OPQ's Perspective on Quality Considerations for Generic Orally Inhaled Drug Products

Complex Generic Drug Product Development Workshop
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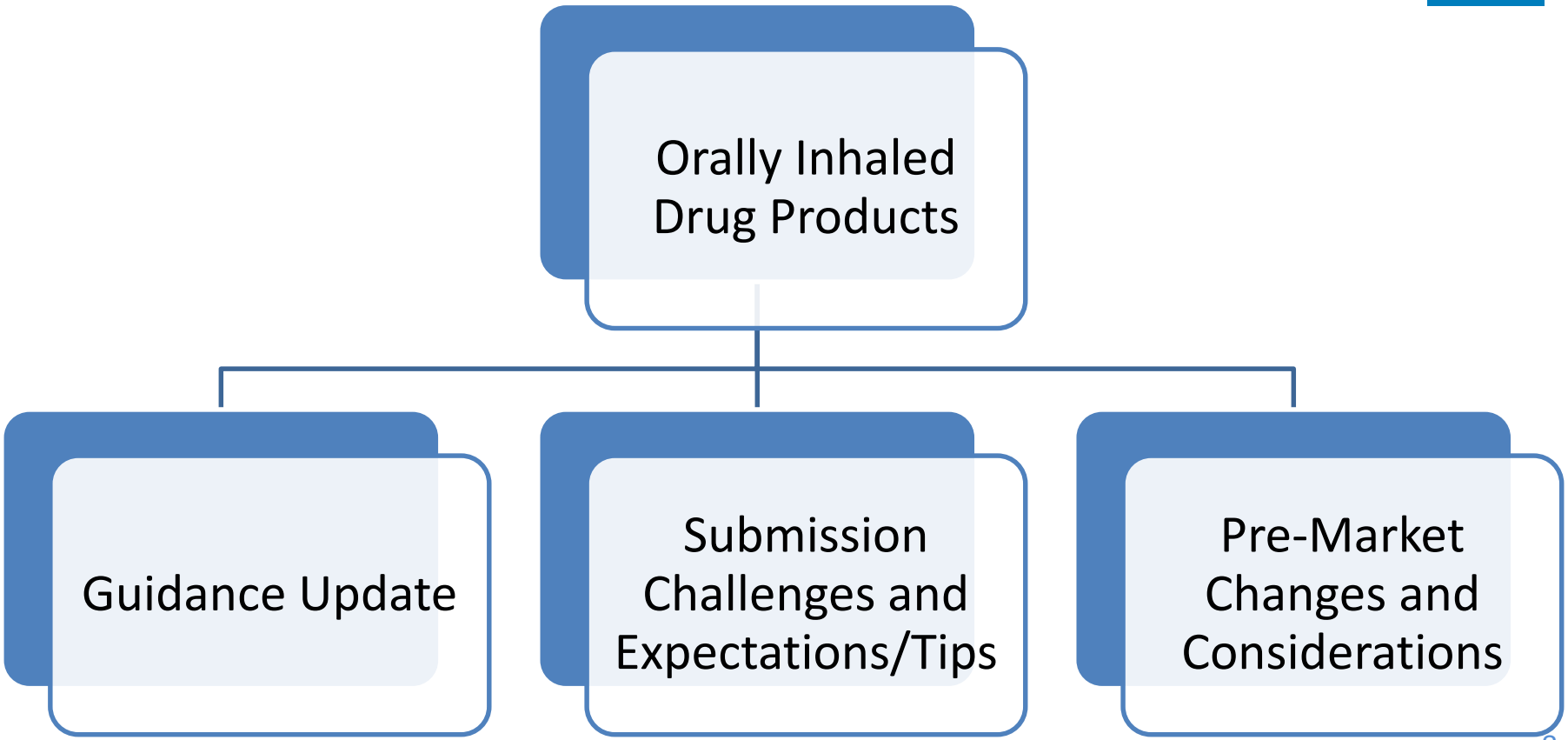
U.S. FOOD & DRUG ADMINISTRATION

Disclaimer

This presentation reflects the views of the speaker and should not be construed to represent the U.S. Food and Drug Administration's views or policies.

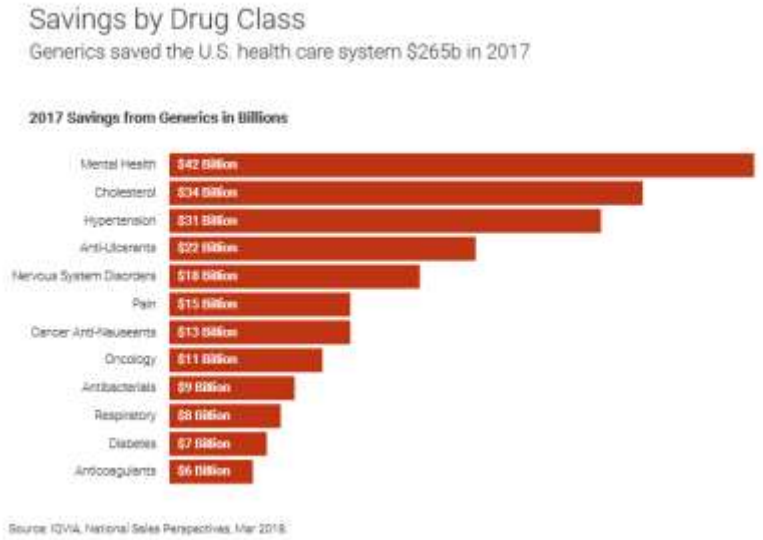
Overview


Orally Inhaled Drug Products
Guidance Update
Submission Challenges and Expectations/Tips
Pre-Market Changes and Considerations

Oral Inhalation Products

- Deliver drug substance(s) to the site of action through inhalation
- Local effect to treat lung diseases -systemic absorption undesirable (e.g., chronic obstructive pulmonary disease (COPD), asthma, as well as respiratory infections and cystic fibrosis)
- Device is integral part of the delivered dose

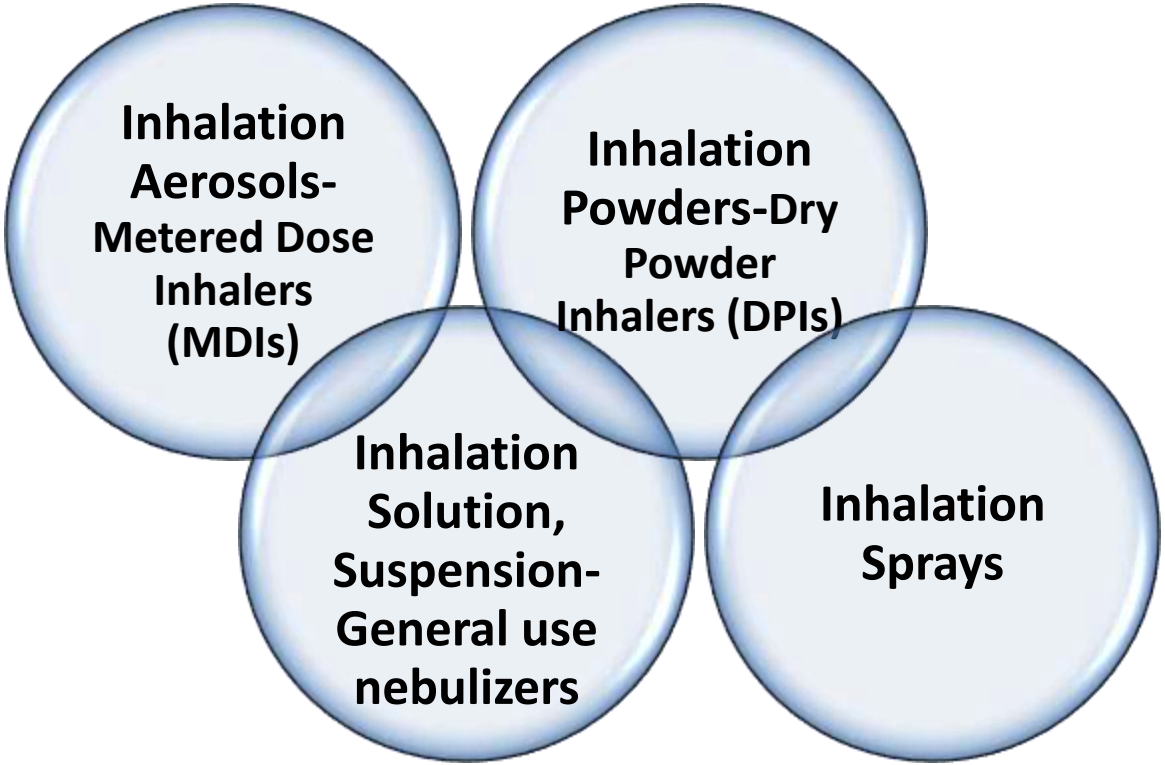
Respiratory Disease Facts & Generic Drug Savings



Looking to the Future- The Route for Inhaled Medications and Inhalation Technology, Pharmaceutical Outsourcing, November/December 2017 Volume 18, Issue 7

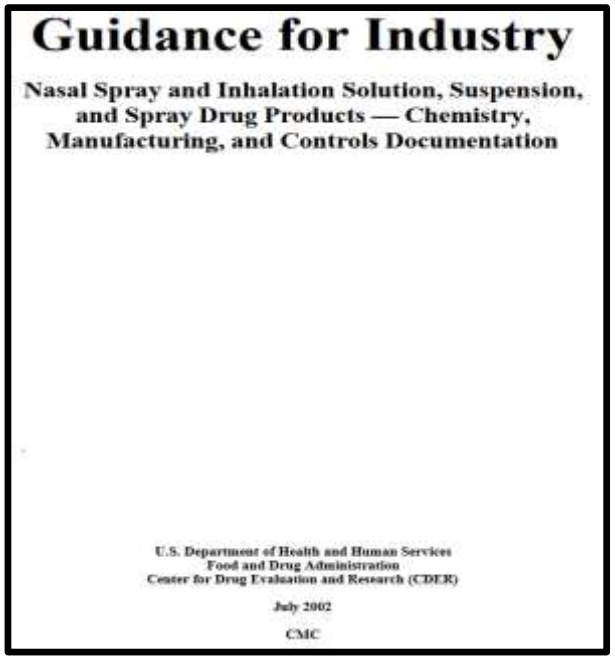
2018 Generic Drug Access & Savings in the U.S, Association for Accessible Medicines (AAM)

Oral Inhalation Products



CDER Drug Guidance

Inhalation solutions/suspensions and Inhalation sprays


Guidance for Industry

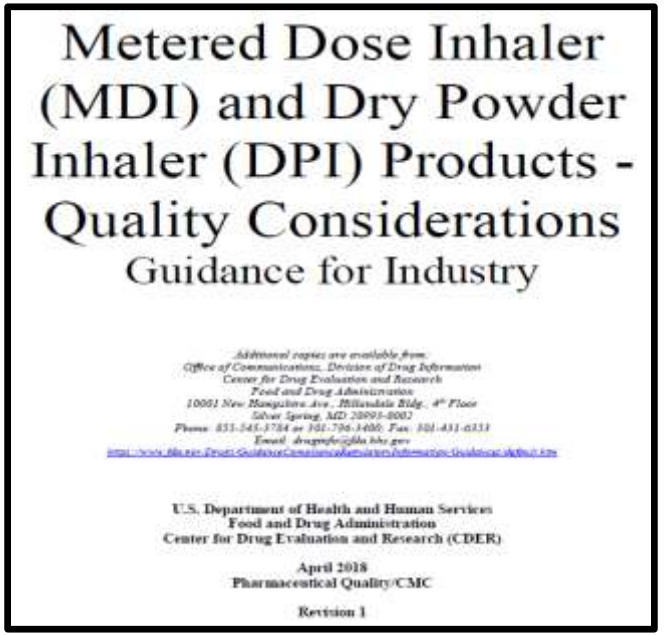
Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

July 2002

CMC

Inhalation aerosols and powders


Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Products - Quality Considerations

Guidance for Industry

Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

April 2018
Pharmaceutical Quality/CMC

Revision 1

Selected Highlights of 2018 Draft:

- MDIs and DPIs is a combination product defined under 21 CFR 3.2(e) and are subject to CGMP requirements applicable to each constituent part (drug, device) of the combination product

- Covers critical features that should be considered during development,
  - Quality Target Product Profiles (QTPP)
  - Critical Quality Attributes (CQAs)
  - Product and Process Development
  - Development of Control Strategy
  - Recommendation for specific characterization studies

FDA guidance for industry on *Current Good Manufacturing Practice Requirements for Combination Products*

Pre-market Submission Challenges for Generic OIDPs- Quality Perspective

Massive volume of information

- A large body of device information
- Complex and lengthy Product Development information
- Miscellaneous: pre-ANDA correspondences, meetings, more types of analytical procedures and validation documents, etc.
- Bridging information package in support of pre-market changes (if proposed)

Understand FDA review disciplines' expectations.
Balance the extent of information to be included into submission.
Clearly present the information to aid assessment.

Challenges Associated with Device Information

- **Location of submission**
  - Current eCTD structure include two locations for (3.2.P.2.4 and 3.P.7) CCS, but not specifically formatted for device information of combination products. Inconsistent locations observed across companies: 3.P.2.4, 3.P.7, 3.2.R, and some (e.g., product characterization/effect of patient use study) in Module 5.

- **Lack of unified guideline and requirement for device development**
  - Multiple guidelines and requirements for device development covering different aspects (product quality, device CGMP, etc.) assessed by different disciplines/sub-disciplines.

Device Information To Be Submitted in ANDA Quality Discipline Expectations

FDA Draft Quality Guidance: MDI and DPI products (04/2018) – Covering expectation for the container closure system (Device constituent part and the PRI/SEC packaging).

3.2.P.2.4 Container Closure System (device/secondary packaging components) development report demonstrating suitability of the proposed CCS for MDIs or DPIs

- Overall description of CCS, critical device function by design, summary of risk management activities (ISO 14971), risk assessment for device attributes and its impact on drug delivery performance characteristics
- Summary data from Product Characterization studies. Device Robustness, Effect of Patient Use, with reference/hyperlink additionally listed in Module 5 as applicable
- Assessment of Materials: Extractables profiles and Leachable study, and toxicological assessment, if needed. Biocompatibility report, Elemental Impurities Risk Assessment
- Summary of changes during development (e.g., device)

Device Information To Be Submitted in ANDA Quality Discipline Expectations

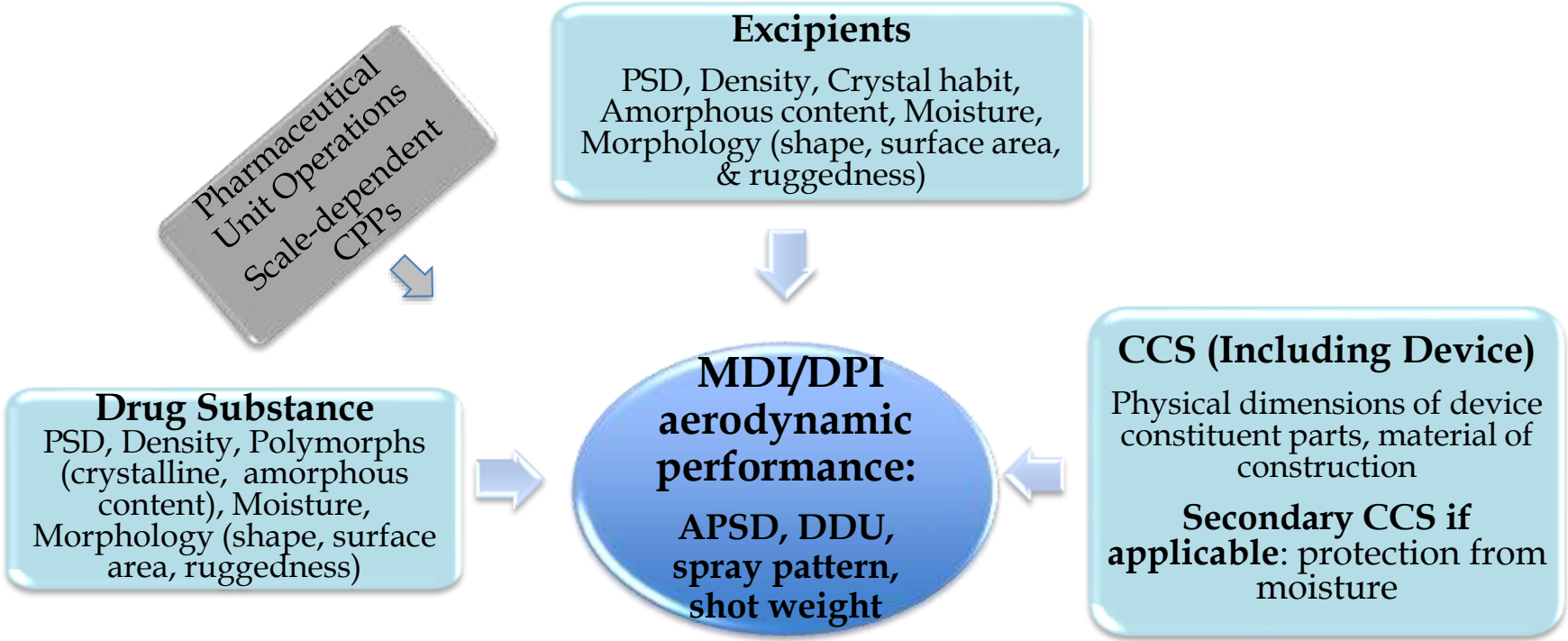
3.2.P.7 CCS (device constituent part and secondary packaging)- Appropriate control strategies

- DMFs # (if referenced) , Device Constituent part, Components, facility responsibility
- Engineering drawings with identified critical dimensions
- Specifications-device constituent parts/subassembly, primary & secondary packaging
- Analytical procedures (including extractables/leachables methods, validation report)
- Representative certification of analysis (registration, clinical, to-be-marketed product) including supplier (device components)
- If Type III DMF has been referenced for manufacture of device constituent parts, manufacturing process and in-process controls are usually not required to be included into ANDA submission. As applicable, this section may hyperlink to unique device constituent manufacturing information in 3.2.R.
- Supportive files for container closure device constituents in section 3.2.R (e.g., device engineering design documentation/Summary reports)

Multi-sources of Variabilities Unique to MDI/DPI Product Development

Upstream Variabilities collectively contribute to variabilities of product performance:

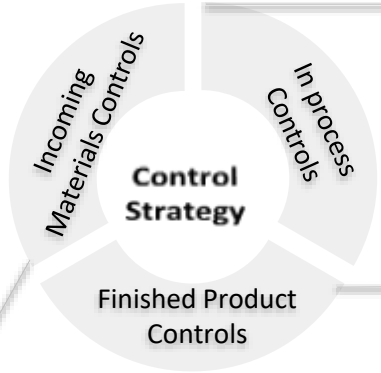
- Lot-to-lot variability of API(s), excipients and device constituent parts, and CCS.



Understanding today's Quality Concept…

Starting point (QTPP, CQAs, Potential Risks-Product/Process)

- Drug substance
  - Micronization
  - Physical Stability
- Excipients
  - Non compendial CQAs
- Device Constituent parts
  - Dimensions
  - Valve functionality
  - Dose counter
  - Actuator orifice
  - Extractables



- MDIs: Homogeneity, Valve performance testing
- DPIs: BU, Moist. content, Fill wt./CU of dosage unit.
- Secondary packaging: Leak test, Seal strength

- DDU and APSD
- Other Quality attributes
- Device attributes: actuation force, resistance to air flow

…shapes our Quality by Design, Design Controls (21 CFR 820.30) Approach

Risk Management

Above approach limits performance and product quality risks

Opportunity

Above approach creates opportunities for lifecycle management

Transparency

Above approach opens up the dialog and strengthens submission quality.

Risk Management for Combination Products

- Risk management activities should be initiated early in the combination product development process.

- Consider using risk assessment tools such as those listed in **ICH Q9 or ISO 14971 *Risk Management – Medical Devices*** (e.g., Failure Modes and Effects Analysis (FMEA), Failure Modes, Effects, and Criticality Analysis (FEMCA), Fault Tree Analysis (FTA), Ishikawa diagram) starting from early product development to identify factors which have the potential to impact product quality and performance, could serve as a basis for developing a suitable framework for risk management for combination products.

Pre-Market Changes

Intended to improve product quality/performance/robustness and process efficiency

Registration batches (stability, pivotal clinical, and in vivo and in vitro bioequivalence)

Should be conducted with final finished form- "to-be-marketed" device, formulation, process

Formulation (change of fine particle ratio of carrier), **Process** (equipment, site), **Device** (composition, design, supplier)

Risk assessment for the change(s), Bridging data, Justification

Information readily available:

- ✓ Promotes efficient and effective ANDA assessment process
- ✓ Reduces number of review cycles
- ✓ Reduces risk of receiving CR major

Pre-Market Changes Recommendations

Communicate with FDA as early as possible

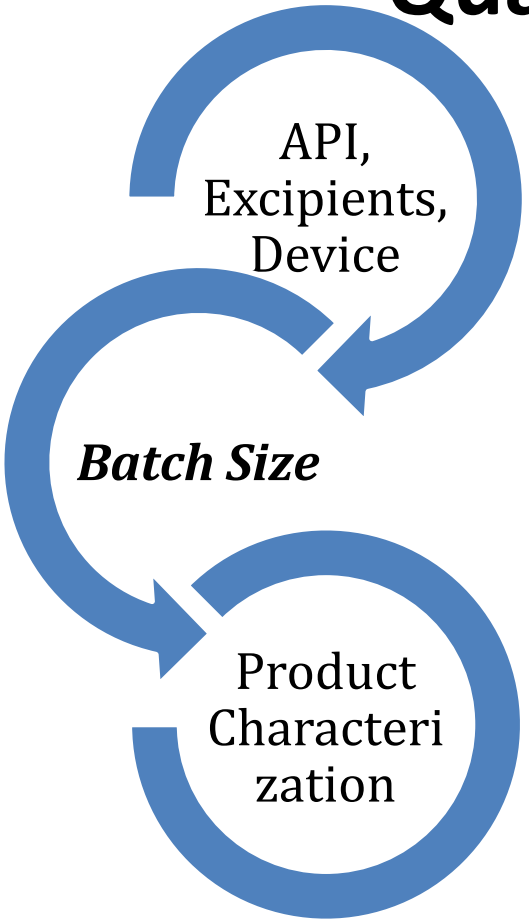
- Identify potential changes as early as possible
- Seek (sub)disciplines' feedbacks on bridging data package
- Prepare submission package per pre-ANDA agreement

Surprises come in full ANDA submission

- Zero communication regarding changes at pre-ANDA phase
- Miscommunication: only partial of changes being discussed with FDA at pre-ANDA phase

The key to avoid major deficiencies is proper communication!!!

Quality Considerations



- Three different lots, of drug substance (discrete lots), Device and Critical Excipients be used for three primary stability batches
- One batch at the proposed commercial production scale and other two should be of at least one-third (1/3) of the proposed commercial
- Conducted on the to-be-marketed configurations and versions of MDI and DPI products
- Three batches with reasonable sample size to support reliability, reproducibility of product quality and performance

Tips of Preparing Submission Package of Complex ANDAs (cont.)

Include, **REVIEWER GUIDE** in Module 1.2 Cover Letter

To aid the reviewer by highlighting pertinent information regarding the content and format of the ANDA. Combination product application- really beneficial!!

- Include a high-level overview of the submission with hyperlinks to submitted information.
- Provide locations for documents not typically included in a submission or documents not placed in more conventional locations;
- Provide any other information that contributes to ease of assessment.

Summary of Changes during Development, Registration/Clinical (with reference links)

Chronological Summary of Key Discussion Points/Agreements with Agency during Development Process

Closing Remarks

- Submission quality and effective and timely communication are key to success, leading to timelier FDA approval and speed U.S. patient access to generic products.
- Encourage Industry to,
  - Adopt science and risk based approaches
  - For potential changes, please communicate with Agency as soon as possible
  - Provide a high degree of assurance there are no unintended consequence of the change

THANK YOU FOR YOUR ATTENTION