CENTER FOR RESEARCH ON COMPLEX GENERICS

Mitigation Strategies for Nitrosamine Drug Substance Related Impurities: Quality and Bioequivalence Considerations for Generics

Welcome Remarks

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June 15, 2023

UNIVERSITY of MARYLAND BALTIMORE

UNIVERSITY OF MICHIGAN

FDA U.S. FOOD & DRUG ADMINISTRATION

Established in 2020, The Center for Research on Complex Generics (CRCG) is a collaboration between the University of Maryland, the University of Michigan, and the FDA.

About CRCG

Our Mission

Increase access to safe and effective generic drugs through enhanced infrastructure/communication, education, and research collaboration across industry, academia and the FDA.

We are dedicated to advancing programs that stimulate scientific dialogue, disseminate current insights, and generate new knowledge about complex generics in support of the FDA's mission to promote and protect the public health.

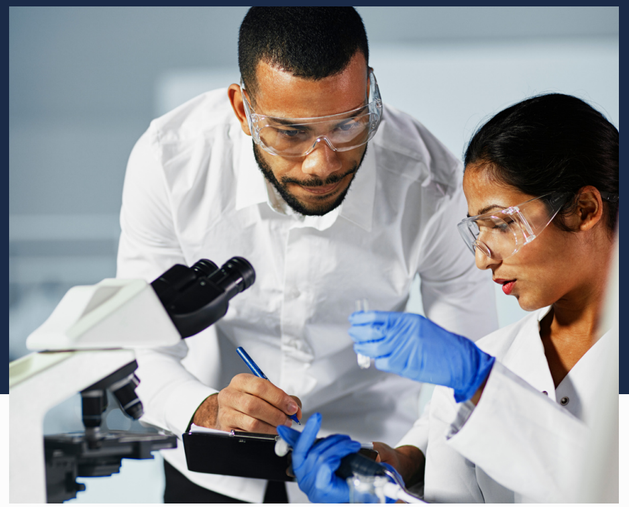
Primary Goals of the CRCG

INFRASTRUCTURE & COMMUNICATION

Establishing core program infrastructure and enhancing communications to advance complex generics development

EDUCATION & TRAINING

Providing education and training through workshops, webinars, hands-on demonstrations, and on-site visits



COLLABORATIVE RESEARCH

Conducting collaborative research and enabling pilot research projects and technological development

Ongoing Engagement to Advance Complex Generics Product Development

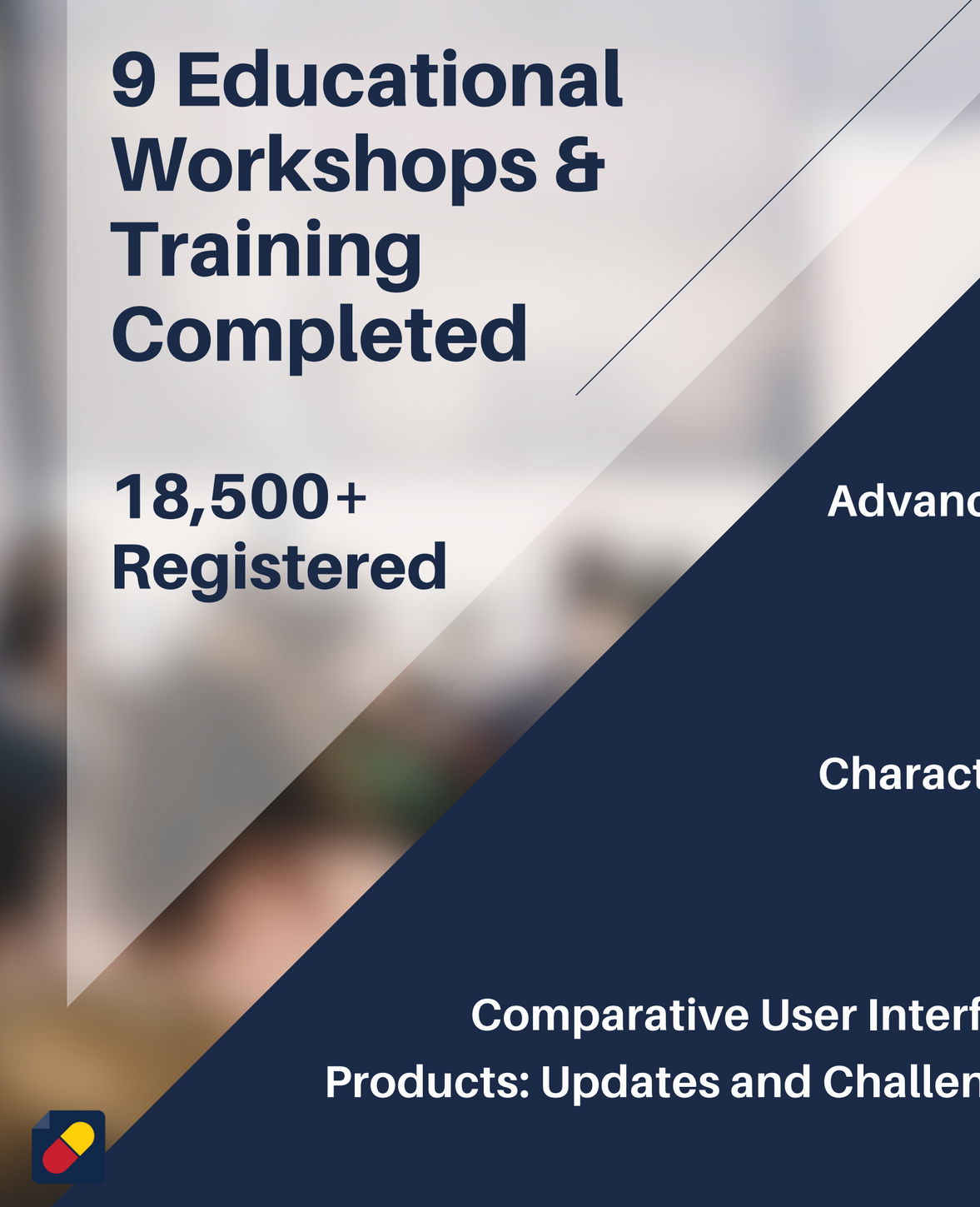
300+ engagements with key complex generics players to understand challenges and opportunities in advancing complex generics product development

Nitrosamines are an ever-growing concern in the generic industry

- General challenges - lack of analytical standards and clarity in the guidance regarding limits, lack of expertise on complex nitrosamines, method development and risk assessment
- Prior focus was on common nitrosamines vs secondary, tertiary, quaternary nitrosamines which are a big issue and were not considered earlier
- Considering lifetime exposure to nitrosamines while several drugs are for acute or chronic care and sometimes used only for a maximum period of 1 week- dosage form and usage (acute vs chronic setting) should be taken into consideration

Nitrosamines are an ever-growing concern in the generic industry

- Methods for complex nitrosamines- difficult to develop a one size fits all method, need to develop methods for each product
- Technical challenges- most nitrosamines are unstable posing a challenge in developing standards. Some are formed during the manufacturing stage, combination of API and excipients sometimes increases nitrosamine level and might potentially require reformulation
- Analytical challenges- Impurity limits specified by the FDA are very stringent and hard to meet across all products and dosage forms and sometimes are not commercially available



9 Educational Workshops & Training Completed

18,500+ Registered

UPCOMING 2023 IN-PERSON（& VIRTUAL） WORKSHOPS & TRAINING

OCTOBER 12

Advances in PBPK Modeling and its Regulatory Utility for Oral Drug Product Development

DECEMBER 7-8

Characterization of Complex Excipients/Formulations

TBD

Comparative User Interface Assessment for Drug-Device Combination Products: Updates and Challenges in Demonstrating Generic Substitutability

Ongoing Research

2 Research projects completed on model-integrated approaches to demonstrate bioequivalence for long-acting injectable generic products

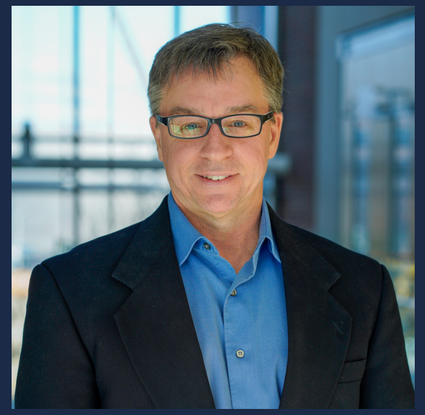
Analytical characterization of ONIVYDE™ and irinotecan liposome

Evaluation of micelle/colloid diffusivity to better parameterized physiologically based pharmacokinetic models for oral drug absorption

Validation of simulated airway mucus models for predicting bioavailability / local exposure of inhaled drugs and characterization of MDI products, particle size, dissolution, particle morphology

Characterization of PLGA-peptides products purity and immunogenicity

CRCG Team



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Thank You for Your Participation!

Opening Remarks by Dr. Robert Lionberger

Director, ORS, OGD, CDER, FDA