FDA Perspective on MDI Propellant Transitions – from New Drug Perspective

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Transitioning to Next Generation Propellants

- Next generation propellants (NGP) are new excipients for orally inhaled drug products → no FDA-approved MDIs containing NGPs
- The role of the propellant in MDIs is complex (more than just an excipient)
- Uncertainty in effect on regional lung deposition that may impact efficacy and/or safety
- Chemical properties of approved HFAs (HFA-134a, HFA-227a) and NGPs (HFO-1234ze, HFA-152a) may be more similar than to phased out CFC propellants
- Too early to tell if there will be any novel issues with the NGPs

Key Concepts for Product Development

- Historically, new inhalation products have required full clinical development programs
- Current knowledge about NGPs and experience with generic MDI development → Opportunity to streamline clinical development with this transition
- Transitioning FDA-approved MDI to NGP
  - Intent to replace currently marketed product (same dose, indication and label)
  - Minimal changes to the device and user interface
  - Abbreviated clinical program likely feasible
- Not previously approved MDI products with NGP
  - Demonstrating comparability between proposed and listed drug product *might* enable reliance on FDA's findings of efficacy/safety and streamlined clinical program
  - Case by case basis

OND Approach to NGP MDI Development

- Current thinking for streamlined development program
- Given early stage of transition and lack of approved NGP products, advice may evolve over time
- Comparative studies between approved reference and NGP test products
- Step-wise approach
- Encourage early, frequent interactions with the Agency

OND Approach to NGP MDI Development

Nonclinical

- Must meet regulatory requirements for nonclinical data for human drug products[1]
- Nonclinical data obtained from NGP manufacturer via letter of authorization to reference DMF
- DMF should contain:
  - Pharmacology (lack of pharmacologic activity)
  - Pharmacokinetics (ADME)
  - Toxicology –

  Inhalation toxicity studies up to 26 and 39 weeks in rodent and non-rodent species

  Genotoxicity

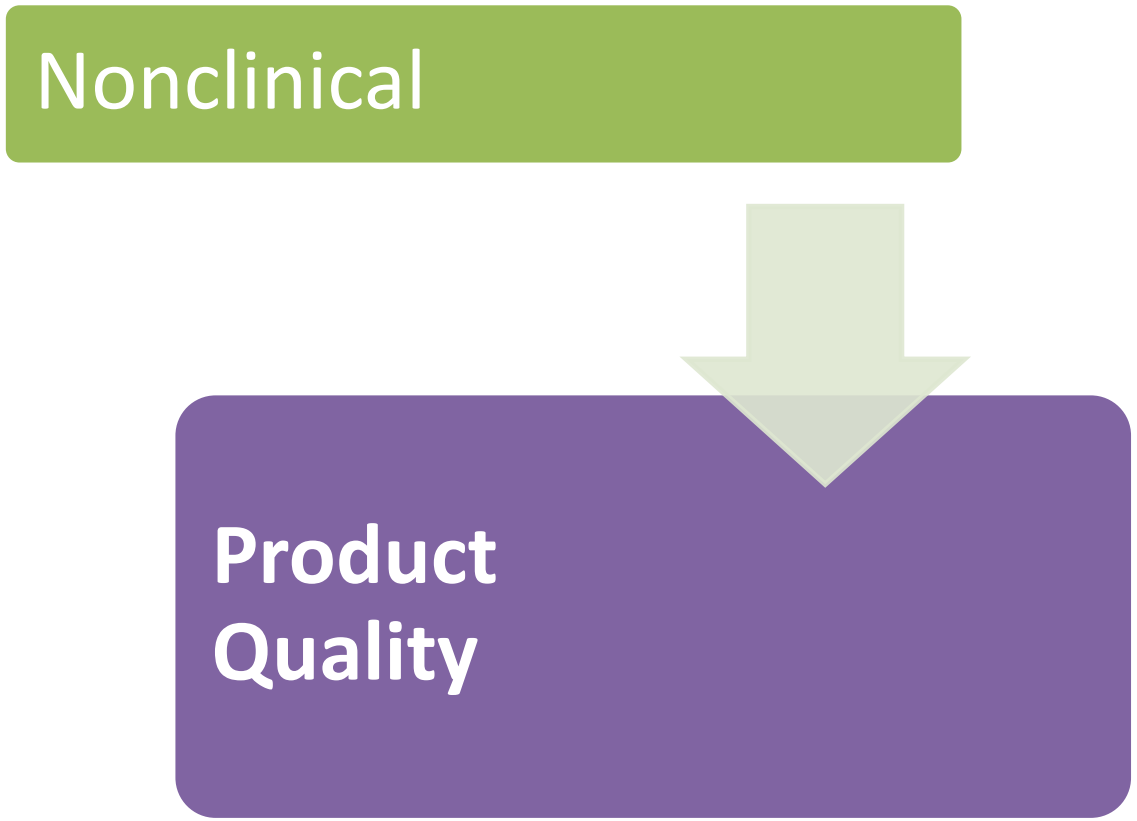
  Carcinogenicity (2yr inhalation study in rats and mice)

  Reproductive and developmental toxicity (DART)

  Other data as appropriate (e.g., juvenile tox)

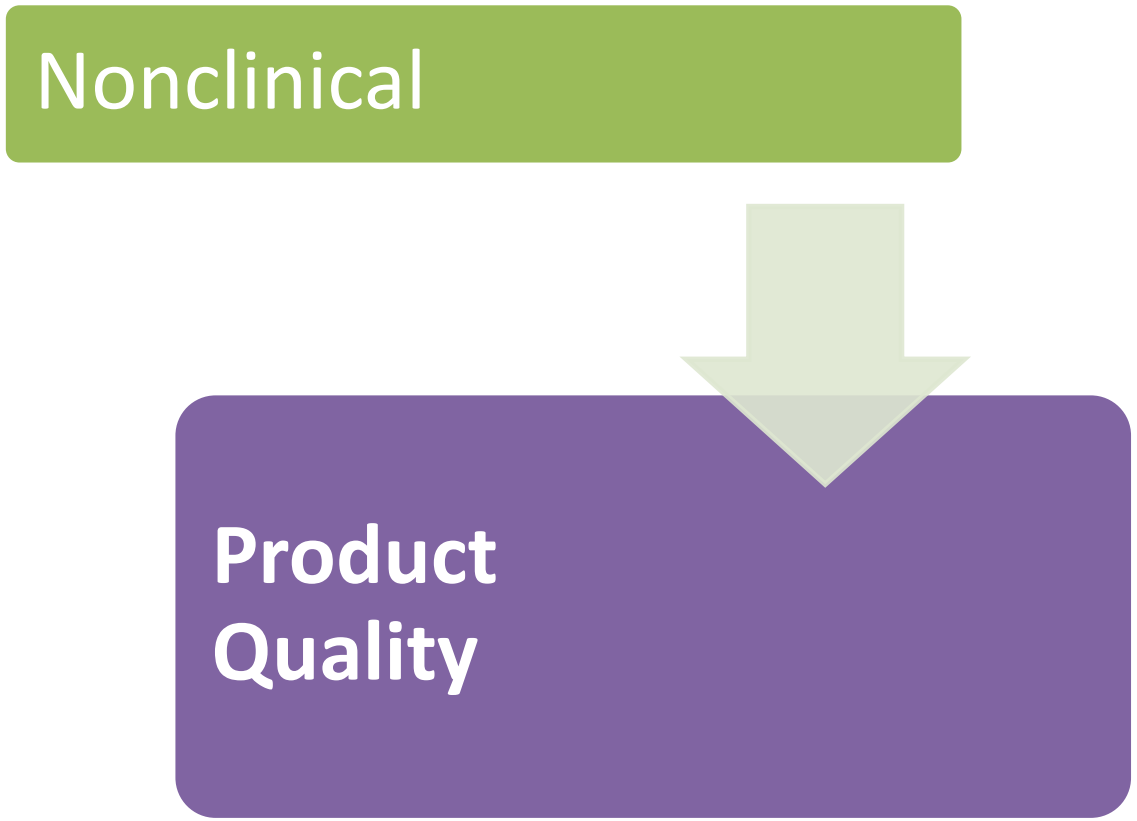
1. IND: 21 CFR 312.23(a)(8)
NDA: 21 CFR 314.50(d)(2)
21 CFR 58 Good Laboratory Practice (GLP) Regulations

OND Approach to NGP MDI Development



- Product quality similarity is foundational first step
- Robust comparison of critical quality attributes between reference and test products
- Streamlined program not appropriate if major differences in *in vitro* data

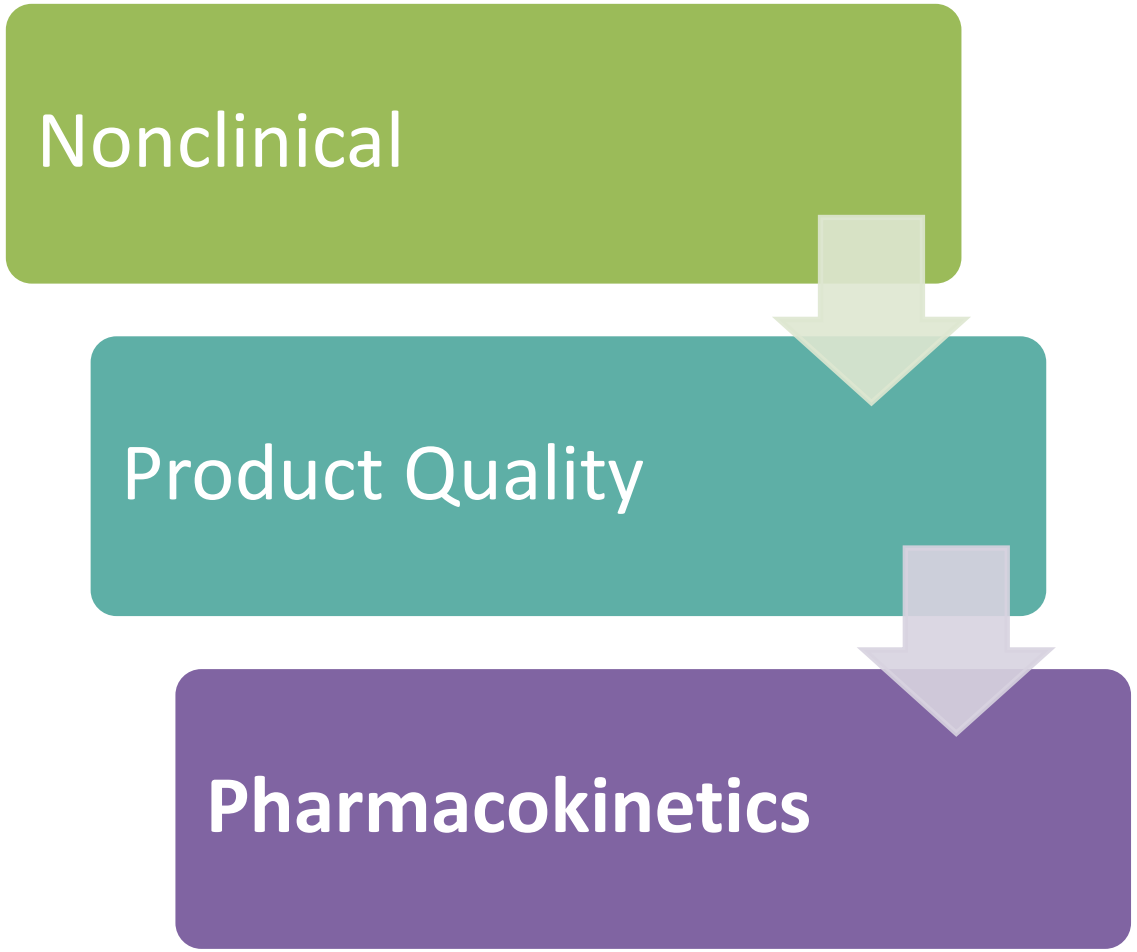
OND Approach to NGP MDI Development



Agency actively working to:

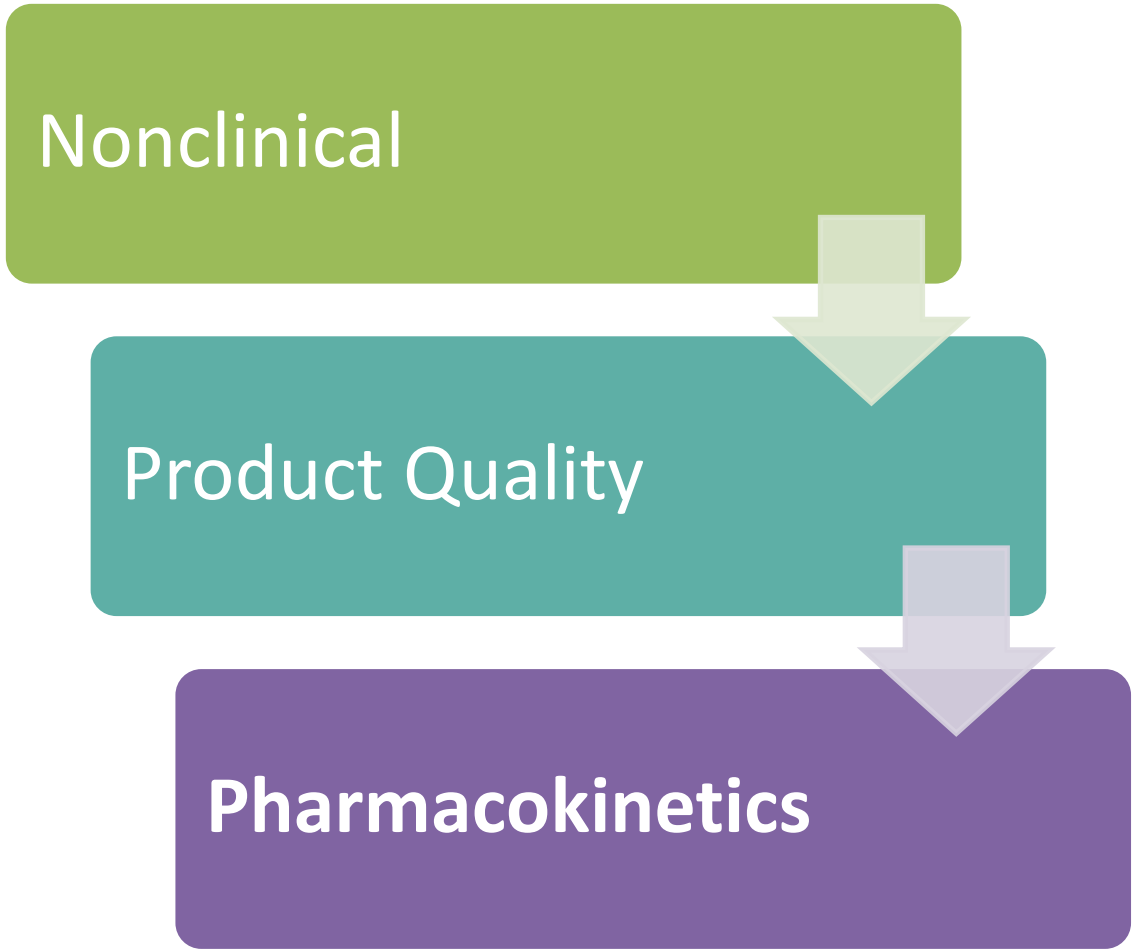
- Identify specific in vitro studies most relevant to clinical performance
- Develop in vitro/in vivo correlation or relationship model
- Identify a safe space in which in vitro characteristics can change w/o impacting product performance

OND Approach to NGP MDI Development



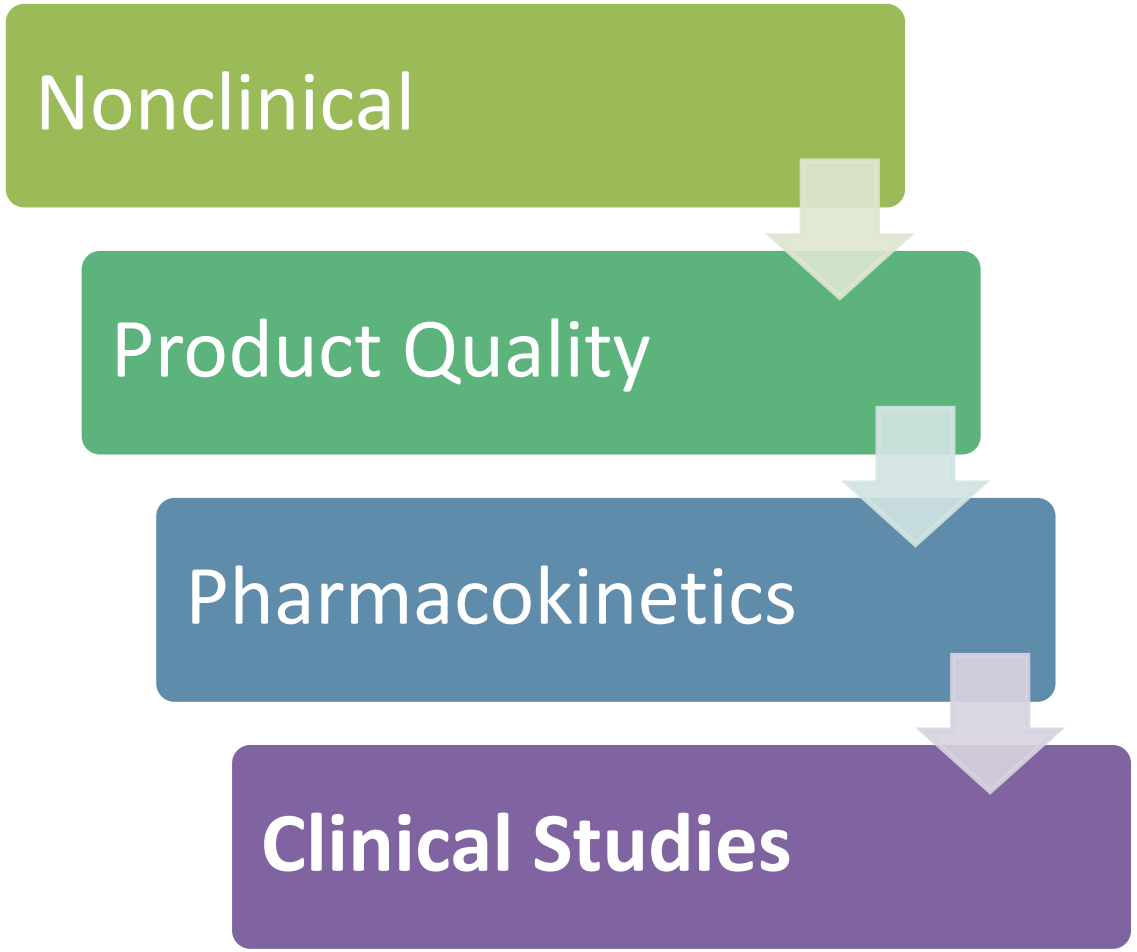
- Pharmacokinetic relative bioavailability study(ies)
  - A sensitive in vivo tool to extend in vitro comparison to demonstrate the comparability between inhalation products with different propellants
  - The PK comparison study may reflect the different deposition/distribution/ absorption of different MDI products in vivo
  - Not routinely required for new inhalation products, but key for streamlined approach

OND Approach to NGP MDI Development



- For drugs with high GI absorption, we recommend:
  - Separate charcoal block study OR
  - Partial AUC approach within same PK study
  - Case by case basis

OND Approach to NGP MDI Development



- In early stages, recommending streamlined clinical program
- Comparative clinical endpoint study to assess for differences in efficacy
  - Pharmacodynamic study
  - Lung function study
- Long-term safety
- Comparative use-related risk analysis

Key Concepts for NGP MDI Clinical Programs

- Study design for comparative clinical endpoint study
  - Depends on API
  - Informed by relevant FDA product specific guidances (PSGs)
  - Treatment arms
    - NGP MDI (test product)
    - Approved HFA MDI (reference product)
    - Assay sensitivity arm (e.g., placebo)
  - Lung function efficacy endpoint → exacerbation data not required

Key Concepts for NGP MDI Clinical Programs

- Local tolerance studies with propellant only (e.g., ciliary function or airway sensitivity reaction studies) not required

- Long-term clinical safety data are required at this time
  - Focus on demonstrating safety of NGP, as safety of API established in HFA MDI program

- Safety study design considerations
  - 12-week treatment duration at maximum recommended dosage
  - Recommend obtaining controlled data with NGP MDI (including the API); propellant-only design may be considered in certain cases

- Anticipate clinical data requirements will change once we have approved NGP MDIs and sufficient safety data

Key Concepts for NGP Propellant Clinical Programs

- Indication and population:
  - Studies may be conducted in a single indicated population (recommend most sensitive)
  - Pediatric patients may be included but not required. Same age indications as reference product may be applied if comparability demonstrated.
  - If no meaningful differences, all indications and labeling claims could carry over

- PREA requirements:
  - Triggered by new indication, dosage form, dosing regimen, route of administration, or active ingredient
  - Does not apply to propellant change for existing approved MDIs
  - Does apply to novel MDIs with NGP

- Use to-be-marketed product throughout program (i.e. in vitro, PK, clinical)

Albuterol MDI Example

- Comparative clinical endpoint study → pharmacodynamic, bronchoprovocation study
  - Single dose, double-blind, double-dummy, randomized, crossover design
  - Asthma study population
  - Post-dose PC_{20} or PD_{20} endpoints
  - Dose scale analysis of pharmacodynamic data to assess for bioequivalence

- Safety study
  - Randomized, double-blind, active-control design
  - 12-week duration
  - Treatment arms: recommend albuterol NGP MDI compared to approved albuterol MDI, but may consider propellant-only MDI study
  - Dosing: scheduled administration (2 inhalations QID) to ensure adequate exposure at maximum recommended dosage

- FDA Albuterol PSG for reference
  - *Draft guidance on albuterol sulfate (August 2024)*
  - https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm

ICS/LABA MDI Example

- Comparative clinical endpoint study
  - Randomized, double-blind, placebo-controlled, multiple-dose design
  - Parallel or cross-over
  - Duration may depend on design → minimum of 4 weeks
  - Treatment arms: NGP MDI, approved HFA MDI, placebo for assay sensitivity
  - Asthma study population
  - Primary endpoints: peak FEV_1/serial FEV_1-time curve (AUC) on Day 1 and trough FEV_1 at end of treatment to assess contribution of each component
  - Assessment of bioequivalence: Determine 90% CI for the test to reference product ratio for the primary endpoints
- Safety study
  - Randomized, double-blind, active-control
  - Minimum 12-week duration
  - Treatment arms: NGP MDI, approved HFA MDI
- FDA PSGs for reference
  - *Draft guidance on fluticasone propionate; salmeterol xinafoate (August 2024)*
  - *Draft guidance on budesonide; formoterol fumarate dihydrate (November 2024)*
  - https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm

Human Factors

- For streamlined programs, we expect no significant difference in device and user interface between the new NGP MDI and approved HFA MDI

- Expect a comparative use-related risk analysis to evaluate for errors and risk
  - Comprehensive and systematic evaluation of all the steps involved in use of product
  - Comparative analyses
    - Labeling comparison
    - Comparative task analysis
    - Physical comparison

- The necessity of a human factors study will depend on the difference between the two products and any changes that may impact the user interface
  - If HF studies are needed, streamlined clinical program may not be appropriate

OND Approach to NGP MDI Development

- Full clinical program might be needed in some scenarios, such as:
  - *In vitro* product quality data and/or PK data not comparable between approved MDI and NGP MDI
  - Major changes to formulation, dose, device, or user interface between approved MDI and NGP MDI
  - Previously not approved MDIs incorporating NGP MDI, unless able to demonstrate comparability to the listed drug

Summary of FDA Approach for Brand Drugs

- Streamlined development program for transitioning to NGPs in approved MDIs depends heavily on comparability in critical quality attributes/PK between products → goal to demonstrate no meaningful differences
- Approach may evolve as we gain experience with and approvals of new NGP MDIs → expect to reduce clinical study requirements
- Different considerations for not previously approved MDIs and for existing MDIs that require substantial changes
  - More extensive clinical programs may be needed
- Early discussion with FDA important regarding scientific and regulatory issues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