BARRIERS AND FACILITATORS INFLUENCING THE DEVELOPMENT OF COMPLEX GENERICS: AN EXPLORATORY STUDY

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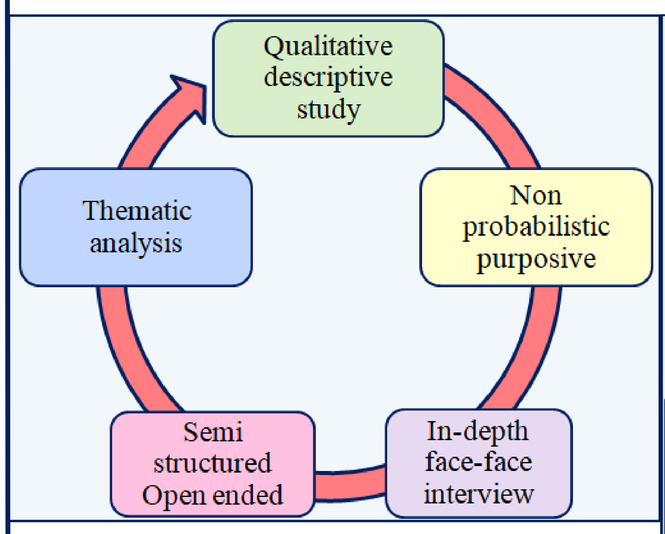
INTRODUCTION

Complex generics are those drug products generally, include products with complex active ingredients, complex formulations, complex routes of delivery, complex dosage forms OR complex drug-device combination products OR other products where complexity or uncertainty concerning the approval pathway or possible alternative approach would benefit from early scientific engagement

OBJECTIVE

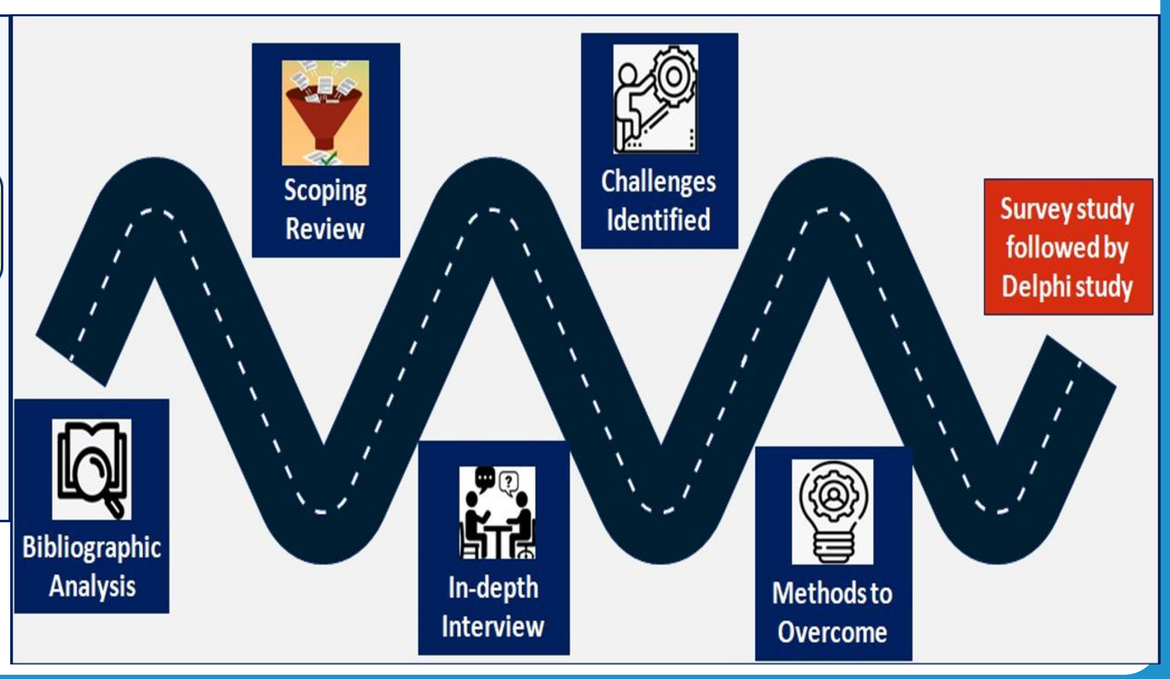
To explore the challenges from the perspective of industrial professionals to identify critical developmental , analytical and regulatory issues encountered.

METHOD



In-depth Interview: 38 participants

Survey : 86 participants



RESULTS

FORMULATION BARRIER

- Complex Oral: Complexity in coatings; Food effect and multiphasic PK complicate BE study design; Layer/coating uniformity; polymer composition and control release phases; robustness to GI conditions; multiparticulate size distribution
- Peptide & Oligonucleotide APIs: Peptide/oligo instability (degradation, aggregation); sensitive to excipients and processing. Chemical/physical instability (deamidation, aggregation); sensitivity to pH; excipients and effect of temperature
- LAI: Batch-to-batch variability driven by polymer source, manufacturing/extrusion conditions, and microstructure. Polymer variability (MW, chemistry); polymer (PLGA) degradation; residual solvent; porosity and microstructure. Process parameters (solvent removal, drying, spray-drying/solvent evaporation)
- Nanoparticle and liposome: Liposome size distribution; lamellarity; PEGylation density; surface charge; internal loading method and leakage rate; Drug loading and stability; Surface modifications (PEGylation); Variation in cryoprotectants concentration
- Topical / Transdermal Products: Physiochemical parameters: vehicle, rheology, particle/crystal state; Vehicle effects (rheology, thermodynamics, particle/crystal state); suspended particle size ; API recrystallization; selection of penetration enhancers or stabilizers; polymorphic changes.

REGULATORY BARRIER

- Topical / Transdermal Products: Evidence of local bioavailability/sameness; demonstrating equivalence across disease states.
- Complex Oral: Food effects and multiphasic PK complicate BE design; Q3 sameness; changes in in-vivo result.
- Peptide & Oligonucleotide APIs: Demonstrating comparable impurity profile; immunogenicity risk and stability.
- LAI: Demonstrating BE or "sameness" without long clinical endpoint trials. Convincing regulators for in-vitro/ modeling evidence. Lack of specification setting for CQAs and manufacturing control that affect the PK/PD.
- Nanoparticle and liposome: Deciding which analyte (total, free, encapsulated) are regulatory-relevant for BE. Demonstrating Q3 sameness (size, surface, composition) and clinical equivalence when no PD biomarker exists.
- OINDPs: Demonstrating evidence of local equivalence. Device changes and non-equivalency. Demonstrate device and formulation sameness
- Drug-Device Combination: Demonstrating device safety/effectiveness; CMC data and device regulatory pathway; stability of formulation after incorporating to device part

ANALYTICAL BARRIER

- OINDPs: High sensitivity to device/formulation/actuation differences (aerosol particle size distribution, plume geometry, spray pattern, emitted dose); Patient and device factors (inhalation flow, technique, anatomy) ;actuator geometry; Variation CMA (suspending agents, viscosity modifiers)
- Drug-Device Combination: Device usability and human factors (patient handling, dose delivery variability); Device sterility and manufacturing controls.
- OINDPs: Demonstrating therapeutic equivalence and stability; APSD measurement; emitted dose repeatability; spray pattern and plume geometry characterization; measuring regional deposition; in-vitro release in anatomical area
- Drug-Device Combination: Measuring delivered dose; spray/jet performance; extractables/leachables profiling, human factors / usability studies. Device compatibility with formulation
- Peptide & Oligonucleotide APIs: Impurity testing; immunogenicity in-vitro assays.
- Complex Oral: Q1/Q2/Q3 sameness; Detecting small coating defects; assays for residual solvents and coating impurities; coating uniformity; In-vitro dissolution methods at different media, agitation, and biorelevant media
- Nanoparticle and liposome: Separate multi-analyte PK (measure both encapsulated and free drug); Measuring size; lamellarity; zeta potential; and leakage lipid composition; assays for serum stability/leakage; Batch-to-batch reproducibility
- LAI: Demonstrating sameness; MW; residual solvent; API impurities; polymer degradation; local drug concentration; In vitro release and associated microstructural characterization; Establishing IVIVC
- Topical / Transdermal Products: Systemic PK/PD endpoints; trace impurities; polymorphs/particle size; ex-vivo permeation tests. Skin variability (disease state, thickness, psoriasis vs healthy skin)

CONCLUSIONS

An interconnection between formulation, analytical, and regulatory challenges in the development of complex generic. Addressing one of these challenges will not be a complete solution to overcome the formulation development barriers. An integrated approach will accelerate the development, regulatory approval and market access of cost effective complex drugs for treating complicated therapies.

REFERENCES

CONTACT INFORMATION