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FDA U.S. FOOD & DRUG ADMINISTRATION

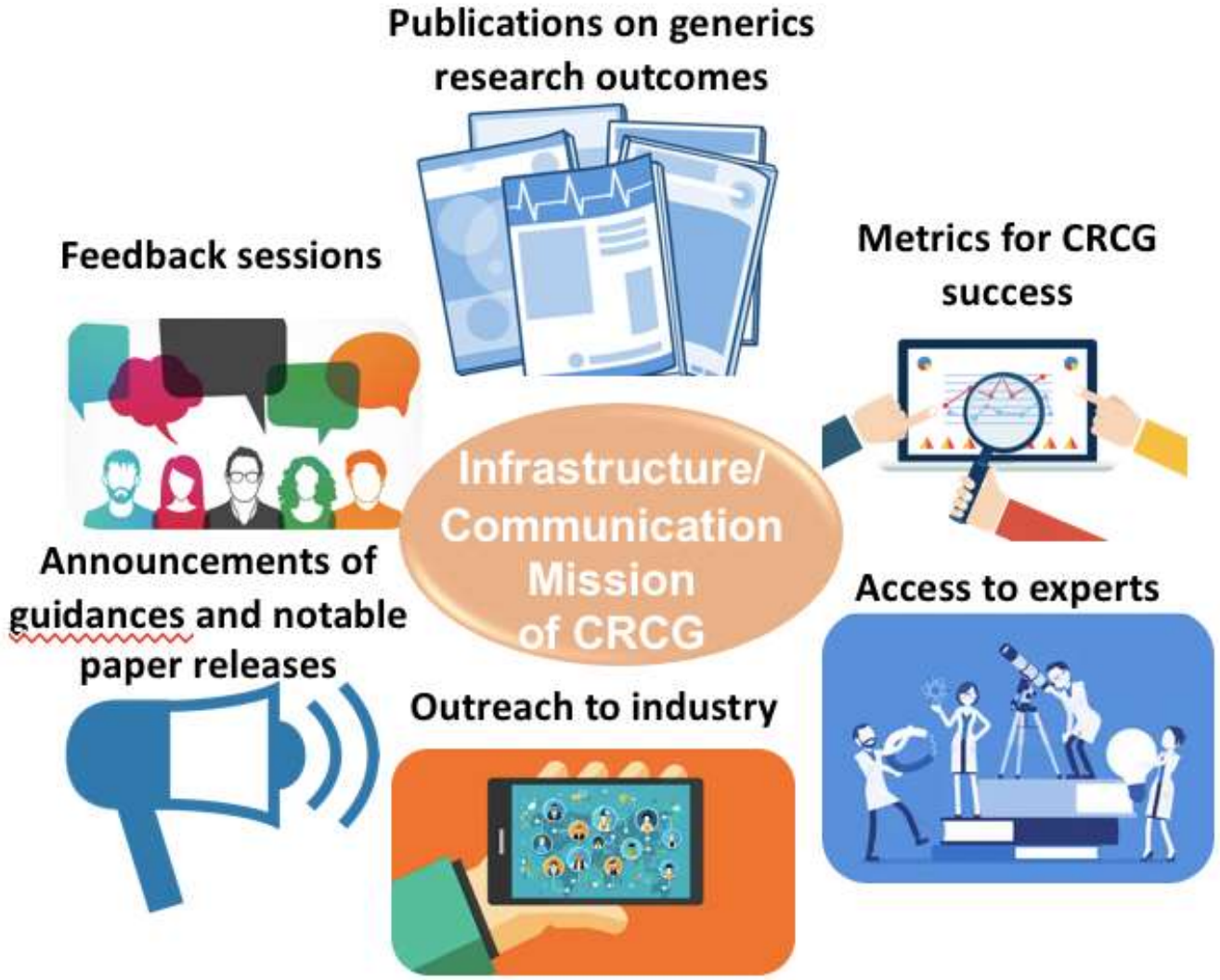
CENTER FOR RESEARCH ON COMPLEX GENERICS

Summary of Interview Feedback from Industry Stakeholders

GDUFA Research Priorities Meeting - June 24, 2021

http://www.complexgenerics.org

Communication Mission of CRCG



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Interviews Structure

- Questions asked:
  - What are the barriers for development of complex generics and "pain points"?
  - Are these barriers due to scientific issues, regulatory challenges, market competition, and ROI considerations?
  - How CRCG could help complex generic products development through research, training, and facilitating communication with the FDA?
- Some interviews were structured with slides and written summaries, and all allowed for open dialogue
- Information will be used to focus CRCG's efforts and help inform FDA's GDUFA funded activities
- The outcomes will be summarized in a peer-reviewed publication

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Interviews

- Stakeholders interviewed (20 organizations, some multiple times)
- Type of products discussed
  - Complex injectables (liposomes, LAI, iron colloids)
  - Inhalation products (DMI)
  - Topical and transdermal products
  - Ophthalmic emulsions and suspensions
  - Orals
- Type of issues discussed
  - CMC issues, BE issues, clinical trial design, use of modeling, PSGs, FDA-industry communications, L&E, and NDMAs

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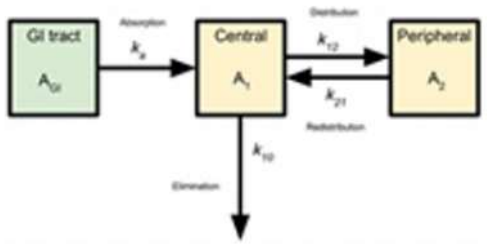
Company Name	Large	Specialty	Trade Org	Type of products mentioned
Perrigo	X			Topical, inhalations, injectables
Apotex	X			Oral, injectables, inhalations, drug-device combo
Teva	X			Injectables, transdermal, inhalations, drug-device, ophthalmic
Viatris	X			Injectables, transdermal, inhalations, drug-device
Sandoz	X			Injectables and inhalations
Cipla	X			All product types
Amneal	X			Injectables, orals, ophthalmic
Sun Pharma	X			Injectables
Fresenius Kabi		X		Injectables
Cosette		X		Topical, locally acting orals, ophthalmic
Solaris Pharma		X		Topical
Nexus		X		Injectables
Xellia		X		Injectables
Capstone		X		Topical, injectables, drug-device combo
AAM			X	Drug-device combo, orals, injectables
PBOA			X	Drug-device combo, inhalations, orals, injectables
Lassman Law			X	PSG for complex products
SAAM			X	Oral, inhalations, ophthalmic, topical

Company	Leachables/ Extractables	Nitrosamines	Changing PSG	FDA-industry communication	Specific CMC Issues	Drug-device combinations	Old and variable ref products	Specific bioequivalence issues
Perrigo	X				X	X	X	X
Apotex	X	X	X	X	X	X	X	
Teva			X	X	X	X		
Viatris	X	X	X	X	X	X		X
Sandoz	X		X	X	X			X
Cipla				X	X	X	X	X
Amneal		X	X	X	X	X	X	
Sun Pharma	X		X		X	X	X	
Fresenius Kabi	X	X	X	X	X		X	
Cosette			X		X			
Solaris Pharma					X		X	X
Nexus	X			X	X	X	X	X
Xellia					X			
Capstone			X	X	X	X	X	X
AAM	X	X	X	X	X	X		
PBOA		X	X	X	X	X	X	X
Lassman Law			X	X	X			
SAAM					X	X		X

BE Studies – Modeling Needs



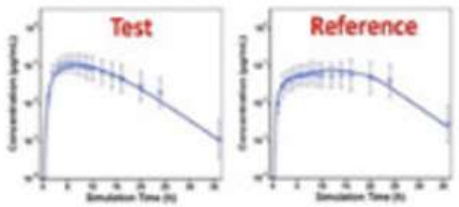
PBPK for inhalation & solid oral dose forms

LAI injectables

Complex products benefitting from modeling

In silico for ophthalmic, topical, oral inhalations

Pop. PK for site of absorption



- Industry concerns:
  - "Finding alternatives for performing clinical end-point studies is important, but generic companies don't want to be trailblazers"
  - "Lack of universally accepted models for complex generics"
  - "Lack of FDA publications on expectations for BE modeling and requirement for model validation."
  - "FDA feedback on model development will be very helpful."
  - "Not sure how the modelling will be reviewed/accepted"
  - "Can we do full modeling or partial modeling to supplement patient data?"

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General CMC Issues

- Analytical methodologies
  - Lack of standardized analytical methodologies for characterization of complex products (examples: particle size and morphology, IVR, immunogenicity, adhesiveness)
  - Difficult to validate some of the non-traditional methods and show discriminative ability
  - "Novel more discriminative methods are developed by the industry but not accepted by the agency as they don't match USP"
  - "Boutique" methods is not easily accessible for some companies (MDRS, SEM, SAXS)
- Extensive analytical requirement in PSGs.
  - "Many requirements are listed on PSGs. Many do not impact product BE. Are all parameters required to be measured?"
  - "Some requirements appear to be of purely of academic interest with no clear scientific rationale or data that supports how parameters impact on BE"

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General CMC Issues

- Q1/Q2 vs. "Q1/Q2 like"
  - In many cases "Q1/Q2 like" products are bioequivalent. Patent limitations to achieve Q1/Q2. "Could product be outside 5% variability requirement?"
  - Q1/Q2 route is too complex to follow, companies opt for clinical studies
  - Difficult to characterize and achieve Q1/Q2 for products with 10+ ingredients
  - Small issues like buffer composition are holding off product approval
  - Differences between RLD label and reverse engineering data
- RLD, API and excipients availability
  - "Difficult to procure (n=3) for low volume, orphan drugs and high price RLDs"
  - "One lot per year is produced for some RLDs, APIs and excipients."
  - "RLD no longer available."

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Highly Variable and Old RLDs

Inherent product variability

- RLD do not pass *in vitro* comparability when compared to itself (release rate, particle size, purity)
- BE studies difficult to match (iron sucrose, PLGA LAI, DMI, topical steroids)
- Discrepancies between label and actual product

Availability of ingredients

- API and excipients sources variable and difficult to obtain
- Some sources only make one batch per year

Outdated technologies and formulations

- Newer technologies control production process, unable to be used because does not meet RLD variability (estradiol cream, topical steroids)
- RLDs could be made more stable with anti-oxidants, but new formulations do not meet Q1/Q2

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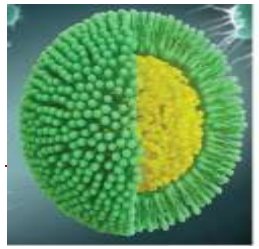
Complex Injectable and Ophthalmic Products



Liposomal Products

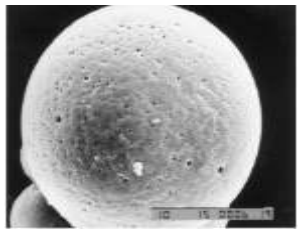
- Establishing and validating methods (i.e. particle size, IVRT, impurities, morphology)
- Too many parameters to measure after BE
- Different morphology but same BE

PLGA Long Acting Injectables

- Establishing and validating methods (i.e. morphology, porosity, IVRT, drug distribution)
- Characterizing aggregates and impurities for immunogenicity
- RLD variability

Iron Sucrose

- Establishing and validating methods (i.e. particle size, morphology, aggregation)
- RLD variability



Ophthalmic Emulsions

- Establishing and validating methods
- RLD variability
- Small Q1/Q2 issues preventing approval

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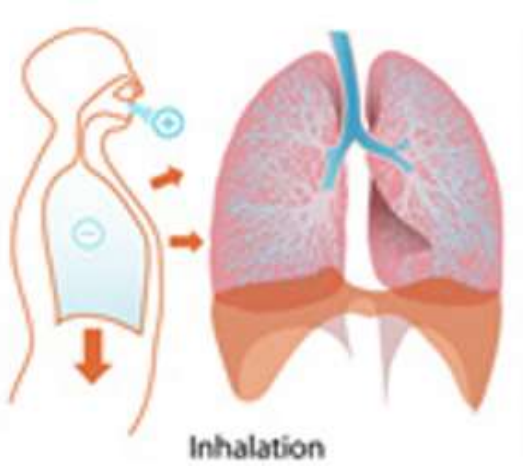
Inhalation Products

DMIs are an important class of products with few generics available that are of high interest to multiple companies



DMI product development considerations

Unique challenges:

batch-batch variability, drug-device combination, patient device use variability, population differences for PK and response

Clinical trials:

large trial requirements, ability to discuss clinical trial design would be beneficial

Standardized methods:

particle size, morphology, physiologically relevant dissolution, modeling (PK, PBPK, pop. PK)

Regulatory requirement differences

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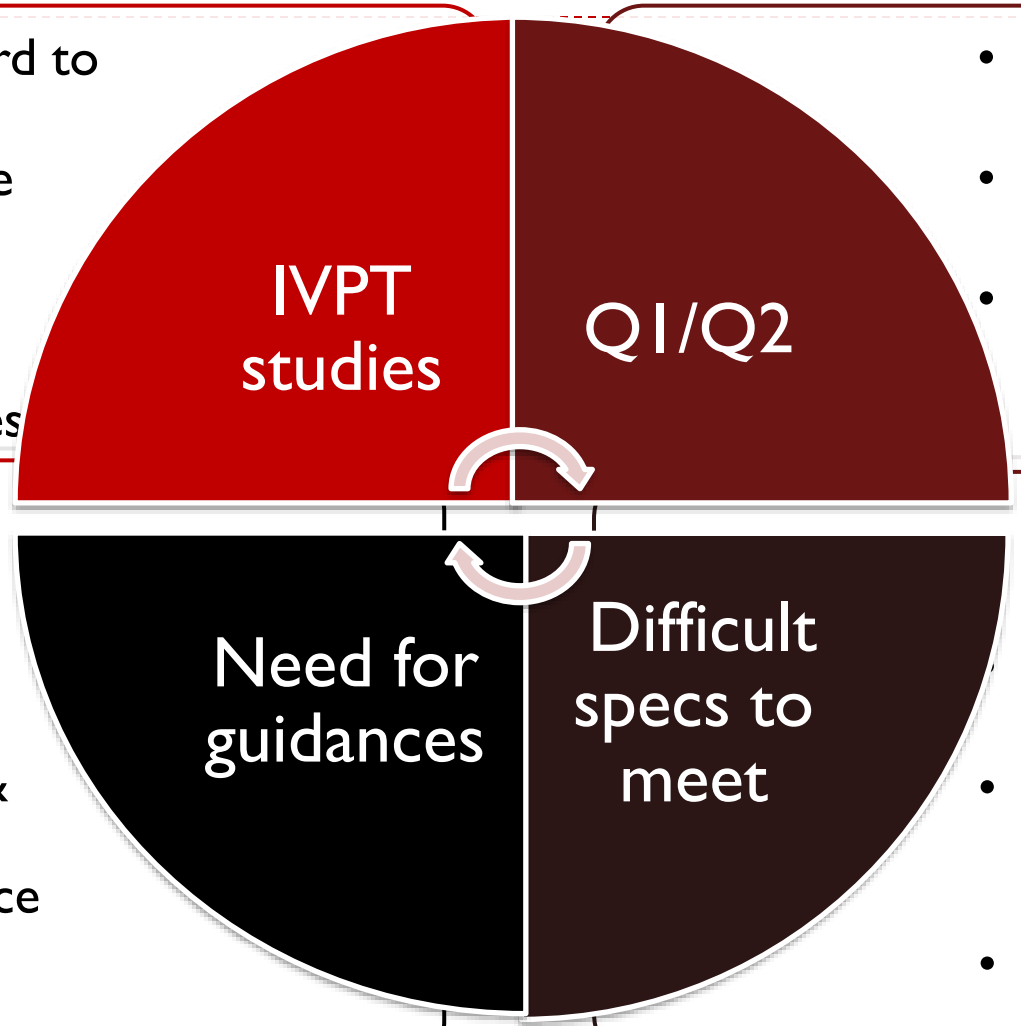
Topical Products

- High variability - statistics hard to pass
- Low drug permeation, sample application
- Donor sample availability throughout study
- No "one size fits all" practices



- Excipients at low levels hard to show equivalence/characterize
- Need alternative BE for products that are only Q1/Q3
- Ink and structural components adhesives limit non Q1/Q2 formulations

- Statistical guidance for IVPT doesn't discuss data outliers
- Impact of crystal formation & release/backing layers on bioavailability and performance
- Permeation enhancers

- N=3 hard to meet → some excipients infrequently
- Need to continue doing adhesion studies for formulations similar to RLD?
- Microscopic appearance study requirements

Clinical Trials Issues

Trial design for clinical end point studies for inhalation products

- Large studies, high variability in formulations and patient device use, expensive
- Looking into modeling alternatives but unsure how FDA will review them
- "Meeting with the agency prior to agree on clinical study design for large/expensive trials will mitigate the risk"

Trial design, duration and recruitment for BE studies

- Long and difficult to recruit studies for LAI products
- Not clear how FDA will review use of modeling LAI and liposomal products
- Need alternative approaches for BE studies based on IVIVC and in vitro characterization
- Limited patient pools, especially drug-naïve patients for cytotoxic drugs

Trial design and execution for "poorly" active not Q1/Q2 equivalent products

- Large studies and highly variable response to drugs
- More expensive to prove equivalency of generic than to approve RLD

Clinical Trials Issues

- "Is FDA open to discussing with EMA and other regulatory agencies trial harmonization?"
- Issues with RLDs sourcing
  - Availability of RLD lots (low volume, orphan and products no longer marketed)
  - The need for geography specific RLD lots for clinical studies
  - Study duration exceeds RLD shelf life
- Bioanalytical concerns
  - How to analyze free vs. encapsulated drug in plasma for liposomal products.
  - Measurement of free iron/bound iron for iron colloids
  - "Multiple failed BE studies due to high product variability and lack of robust bioanalytical methods."
- LAR products (site of injection vs. bioequivalence)
- Correlation between adhesion and bioequivalence for transdermal products

Leachables and Extractables

"USP <661/661/1/661.2> only used as baseline"
"Same scrutiny for cream containers and applicators,"
"Inability to defend position in a two-way dialogue"

Unclear FDA expectations

Delay of approval

"9 out of 10 programs delayed by L&E questions"
Need to repeat expensive studies for L&E
"Even low risk products have to go back and generate additional L&E data"

"Same product submitted under different company names – completely different reviews"

Inconsistency of reviews for similar/same products

Communication and Guidance Concerns

Utility of FDA-Industry Meetings

- Pre-ANDA most useful → need more than one
- Mid-review and post-CRL limited in utility, constrained
- Desire for direct communication with FDA to solicit feedback on study design

Missed Deadlines/ Deficiencies

- Seeking to receive and address most of the FDA requests during 1st review cycle
- "Missed GDUFA goal dates due to complex review issues leading to unpredictability"

Changes in PSGs

- "Involve industry in development of PSGs"
- Updated requirements lead to delays and redevelopment → hinders economic viability
- Unclear what standards a filing held to if new PSG is release after filing

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CRCG Strategic Plan to Address Industry Concerns

- Addressing CMC concerns
  - Perform reverse engineering for high interest and highly variable RLDs
  - Establish and characterize the performance on non-standard analytical methods
  - Establish "boutique" characterization methods and make them available to industry
  - Understand the impact of "Q1/Q2 like" or morphological differences on BE
  - Develop a library of RLD, API and critical excipients lots available to generic industry
  - Work on development of analytical characterization for upcoming new product classes (example: RNA therapeutics)

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CRCG Strategic Plan to Address Industry Concerns

- Addressing Modeling and Clinical Trials Concerns
  - Work with industry stakeholders and FDA to develop acceptable and "standard" models for inhalation, ophthalmic, LAI and topical products
  - Jointly develop an understanding of model validation requirements
  - In collaboration with industry, explore alternatives to BE studies based on in vitro characterization and IVIVC for select products
  - Re-examine BE requirements for highly variable RLDs
  - Work with FDA and other regulatory agencies on harmonization of clinical trials design requirement

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CRCG Strategic Plan to Address Industry Concerns

- Addressing Industry Concerns
  - Work with the agency to address concerns around L&E reviews
  - Work on development of analytical characterization methods and risk assessment for different NDMAs
  - Organize workshops on specific types of complex products and newly developed regulatory guidances to provide clarifications and to solicit industry feedback
  - Be able to foresee potential scientific questions for products with patent expiries in 5-10 years

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Acknowledgements

- FDA U18 FD007054 grant from GDUFA funding
- Multiple generic companies and trade organizations that had been interviewed by CRCG
- Dr. Sameersingh (Sam) Raney, FDA grant manager
- Dr. Lisa Parks, AAM
- Dr. James Polli, University of Maryland, CRGG co-director
- Dr. Vishalakshi (Visha) Krishnan, CRCG manager
- Ms. Jill Coghlan, U-M Ph.D. candidate