

IV. Paperwork Reduction Act of 1995

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Dated: September 22, 2017.

Leslie Kux,

Associate Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

[Docket No. FDA–2017–N–5442]

Leveraging Quantitative Methods and Modeling To Modernize Generic Drug Development and Review; Public Workshop; Request for Comments

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of public workshop; request for comments.

SUMMARY: The Food and Drug Administration (FDA, the Agency, or we) is announcing the following public workshop entitled “Leveraging Quantitative Methods and Modeling to Modernize Generic Drug Development and Review.” The purpose of the public workshop is to engage stakeholders in a discussion of current and emerging scientific approaches and applications for the conduct of quantitative modeling and simulations in generic drug development, especially for complex and locally acting products, and to gain input regarding opportunities and knowledge gaps related to the use of quantitative modeling and simulation to inform regulatory decision making through the product lifecycle. FDA will use the information gained through the workshop to support product-specific guidance development, improve pre-abbreviated new drug applications (ANDA) interactions with applicants, increase the quality and efficiency of regulatory reviews, and identify a next generation modeling and simulation toolset for complex and locally acting products.

DATES: The public workshop will be held on October 2 and 3, 2017, from 8:30 a.m. to 4:30 p.m. Submit either electronic or written comments on this

public workshop by November 3, 2017. See the **SUPPLEMENTARY INFORMATION** section for registration date and information.

ADDRESSES: The public workshop will be held at FDA’s White Oak Campus, 10903 New Hampshire Ave., Bldg. 31, Great Room, Silver Spring, MD 20993. Entrance for the public workshop participants (non-FDA employees) is through Building 1 where routine security check procedures will be performed. For parking and security information, please refer to <https://www.fda.gov/AboutFDA/WorkingatFDA/BuildingsandFacilities/WhiteOakCampusInformation/ucm241740.htm>.

You may submit comments as follows. Please note that late, untimely filed comments will not be considered. Electronic comments must be submitted on or before November 3, 2017. The <https://www.regulations.gov> electronic filing system will accept comments until midnight Eastern Time at the end of November 3, 2017. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is 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–2017–N–5442 for “Leveraging Quantitative Methods and Modeling to Modernize Generic Drug Development and Review.” Received comments, those filed in a timely manner (see **ADDRESSES**), will be placed in the docket and, except for those submitted as “Confidential Submissions,” publicly viewable at <https://www.regulations.gov> or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday.

- **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.gpo.gov/fdsys/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.

FOR FURTHER INFORMATION CONTACT:

Lanyan (Lucy) Fang, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 75, Rm. 4686, Silver Spring, MD 20993, 301-796-5005, email: Lanyan.fang@fda.hhs.gov; or Liang Zhao, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 75, Rm. 4702, Silver Spring, MD 20993, 240-402-4468, email: Liang.zhao@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background

To enhance dialogue regarding modeling and simulation and communication of recent advances in modeling and simulation, including those supported by the Generic Drug User Fee Amendments regulatory science research program, FDA plans to hold a public workshop to (1) engage stakeholders in a discussion of current and emerging scientific approaches and applications for the conduct of quantitative modeling and simulations in generic drug development, especially for complex and locally acting products, and (2) gain input regarding opportunities and knowledge gaps related to the use of quantitative modeling and simulation to inform regulatory decision making through the product lifecycle.

Modeling and simulation has been increasingly used in drug development, providing a framework for synthesizing information and extrapolating beyond what has been studied. Model-informed drug development (MIDD) approaches can be applied to brand drug products approved pursuant to a new drug application (NDA), and generic drug products approved pursuant to an ANDA. MIDD holds particular promise in key opportunity areas including pharmacokinetic/pharmacodynamics (PK/PD) models, physiologically based pharmacokinetic (PBPK) or absorption models, systems pharmacology, quantitative risk modeling, and emergent machine learning tools. These application areas can leverage the large pharmaceutical data sets (big data) available to FDA and other organizations. Quantitative approaches have been used to address significant scientific and regulatory issues in all phases of the product lifecycle: from pre-investigational new drug applications through NDAs, ANDAs, and post-approval evaluation of new

and generic drugs. Given the broad applications of modeling and simulation through the entire lifecycle of a product, there is a need to identify best practices to improve the routine use and acceptance of modeling and simulation for regulatory decision making.

The purposes of the workshop are to:

- (1) Engage global stakeholders and share experience and vision on using quantitative approaches in regulatory decision making for generic drug development and product lifecycle management;
- (2) Identify and prioritize potential areas for global harmonization for tools to inform regulatory decision making;
- (3) Share the current state of knowledge and practice in utilizing quantitative methods and modeling for generic drug development and review by case demonstrations and by integrating experience and lessons learned from new drug product development and reviews;
- (4) Identify opportunities for complex and locally acting product development and discuss approaches and principles in using quantitative methods and modeling to aid product-specific guidance development, pre-ANDA interactions between FDA and prospective applicants, ANDA reviews, and postmarket performance monitoring; and
- (5) Discuss next generation quantitative method and modeling toolsets, future directions, and application areas beyond currently available tools.

There is a paradigm shift to a risk-based product-specific regulatory approach for generic drugs. Examples of this transition include recommendations for partial AUC (area under the concentration-time curve) for some modified release drugs and replicate study bioequivalence (BE) recommendations for narrow therapeutic index (NTI) drugs. These product-specific guidances are driven by the therapeutic significance of either the exposure-response relationships for safety and efficacy (NTI drugs) or the difference in the shape of PK profiles. Modeling and simulation toolsets direct the design and evaluation of PK or comparative clinical endpoint BE studies, help evaluate clinical endpoint sensitivity and feasibility, and enable the assessment of alternative BE approaches. Overall, quantitative methods and modeling support better and faster decisions during the generic drug development and review process because they integrate knowledge accumulated during and after new drug product development, including in vitro in vivo correlation for formulation

design, absorption, distribution, metabolism, and excretion properties, population PK, and exposure-response relationships for efficacy and safety.

There is also a growing recognition that analysis of large datasets helps organizations and individuals make better decisions. Emerging methodologies that enable the Agency to take advantage of big data will impact how generic drugs are developed, reviewed, and monitored. Knowledge extracted from large datasets can provide FDA the opportunity to improve the focus of regulatory review, modernize BE assessment criteria, and efficiently manage workload by predicting future ANDA applications. Further, such knowledge will support industry's efforts to optimize their generic drug portfolios to meet upcoming patient and market needs. The public workshop will focus on the use and advance of quantitative methods and modeling in modernizing generic drug development, regulatory review, and product lifecycle management.

II. Scope of Public Input Requested

FDA seeks input on a range of topics related to the conduct of modeling and simulation by pharmaceutical industries and by FDA and on the interpretation and use of simulations for risk-based regulatory assessment. They include:

- (1) Opportunity areas for model-informed generic drug development and review
 - (2) Risk-based BE standard for complex and locally acting products:
 - a. Under what circumstances would alternative approaches to the product-specific BE guidances be encouraged?
 - b. What can serve as evidentiary data when proposing alternative BE approaches?
 - c. What are the scientific and regulatory challenges in using a model-based BE approach?
 - (3) Emerging quantitative methods and modeling in assisting regulatory decision making for drug development and product life cycle management:
 - a. What are the areas (e.g., excipient selection, molecular target/mechanism of action-safety profile association, universal exposure response models for drugs with the same target) that can benefit most in the big data era and what will be the regulatory impact and implications?
 - b. What are the potential new methods, including but not limited to, machine learning and their application areas in assisting drug development and review?
 - (4) Post-approval evaluation of the substitutability of generic products for

the corresponding reference listed drugs or reference standards:

a. How to effectively integrate systems pharmacology, PBPK, and the exposure-clinical response relationship to evaluate product risk and assist BE evaluation?

b. What will be the next generation methodologies in postmarket signal detection to evaluate product substitution or compare product performance using the Sentinel database or complementary toolsets?

III. Participating in the Public Workshop

Registration: Persons interested in attending this public workshop must register online at https://survey.co1.qualtrics.com/jfe/form/SV_3eiJOCsnrPdTZU9. Please provide complete contact information for each attendee, including name, title, affiliation, address, email, and telephone.

Registration is free and based on space availability, with priority given to early registrants. Persons interested in attending this public workshop must register by September 25, 2017, midnight, Eastern Standard Time. Early registration is recommended because seating is limited; therefore, FDA may limit the number of participants from each organization.

If you need special accommodations due to a disability, please contact Lanyan (Lucy) Fang (see **FOR FURTHER INFORMATION CONTACT**) no later than 7 days before the workshop.

Requests for Oral Presentations: During online registration you may indicate if you wish to present during a public comment session, and which topic(s) you wish to address. We will do our best to accommodate requests to make public comments. Individuals and organizations with common interests are urged to consolidate or coordinate their presentations, and to request time for a joint presentation, or to submit requests for designated representatives to participate in the focused sessions. Following the close of registration, we will determine the amount of time allotted to each presenter and the approximate time each oral presentation is to begin, and will select and notify participants by September 27, 2017. All requests to make oral presentations must be received by the close of registration on September 25, 2017. If selected for presentation, any presentation materials must be emailed to Lanyan (Lucy) Fang (see **FOR FURTHER INFORMATION CONTACT**) no later than September 28, 2017. No commercial or promotional material will be permitted to be presented or distributed at the public workshop.

Streaming Webcast of the Public Workshop: This public workshop will also be webcast. A live webcast of this workshop will be viewable at <https://collaboration.fda.gov/dqmm1017> on the day of the workshop.

If you have never attended a Connect Pro event before, test your connection at https://collaboration.fda.gov/common/help/en/support/meeting_test.htm. To get a quick overview of the Connect Pro program, visit https://www.adobe.com/go/connectpro_overview. FDA has verified the Web site addresses in this document, as of the date this document publishes in the **Federal Register**, but Web sites are subject to change over time.

Transcripts: Please be advised that as soon as a transcript of the public workshop is available, it will be accessible at <https://www.regulations.gov>. It may be viewed at the Dockets Management Staff (see **ADDRESSES**). A link to the transcript will also be available on the internet at <http://www.fda.gov/Drugs/NewsEvents/ucm554182.htm>.

Dated: September 26, 2017.

Anna K. Abram,

Deputy Commissioner for Policy, Planning, Legislation, and Analysis.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Prospective Modification of Exclusive Patent License Potent and Selective Analogues of: Monamine Transporters; Methods of Making; and Uses Thereof

AGENCY: National Institutes of Health, HHS.

ACTION: Notice.

SUMMARY: The National Institute of Drug Abuse, an institute of the National Institutes of Health, Department of Health and Human Services is contemplating the modification of grant of an Exclusive Patent License to EncepHeal Therapeutics, Inc., located in Winston-Salem, North Carolina, to practice the inventions embodied in the patent applications listed in the Supplementary Information section of this notice.

DATES: Only written comments and/or applications for a license which are received by the National Institute on Drug Abuse's Technology Transfer Office on or before October 17, 2017 will be considered.

ADDRESSES: Requests for copies of the patent application, inquiries, and comments relating to the contemplated modification of the Exclusive Patent License should be directed to Martha Lubet, Ph.D., Technology Transfer Manager, NCI TTC, 9609 Medical Center Drive, Room IE350, MSC 9702, Rockville, MD 20850. Telephone: 240 276-5508. Facsimile: 240 276-5505. Email: lubetm@mail.nih.gov.

SUPPLEMENTARY INFORMATION: The following represents the intellectual property to be licensed under the prospective agreement:

U.S. provisional application 61/774,878, filed March 8, 2013 entitled "Potent and Selective Inhibitors of Monamine Transporters; Methods of Making; and Uses Thereof" [HHS Ref. No. E-073-2013/0-US-01];

PCT application PCT/US2014/021514, filed March 7, 2014 entitled "Potent and Selective Analogues of: Monamine Transporters; Methods of Making; and Uses Thereof" [HHS Ref. No. E-073-2013/0-PCT-02];

U.S. application 14/772,486, filed September 3, 2015 entitled "Potent and Selective Analogues of Monamine Transporters; Methods of Making; and Uses Thereof" [HHS Ref. No. E-073-2013/0-US-06];

EPO application 14714043.8, filed September 1, 2015 entitled "Potent and Selective Analogues of Monamine Transporters; Methods of Making; and Uses Thereof" [HHS Ref. No. E-073-2013/0-EP-05];

Australian application 2014225550, filed September 8, 2015 entitled "Potent and Selective Analogues of Monamine Transporters; Methods of Making; and Uses Thereof" [HHS Ref. No. E-073-2013/0-AU-03];

Australian application 2017202849, filed April 28, 2017 entitled "Potent and Selective Analogues of Monamine Transporters; Methods of Making; and Uses Thereof" [HHS Ref. No. E-073-2013/0-AU-07];

Canadian application 2903746, filed September 2, 2015 entitled "Potent and Selective Analogues of Monamine Transporters; Methods of Making; and Uses Thereof" [HHS Ref. No. E-073-2013/0-CA-04];

The patent rights to these inventions have been assigned to and/or exclusively licensed to the Government of the United States of America.

The Government previously announced its intention to grant an exclusive license to EncepHeal at FR 80:245 (December 22, 2015), pp. 79595-79596.

The Notice of Intent to Grant (NOITG) specified a Field of Use as "Use of