Center for Research on Complex Generics (CRCG)

Call for Proposals

Best Practices for Establishing the Suitability of a Model Integrated Approach to Demonstrate the Bioequivalence of Long Acting Injectable Products

Background

Model integrated approaches are increasingly being utilized by the generic drug industry to support a demonstration of bioequivalence (BE), especially for complex generic products (e.g., long acting injectable drug products) for which in vivo BE studies are challenging to conduct. Model integrated approaches have the potential to overcome these challenges, which have represented barriers to the development of complex generics.

The CRCG (www.complexgenerics.org) is inviting proposals from experts in the field of modeling and simulation to illustrate how a given model integrated approach can be demonstrated to be suitable to support an establishment of BE. Selected proposals will receive an award of $100,000.00 from the CRCG so that all the components of the demonstration can be developed and presented for discussion at a workshop tentatively planned for November 30, 2021 on *"Best Practices for Establishing the Suitability of a Model Integrated Approach to Demonstrate the Bioequivalence of Long Acting Injectable Products."*

The CRCG envisions that this free workshop will provide an open forum for deliberation and collaboration, and will help to develop consensus about best practices for the development and regulatory assessment of model integrated BE approaches. A specific model integrated approach for BE assessment, using real-world case studies relevant to

long acting injectable products, will be a common theme for all the proposals. A specific goal of this funding opportunity (and the associated free workshop) is to facilitate enhanced collaborations among industry, academia, and the FDA that will establish best practices for model-integrated approaches to support a demonstration of BE and, thereby, expedite the development of complex generic long acting injectable products. The ultimate goal is that the insights gained from the model-integrated analysis of real-world case studies discussed at the workshop, and the best practices established for demonstrating the suitability of these models and model integrated approaches, will enhance patient access to numerous types of complex generic products whose development can be facilitated by similar model integrated BE approaches.

Funding opportunity description

This opportunity calls for proposals that are targeted to develop and assess a model integrated BE analysis for long acting injectables based on real-world case studies. If funded, further work would be performed to illustrate how the model integrated approach would be shown to be suitable to support a demonstration of BE, and this work would be presented and discussed at the aforementioned workshop tentatively planned for November 30, 2021. The emphasis of the proposal should be on the application of a model integrated approach to support the innovative study designs and data analyses for BE assessment. Successful proposals will clearly demonstrate how the model integrated approach can be used to compare/determine/optimize novel study designs that are more efficient than the conventional pharmacokinetic (PK) BE study designs.

The awardees are expected to share their experiences and insights gained from the real-world case studies through a presentation at the workshop and through open forum discussions among relevant stakeholders and other invited experts in the field. The intention is to develop best practices for regulatory applications of model-integrated BE approaches in a collaborative manner, and to publish the case studies in scientific literature.

These studies may include, but are not limited to, the evaluation of model integrated approaches to support the development and evaluation of novel study designs, reducing study duration, reducing the number of subjects in a study, developing alternative BE metrics, and innovating other statistical BE analysis methods associated with novel designs. The expectation is that best practices for model development, verification and validation will be appropriately identified, taking into consideration the challenges encountered in a real-world scenario for a generic drug development. Ideally, the proposal should include, at a minimum, overall plans for:

1) demonstrating the application of model-integrated BE approaches to reduce the barrier (e.g., sample size and/or study duration reductions) for generic long acting injectable drug product development and regulatory assessment through the proposed study:

- Applicants may refer to publicly available PPK models for long acting injectable products in the literature (e.g., Sharan et al., 2021[1], Zhao et al., 2018[2]) to develop the proposals.
- Once the awardees are selected, the CRCG may provide a dummy dataset for the awardee to further refine the literature model for the proposed study

2) proposing best practices for the development and assessment of a model integrated approach for BE demonstration. For example, for novel BE study designs:

- What validation will be required if a new BE study is being proposed based on virtual simulation conducted using a population PK (PPK) model from a reference listed drug (RLD) holder (either one that is already published, or one that is updated with additional study data by a generic drug applicant)? How can a published/modified PPK model from an RLD holder best be used to identify the most efficient study design for demonstrating BE?

    i. **Shortened Study Duration:** What validation will be needed for a BE study where the commonly recommended steady state is only partially conducted, e.g., 2-3 dose administrations, and the data from the limited clinical study is used to simulate steady state PK data, and a BE assessment is conducted on the simulated steady state PK BE data? What if a different BE metric and/or limit is proposed that can ensure BE at steady state?
    ii. **Lower Sample Size:** What validation will be required if the BE study is conducted in a limited number of subjects/patients (not adequately powered to demonstrate BE), but then the collected clinical data with the limited number of subjects is used to perform a virtual BE simulation with a higher number of subjects that provide adequate statistical power (e.g., 80%), and BE is assessed using this virtual BE dataset?
    iii. **Other options:** Any other considerations, e.g., two-stage designs for BE demonstration?

3) proposing expectations on the pre-specified modeling analysis plan (MAP) that corresponds to the proposed model integrated BE study design.

[1] Sharan S, Fang L, Lukacova V, Chen X, Hooker AC, Karlsson MO. Model-Informed Drug Development for Long-Acting Injectable Products: Summary of American College of Clinical Pharmacology Symposium. Clin Pharmacol Drug Dev. 2021 Mar;10(3):220-228.

[2] Zhao, L., Kim, M.-J., Zhang, L. and Lionberger, R. (2019), Generating Model Integrated Evidence for Generic Drug Development and Assessment. Clin. Pharmacol. Ther., 105: 338-349.

- Proposals should also include details of the plan to determine which part of the MAP should be pre-specified, and where post-hoc analysis can and/or should be allowed.

Funds Available and Anticipated Number of Awards

Two awards will each provide a 6-month of support to produce study results for presentation and discussion at the workshop tentatively planned for November 30, 2021, and contribute to other post-workshop activities.

It is anticipated that up to 2 awards will be made, not to exceed $100,000.00 in total costs (direct plus indirect), per award.

Up to 2 runner up proposals may be selected that are not funded, but given an opportunity to present their studies at the workshop.

Expected Deliverables

The awarded proposals are expected to 1) submit their results in a presentation format for a workshop tentatively planned for November 30, 2021 (presentations would be due two weeks prior to the workshop) and 2) submit a detailed final report summarizing their study outcomes, which will be adapted for publication in scientific journals[3].

If the proposed research is not concluded in time for the workshop (tentatively planned for November 30, 2021), the awardees are expected to present the concept and details of their proposed approach based on their research up to that date, and to openly discuss proposed solutions to the problems they encountered when developing their approach (with disclosure of supporting data and relevant information).

Application Details

Applications are due by 11:59 pm ET on Friday, May 14, 2021. Applications should be emailed as a single PDF file to complexgenerics@rx.umaryland.edu

Although a letter of intent is not required, is not binding, and does not enter into the review of a subsequent application, the information that it contains allows the CRCG staff to estimate the potential review workload and plan the review. By April 13, 2021 at 5pm ET, prospective applicants are asked to submit a letter of intent that includes the following information: Descriptive title of proposed activity; Name(s), email address(es), and telephone number(s) of the Program Director(s)/Principal Investigator(s); Names of

[3] By accepting the award, the awardee agrees that the material presented at the workshop and the content of the final report can become a part of a manuscript for hers/his study. The awardee agrees to collaborate with the workshop organizers and other presenters in drafting a manuscript to summarize the workshop.

other key personnel; Participating institution(s); and Title of this funding opportunity. The letter of intent should be sent to: complexgenerics@rx.umaryland.edu

A technical session will be held for prospective applicants in April 2021. The conference call information will be provided to prospective applicants that submit a letter of intent. The technical session will provide an overview of the submission requirements and allow prospective applicants an opportunity to ask questions regarding the application process. Participation in the technical session is optional, but strongly encouraged.

Applications should include a cover page, quad chart, white paper proposal, and a budget. A cover page (one page) should include information about the applicant, including elements relevant to applicant eligibility (see the section below on 'Eligible Organizations'). A quad chart (one page) and white paper (10 pages maximum, plus 2 page maximum addendum) should address this call for proposals, using Stage 1 Quad Chart and Stage 1 White paper instructions in FDABAA-21-00123 FY21 FDA Broad Agency Announcement (BAA) for Advanced Research and Development of Regulatory Science (https://govtribe.com/opportunity/federal-contract-opportunity/fy21-fda-broad-agency-announcement-baa-for-advanced-research-and-development-of-regulatory-science-fdabaa2100123). A budget page (one page) should include a budget and budget justification. All applications should include a data sharing plan that describes the applicants intentions related to public disclosure and publication of data and information developed in conjunction with the award.

Reviewers will consider each of the review criteria below in the determination of scientific merit.

Relevance (30 Points)

Does the project address an important problem or a critical barrier to progress in the field? Is the prior research that serves as the key support for the proposed project rigorous? If the aims of the project are achieved, how will the outcome help provide a practical path forward for the given challenge? How will successful completion of the aims change the concepts, methods, technologies that drive this field?

Investigator(s) (20 Points)

Are the PD(s)/PI(s), collaborators, and other researchers well suited to the project? If Early Stage Investigators or those in the early stages of independent careers, do they have appropriate experience and training? If established, have they demonstrated an ongoing record of accomplishments that have advanced their field(s)? If the project is collaborative or multi-PD/PI, do the investigators have complementary and integrated expertise; are their leadership approach, governance and organizational structure appropriate for the project?

Innovation (20 Points)

Does the application challenge and seek to shift current research paradigms by utilizing novel theoretical concepts, approaches or methodologies, or interventions? Are the concepts, approaches or methodologies, or interventions novel to one field of research or novel in a broad sense? Is a refinement, improvement, or new application of theoretical concepts, approaches or methodologies, or interventions proposed?

Approach (30 Points)

Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the project? Have the investigators included plans to address weaknesses in the rigor of prior research that serves as the key support for the proposed project? Have the investigators presented strategies to ensure a robust and unbiased approach, as appropriate for the work proposed? Are potential problems, alternative strategies, and benchmarks for success presented? If the project is in the early stages of development, will the strategy establish feasibility and will particularly risky aspects be managed

Applicants will be notified of award decisions by May 21, 2021. Applicants may or may not receive review feedback.

Awards are generally subject to the terms and conditions, cost principles, and other considerations described in the HHS Grants Policy Statement (https://www.hhs.gov/sites/default/files/grants/grants/policies-regulations/hhsgps107.pdf). Additional funding restrictions and requirements may be part of any award.

Eligible Organizations

Higher Education Institutions

- Public/State Controlled Institutions of Higher Education
- Private Institutions of Higher Education

The following types of Higher Education Institutions are always encouraged to apply for FDA support as Public or Private Institutions of Higher Education:

- Hispanic-serving Institutions
- Historically Black Colleges and Universities (HBCUs)
- Tribally Controlled Colleges and Universities (TCCUs)
- Alaska Native and Native Hawaiian Serving Institutions
- Asian American Native American Pacific Islander Serving Institutions (AANAPISIs)

Nonprofits Other Than Institutions of Higher Education

- Nonprofits with 501(c)(3) IRS Status (Other than Institutions of Higher Education)
- Nonprofits without 501(c)(3) IRS Status (Other than Institutions of Higher Education)

For-Profit Organizations

- Small Businesses
- For-Profit Organizations (Other than Small Businesses)

Governments

- State Governments
- County Governments
- City or Township Governments
- Special District Governments
- Indian/Native American Tribal Governments (Federally Recognized)
- Indian/Native American Tribal Governments (Other than Federally Recognized)
- U.S. Territory or Possession

Other

- Independent School Districts
- Public Housing Authorities/Indian Housing Authorities
- Native American Tribal Organizations (other than Federally recognized tribal governments)
- Faith-based or Community-based Organizations
- Regional Organizations
- Non-domestic (non-U.S.) Entities (Foreign Institutions)

Foreign Institutions

Non-domestic (non-U.S.) Entities (Foreign Institutions) **are** eligible to apply.

Non-domestic (non-U.S.) components of U.S. Organizations **are** eligible to apply.

Foreign components, as defined in the HHS Grants Policy Statement (https://www.hhs.gov/sites/default/files/grants/grants/policies-regulations/hhsgps107.pdf), **are** allowed.

Application Submission Contact: complexgenerics@rx.umaryland.edu