CENTER FOR RESEARCH ON COMPLEX GENERICS

Challenges and Opportunities Related to the Development of Generic Drugs

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UNIVERSITY of MARYLAND BALTIMORE

UNIVERSITY OF MICHIGAN

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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

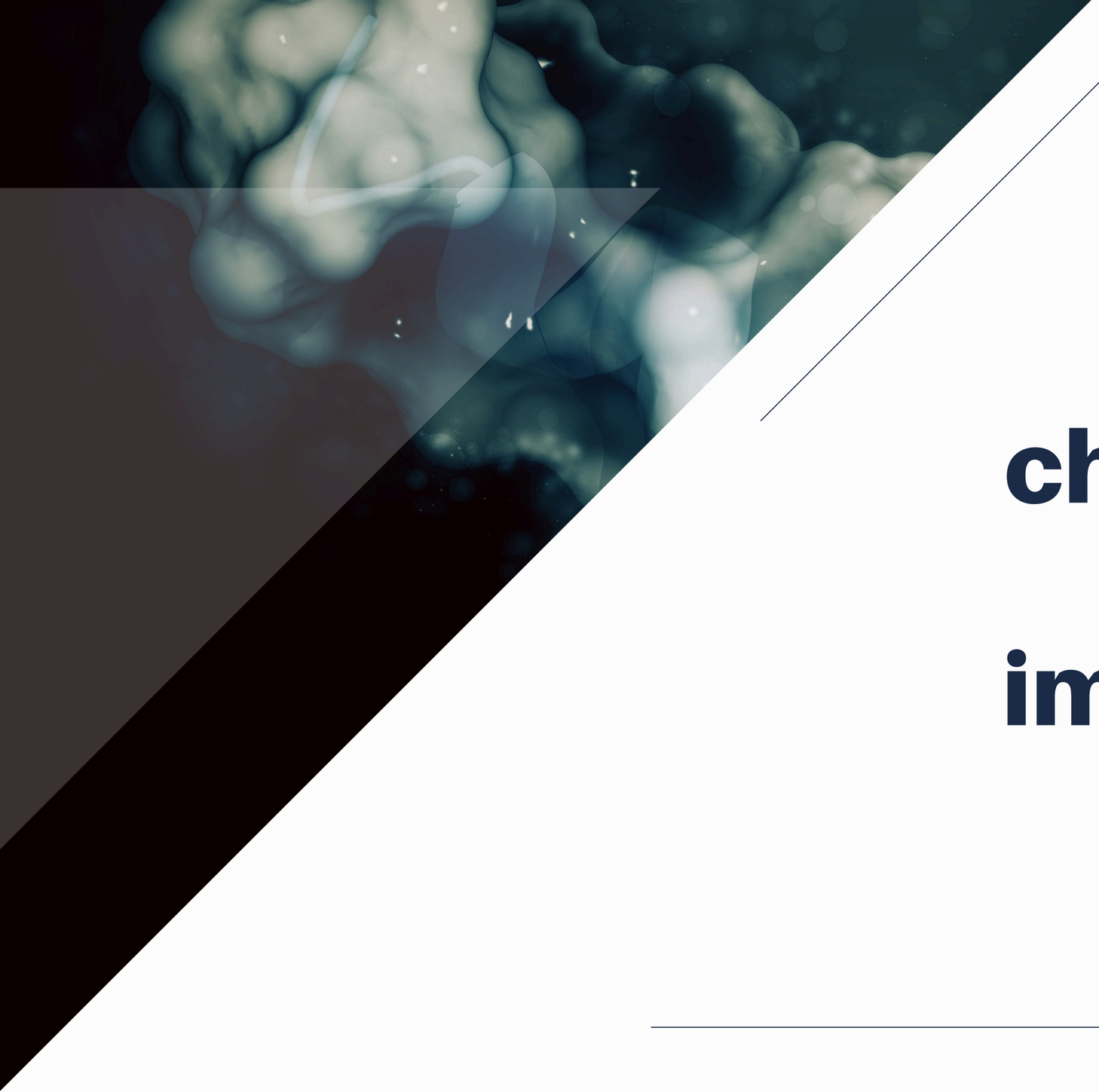
Conducting collaborative research and enabling pilot research projects and technological development

Ongoing Engagement to Advance Complex Generics Product Development

Periodic interviews with key complex generics players to understand challenges and opportunities in advancing complex generics product development

Scientific Methods Associated with FDA's Bioequivalence Recommendations - Implementation Challenges

- Complex API's characterization and immunogenicity
- Complex products including LAI, inhalation, complex injectables, drug-device combinations
- Non-complex dosage forms M13A



Complex API’s characterization and immunogenicity

Need for Clarification on Guidance for Nonclinical Safety Assessment of Oligonucleotide Therapeutics (ONTs)

In Vitro Assays

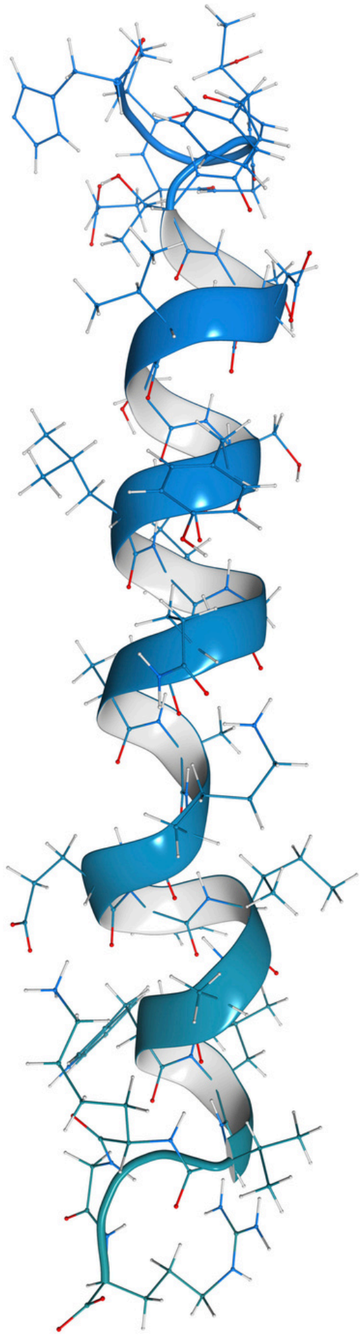
- Appropriateness of assays for evaluating both innate and adaptive immune responses
- Criteria to determine “sensitivity, specificity, and reproducibility” of immunogenicity assays
- Positive and negative controls for in vitro immunogenicity risk assessment
- Distinguishing immune response triggered by the oligonucleotide vs impurities
- Immunogenicity assessments at different stages of product development cycle – regulatory requirements

Impurities

- Identification and qualification parameters and thresholds for impurities
- Impurity characterization- co-eluting impurities, mixtures
- Immunogenicity and inflammation risk assessment
- Comparability of impurities in test product
- In vitro/in vivo studies required to qualify impurities
- Appropriate fit-for-purpose parameters for validation of in vitro assays

Alternate Approaches

- Orthogonal methods for demonstrating API sameness
- In-silico model to predict immunogenicity risk



Gaps, Evolving Expectations and Lack of Standardization with Immunogenicity Risk Assessment for Complex Peptides

- Lack of universally accepted protocols or benchmarks for assessing immunogenicity leads to challenges with study design and regulatory compliance
- Need for clarifications in guidelines for:
  - HCP impurities from peptide synthesized with fermentation technology
  - Peptide less than 9-amino acids
  - Impurity specifications for PEGylated peptides
  - Impurity specification for oral peptides
  - When to and how to qualify impurities for synthetic peptides
- Regulatory harmonization challenges for complex peptides
- Divergent regulatory standards, not fully aligned with international agencies. Key areas of divergence- analytical characterization requirements, impurity and impurity profiling threshold, bioequivalence and immunogenicity standards

Complex products including LAI, inhalation, complex injectables, drug-device combinations

Complex Injectables- Bioequivalence Challenges

- Major challenge remains the same, i.e., BE to the RLD
- Need for clarity on the physical characterization methods to characterize the RLD, prior to expensive clinical / BE studies
- Some equipment / methods published by FDA and others are not available at major CROs for the physical characterization
- Need for specifications to compare with RLD for Q3 characterization, when several orthogonal methods are to be used
- Lack of compendial dissolution methods, along with lack of physical standards such as molecular weight and system suitability standards
- Need for guidance on biorelevant simulation studies to compare with the RLD
- Patient BE challenges for LAIs- compliance, missing samples, drop-outs, recruitment, variability within multi-centric studies
- Considerations for alternate BE pathway for e.g., in vitro studies, single dose PK studies etc. in lieu of in vivo steady-state study for extended release injectable suspensions

BE Challenges with Complex Inhalables - Fewer Generics in the US vs Other Highly Regulated Markets

- Challenge with RLD variability for PK studies & establishing BE, given tight criteria for BE
- BE testing for several individual parameters bears an inherent statistical risk to get false-negative outcome (alpha error 5 %)
- Lack of clarity on spray pattern/plume geometry (e.g., automated method required) delaying development timeline
- Need for guidance on BE requirements for adapting to LGWP based generic formulations
- Need for clarity around requirements for new BE techniques that are introduced, and more realistic & validated in vitro options
- Lack of guidance on alternate approaches and limitations:
  - Development of a discriminatory dissolution method is very difficult
  - Sample preparation for dissolution/MDRS requires equipment not commercially available
  - Method and equipment for inhalation products
- Need for clarity on studies to establish Q1/Q2 in addition to in vitro and PK studies that establish BE
- Considerations for other designs (e.g., non-inferiority) for clinical endpoint studies
- Need for guidance on use of modeling approaches to extrapolate pilot BE study to pivotal BE study, if the test product process and composition is equivalent to exhibit batch

Drug-Device Combination Products (DDCPs)and Human Factor Studies Continue to Pose Challenges

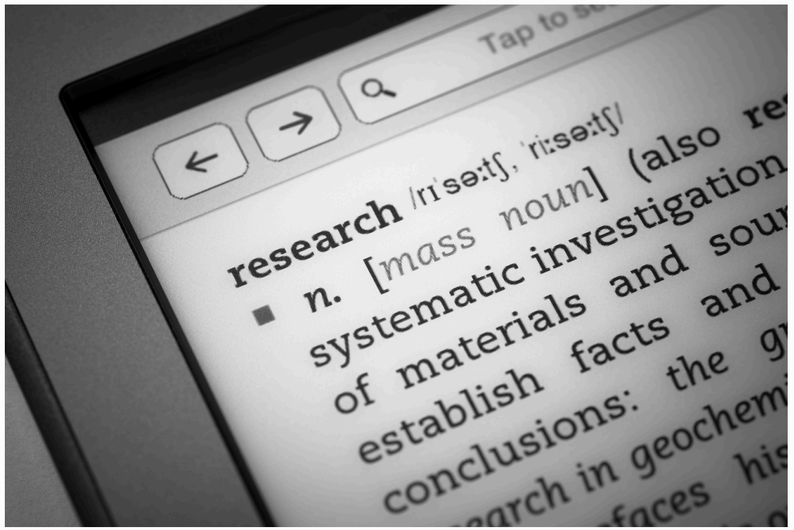
- Challenging approval standards- Q1/Q2, same “Instructions for Use”, similarity of device, lack of stepwise approach to BE requirements
- Human factor studies are expensive, never identical to RLD, evaluated quantitatively rather than qualitatively yielding little meaningful information about safety and effectiveness, burdensome for highly variable RLDs
- Need for guidance regarding acceptable non-inferiority margins in comparative use human factors studies
- Need for a common ground where ‘other differences’ between test and RLD combination products could be effectively managed
- FDA has been wary of adopting or accepting certain scientific methods that sponsors consider commonplace or routine

Non-complex dosage forms M13A

Challenges and Need for Alternate Approaches - IR and MR products

- FDA revision of PSG to remove fasting/fed studies for conventional IR formulations is helpful in reducing BE burden on generic industry
- Requirement for multiple BE studies on multiple strengths for MR products- potential for modeling approaches to waive certain BE studies (e.g., on lower strengths fasting/fed)?
- While modeling approaches are encouraged, IVIVC or biopredictive dissolution development is a very challenging task for some dosage forms
- ICH 13B – Need for statistical approaches for dissolution similarity owing to tightened dissolution variability criteria (SD <8%) in new guidance
- ICH 13C – Need for harmonization of statistical approaches (e.g., USFDA – RSABE approach, EMA – widening of CI limits approach for Cmax, Canada – widening of CI limits approach for AUC)
- Need for clarification on significance or clinical relevance of partial AUCs
- Need for scientifically sound options to waive fed study for high-risk products- amount of data available to generic industry to employ modeling approaches may vary
- Inconsistent interpretation and adoption of M13A by other regulators

A Few Potential Research Opportunities



- Delineating mechanism of formation of anti-drug antibodies against ONTs - a barrier for ONT approvals
- Investigate use of recombinant API as a generic of a peptide through the 505(j) pathway
- Establish robust, refined, realistic and validated in vitro BE tests for complex inhalation products
- Develop biorelevant in silico/modeling frameworks to establish BE for complex injectables and inhalables
- Alternative approaches to comparative use human factors studies for DDCPs

Summary

- CRCG has been effective in identifying concerns, challenges and potential areas of research focus to facilitate generic drug development
- We appreciate the continued collaboration with the FDA and relationships we have established with generic industry stakeholders that has increased our understanding of critical factors that impact generic drugs and ability to bring these issues up to the FDA
- There continues to be a strong need for development of alternative approaches to BE and end-point studies for complex products
- There is a need for collaborative research efforts on several topics identified by CRCG
- There is a significant gap in and need for knowledge sharing, publications and case studies for robust, realistic and validated methods for in vitro and in vivo approaches, alternate approaches and in silico models to establish BE for several complex product categories

17 Educational Workshops & Training Completed

33,600+ Registered

2025 IN-PERSON (& VIRTUAL) WORKSHOPS & TRAINING

SEPTEMBER TBD

Mastering Particle Size Analysis: A Step-By-Step Illustration of Techniques and Best Practices

OCTOBER 15-16

Modeling and Artificial Intelligence in Generic Drugs: Regulatory Insights and Future Trends

NOVEMBER 19-20

Visionary Standards: Advancing Science and Regulation in Generic Ophthalmic Products

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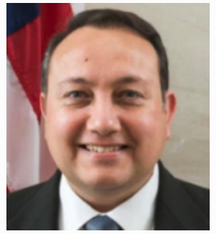

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Thank You !