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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2026-N-0005]

Biomarker Incubator: Urinary Kidney Safety Biomarkers; Request for Information

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; request for information.

SUMMARY: The Center for Drug Evaluation and Research (CDER) of the Food and Drug Administration (FDA or Agency) is announcing a request for information regarding a regulatory science initiative. The aims of the initiative are to advance biomarker validation through the compilation of data from multiple sources and through a specific pilot project focused on aggregating data for biomarkers of drug-induced kidney injury. The purpose of this notice is to inform the public of the aims of this initiative, to encourage human data submission and sharing, and to identify opportunities to enhance interactions between relevant stakeholders and FDA. The Agency intends to use the information submitted to inform future activities related to data sharing, biomarker development, and broader translation of biomarkers of drug-induced kidney injury.

DATES: Either electronic or written comments on the notice must be submitted by **[INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]**.

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. The https://www.regulations.gov electronic filing

system will accept comments until 11:59 p.m. Eastern Time at the end of **[INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]**. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are received on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: https://www.regulations.gov. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to https://www.regulations.gov will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on https://www.regulations.gov.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2026-N-0005 for "Biomarker Incubator: Urinary Kidney Safety Biomarkers; Request for Information." Received comments filed in a timely manner (see **ADDRESSES**) will be placed in the docket and, except for those submitted as "Confidential Submissions," will be publicly viewable at https://www.regulations.gov or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on https://www.regulations.gov. Submit both copies to the Dockets Management Staff. If you do not wish your

name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to https://www.regulations.gov and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

FOR FURTHER INFORMATION CONTACT: Yvonne Knight, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 2142, Silver Spring, MD 20993, 301-796-2133, Yvonne.Knight@fda.hhs.gov, with the subject line "Kidney Biomarker for CDER."

SUPPLEMENTARY INFORMATION:

I. Background

CDER in partnership with the Quantitative Medicine Center of Excellence is undertaking a regulatory science initiative to aggregate biomarker data from multiple sources (e.g., clinical trials from multiple drug development programs) for the purpose of validating biomarkers for use in drug development. This notice seeks to: (1) inform the public of this initiative, herein referred to as the "Biomarker Incubator"; (2) request

voluntary submission of human data to support the goals of the pilot phase of the Biomarker Incubator initiative; and (3) obtain input on the scope and direction of the Biomarker Incubator initiative.

The 21st Century Cures Act established a formal pathway for biomarker qualification, codified under section 507 of the Federal Food, Drug, and Cosmetic Act, through which FDA may qualify a biomarker for a specific context of use in drug development following a structured evidentiary review process. The qualification process often relies on assembly of data from academic or industry-sponsored studies, typically through consortia. Biomarker data are commonly generated within individual drug development programs for various purposes, such as to evaluate pharmacodynamic responses and safety in early phase trials or to complement assessments of efficacy in later phase trials. FDA may identify a need to characterize a biomarker to inform regulatory decision-making where qualification activities are not being considered. As such, FDA staff often undertake research efforts to assemble human data from different programs to better characterize biomarker relationships with outcomes and develop endpoints that may be used to expedite drug development. Examples of disease areas where these efforts have been undertaken by the Agency include pulmonary hypertension, schizophrenia, and hepatitis C (Chen et al. 2013; Kalaria et al. 2021; Kalaria et al. 2020). However, these biomarker characterization studies are complicated by heterogeneity in data collection protocols, the possibility that assays used to measure the biomarker or biomarkers may not be valid, the absence of standardized submission formats, and a limited volume of data (because such data are viewed as exploratory and not uniformly submitted to FDA). Therefore, CDER is seeking to develop infrastructure

that could help us understand best practices for biomarker data generation, streamline processes for requesting voluntary data submission, and create a platform to analyze data. Ultimately, improving CDER's ability to evaluate novel biomarkers could facilitate the generation of higher quality biomarker data, expanded use of novel biomarkers, more consistent interpretation of findings from biomarker studies, and development of novel endpoints that can support a range of regulatory and drug development decisions. The initiative outlined in this notice is intended to complement FDA's existing qualification framework by strengthening FDA's review of formal qualification submissions and advancing the use of biomarkers that may not be in the qualification pipeline.

II. Pilot Project

FDA has focused on advancing the use of biomarkers of drug-induced kidney injury (DIKI) as a pilot project under this Biomarker Incubator initiative. In 2018, FDA qualified a panel of biomarkers (including the six biomarkers listed in this notice) for use in conjunction with traditional measures to aid in the detection of kidney tubular injury in phase 1 trials with healthy volunteers when there is an a priori concern that the drug may cause renal tubular injury in humans. The qualification submission was based on data submitted jointly by the Foundation for the National Institutes of Health Biomarkers Consortium and the Predictive Safety Testing Consortium of the Critical Path Institute (C-Path).

Following the qualification of the panel of six biomarkers, other efforts were made to advance biomarker use in drug development. C-Path created the Biomarker Data Repository (BmDR) in 2019, starting with a focus on urinary kidney safety biomarkers with intent to expand to other organ safety biomarkers. The goal of the BmDR is to

compile and provide stakeholders with large, reliable datasets containing masked, deidentified nonclinical and clinical study data on translational safety biomarkers. In May 2022, C-Path also convened the "International 2022 Drug-induced Kidney Injury Biomarker Workshop." Participants in this workshop highlighted an unmet need for better tools to detect DIKI at earlier and reversible stages, which would protect study participants by reducing clinically significant DIKI. Further, patient representatives attending the workshop expressed desire to share their data to support safety and drug development.

As part of CDER's efforts to assess the performance and use of qualified and exploratory biomarkers of DIKI in drug development, and to complement the data accumulating through the BmDR, FDA began aggregating data on urinary kidney safety biomarkers that had previously been submitted to FDA. The Agency also requested voluntary submission of data from specific companies that had generated such data but had not yet submitted those data to FDA. These data were not expected to be in the BmDR already and were limited in size and scope. Specific urinary kidney safety biomarkers of interest for the previously mentioned efforts and the current request include cystatin C (CysC), osteopontin (OPN), kidney injury molecule-1 (KIM-1), N-acetyl-β-D-glucosaminidase (NAG), lipocalin-2 (LCN2)/neutrophil gelatinase-associated lipocalin (NGAL), and apolipoprotein J (APOJ)/clusterin (CLU). The specific objectives of FDA's pilot project for urinary kidney safety biomarker data are to: (1) assess data availability and quality; (2) pool data from a range of clinical trial participants, drug programs, and phases of development; (3) perform analyses characterizing intersubject and intrasubject variability, expected ranges for subpopulations, time-course for changes,

use and quality of different assay methodologies, and the predictive performance compared to conventional biomarkers; and (4) establish a process and platform for identifying, requesting, receiving, storing, and analyzing data to support biomarker use in drug development.

III. Request for Information

This request for information aims to provide an opportunity for stakeholders--including both commercial drug developers and academic investigators--to share with FDA deidentified subject-level data on these biomarkers and experiences and challenges in applying these biomarkers in drug development.

A. Voluntary Data Submission

If data use agreements allow and data owners are willing, FDA is requesting that data owners submit any shareable human data that have not already been or are not in the process of being submitted to FDA or C-Path's BmDR. This submission can be accomplished under an existing Investigational New Drug (IND) application, with a cover letter indicating any data use restrictions, or under a new pre-IND (for submissions that are not associated with an existing IND or need to be isolated and deidentified from an existing IND). Additionally, data owners may submit a response to this information request, including a desired approach to facilitate voluntary submission of exploratory data.

FDA emphasizes the importance of storing and sharing data using the most updated terminology standards as outlined in the final guidance for industry *Providing Regulatory Submissions in Electronic Format — Standardized Study Data* (June 2021). Adherence to data standards may improve data quality and reliability. The Agency

requests that datasets be submitted in Clinical Data Interchange Standards Consortium (CDISC) format and contain deidentified subject-level data that includes clinical and demographic information, pharmacokinetic data, and urinary kidney safety biomarker data. Any dataset submitted should follow the format of one record per subject per parameter per treatment group per time point (if applicable). An example of a data structure that would be acceptable is provided in Table 1. The study protocol or a protocol synopsis, and NCT number, if available, should be included to aid in data interpretation. A description of the assay for each biomarker should also be submitted along with any available analytical validation reports that support the reliability, accuracy, and precision of assays used to measure the various urinary kidney safety biomarkers. The assay description should include the analytical method (e.g., ELISA), manufacturer, controls, lower limit of quantitation, within- and between-run precision, assay linearity, and percent recovery.

Table 1.--Data Structure Example (Requested Data File Formats: .csv, .xlsx, .xpt, or .xml)

Variable name	Description	Format	Comment
STUDYID	Study ID	Char	
USUBJID	Unique subject ID	Char	
TRTP	Planned treatment	Char	
TRTA	Actual treatment	Char	
SEX	Sex	Char	M or F
AGE	Age at baseline	Num	Years
RACE	Race	Char	
ETHNIC	Ethnicity	Char	The ethnicity of the subject. Submitters should refer to the guidance for industry *Collection of Race and Ethnicity Data in Clinical Trials* (2016) regarding the collection of ethnicity.
COUNTRY	Country	Char	Country of the investigational site in which the subject participated in the trial.
ARM	Description of planned arm	Char	Name of the arm to which the subject was assigned. If the subject was not assigned to an arm, ARM is null, and ARMNRS is populated. With the

			exception of studies that use multistage arm assignments, the name provided must be a value of ARM in the Trial Arms Dataset.
ARMNRS	Reason ARM is Null	Char	A coded reason that Arm variables and/or actual Arm variables are null. Examples: "SCREEN FAILURE", "NOT ASSIGNED", "ASSIGNED, NOT TREATED", "UNPLANNED TREATMENT". It is assumed that if the Arm and actual Arm variables are null, the same reason applies to both Arm and actual Arm.

Table 1.--Data Structure Example (Requested Data File Formats: .csv, .xlsx, .xpt, or .xml)

Variable name	Description	Format	Comment
HGT	Baseline height	Num	cm
WGT	Baseline weight	Num	kg
BMI	Body mass index	Num	kg/m^2
EGFR	Baseline eGFR	Num	ml/min per 1.73 m^2
CMAX	Cmax	Num	ng/ml, if collected for a drug
TMAX	Tmax	Num	H, if collected for a drug
AUCLAST	AUC 0-last	Num	ng*h/ml, if collected for a drug
AUCINF	AUC 0-INF	Num	ng*h/ml, if collected for a drug
ATP	Analysis time point	Char	e.g., Baseline, day 1, (add time points per schedule of assessments)
LBNAM	Vender name	Char	The name or identifier of the laboratory/machine that performed the test.
PARAMCD	Parameter code	Char	From CDISC SDTM standards - 2024: KIM1: Kidney injury molecule 1 LCN2: Lipocalin-2, also known as NGAL / neutrophil gelatinase-associated lipocalin NAGASE: N-acetyl-beta-D-glucosaminidase APOJ: Apolipoprotein J, also known as CLU / clusterin CYSTATC: Cystatin C OPN: Osteopontin CREAT: Creatinine eGFR: Estimated glomerular filtration rate UACR: Urine albumin-to-creatinine ratio UPCR: Urinary protein-to-creatinine ratio
UNITS	Parameter units	Char	CDISC standards - 2024 (parameter – urine creatinine normalized parameter): KIM1: ng/mL – ng/mg LCN2: ng/mL – ng/mg NAGASE: U/mL – U/mg APOJ: ng/mL – ng/mg CYSTATC: ng/mL – ng/mg OPN: ng/mL – ng/mg CREAT: mg/mL
BASE	Baseline parameter value	Num	
AVAL	Parameter value	Num	
AVALU	Parameter unit	Char	

CHG	Change from baseline	Num	
MHSEQ	Sequence number	Char	The medical history dataset includes the subject's prior history at the start of the trial. Examples of subject medical history information could include general medical history, gynecological history, and primary diagnosis.

Table 1.--Data Structure Example (Requested Data File Formats: .csv, .xlsx, .xpt, or .xml)

Variable name	Description	Format	Comment
LBCAT	Category for lab test	Char	e.g., urinalysis, urine chemistry
LBSPEC	Specimen type	Char	e.g., urine, serum
LBLLOQ	Lower limit of quantitation	Num	Same units as parameter
LBULOQ	Upper limit of quantitation	Num	Same units as parameter

B. Additional Information

CDER requests that stakeholders comment on the following topics:

1. To improve public health and more optimally inform drug development, the Agency is interested in derisking the process for data sharing, overall, and specifically, with regulatory authorities. For this Biomarker Incubator initiative, efforts to request data voluntarily have been piloted on a small scale (at the individual IND level). If there are considerations or barriers that could be addressed to support future data-sharing efforts, the Agency is interested in addressing those considerations in future voluntary data requests.

2. FDA seeks to identify and prioritize potential topics related to voluntary data sharing with interested parties for possible future inclusion in public workshops. Please comment on specific topics that may be of value for public discussion. Topics can be related to specific data-sharing matters or specific biomarkers of

interest where discussion of translation would facilitate coordinated research efforts.

3. Please provide input on specific biomarkers that are commonly collected but not yet accepted as an endpoint and have the potential to significantly support regulatory decisions related to safety or efficacy, for which aggregation of data across multiple programs may advance drug development.

IV. References

The following references are on display at the Dockets Management Staff (see **ADDRESSES**) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; these are not available electronically at https://www.regulations.gov as these references are copyright protected. Some may be available at the website address, if listed. Although FDA verified the website addresses in this document, please note that websites are subject to change over time.

Chen J, J Florian, W Carter, RD Fleischer, TS Hammerstrom, PR Jadhav, W Zeng, J Murray, and D Birnkrant, 2013, Earlier Sustained Virologic Response End Points for Regulatory Approval and Dose Selection of Hepatitis C Therapies, *Gastroenterology*, 144(7):1450–1455.e2, epub ahead of print March 5, 2013, doi: 10.1053/j.gastro.2013.02.039.

Kalaria SN, TR Farchione, R Uppoor, M Mehta, Y Wang, and H Zhu, 2021, Extrapolation of Efficacy and Dose Selection in Pediatrics: A Case Example of Atypical

Antipsychotics in Adolescents With Schizophrenia and Bipolar I Disorder, *Journal of Clinical Pharmacology*, 61: S117–S124, doi: 10.1002/jcph.1836.

Kalaria SN, TR Farchione, MV Mathis, M Gopalakrishnan, I Younis, R Uppoor, M Mehta, Y Wang, and H Zhu, 2020, Assessment of Similarity in Antipsychotic Exposure-Response Relationships in Clinical Trials Between Adults and Adolescents With Acute Exacerbation of Schizophrenia, *Journal of Clinical Pharmacology*, 60(7): 848–859, doi: 10.1002/jcph.1580.

(Authority: 21 CFR part 10 and 21 USC 357.)

Grace R. Graham,

Deputy Commissioner for Policy, Legislation, and International Affairs.

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