Development of Enhanced Analytical Tools for Evaluation of Complex Generic Products

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OPQ's Proactive Science and Research Approach

- The **science program** is designed to maintain preparedness.
  - Consumer complaints
  - Public health issues
- The **research program** is "forward looking."
  - New and emerging technologies for analytics and manufacturing
  - Advanced analytics (instrument and modelling)
  - Forecasting generics for newly-approved NDAs
  - Complex Drugs in NME and generic drugs

OTR's Role in Generic Drug Science

- Laboratory consults
  - Method evaluation (verification)
  - Product quality
  - Pharmaceutical equivalence and bioequivalence (in vitro approaches)
- Training
  - Provide training to quality assessment staff
- Guidance and Standard development
  - Provide laboratory data to support product specific guidances (PSG) and general guidances
  - Develop improved testing methods for quality and equivalence standards

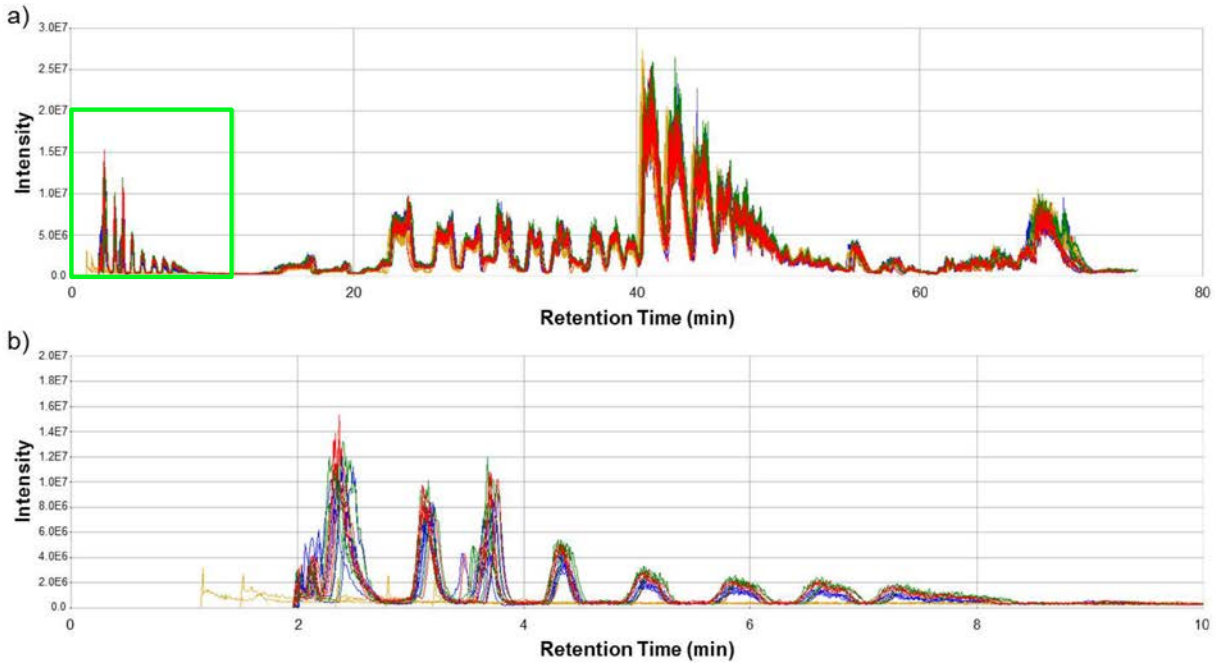
Elements of Providing PSG for Complex Generics

- Bioequivalence study recommendations
  - Systemic or local site of action
  - In vitro or in vivo approach
- Extent of analytical characterization of sameness
  - What attributes need to be the same and which can differ in a generic?
- Standard for analytical characterization
  - Equivalence test (statistical criteria)
  - Quality range approach (mean ± X SD)
  - Qualitative comparison (visual displays)
  - Quantitative comparison (statistical methodology)
- Device similarity and human factor studies

Examples of Complex APIs and Challenges

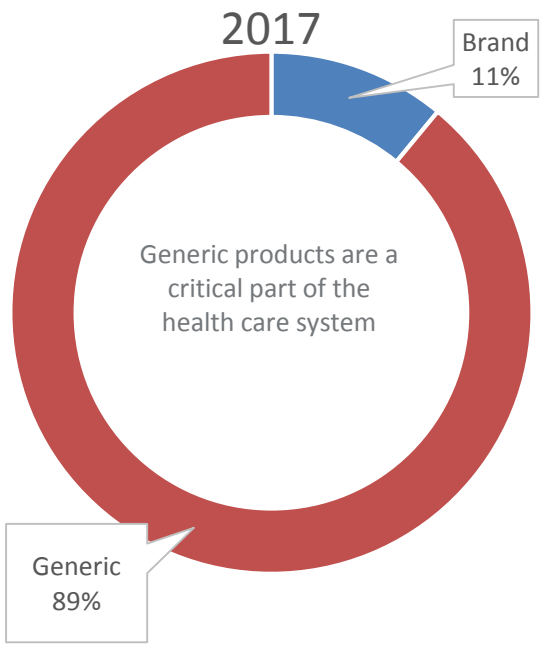
- Peptides including lipopeptides
  - Peptide-related impurity analysis
  - Non-clinical immunogenicity assessments on impurities
- Polymeric compounds
  - Sameness assessment
- Oligonucleotides
  - Characterizations for establishing identity
  - Impurity analysis for related-substances

LC-MS: Differential Analysis of Glatiramer Acetate



Rogstad et. al. Analytical and Bioanalytical Chemistry, 407, 29, **2015**, 8647-8659.

Challenges to Determine Equivalence of Complex Generics



Standards for approval of a generic, compared to Reference Listed Drug (RLD):

- Same *active ingredient(s)*
- Same *strength*
- Same *dosage form*
- Same *route of administration*
- Same *indication(s)*

Pharmaceutical equivalent

- ***Bioequivalent*** to RLD
- May differ in color, shape, excipients and packaging

But for complex drug products below, applying the standard approach can be challenging, for example:

- Complex Active Ingredients
  - LMWH, peptides, complex mixtures, natural source products
- Complex Formulations
  - Liposomes, iron colloids, nanomaterials, **emulsions**
- Complex Route of Delivery
  - **Locally acting drugs**
- Complex Drug-Device Combinations
  - DPI, MDI, nasal spray, transdermal system

Example: cyclosporine ophthalmic emulsions

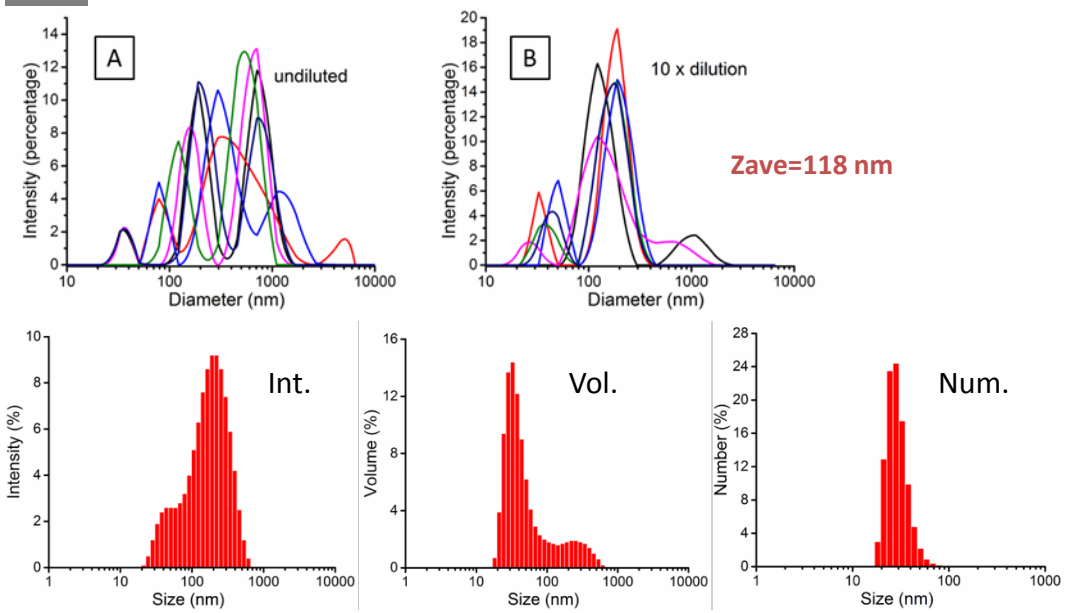
- Reference listed drug: Restasis® (cyclosporine ophthalmic emulsion) 0.05%
- Indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with kerato-conjunctivitis sicca
- Locally acting topical ophthalmic emulsions (o/w)
- Typical BE studies are not feasible (in vivo PK or PD)
- **Globule size distribution** is one of the critical in vitro physicochemical property to determine BE*

*https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm358114.pdf

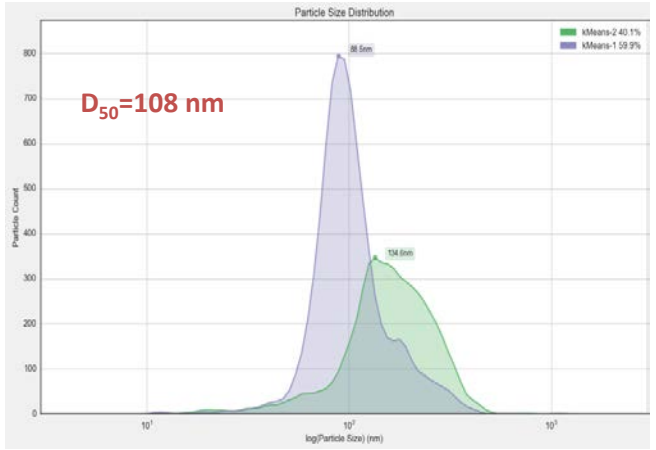
Particle Size and Size Distribution (PSD): cyclosporine emulsion

Challenge: what is the size? How to compare?

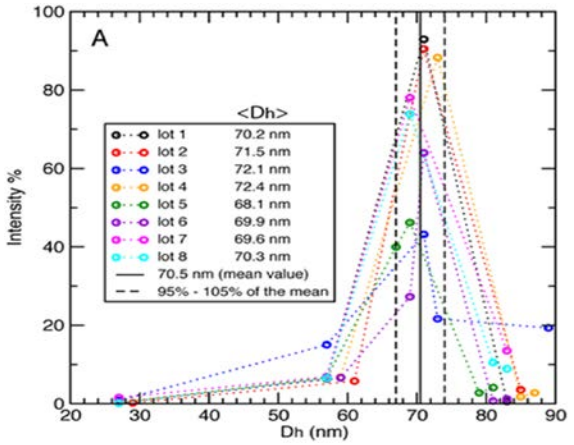
DLS



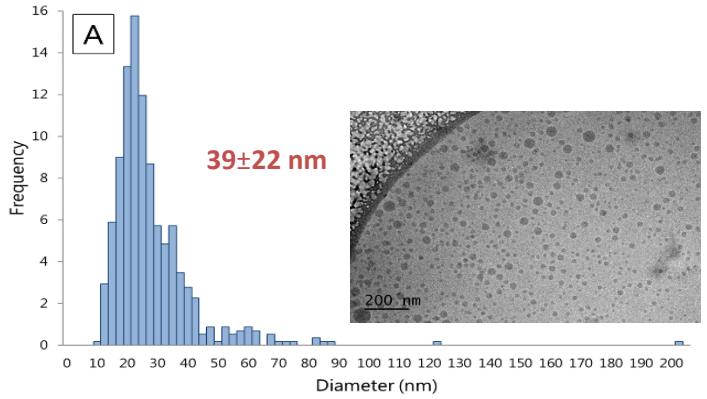
NTA



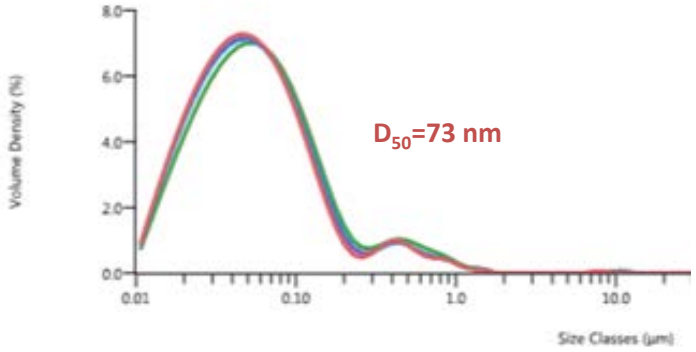
DOSY NMR



Cryo-TEM



LD

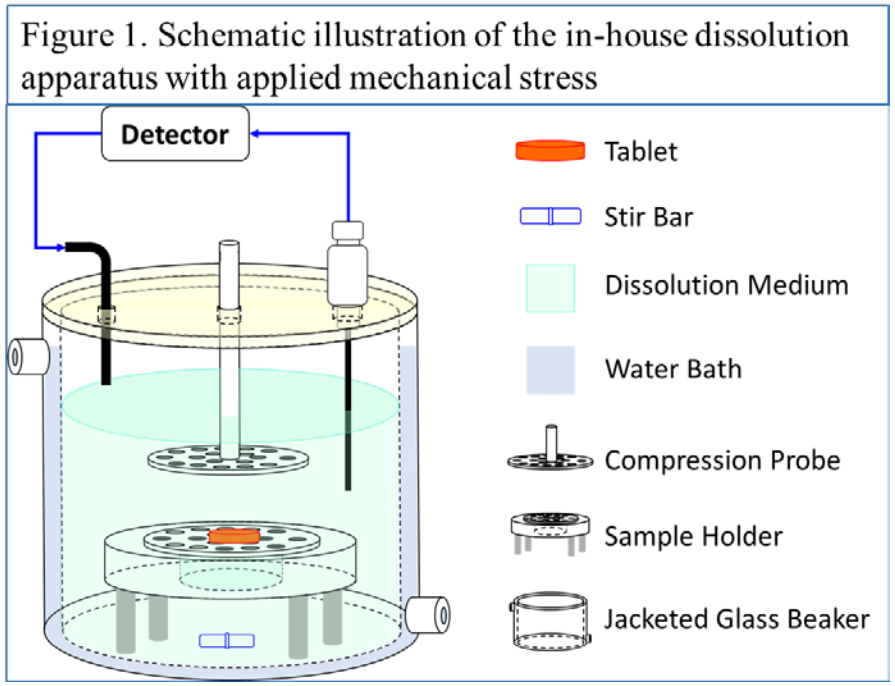


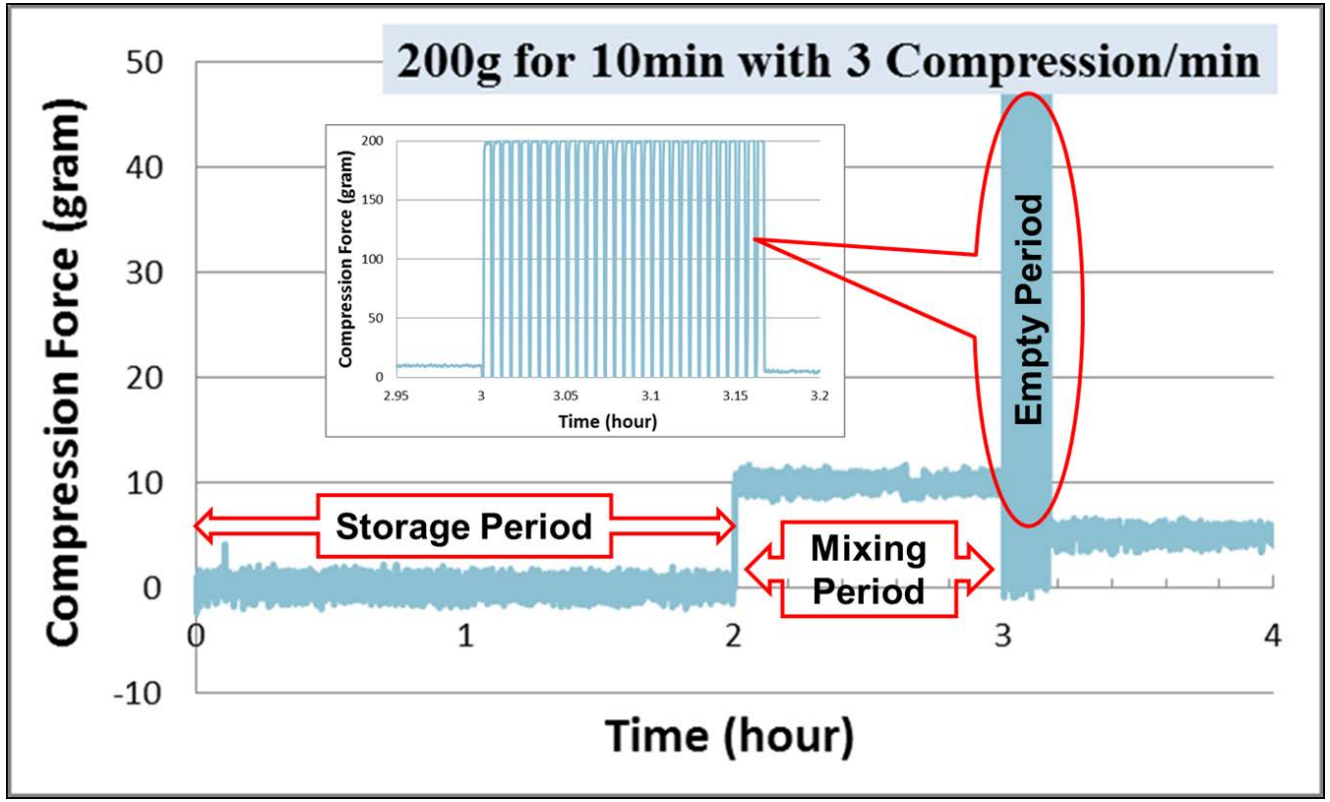
Why is size of the product important?

- It likely affects drug distribution
- It may impact overall drug release

P. Petrochenko, N. Pavurala, Y. Wu, S. Y Wong, H. Parhiz, K. Chen, S.M. Patil, H. Qu, P. Buoniconti, A. Mohammad, S. Choi, D. Kozak, M. Ashraf, C.N. Cruz, J. Zheng, X. Xu. Analytical Considerations for Measuring the Globule Size Distribution of Cyclosporine Ophthalmic Emulsions. International Journal of Pharmaceutics (2018). 550(1-2), 229-239

Biorelevant Dissolution Method - Simulate GI Contraction During Dissolution Testing

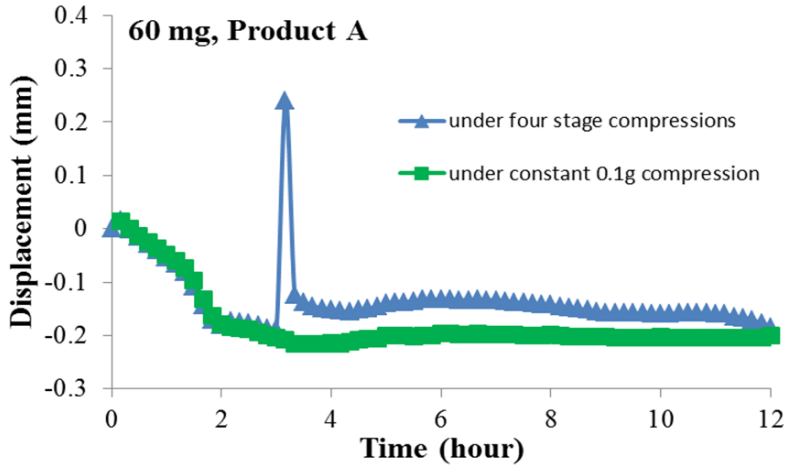


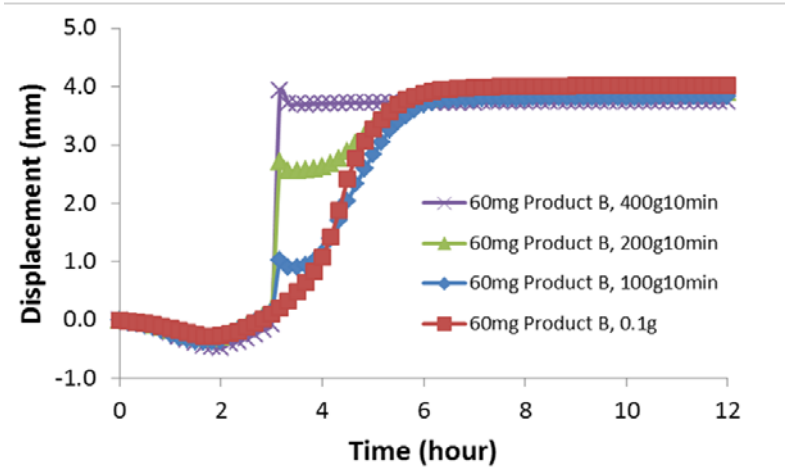


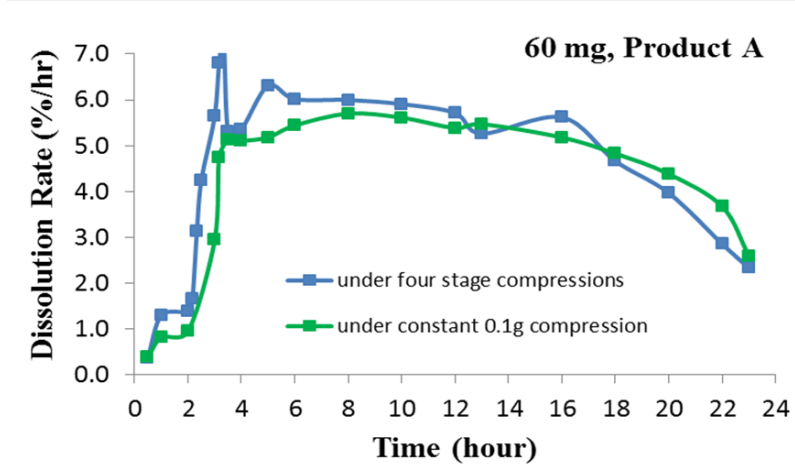
Biorelevant dissolution testing

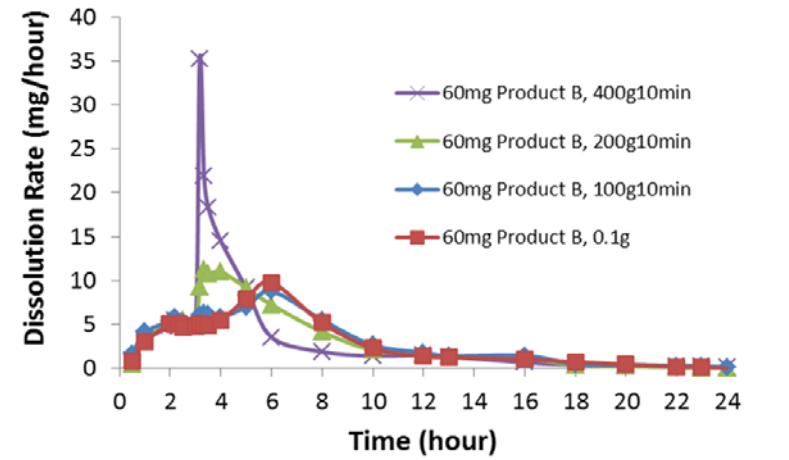
- In house apparatus to simulate GI contraction
- Biorelevant dissolution medium

Case Study: Effect of Simulated GI Contraction on Drug Release of Nifedipine ER Tablet









- Product A (osmotic pump, RLD) delivered drug substance at a constant rate, largely independent of the simulated GI contraction.
- Products B (polymer based tablet, generic) deformed significantly under compression.
- The various levels of simulated GI contractions resulted in different drug release rates for polymer based generic product.

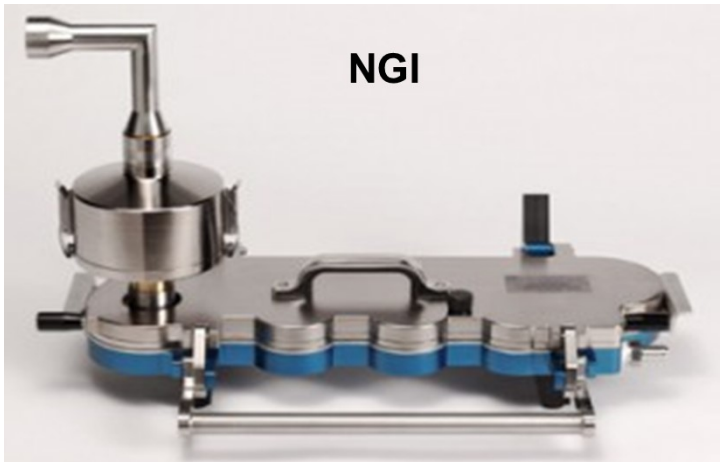
Evaluation of Abbreviated Impactor Measurement (AIM) Methods for Characterization of Orally Inhaled Products (OIPs)

Background:

- Cascade impactors (CIs) are widely used for characterization of inhalation products.
  - Extremely time-consuming and labor-intensive
- Abbreviated impactor measurement (AIM) concept has been highly advocated by various groups.
  - Faster and less expensive

Objective:

- Evaluate the suitability of AIM methods for characterization of OIPs as a quality control test.



Full Resolution CI

AIM

Evaluation of Abbreviated Impactor Measurement (AIM) Methods for Characterization of Orally Inhaled Products (OIPs)

Three drug candidates were tested during 3-month 40°C/75%RH accelerated stability study.

- Advair HFA (230/21) (MDI)
- Advair Diskus (100/50) (DPI)
- Proair RespiClick (DPI)

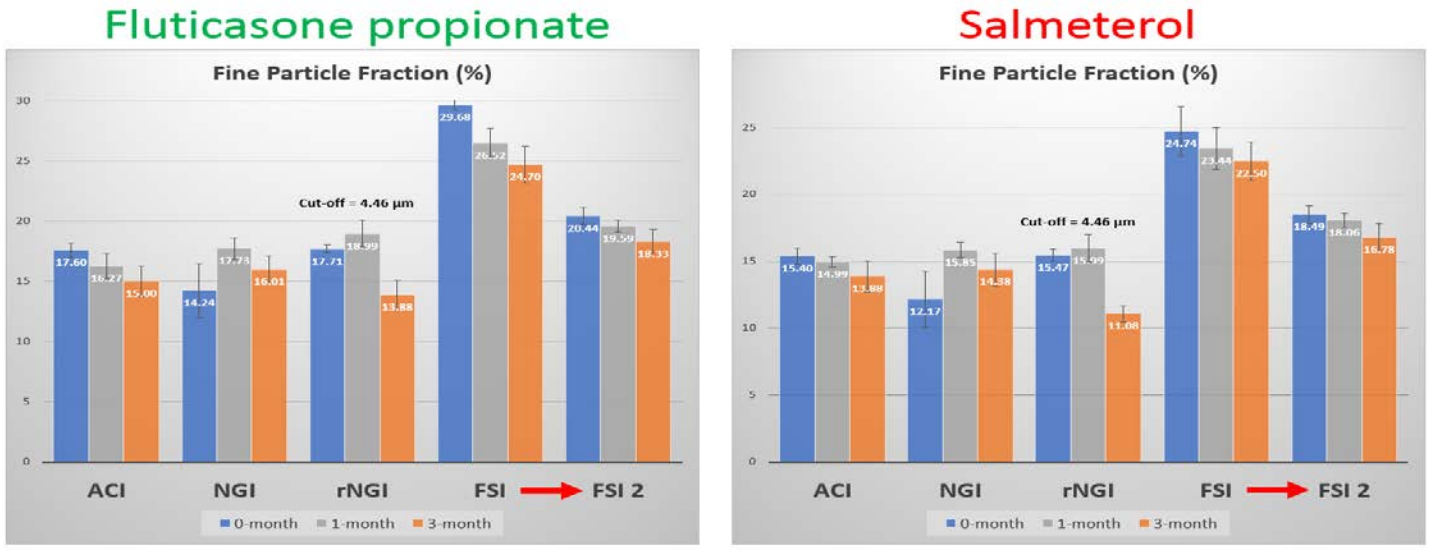


Figure 1. Comparison of Fine Particle Fraction (FPF) results obtained from ACI, NGI, rNGI, and FSI for the two APIs (Fluticasone Propionate and Salmeterol) in Advair Diskus (100/50) Inhalation Powder.

Findings:

- AIM methods may not provide equivalent results to full resolution impactors.
- Appropriate method development and validation are needed in order to use an AIM method as a fast-screening tool for product development and quality control.

In Vitro Permeation Test (IVPT)

- Purpose of IVPT:
  - To determine in vitro drug permeation from topical or transdermal formulations across cadaver skin samples mounted in diffusion cells.
- IVPT Apparatus:
  - Static Diffusion Cells (Franz Cells)
  - (Dynamic) Flow-Through Diffusion Cells
- Analytical Characterization Methods:
  - Raman imaging for understanding formulation properties and drug distribution
  - HPLC, UPLC, LC-MS for quantification of drug permeated through or retained in the skin samples

Examples of Complex TDS Studied

- Acyclovir Topical Cream:
  - IVPT to determine the effect of formulation and manufacturing process variables on Q3 of the cream in comparison to the RLD
  - Studied Q3 includes: API particle size distribution and rheological characteristics (i.e. viscosity and yield stress)
  - IVPT was also used for the assessment of product sameness
- Estradiol Drug-in-adhesive Matrix Type Transdermal System:
  - Characterization of cold flow (CF) occurred during storage
  - IVPT to evaluate differences in product performance with and without CF.
- Testosterone gel:
  - IVPT to evaluate the effect of permeation enhancers on skin permeation flux

International Journal of Pharmaceutics 2014, 475, 1-2, 110-122.
International Journal of Pharmaceutics 2014, 477,1-2,73-80.
Journal of Pharmaceutical Sciences 2017, 106, 1805-1813.

Summary and Conclusions

- Generic drug science and research are an integral part of OPQ's work (with laboratory capability)
- Science provides a foundation for research readiness
- Research facilitates streamlined evaluation and monitoring of complex generic drug quality and equivalence to brand-name drugs
- Science and research together promote the development of proactive tools to assess complex drugs

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