FDA's Current Perspectives on the Propellant Transition: Work Towards Global Harmonization

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Outline

- FDA-CRCG Workshop Overview.
- Considerations for hydrofluoroalkane (HFA) to Next Generation Propellant (NGP) Transition for U.S. approved metered dose inhalers (MDIs).
- Current Considerations on Data Requirements.
- Comparative Studies – HFA vs. NGP MDIs.
- Areas for Global Harmonization.
- Conclusions.

FDA-CRCG Public Workshop

- **FDA-CRCG Workshop: Navigating the Transition to Low Global Warming Potential Propellants**
  - December 4-5, 2024
  - University of Shady Grove, Rockville MD
- **Objectives:**
  - Cover scientific and regulatory considerations regarding the data requirements to support an MDI transition program for brand name and generic drug products.
  - Engage subject matter experts from academia, industry, and health and regulatory agencies to discuss the current scientific understanding and challenges for NGP MDI transition development programs.

- **Day 1**
  - Session 1: Propellant Transition of New Drug MDIs
  - Session 2: Current Industry Experience on MDI Development for Propellant Transitions
  - Session 3: Small Group Working Sessions
- **Day 2**
  - Session 1: Generic MDI Development for Propellant Transitions and the Generic Industry Experience
  - Session 2: The Global Propellant Transition
  - Session 3: Lessons Learn/Closing Remarks

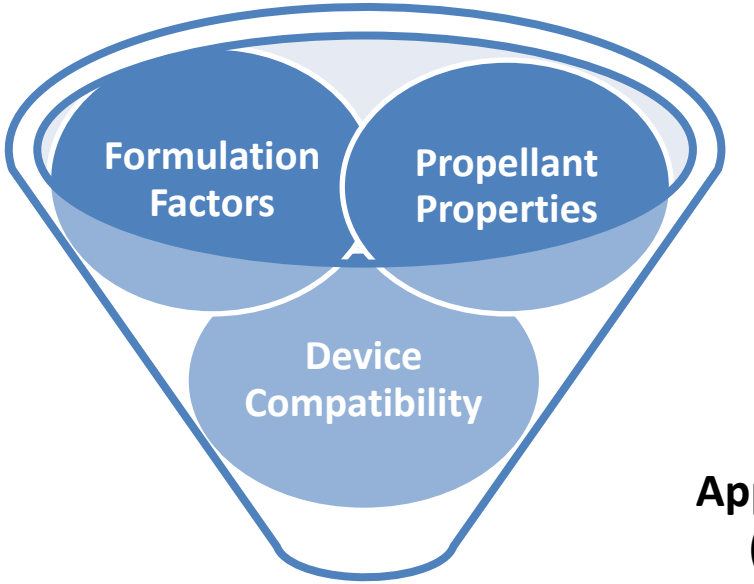
CRCG Website Link: https://www.complexgenerics.org/education-training/navigating-the-transition-to-low-global-warming-potential-propellants/

Considerations on HFA to NGP Transition

- **Match strength.**
  - ***Amount (mg)*** per inhalation (i.e., actuation).
- **Consider indications and labeling for MDIs replacing an approved HFA version.**
- **Minimize changes to the device and user interface.**
  - Consider ***use***, ***storage***, ***cleaning***, ***priming***, and ***repriming.***
- **Demonstrate comparability/bioequivalence(BE) between HFA MDI and NGP MDI.**
- **Guidance and Communications.**
  - Advice may ***evolve*** over time.
  - We strongly encourage ***direct and frequent interactions*** with the Agency.

HFA to NGP Transition for Existing MDI Products

Goals



Similarity in Aerosol Performance and Usability

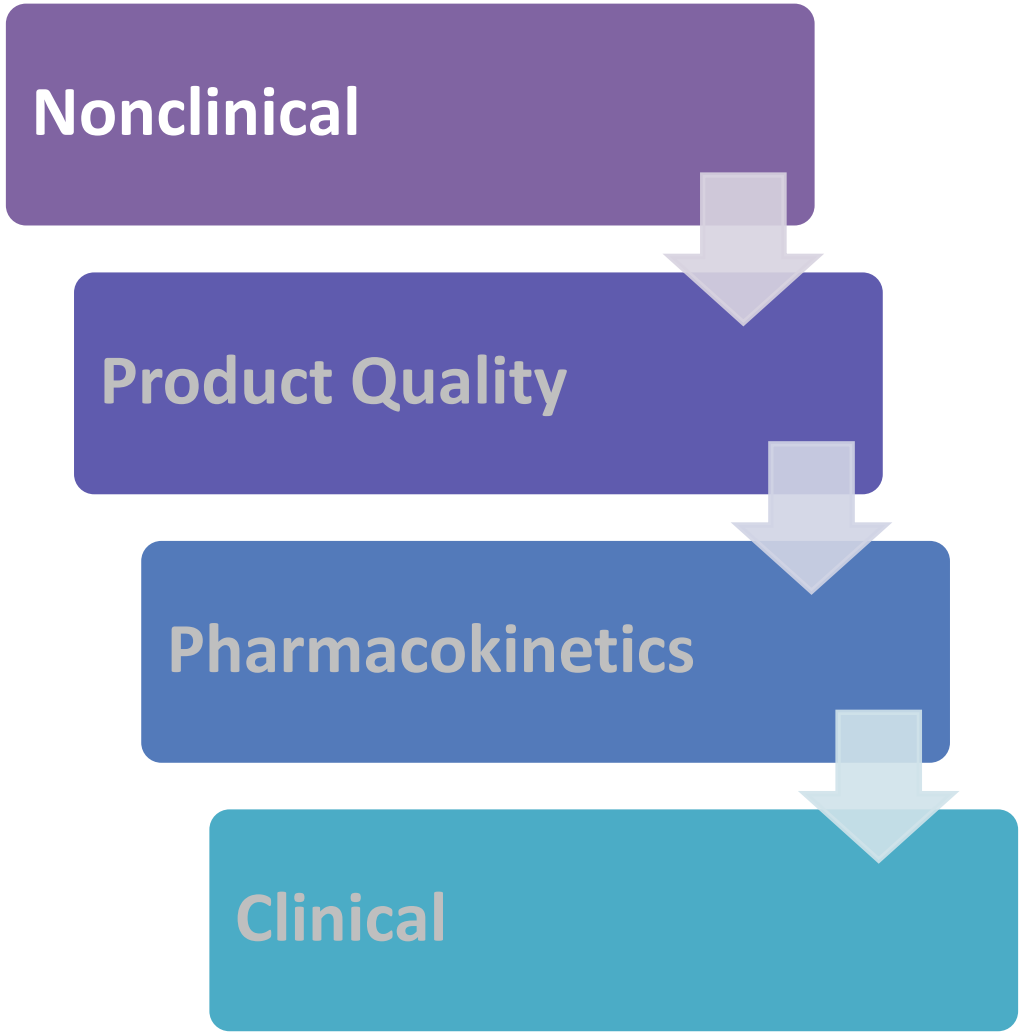
Data Requirement Considerations

Initial Applications (NDAs)

- Nonclinical
- Product Quality
- Pharmacokinetics
- Clinical

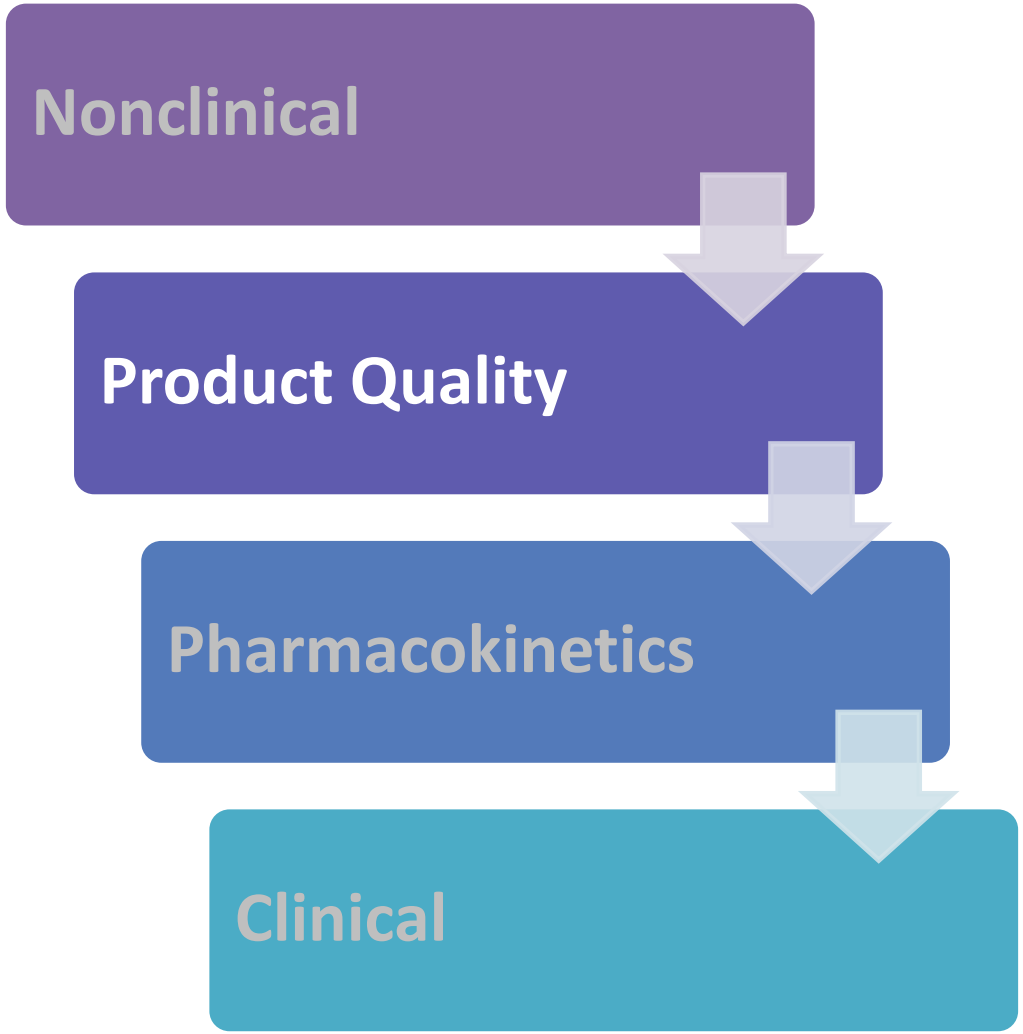
Abbreviated/ Supplemental Pathways (NDAs/ANDAs)

Nonclinical Data



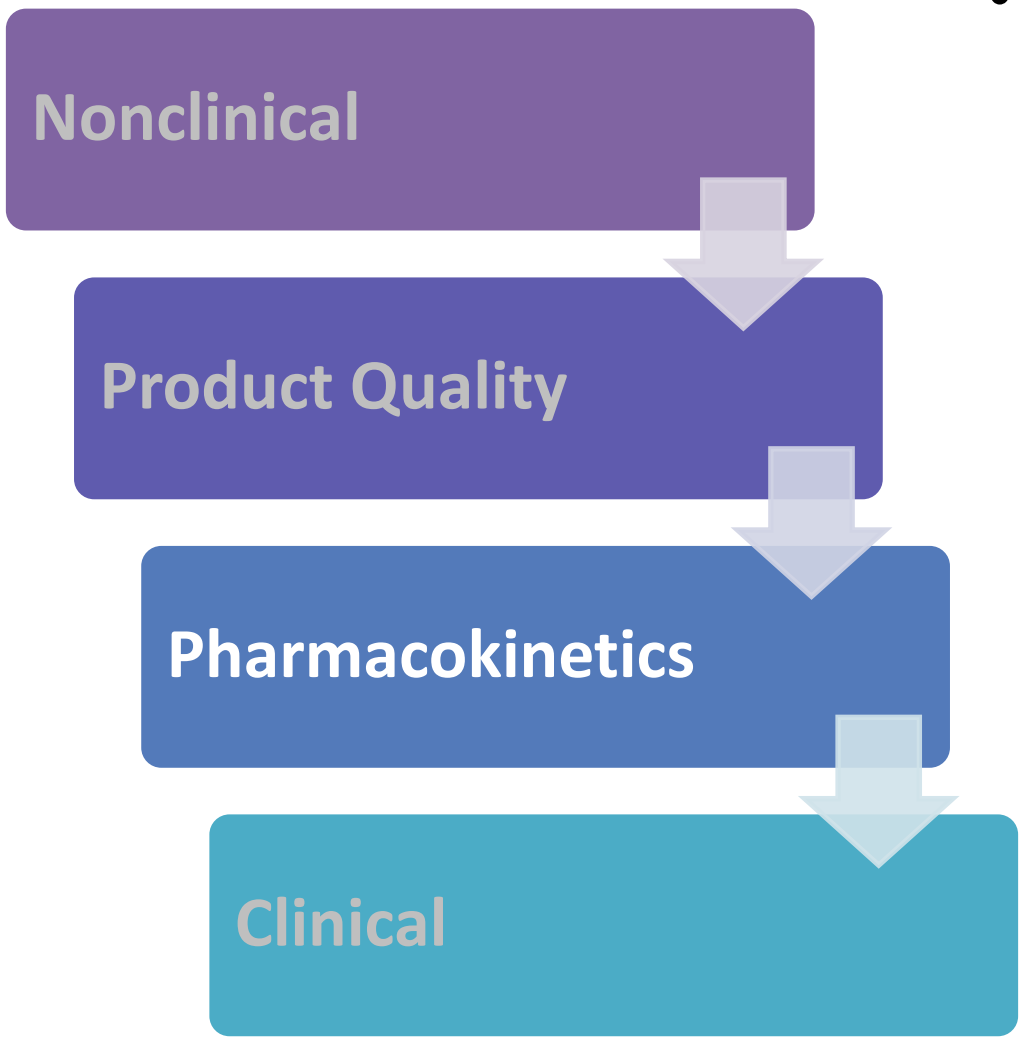
- **Currently, NGPs (HFA-152a and HFO-1234ze) are novel excipients.**
  - Currently, **no existing safety data** on proposed level and duration of exposure or route of administration.
- **Sponsors of MDIs must provide adequate nonclinical safety information (pharmacology and toxicology) to support the intended clinical use of propellants in IND and NDA applications.**
- **Nonclinical data of excipients generally submitted and reviewed under drug master files (DMFs).**
- **Nonclinical data obtained from NGP manufacturer via letter of authorization to DMF.**
- **NGP Propellants (HFA-152a and HFO-1234ze)**
  - Appear to have **similar nonclinical safety profiles** as HFA propellants.
  - **In vivo formulation/interaction studies in animals** may ***no*** longer be necessary in the NGP switch programs once DMF requirements are met.

Product Quality



- **Product quality similarity is the foundational first step, should be comprehensive, and data driven.**
- **Robust comparison of critical quality attributes between HFA and NGP products.**
  - **Product-specific guidances (PSGs)** can be consulted.
  - **Bioequivalence (BE)** should be evaluated.
  - Comparative in vitro characterization is desired.
  - **Justification** for any **observed differences**.
- **Major differences in in vitro performance may require additional data/justifications.**
  - Streamlined approach to approval may ***not*** be appropriate in all situations.

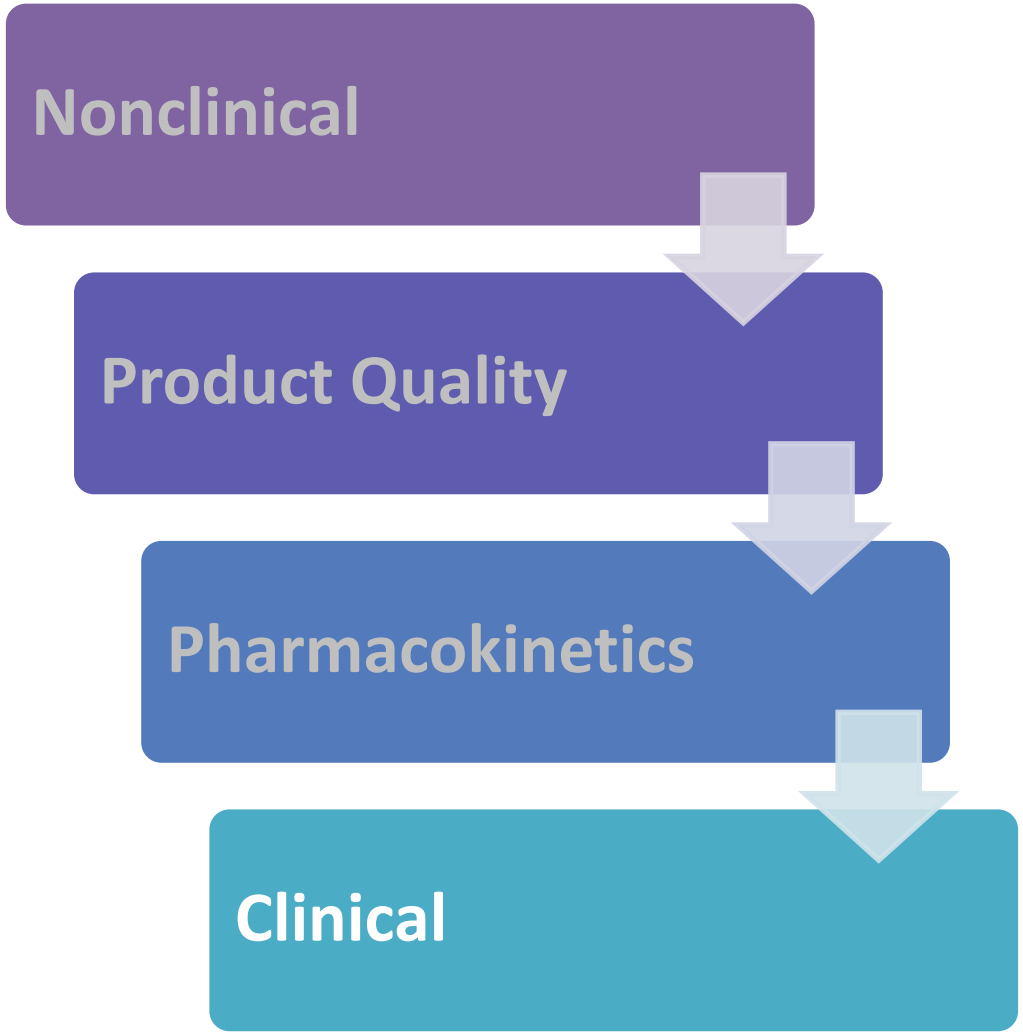
Pharmacokinetics



- **Pharmacokinetic studies to assess bioavailability (BA) and inform on systemic safety.**
  - **Single dose crossover in healthy adults** with appropriate washout.
    - **Treatments**: HFA MDI and NGP MDI.
    - **Dose**: Minimum number of inhalations required for systemic exposure detection.
    - **PK Endpoints:** C_{max}, AUC_t, $AUC_{inf.}$
    - With and without charcoal depending on API(s).
      - Applicants considering alternatives to conducting charcoal-block PK studies (e.g., **partial area under the curve (pAUC), in silico methods**) for assessment of systemic BA from the ***lung dose, are strongly encouraged to discuss with FDA***.

API: Active Pharmaceutical Ingredient

Clinical



- **Initial Applications (NDAs)**
  - Efficacy: comparative clinical endpoint/PD study.
    - Refer to PSGs on MDIs as reference for study designs.
  - Safety: Long term clinical safety (at this time).
    - Focus on demonstrating safety of the NGP, as safety of API established within HFA MDI program.
    - Randomized, double-blind, active control design.
  - Full clinical programs may **not** be needed if reliable in vitro and PK comparability is demonstrated.
- **Streamlined Clinical Program**
  - **In vitro** comparability.
  - **PK** comparability.
  - No significant differences in **device** and **user interface.**

Studies to Demonstrate Comparability/BE

Option 1^

Formulation Sameness
- No difference in inactive ingredients or other aspects of the formulation relative to the RS that may significantly affect local or systemic availability of API (e.g., Q1/Q2 sameness to RS)

Q1: qualitative; Q2: quantitative; RS: reference standard

In Vitro Studies
- SAC, APSD, Spray Pattern, Plume Geometry, Priming/Repriming, rAPSD, Dissolution*

SAC: Single Actuation Content; APSD: aerodynamic particle size distribution; rAPSD: realistic APSD

**When BA of API is dissolution limited*

Comparative Characterization Studies
- Particle Morphology of the Emitted Dose**

***When formulations are more complex*

In Vivo Studies
- PK BE Study, PK BE Study With Charcoal Block***

****When GI absorption of API affects systemic BA*

PK: Pharmacokinetic

Additional Information
- Optional Computational Modeling Study(ies)
- Device Similarity (in design and user interface) to the RLD

Option 2^

Formulation Sameness
- None (e.g., Q1/Q2 or non-Q1/Q2 the same to the RS)

In Vitro Studies
- SAC, APSD, Spray Pattern, Plume Geometry, Priming/Repriming

Comparative Characterization Studies
- Particle Morphology of the Emitted Dose**

***When formulations are more complex*

In Vivo Studies
- PK BE Study, PD/CCEP BE Study

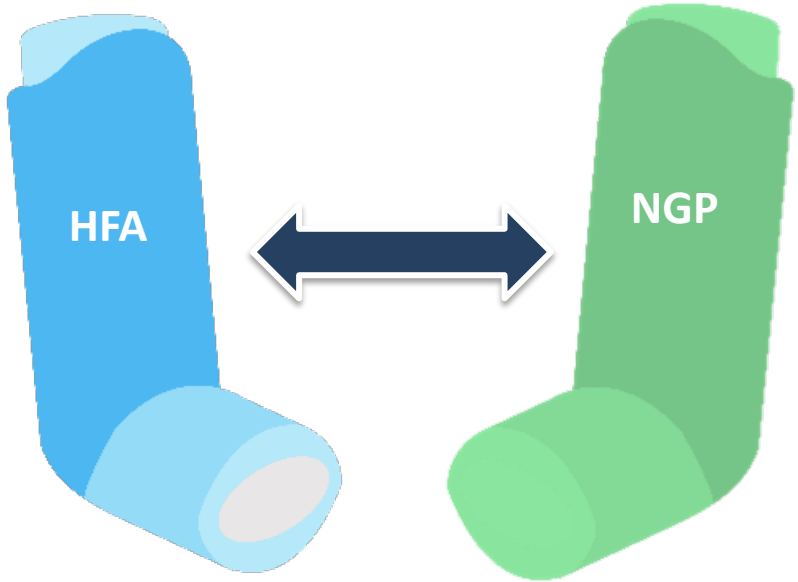
PD: pharmacodynamic; CCEP: Comparative Clinical Endpoint

Additional Information
- Optional Computational Modeling Study(ies)
- Device Similarity (in design and user interface) to the RLD

^ Refer to the PSG on the MDI drug product of interest for the specific recommended BE studies.

Studies to Demonstrate Comparability/BE

- **Comparisons from HFA to NGP MDIs should be established.**
- **Allow for differences in inputs (formulation/device) that do *not* impact in vitro and in vivo performance, safety, and efficacy.**
- **Leverage existing knowledge on HFA MDI and scientific literature.**
- **Use PSGs on MDI products as guidelines.**
  - May consider Option 1 BE approach (**in vitro + PK**) with justifications that formulation differences will not affect local or systemic bioavailability of API(s).
  - **Updates to follow** to work towards global harmonization in comparability/BE requirements.
- **Focus on matching key characteristics first.**
  - In Vitro: **SAC/DDU** and **APSD/rAPSD**
  - In Vivo: **PK study without charcoal**
- **When to consider stepwise approach?**
  - Understanding the ***in vitro-in vivo relationship(s) is critical.***



API: Active Pharmaceutical Ingredient
SAC: Single Actuation Content
DDU: Delivered Dose Uniformity
APSD: Aerodynamic Particle Size Distribution
rAPSD: realistic APSD

Comparative/BE Study Challenges

- **Current U.S. recommendations include both in vitro and in vivo studies rather than a stepwise approach.**
  - **Additional in vitro studies**: realistic APSD (**rAPSD**), **dissolution**,* and **comparative particle morphology.****
  - Need for standardization of rAPSD and dissolution methods.
- **PK BE study with charcoal block?**
  - Need for **standardization of charcoal dosing.**
  - Harmonization on when **pAUCs** in PK studies without charcoal can be used over charcoal PK studies.

Dissolution is recommended when dissolution is rate-limiting stop in BA of the API
****Recommended when have more complex formulations (e.g., particle engineering)***

- **Consider in silico modeling to support your application.**
- **Communicate early and often.**
  - Prospective applicants are highly encouraged to discuss their development plans with the Agency to gain feedback.
- **Agency's thinking on establishing BE *may evolve* as scientific understanding and experience is gained.**

Work Towards Global Harmonization

- **While regulations may differ in each country, an attempt to harmonize data requirements, study designs, and statistical evaluation is possible.**
- **Areas for consideration:**
  - Find ways to **minimize the need for clinical data** via sharing gained experience.
  - Amount and types of **NGP safety data.**
  - Applicability of **propellent only studies** for local tolerance (ciliary function and airway sensitivity).
  - Identify and agree upon **key in vitro studies** needed to demonstrate comparability/BE.
  - Clarify the appropriate design for **charcoal block PK studies,** when they are needed, and when other approaches may be applicable.

Work Towards Global Harmonization

- **Continue frequent and open communication**
  - **Application-specific communication pathways**
    - Written communication and formal meetings for IND and NDA-specific discussions.
      - FDA final guidance for industry, *Best Practices for Communication Between IND Sponsors and FDA During Drug Development* (December 2017) (https://www.fda.gov/media/94850/download).
      - FDA draft guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (September 2023) (https://www.fda.gov/media/172311/download).
    - Controlled correspondences and pre-ANDA product development meetings for ANDA-specific discussions.
      - FDA final guidance for industry, *Controlled Correspondence Related to Generic Drug Development* (March 2024) (https://www.fda.gov/media/164111/download).
      - FDA final guidance for industry, *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* (October 2022; Rev 1) (https://www.fda.gov/media/107626/download).
    - FDA-EMA Parallel Scientific Program Plan if you plan to submit to U.S. and EU.*
  - Between **regulators.**
  - At **scientific meetings** and **public workshops.**

* https://www.fda.gov/media/105211/download

* https://www.fda.gov/drugs/generic-drugs/fda-ema-parallel-scientific-advice-pilot-program-complex-generichybrid-products

Conclusions

- **December 2024 FDA-CRCG Workshop provided an opportunity for conversation with all stakeholders on the need for collaboration and harmonization to ensure an efficient and successful NGP transition of HFA MDIs.**
- **For approved HFA MDIs to transition to NGP MDIs.**
  - Match **strength**, **indications**, and **labeling.**
  - Leverage past **knowledge** and **experience.**
  - **Minimize changes** when possible.
  - NGP is currently a **novel excipient** that will require nonclinical safety data initially.
  - Once propellant safety is established, find ways to minimize need for clinical studies.
    - Demonstrate **in vitro** and **PK comparability.**
    - Understand **in vitro-in vivo relationship(s).**
- **While challenges for harmonizing data requirements remain, frequent communications between key stakeholders can ensure efforts toward harmonization of the NGP transition process are successful.**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