CENTER FOR RESEARCH ON COMPLEX GENERICS

Industry Interview Feedback on the Main Challenges in the Development of Complex Generics

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Generic Drug Science and Research Initiatives Public Workshop
May 21, 2024

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

14 Educational Workshops & Training Completed

27,400+ Registered

UPCOMING 2024 In-Person (&Virtual) Workshops &Training

OCTOBER 7 - 8

Scientific and Regulatory Considerations for Assessment of Immunogenicity Risk for Generic Peptide and Oligonucleotide Drug Products: Present State and Future Directions

NOVEMBER 7

Updates on Approaches to Acceptable Intakes of Nitrosamine Drug Substance Related Impurities (NDSRIs) and Bioequivalence Assessment for Reformulated Drug Products

DECEMBER 4 - 5

Navigating the Transition to Low Global Warming Potential Propellants

Research Projects

- Research and education needs for complex generics
- Towards best practice in novel bioequivalence studies of long-acting injectable products: A complete framework for model-integrated design with the MonolixSuite
- Accelerating generic drug development using an MIBE approach
- Evaluation of micelle/colloid diffusivity to better parameterized physiologically based pharmacokinetic models for oral drug absorption
- Reverse engineering, IVR and small-scale manufacturing of ONIVYDE™
- Reverse engineering of Invega Sustenna® (paliperidome palmitate suspension)
- Scientific challenges and opportunities in the development of complex generics
- Best Practices and Standards in Nanotechnology
- Lack of effect of antioxidants on BCS Class III drug permeability
- Mitigation of nitrosamine formation in solid dosage form through formulation

Ongoing Engagement to Advance Complex Generics Product Development

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

Industry Engagement and Research Methodology

Establish Relationships

- Small, medium and large generic companies
- Trade Organizations (AAM, Pharma-Bio, etc.)
- CROs and CMOs
- Other generics stakeholders
- FDA

Periodic Meetings

- Every 3-4 months with generic industry stakeholders
- Monthly and weekly meetings with the FDA

Data, Analysis and Outcome

- Interview notes summarized and analyzed
- Key challenges identified
- Challenges shared with FDA during monthly and weekly meetings
- Publication of findings

Key Topics Impacting Generic Industry Stakeholders

Characterization of Complex Generics

- Complex Formulations and Excipients
- Peptide Immunogenicity

Nitrosamines

Drug Device Combination and Human Factor Studies

Clinical Trial Design and Alternative Approaches to End Point

Intellectual property

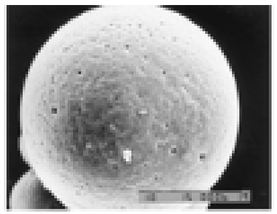
Timeliness of guidelines, communication

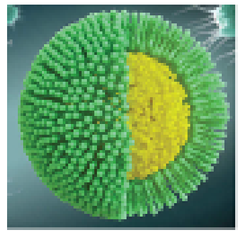
Challenges with characterization of complex generics

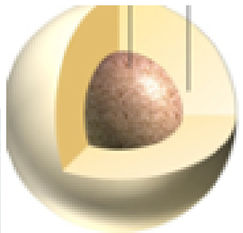
Challenges with translating guidance into the development program- there are still lot of questions and lack of clarity on incorporating them for inhalables, ophthalmic, and injectables.

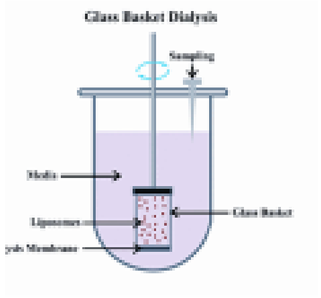
Need for better CMC controls and analytical characterization methods potentially prescribed in collaboration with USP and prescribed publication on analysis.

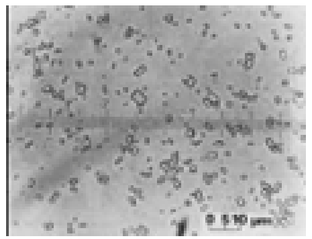
For peptides, when it comes to sameness studies and immunogenicity (heavy focus) requirements need more guidance and clear expectations

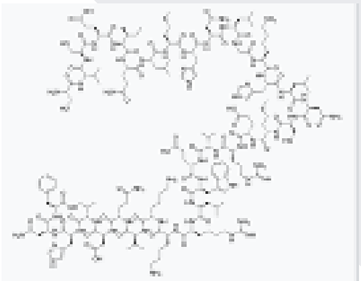












Nitrosamines are an ever-growing concern in the generic industry

- Complex nitrosamines impact large number of products
- Increases development cost and timeline
- Difficult to control supply chain, leading to potential shortages
- Lack of analytical standards and clarity in the guidance regarding limits, lack of expertise on complex nitrosamines, method development and risk assessment

- Complex nitrosamines require organic synthesis of standards for analytical development
- Analytical characterization is complicated
- Issues with formulation stability long term and nitrosamine levels during manufacturing stage, combination of API and excipients

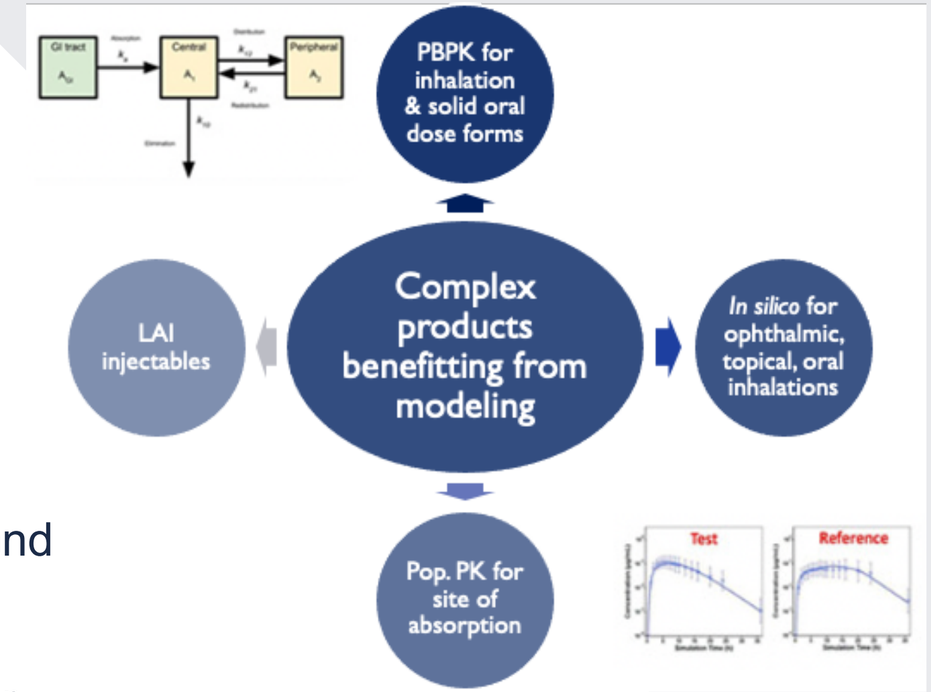
- Simple and complex nitrosamines are treated the same by the guidance
- No toxicology data is available for complex nitrosamine as well as limited data for simple nitrosamines
- Use of lifetime exposure nitrosamine limits for products with only 1 week treatment

Drug-device combination products and human factor studies pose unique challenges

- 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

Challenges and need for alternate approaches to clinical trial design and end point

- Complex characterization, non-standard analytical methods, batch-batch variability, drug-device combination, patient device use variability, population differences for PK and response
- Clinical end-point studies (>$30MM), inter and intra-patient variability underscore need for alternate approaches that combine in vitro characterization and in silico modeling methods
- Model-based alternatives to bioequivalence studies to speed up the development process and reduce costs
- Lack of case studies even though the agency is engaged, enthusiastic and willing to work on these issues
- Need for global harmonization in acceptance of modeling approaches for approval of generic drugs across multiple agencies



Intellectual property (IP) interferes with the progress of generic development

- IP blocks companies from making acceptable “mimics” of the innovator.
- If a generic does not meet all RLD specifications due to concerns over prior art, it impacts approval
- The uncertainty of new patent claims, makes it challenging to predict infringement, design clinical studies and begin scaling up manufacturing
- Inability to access device or work around the patents and trademarks to make it substitutable
- Trade dress can prevent companies from using the same device shape, color and/or delivery design that are crucial for optimal dosing or patient usage

Summary

- CRCG has been effective in identifying concerns, challenges and potential areas of research focus to facilitate generic drug development.
- We appreciate the 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 is a need for development of PSG for products before they come off patent especially for orphan indications and RNA-based therapeutics
- There is a strong need for development of alternative approaches to BE and end-point studies for complex products
- There is a need for a collaborative research efforts on nitrosamines with respect to analytical characterization, toxicology evaluation, and excipient control
- There is a need for publications and specific case studies around analytical characterization, in silico models and immunogenicity of specific complex products based on GDUFA research and development of standard methodologies

CRCG Contact & Media Platforms

Email: info@complexgenerics.org

Website

Learn more about the Center & signup for listserv

www.complexgenerics.org

YouTube Channel

Recordings from CRCG events will be posted here. Subscribe for updates.

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Social Media

Please follow CRCG for event related updates.

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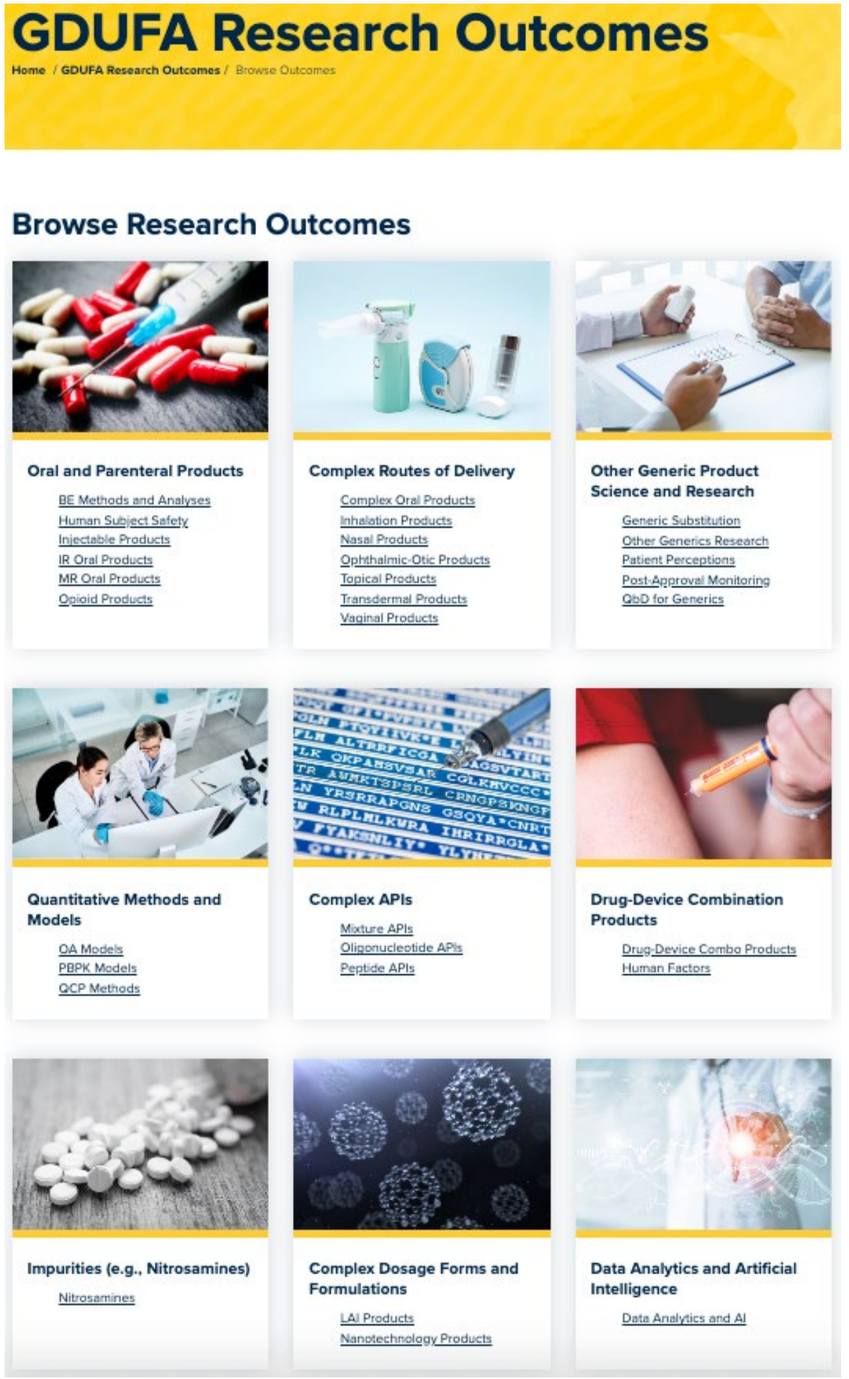
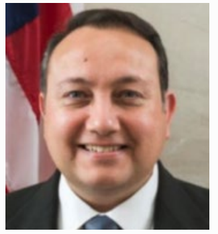
CRCG Website - GDUFA Research Outcomes Database

Access to a searchable GUDFA research outcomes database which contains important scientific resources and results arising from GDUFA-funded research across the major GDUFA science and research priority areas - including scientific publications, presentations, and posters from GDUFA-funded research.



Acknowledgements

- FDA U18 FD007054 grant from GDUFA funding
- Generic companies and stakeholders interviewed by CRCG
- Dr. Robert Lionberger, Director, ORS, OGD, FDA
- Dr. Sameersingh (Sam) Raney, Associate Director/Chief Scientific Advisor, ORS, OGD, FDA & CRCG Program Officer
- FDA CRCG Program Oversight Committee Members
  - Dr. Andrew Babiskin, Team Lead, DQMM, ORS, OGD, FDA
  - Dr. Wenlei Jiang, Senior Advisor for Innovation and Strategic Outreach, ORS, OGD, CDER
  - Dr. Xiaoming Xu, Division Director, DPQR, OTR, OPQ, FDA
- CRCG Team
  - Dr. James Polli, University of Maryland, CRGG co-Director
  - Dr. Vishalakshi (Visha) Krishnan, CRCG Associate Director
  - Dr. Jill Coghlan, U-M PhD
  - Dr. Alyssa Marconi, U-M PharmD
  - Dana Hammell, Events Coordinator CRCG
  - Jennifer Dick, Administrative Assistant CRCG



Thank You !