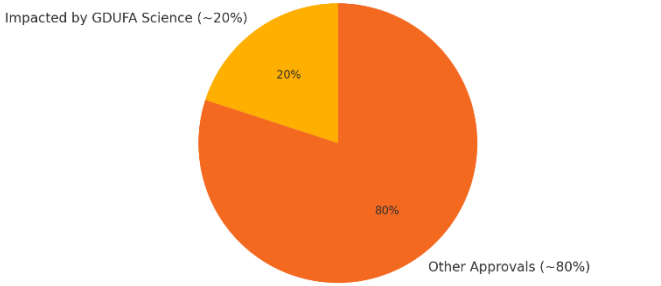
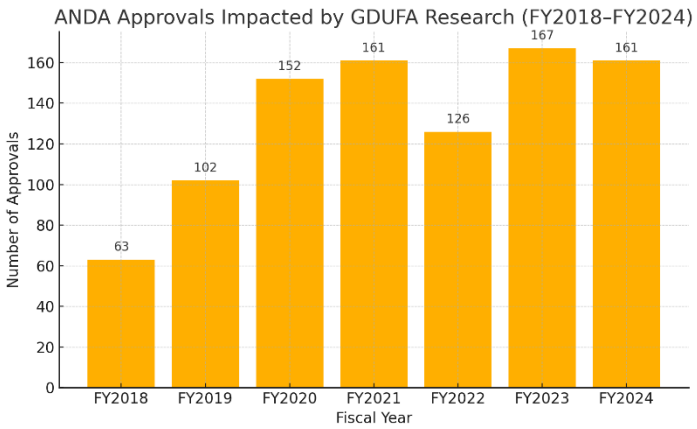
Perspectives on Current Quality and Bioequivalence Challenges for Complex Products

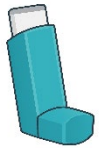
Andre O'Reilly Beringhs, Ph.D.
Staff Fellow – ORS/OGD/CDER/FDA

Renishkumar Delvadia, Ph.D.
Senior Staff Fellow – OPQ/CDER/FDA

GDUFA-driven Breakthroughs Pave the Way to ANDA Approvals







Budesonide; Formoterol Fumarate Metered Dose Inhaler
Reduced need of clinical endpoint bioequivalence studies

Naltrexone for Extended-Release Injectable Suspension
Alternative methods to support drug product sameness

Cyclosporine Ophthalmic Emulsion
Q1/Q2/Q3 microstructure fingerprinting in lieu of in-vivo trials

The takeaway is simple: GDUFA regulatory-science investments pay tangible dividends in faster, lower-cost approvals, especially for complex generic products

Topical Dermatological and Transdermal Products

Topic	Quality/Bioequivalence Challenges	Exploratory Ideas
Topical Semisolids	• IVPT implementation • Q3 assessment for products with compositional differences	• Q3 'safe space' and performance relationship
Integrated Modeling	• Model validation and implementation • No model-only BE approaches in PSGs	• Totality-of-evidence via Q3 + modeling
Transdermal and Topical Delivery Systems	• Lack of biorelevant in vitro adhesion tests • Skin irritation and sensitization	• Skin-mimetic adhesion tests

Inhalation and Nasal Products

Topic	Quality/Bioequivalence Challenges	Exploratory Ideas
Dry Powder Inhalers (DPIs)	• High inter-batch variability • Particle-aerosol performance link	• High-res morphology mapping • Variability deconvolution studies
Metered Dose Inhaler (MDIs) & Next Generation Propellants	• Spray/APSD variability with new propellants; • BE framework or design space	• Map formulation-device interactions • PBPK and in vitro - in silico models
Nasal and Nose-to-Brain Products	• No validated regional deposition models • Unclear CNS delivery target site	• Develop 3D nasal models with deposition readouts • Pilot CNS surrogate endpoints in preclinical models

Complex Injectables

Topic	Quality/BE Challenges	Exploratory Ideas
In-situ Forming Depots	• Validated in vitro models for depot formation • High variability from injection factors	• Injectability rigs and imaging • Physiologically-relevant dissolution models
Nanoparticle-based Injectables	• Impact of albumin-bound stabilizers on nanoparticle BE and quality	• Profile stabilizer levels • Risk-assessment framework for stabilizer differences
Q1/Q2 Flexibilities	• Impact of minor formulation differences on BE	• Q3/Q4 fingerprinting + PBPK modeling • Science-based “safe-harbor” for formulation variations

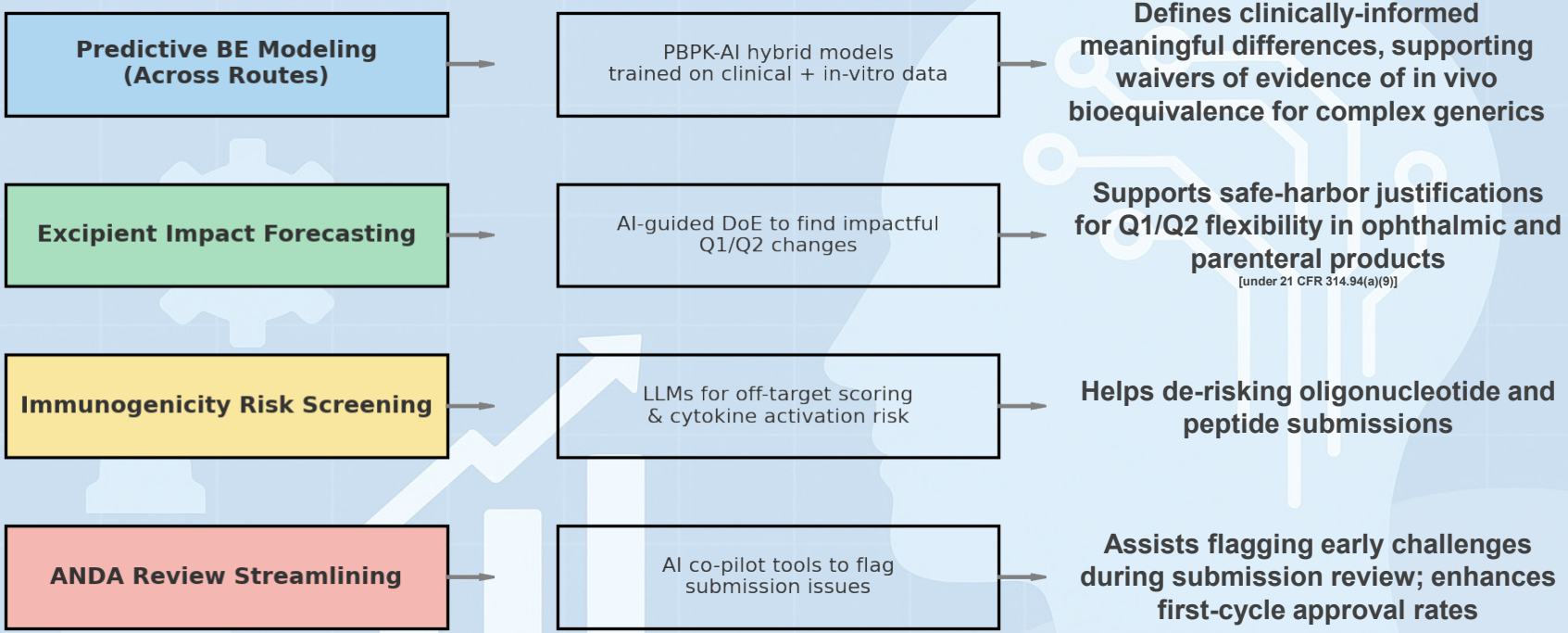
Ophthalmic and Otic Products

Topic	Quality/Bioequivalence Challenges	Exploratory Ideas
Intra-ocular Implants	• Predict long-term ocular PK • Structure-release relationships	• Modular toolkit (micro-CT, Raman, USP 4) • PBPK modeling
Posterior-segment Depots	• Q1/Q2/Q3 impact on vitreous depot behavior	• Use vitreous-mimic chamber • IVIVC models
Permissible Excipient Differences	• Impact of Q1/Q2 differences • Equivalent substitutes	• AI-based Q3 fingerprinting with in/ex vivo data
Otic Suspensions & Gels	• In vitro model reflecting middle ear permeability	• Tympanic organ-chip with real-time permeation for PK prediction

Peptide and Oligonucleotide Products

Topic	Quality/Bioequivalence Challenges	Exploratory Ideas
Oral and Nasal Peptides	• In vitro models for enhancer-driven absorption • Simulation of mucosal dynamics	• Epithelial perfusion models with real-time protease/enhancer tracking
Depot-forming Peptides	• Tools to model long-acting depot PK • Depot structure-PK linkage	• SANS/SAXS + depot-shrinkage imaging with subQ release modeling
Oligonucleotides	• Impurity characterization • Potential off-target and/or immunogenicity risks	• Orthogonal impurity profiling platforms for low-level process- and sequence-related impurities

AI Tools Applied to Complex Generics



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