Overview of Complex Generic Inhalation and Nasal Drug-Device Combination Products

The DIA/FDA Complex Generic Drug-Device Combination Products Conference 2020

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October 19, 2020

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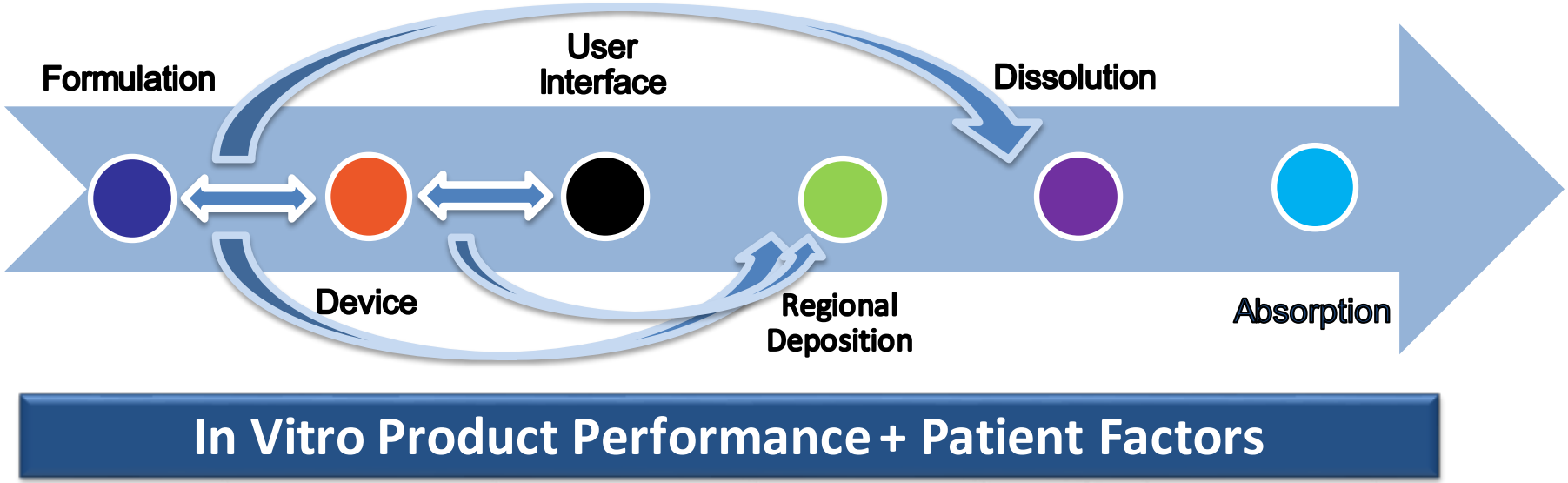
Locally-Acting OINDPs: Challenges for Establishing BE

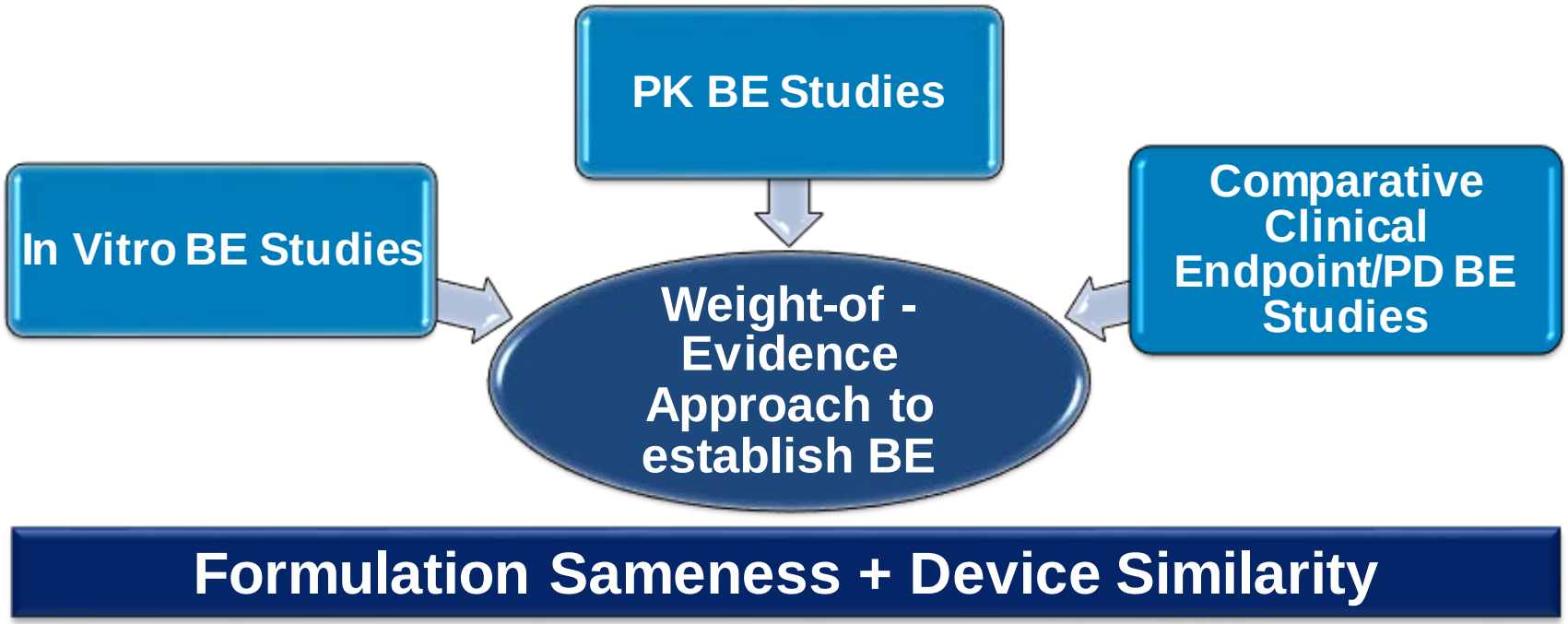
- Developing generics for **locally-acting OINDPs** is challenging because of the ***multiple factors that can influence drug delivery to the site of action***



OINDPs: Orally Inhaled and Nasal Drug products
BE: Bioequivalence

Establishment of BE for OINDPs

- **To Address Challenges for locally-acting OINDPs → *Weight-of-Evidence Approach***
  - ***Locally-acting nasal suspensions, metered dose inhalers (MDIs), dry powder inhalers (DPIs)***



PK: pharmacokinetic
PD: pharmacodynamic

Recommended In Vitro BE Studies

- Sensitive for detecting differences between formulations (if present)
- Less variable and easier to control than comparative clinical endpoint BE studies
- Conducted with all strengths, at least 3 batches of test (T) and reference (R) products, with no fewer than 10 units from each batch
- SAC and APSD are critical attributes believed to affect the total and regional deposition of drugs in the lung
- SAC and APSD dependent on, and sensitive to, product- and process-related factors (e.g., API/Carrier physicochemical properties, device properties, process conditions)
- For MDIs and nasal suspensions, priming / repriming studies are recommended if required by the R product (e.g., not recommended for breath-actuated MDIs)

DPIs

- **SAC**
  - Beginning (B), middle (M) and end (E) lifestages
  - 3 flow rates
- **APSD**
  - B and E lifestages
  - 3 flow rates

MDIs

- **SAC**
  - B, M and E lifestages
- **APSD**
  - B and E lifestages
- **Spray Pattern**
  - B lifestage
  - 2 distances from actuator mouthpiece
- **Plume Geometry**
  - B lifestage
- **Priming / Repriming**
  - (if required by the R product)

Nasal Suspensions

- **SAC**
  - B and E lifestages
- **Droplet Size Distribution by Laser Diffraction (LD)**
  - B and E lifestages
  - 2 distances from actuator orifice
- **Drug in Small Particles/Droplets**
  - B lifestage
- **Spray Pattern**
  - B lifestage
  - 2 distances from actuator orifice
- **Plume Geometry**
  - B lifestage
- **Priming / Repriming**
  - (if required by the R product)

SAC: Single Actuation Content
APSD: Aerodynamic Particle Size Distribution

API: Active Pharmaceutical Ingredient

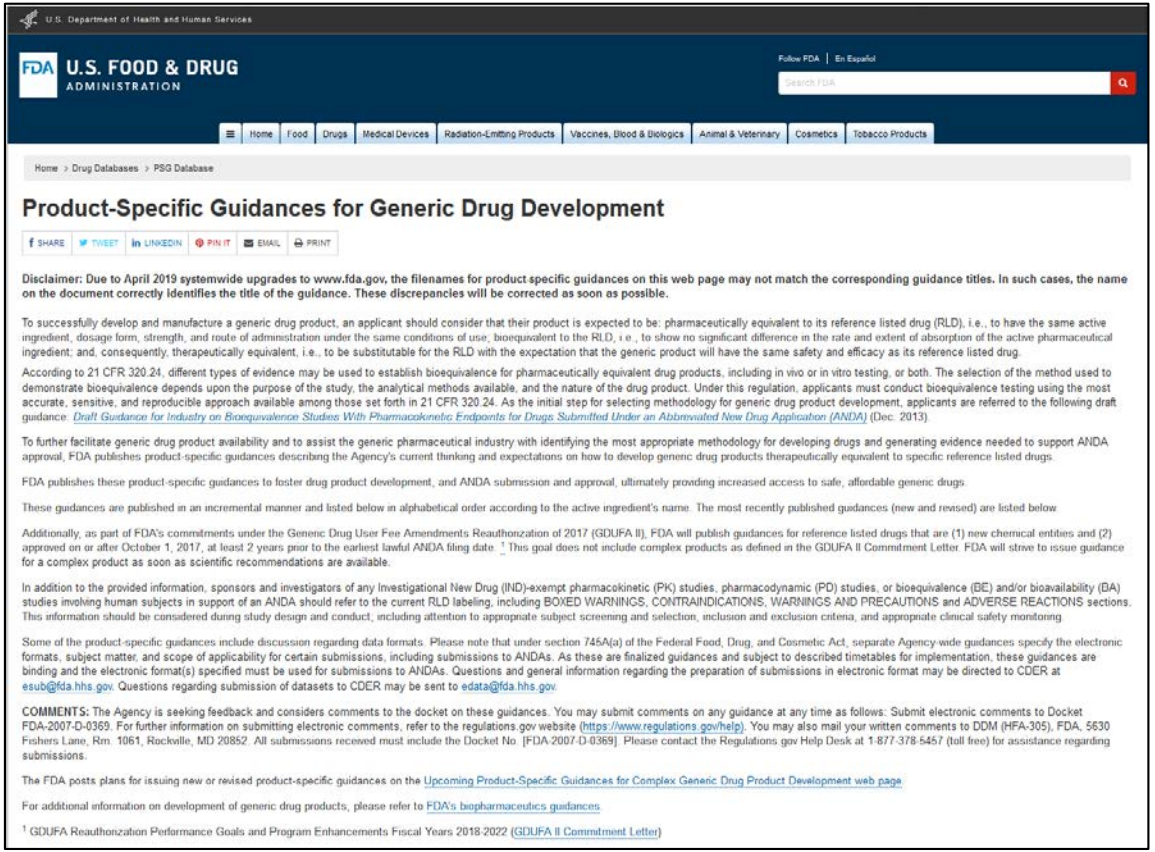
Recommended In Vivo Pharmacokinetic BE Studies

In Vivo BE Parameter	DPIs	MDIs	Nasal Suspensions
Study Design	Fasting, single-dose, two-way crossover, comparative PK study		
Objective	Determine differences in systemic exposure between drug products		
Strengths	All strengths should be tested since the relationship between PK dose proportionality across multiple strengths, in vitro performance parameters, and product characteristics are not well understood		
Dose	A minimum number of inhalations sufficient for PK characterization using a sensitive analytical method		
Study Population	Healthy subjects		
BE Endpoints and Criteria	The 90% confidence interval for the geometric mean T/R ratios for AUC and Cmax should fall within the limits of 80 – 125%		

Recommended In Vivo Comparative Clinical Endpoint / Pharmacodynamic BE Studies

In Vivo BE Parameter	DPIs	MDIs	Nasal Suspensions
Study Design	• Randomized, placebo-controlled, parallel or crossover comparative clinical endpoint (CEP) or pharmacodynamic (PD) BE study • Comparative CEP should contain a placebo run-in period followed by the treatment period of placebo, T, and R • Study sensitivity: Comparative CEP (effect over placebo), PD study (adequate dose-response)		• Randomized, placebo-controlled, parallel-group comparative CEP BE study • Comparative CEP should contain a placebo run-in period followed by the treatment period of placebo, T, and R • Study sensitivity: Comparative CEP (effect over placebo)
Objective	Determine differences in local delivery at the site of action between drug products		
Strengths	Lowest labeled dose (comparative CEP study)		
Dose	Single or multiple-dose (based on mechanism of action)		Multiple-dose
Study Population	One patient population indicated in the approved labeling		
BE Endpoints and Criteria	The 90% confidence interval for the geometric mean T/R ratios for the endpoint(s) should fall within the limits of 80 – 125%		Change from the baseline mean reflective Total Nasal Symptom Score (rTNSS) to the treatment mean rTNSS (in absolute units)

Website for Product-Specific Guidances



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Product-Specific Guidances for Generic Drug Development

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Disclaimer: Due to April 2019 systemwide upgrades to www.fda.gov, the filenames for product specific guidances on this web page may not match the corresponding guidance titles. In such cases, the name on the document correctly identifies the title of the guidance. These discrepancies will be corrected as soon as possible.

To successfully develop and manufacture a generic drug product, an applicant should consider that their product is expected to be: pharmaceutically equivalent to its reference listed drug (RLD), i.e., to have the same active ingredient, dosage form, strength, and route of administration under the same conditions of use; bioequivalent to the RLD, i.e., to show no significant difference in the rate and extent of absorption of the active pharmaceutical ingredient; and, consequently, therapeutically equivalent, i.e., to be substitutable for the RLD with the expectation that the generic product will have the same safety and efficacy as its reference listed drug.

According to 21 CFR 320.24, different types of evidence may be used to establish bioequivalence for pharmaceutically equivalent drug products, including in vivo or in vitro testing, or both. The selection of the method used to demonstrate bioequivalence depends upon the purpose of the study, the analytical methods available, and the nature of the drug product. Under this regulation, applicants must conduct bioequivalence testing using the most accurate, sensitive, and reproducible approach available among those set forth in 21 CFR 320.24. As the initial step for selecting methodology for generic drug product development, applicants are referred to the following draft guidance: *Draft Guidance for Industry on Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application (ANDA)* (Dec. 2013).

To further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval, FDA publishes product-specific guidances describing the Agency's current thinking and expectations on how to develop generic drug products therapeutically equivalent to specific reference listed drugs.

FDA publishes these product-specific guidances to foster drug product development, and ANDA submission and approval, ultimately providing increased access to safe, affordable generic drugs.

These guidances are published in an incremental manner and listed below in alphabetical order according to the active ingredient's name. The most recently published guidances (new and revised) are listed below.

Additionally, as part of FDA's commitments under the Generic Drug User Fee Amendments Reauthorization of 2017 (GDUFA II), FDA will publish guidances for reference listed drugs that are (1) new chemical entities and (2) approved on or after October 1, 2017, at least 2 years prior to the earliest lawful ANDA filing date. [1] This goal does not include complex products as defined in the GDUFA II Commitment Letter. FDA will strive to issue guidance for a complex product as soon as scientific recommendations are available.

In addition to the provided information, sponsors and investigators of any Investigational New Drug (IND)-exempt pharmacokinetic (PK) studies, pharmacodynamic (PD) studies, or bioequivalence (BE) and/or bioavailability (BA) studies involving human subjects in support of an ANDA should refer to the current RLD labeling, including BOXED WARNINGS, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS sections. This information should be considered during study design and conduct, including attention to appropriate subject screening and selection, inclusion and exclusion criteria, and appropriate clinical safety monitoring.

Some of the product-specific guidances include discussion regarding data formats. Please note that under section 745A(a) of the Federal Food, Drug, and Cosmetic Act, separate Agency-wide guidances specify the electronic formats, subject matter, and scope of applicability for certain submissions, including submissions to ANDAs. As these are finalized guidances and subject to described timetables for implementation, these guidances are binding and the electronic format(s) specified must be used for submissions to ANDAs. Questions and general information regarding the preparation of submissions in electronic format may be directed to CDER at esub@fda.hhs.gov. Questions regarding submission of datasets to CDER may be sent to edata@fda.hhs.gov.

COMMENTS: The Agency is seeking feedback and considers comments to the docket on these guidances. You may submit comments on any guidance at any time as follows: Submit electronic comments to Docket FDA-2007-D-0369. For further information on submitting electronic comments, refer to the regulations.gov website (https://www.regulations.gov/help). You may also mail your written comments to DDM (HFA-305), FDA, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All submissions received must include the Docket No. [FDA-2007-D-0369]. Please contact the Regulations.gov Help Desk at 1-877-378-5457 (toll free) for assistance regarding submissions.

The FDA posts plans for issuing new or revised product-specific guidances on the Upcoming Product-Specific Guidances for Complex Generic Drug Product Development web page.

For additional information on development of generic drug products, please refer to FDA's biopharmaceutics guidances.

[1] GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (GDUFA II Commitment Letter)

- ~ 70% of all MDI and DPI products have PSGs
- > 60% of all nasal products have PSGs

https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm

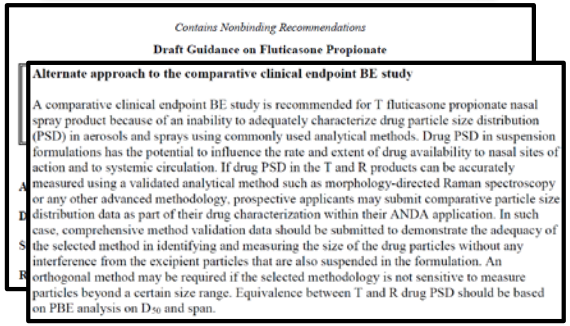
Addressing the Challenges from the Comparative CEP BE STUDY

Alternative BE Approaches

Comparative CEP Challenges:

- **Higher Variability and Lower Sensitivity than Other BE Methods**
- **Time and Cost**

Nasal Suspensions



Contains Nonbinding Recommendations

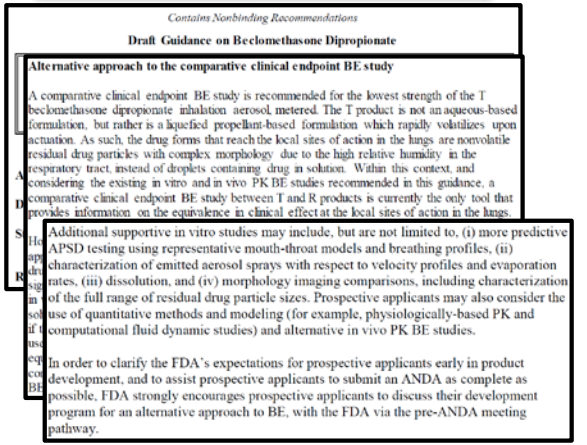
Draft Guidance on Fluticasone Propionate

Alternate approach to the comparative clinical endpoint BE study

A comparative clinical endpoint BE study is recommended for T fluticasone propionate nasal spray product because of an inability to adequately characterize drug particle size distribution (PSD) in aerosols and sprays using commonly used analytical methods. Drug PSD in suspension formulations has the potential to influence the rate and extent of drug availability to nasal sites of action and to systemic circulation. If drug PSD in the T and R products can be accurately measured using a validated analytical method such as morphology-directed Raman spectroscopy or any other advanced methodology, prospective applicants may submit comparative particle size distribution data as part of their drug characterization within their ANDA application. In such case, comprehensive method validation data should be submitted to demonstrate the adequacy of the selected method in identifying and measuring the size of the drug particles without any interference from the excipient particles that are also suspended in the formulation. An orthogonal method may be required if the selected methodology is not sensitive to measure particles beyond a certain size range. Equivalence between T and R drug PSD should be based on PBE analysis on D_{50} and span.

- *Fluticasone Propionate Nasal Spray, Metered* (Jun 2020)
- *Fluticasone Furoate Nasal Spray, Metered* (Jun 2020)
- *Budesonide Nasal Spray, Metered* (May 2019)
- *Azelastine Hydrochloride; Fluticasone Propionate Nasal Spray, Metered* (Jun 2020)
- *Mometasone Furoate Nasal Spray, Metered* (Jun 2020)
- *Triamcinolone Acetonide Nasal Spray, Metered* (Jun 2020)

Solution-Based MDIs



Contains Nonbinding Recommendations

Draft Guidance on Beclomethasone Dipropionate

Alternative approach to the comparative clinical endpoint BE study

A comparative clinical endpoint BE study is recommended for the lowest strength of the T beclomethasone dipropionate inhalation aerosol, metered. The T product is not an aqueous-based formulation, but rather is a liquefied propellant-based formulation which rapidly volatilizes upon actuation. As such, the drug forms that reach the local sites of action in the lungs are nonvolatile residual drug particles with complex morphology due to the high relative humidity in the respiratory tract, instead of droplets containing drug in solution. Within this context, and considering the existing in vitro and in vivo PK BE studies recommended in this guidance, a comparative clinical endpoint BE study between T and R products is currently the only tool that provides information on the equivalence in clinical effect at the local sites of action in the lungs.

Additional supportive in vitro studies may include, but are not limited to, (i) more predictive APSD testing using representative mouth-throat models and breathing profiles, (ii) characterization of emitted aerosol sprays with respect to velocity profiles and evaporation rates, (iii) dissolution, and (iv) morphology imaging comparisons, including characterization of the full range of residual drug particle sizes. Prospective applicants may also consider the use of quantitative methods and modeling (for example, physiologically-based PK and computational fluid dynamic studies) and alternative in vivo PK BE studies.

In order to clarify the FDA's expectations for prospective applicants early in product development, and to assist prospective applicants to submit an ANDA as complete as possible, FDA strongly encourages prospective applicants to discuss their development program for an alternative approach to BE, with the FDA via the pre-ANDA meeting pathway.

- *Beclomethasone Dipropionate Inhalation Aerosol, Metered* (May 2019)
- *Beclomethasone Dipropionate Inhalation Aerosol, Metered* (Mar 2020)

Alternative BE Approaches: Solution MDIs

If a generic shows formulation sameness (Q1/Q2) and device similarity to the RLD, additional supportive information may provide a foundation to help ensure the ***equivalence to local site of action*** (lungs):

More Predictive APSD Testing (representative mouth-throat models and breathing profiles)
- Understand impact of patient variability

Characterization of Emitted Sprays (velocity profiles and evaporation rates)
- Understand droplet size and evaporation process of formulation emitted from the device

Morphology Imaging Comparisons (characterization of full range of residual drug particle sizes)
- Understand residual particle morphology and size distribution of formulation emitted from the device

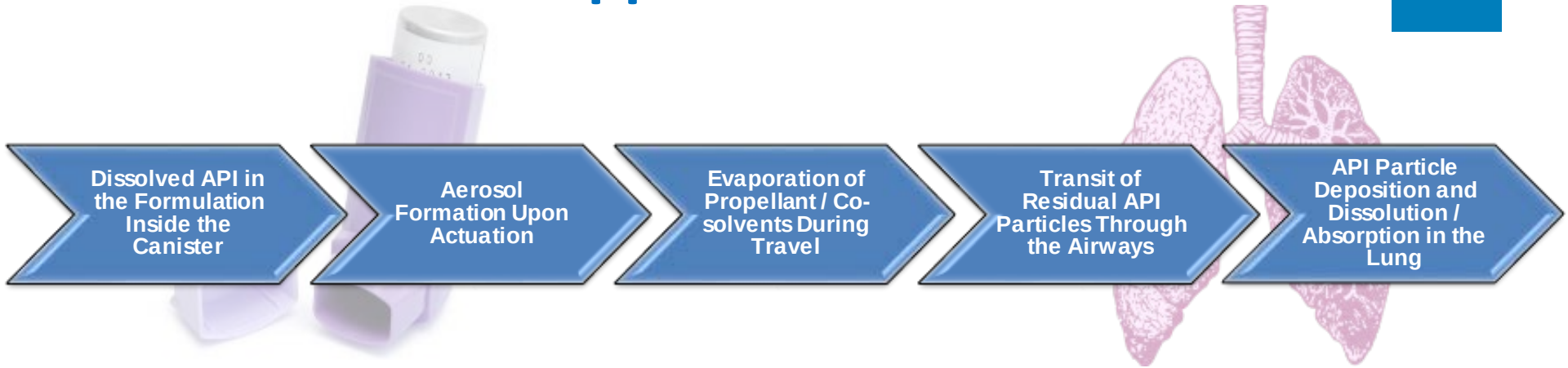
Dissolution
- Understanding how API dissolved at the site of action for absorption once deposited

Quantitative Methods and Modeling (e.g., physiologically-based PK; computational fluid dynamic studies)
- In vitro-in vivo correlations (IVIVCs; bridge gap between in vitro product performance and regional drug deposition)

Alternative PK BE Studies
- Understanding how PK studies may correlate to local deposition

RLD: Reference Listed Drug

Alternative BE Approaches: Solution MDIs



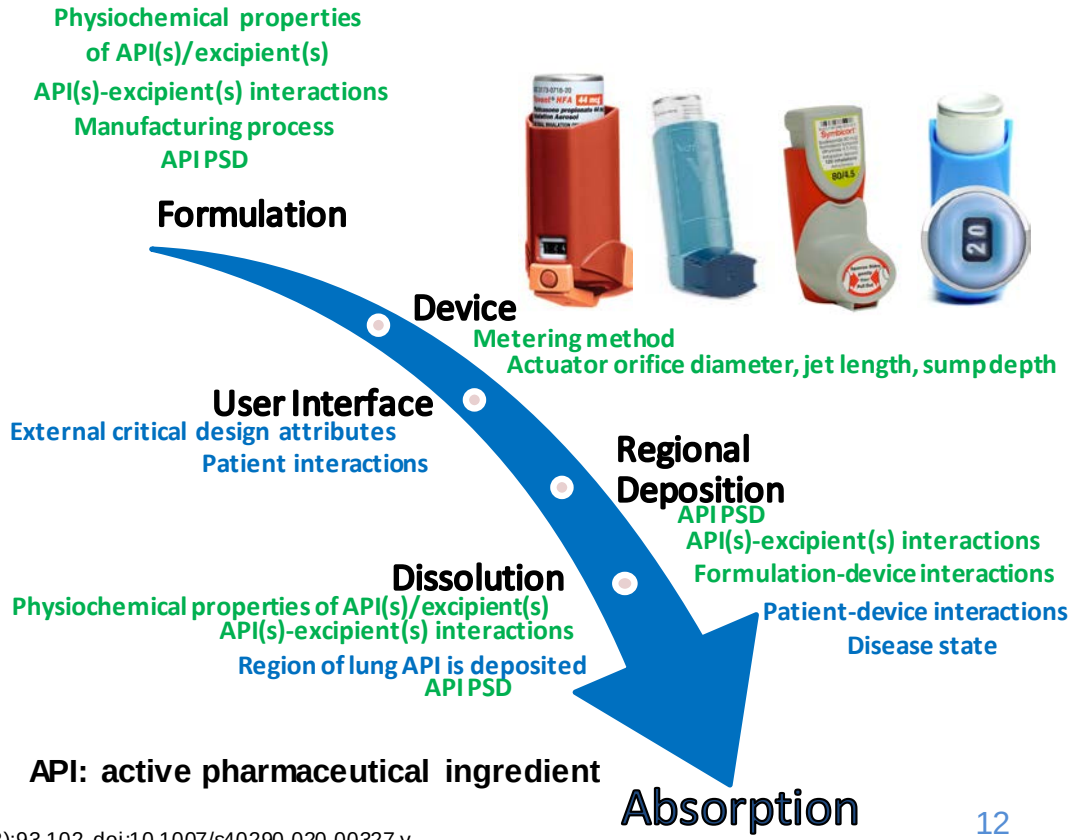
- Local delivery of the API to the site of action is a complex, multi-step process with each step impacting the next
- The comparative CEP BE study incorporates all steps from actuation to deposition, including those shown above, when evaluating whether a T and R OIDP have equivalent local drug delivery
- Similarly, an alternative approach to the comparative CEP BE study is recommended to contain in vitro, in silico, and/or alternative in vivo studies (e.g., PK BE study) to account for the different steps/factors impacting local delivery of the API to the site of action
- Like the weight-of-evidence approach for OINDPs, the selected studies in the alternative BE approach are recommended to **work together** to provide a **comprehensive evaluation of the local drug delivery**, in order to establish equivalence
- In silico approaches may be useful for demonstrating how results from different alternative BE studies work together to establish equivalence in local drug delivery
- The types of alternative BE studies to include may depend on the ***specific OIDP dosage form*** and ***formulation***

https://www.dreamstime.com/stock-photos-asthma-inhaler-image24790423

OIDP: Orally Inhaled Drug Product

What About Alternative BE Approaches for Other OIDPs?

- **Specific *Additional* Challenges for Suspension MDIs**
  - Understanding interaction of ***suspended API*** in the canister and emitted from the actuator
    - Formulation, device, formulation-device interactions that influence regional deposition and absorption of the API
      - Manufacturing process
      - Physiochemical properties of API(s)/excipient(s)
      - API particle size distribution (PSD)
      - Excipient(s) (type and amount)
      - Actuator design



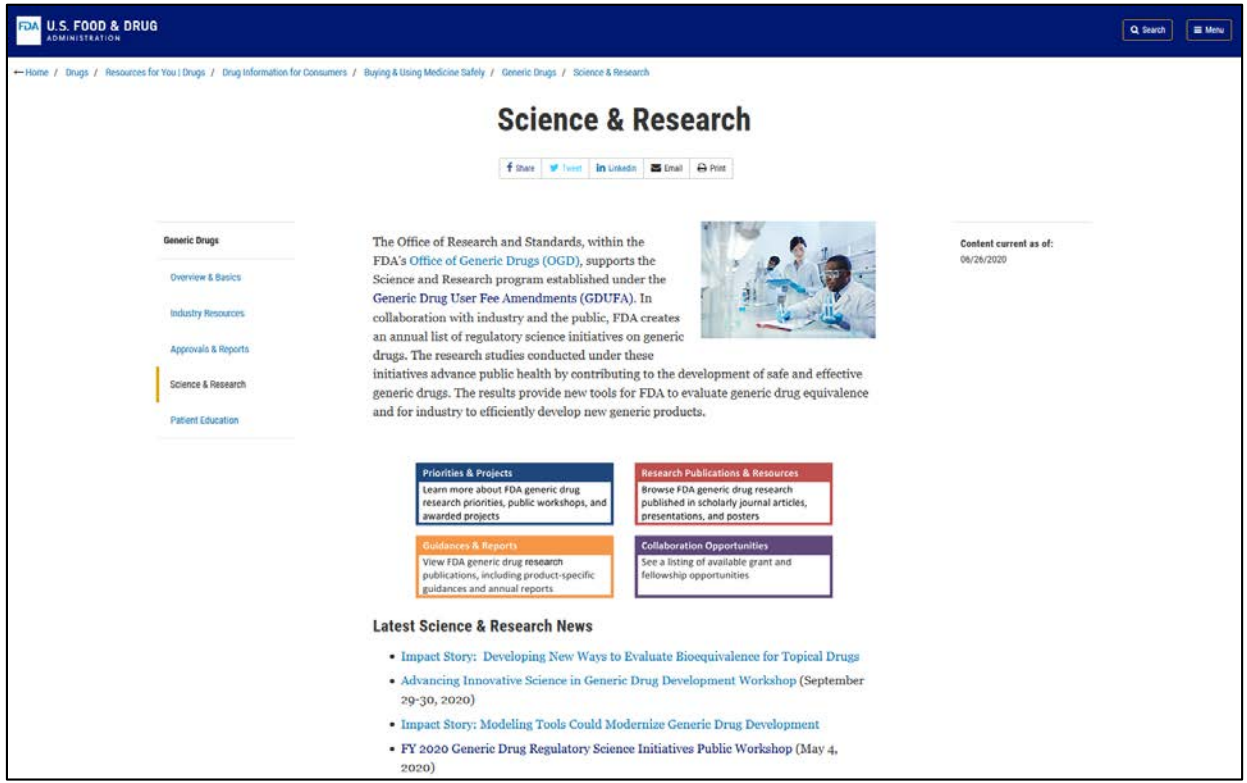
Newman, Bryan, et al.. ***Pharmaceutical Medicine.*** 2020;34(2):93-102. doi:10.1007/s40290-020-00327-y

General Considerations for Alternative BE Approaches for OIDPs

- **Approaches should address sameness of delivery at the *site of action***
- **Alternative approaches may be proposed**
  - If scientific proposal is for a product that does not have a PSG, is outside what is issued in a PSG, or contains complex development issues, it is ***highly encouraged*** to the firm to submit a **pre-ANDA Product Development Meeting Request**
    - Refer to FDA guidance for *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* (October 2017)
    - Approaches should be scientifically justified with a comprehensive, significant body of data, and evaluated as statistically meaningfully as possible

Due to the complexity of many different factors that can affect generic product performance, critical key attributes for any MDI or DPI may be ***product-specific.*** It is vital to understand key quality attributes of your generic product (in vitro performance) in comparison to the RLD that will influence in vivo BE (deposition and absorption of the API to the site of action) as to establish an appropriate alternative BE approach to the CCEP or PD BE study.

Regulatory Science Initiatives



- Research efforts for addressing the challenges with developing an OINDP are ongoing

- If a firm plans to propose an alternative BE approach, we **highly encourage** visiting our GDUFA regulatory science website to view the ongoing projects and outcomes, which can be informative for a generic's development program

Conclusions

- **OINDPs are complex drug-device combination products with multiple factors contributing to their performance**
- **Establishment of BE for locally-acting OINDPs occurs through the *weight-of-evidence approach***
- **To address the challenges with comparative CEP BE studies, the Agency has provided recommendations on *alternative approaches for establishing BE* in lieu of the comparative CEP studies with locally-acting nasal suspensions and solution-based MDIs**
- **Alternative approaches are recommended to evaluate the multiple processes contributing to local drug delivery when establishing BE between a T and R solution-based MDI**
- **The types of studies include as part of an alternative BE approach to a comparative CEP study will be *product-specific*, as differences in dosage form and formulation will give rise to different areas of uncertainty**
- **Firm's are *highly encouraged* to submit a pre-ANDA Product Development Meeting Request for communication and seeking Agency's feedback and comments on alternative BE study proposal**
  - Approaches should be scientifically justified with a comprehensive, significant body of data, and evaluated as statistically meaningfully as possible

Acknowledgements

- Denise Conti, Ph.D.
- Elizabeth Bielski, Ph.D.
- Sneha Dhapare, Ph.D.
- Liangfeng Han, M.D., Ph.D.
- Markham Luke, M.D., Ph.D.
- Lei K. Zhang, Ph.D.
- Robert Lionberger, Ph.D.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