intends to revise its requirements pertaining to exemptions from IRB review to align with the human subject protection regulations found at 45 CFR 46. However, until FDA promulgates these regulations, we do not intend to object to an IRB allowing for certain exemption determinations currently available under 45 CFR 46.104 when the IRB finds and documents that:
> - The clinical investigation involves no more than minimal risk (as defined in 21 CFR 50.3(k) or 56.102(i)) to the subjects;
> - The exemption determination will not adversely affect the rights and welfare of the subjects;
> - Consent appropriate to the activities will be obtained, but would not require all the elements of consent at 21 CFR 50.25 except that any consent form or process must include element 21 CFR 50.25(a)(5);
> - Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

Promulgation of these changes in the guidance will greatly reduce administrative burden between the regulations governing human subjects research, adhere to appropriate human subjects protections provided by the Common Rule, and accelerate minimal risk FDA-regulated research.

We appreciate the opportunity to comment on this guidance document and your commitment to improve efficiency for IRBs and clinical investigators involved in minimal risk research. If you have any questions concerning our comments, please contact Agnes Balla, Research Policy Manager, at agnes.balla@ucop.edu.

Sincerely,

Lourdes G. DeMattos
Associate Director
Research Policy Analysis & Coordination
University of California, Office of the President