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PRESCRIPTION DIVISION

Qualifying Container Closure Systems for OINDP: Current & Future Regulatory Expectations

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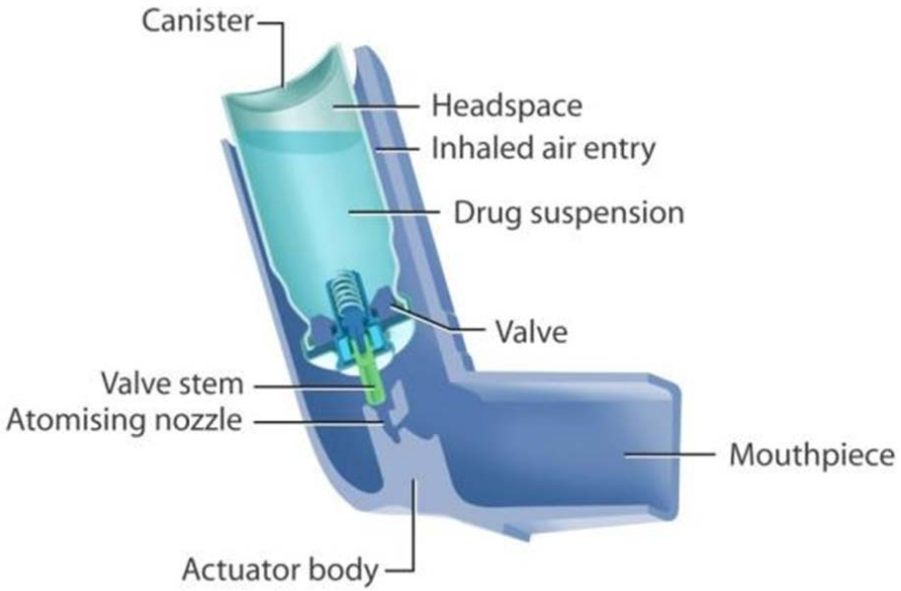
Objectives

- Container-Closure System Attributes
- Extractables
- Regulatory Expectations
  - Asian Market
  - Regulated Market
- Bridging to Regulated Markets
- Future Considerations

Container-Closure Systems



- Elastomers, plastic polymers, glass, stainless steel, aluminum
- Attributes ensure safety, stability and reproducible delivery
- Device performance requirements vary by country

Extractable & Leachable Requirements

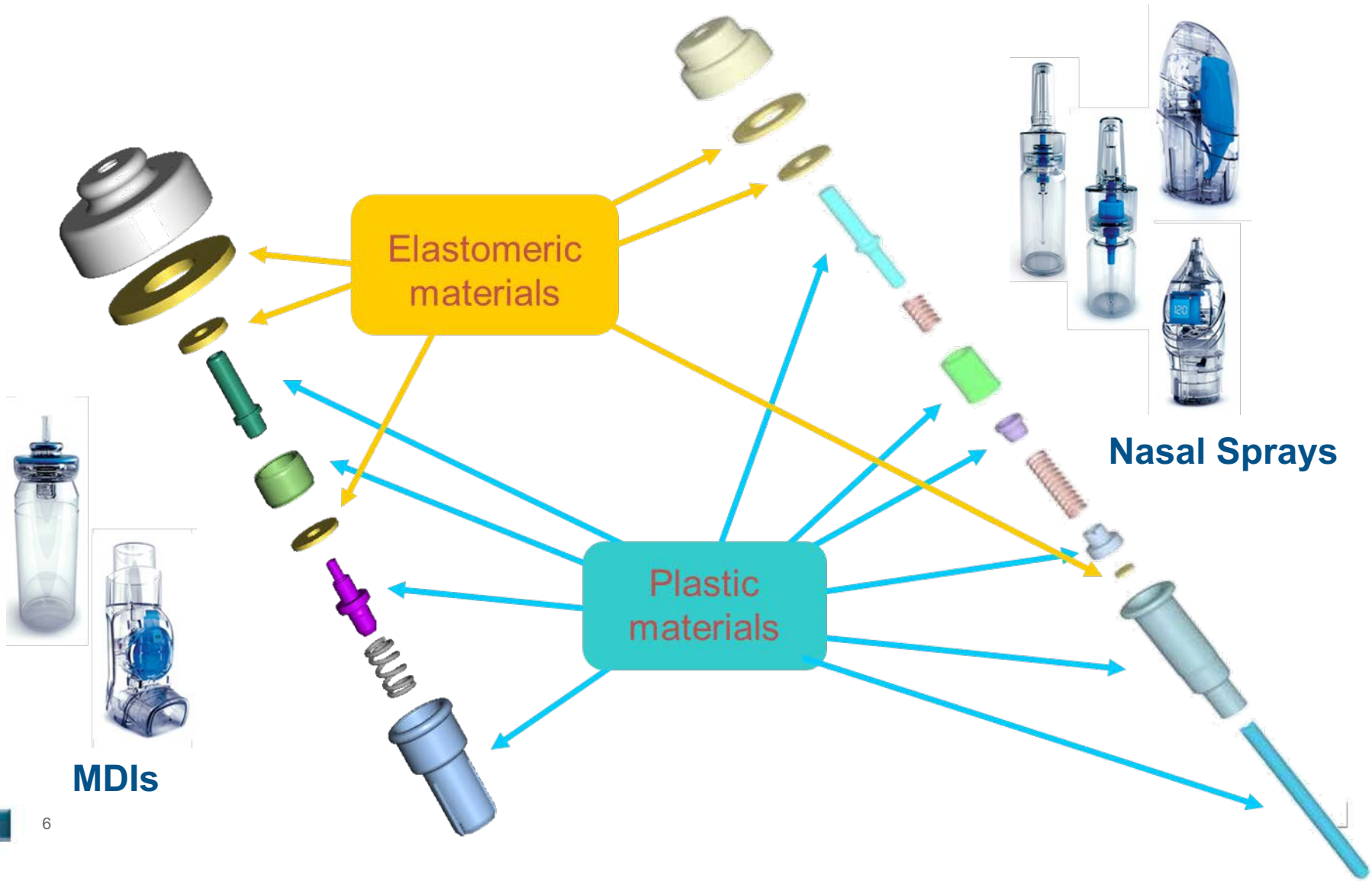
Highly Regulated			Evolving Regulations		
Development Data Routine Controls (QC)			Development Data		N/A
US	EU	BR	China	SE Asia	India
					

Container-Closure Systems

- Device must be registered with CFDA
  - No Drug Master File (DMF) System
- Device Supplier provides information to CFDA
  - Extractables → development data submitted
- Select Supplier with CFDA registration
- 2015 projected release for Chinese Pharmacopeia
  - Addition of multi-stage cascade impaction testing
  - Pharmaco testing expectation

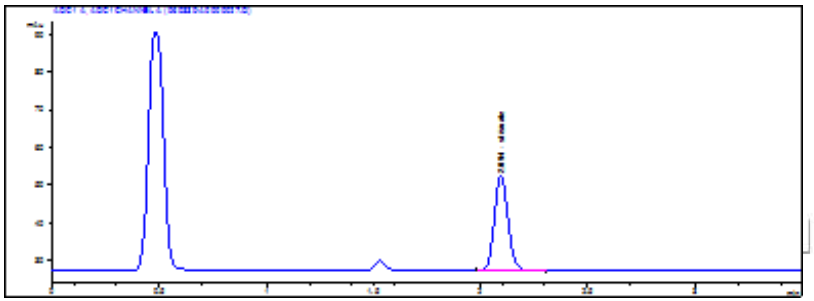
CFDA 国家食品药品监督管理总局 China Food and Drug Administration

Principle Extractable Sources



Identify Potential Extractables

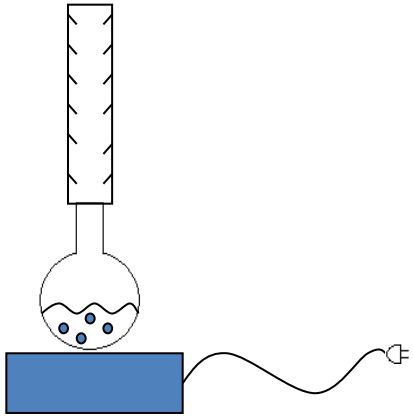
- Additives (antioxidants, stabilizers, lubricants) used to improve:
  - processing
  - device assembly
  - shelf life
- Residual products (oligomers, vulcanization agent…)
- Degradation products from additives, polymers
- By-products from polymerization
- The more details provided by raw material suppliers, the easier the controlled extraction studies

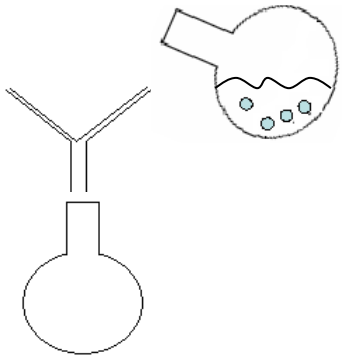


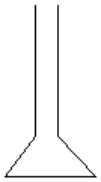
Controlled extraction studies

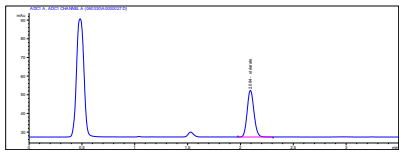
Thin films

Powder



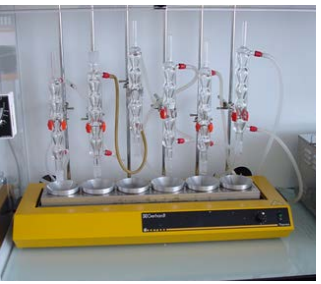






Sample prep | **Extraction technique** | **Filtration** | **Evaporation of extraction solvent** | **Sample Solution prep** | **Chromatographic analysis**

Materials



Microwave oven
Reflux
Soxhlet
Sonication
Accelerated Solvent Extractor...

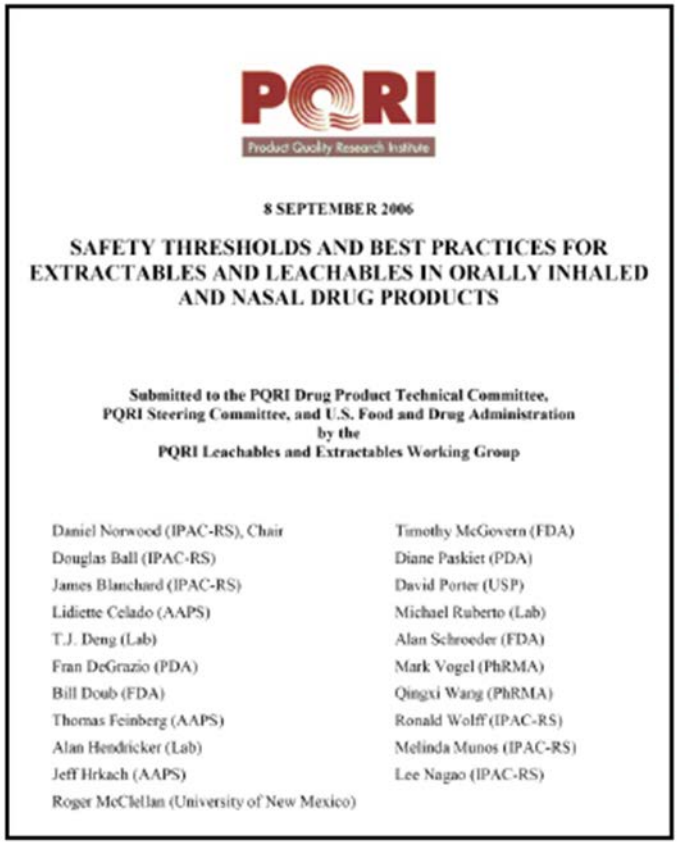
Solvents of different polarities:

Dichloromethane
Water
Isopropanol
Hexane
etc…

HPLC-UV
HPLC-ELS
HPLC-MS
GC-FID
GC-MS
GC-NCD
GC-TEA
GC-NPD

PQRI Extractable and Leachable Guidelines

- Prescriptive guidelines
- Determine Analytical Evaluation Thresholds (AET)
- Safety Thresholds
  - Qualification Threshold (QT)
    - 5 mcg/day
  - Safety Concern Threshold (SCT)
    - 0.15 mcg/day



PQRI
Product Quality Research Institute

8 SEPTEMBER 2006

SAFETY THRESHOLDS AND BEST PRACTICES FOR EXTRACTABLES AND LEACHABLES IN ORALLY INHALED AND NASAL DRUG PRODUCTS

Submitted to the PQRI Drug Product Technical Committee, PQRI Steering Committee, and U.S. Food and Drug Administration by the PQRI Leachables and Extractables Working Group

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Extractable Studies Process

Extractable screening for identification → Development / Validation of analytical methods capable of quantifying extractables → Controlled extraction studies on materials

Material is validated in terms of extractables

Measurement of extracts on several batches of raw materials → Establishment of specifications → Implementation of routine controls

Possible DMF* submission or Registration by Device Manufacturer

**DMF: Drug Master File*

Setting Extractables Specifications: Routine Controls

- For extractables to be monitored, specifications are established for each material based on:
  - Measurement of extracts profile from several batches
  - Limits are set:
    - ✓ For each extractable to be monitored
    - ✓ For unknowns as a reporting limit (e.g limit of quantification of the method)

- Based on extractables profile, appropriate routine quality controls are implemented:
  - Systematic control of each batch upon reception
  - Verification of the consistency of packaging material from batch to batch and avoid new impurities (e.g. contamination)
  - To guarantee that the manufacturing process is under control

Device Quality Agreement

- Commitment to test incoming materials
- Quality Agreement criterion will vary by market regulations

Device quality agreement inclusions	Objective	Reference
Food contact certificate	Ensure that the materials used in the CCS conform to the minimum considered generally safe	e.g 21 CFR 177, EU 10/2011
USP monograph compliance	Assure compliance with plastic, rubber & toxicology standard tests etc.	e.g. USP <661> plastics, USP <381> Elastomers, USP <87,88> biological reactivity tests etc.
International GMP or ISO compliance	Compliance with accepted international quality standards	ISO 9001, 13485, 15378, 21 CFR 210
Standard performance limits (release testing)	Compliance with accepted performance standards for OINDPs	USP <601>, FDA (5), EP Inhalanda & Nasalia

Certificate of Analysis (CofA)

- Metrics based on internal company standards or regulatory expectations
- Items included in CofA can be tailored for Pharmaco requirements

Example CofA nitrile elastomers in nasal pumps for the US market	
Characteristic / Analytical test	**Units of measure**
Identification	Infra-red profile
Dimensional, metrology	Technical drawings
Extractables	
PNAs	ppm
Acrylonitrile monomer	ppb
Fatty Acids	mg/g
Semi-volatiles	mg/g
Nitrosamines	ppb

Additional Considerations for Selection

- Container Closure Manufacture
  - ISO 15378, GMP and/or Quality Agreement
  - Site of manufacture
- Market Expectations
  - End user requirements
  - Economic considerations
  - Regional differences within a population

Twister DPI,
Aptar Pharma

Starhaler, Sun
Pharma

Regulated Markets

- Innovator
  - FDA Chemistry Manufacturing and Control Guidances
  - EMA CHMP Guidelines
  - Well established for nasal and pulmonary drug products
- Generic
  - FDA and Brazil detailed BE pathways
  - EMA outlines BE approach
- Super Generic
  - 505(b)(2) (US)
  - Similar (BR)

505(j) Abbreviated New Drug Application (ANDA)

- Bioequivalence
  - Demonstrate equivalent rate and extent of absorption
  - Reduced scope of in vivo and/or in vitro comparison
  - Full CMC still needed
- Global approaches to bioequivalence
  - EMA applies step wise approach to BE
  - FDA applies weight of evidence
  - Required tests and statistical approaches differ

FDA Drug Specific Guidance: Albuterol MDI BE Expectations

- Dose Counter
  - Required if present on RLD
  - May need to demonstrate robustness and accuracy
    - In vitro and in-use (suggests patient handling)
- Single Actuation Content (SAC)
- Aerodynamic Particle Size Distribution (APSD)
- Spray pattern
- Plume geometry
- Priming and Repriming
- Note PK and PD studies required for full BE

Fluticasone Proprionate/Salmeterol Xinafoate DPI

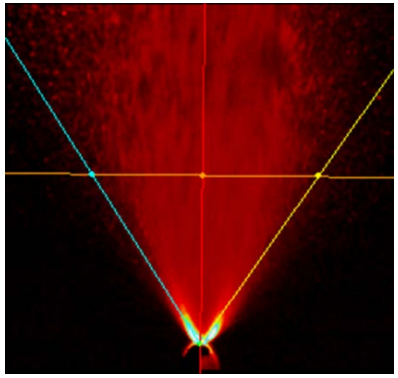
- In vitro and in vivo required
  - Clinical endpoint and PK
- All strengths
- SAC and APSD at 3 flow rates
  - SAC 2L; Population Bioequivalence (PBE) stats
  - APSD 4L; PBE Impactor Stage Mass (ISM) and submit CI profiles
- Device comparability necessary
  - Same device resistance
  - Internal mechanism can differ
- Robustness of T product required
  - **In vitro and in-use**

In Vitro BE for Nasal Sprays Across Regulatory Bodies

FDA	Brazil (ANVISA)	EMA
Droplet Size	Droplet Size	Droplet Size officially
Single Actuation Content Uniformity	Single Actuation Content Uniformity	Other in vitro tests appear to be used
Spray Pattern	Spray Pattern	
Prime Reprime	Prime Reprime	
Particle Size	Number of Metered Doses	
Plume Geometry	Pump Delivery	
Particles < 10µm		

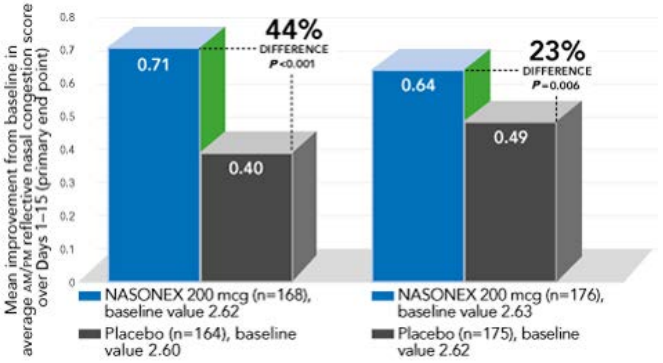
FDA and Brazil Generic Pathways

Agency	Bioequivalence (BE)	Pharmaceutical Equivalence (PE)
FDA	In Vivo and/or In Vitro	Definition does not exist
ANVISA	In Vivo	In Vitro



In Vitro
Plume Geometry

In Vivo
Pharmacokinetics (PK)



In Vivo
Clinical Endpoint

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Brazil PE Tests

In Vitro Test	Metric for Statistics	Similarity to FDA BE
Contents of an actuation on the total contents of the device (single actuation content uniformity)	Mass (µg) of drug	Same
Dose mass (pump delivery)	Spray weight (mg) No stats	Not required
Droplet size distribution	D50 Span	Same
Spray pattern	Ovality Area	Same
Number of doses	Count No stats	Not required
Load and reload (prime and reprime)	Mass of drug Meet 95-105% LC	Three orientations required not one Stats required

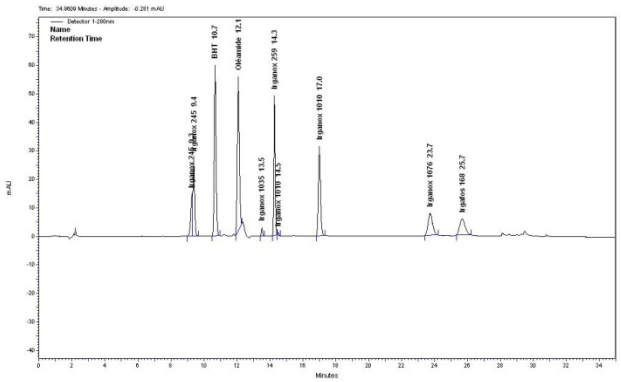
US FDA ANDA Notes

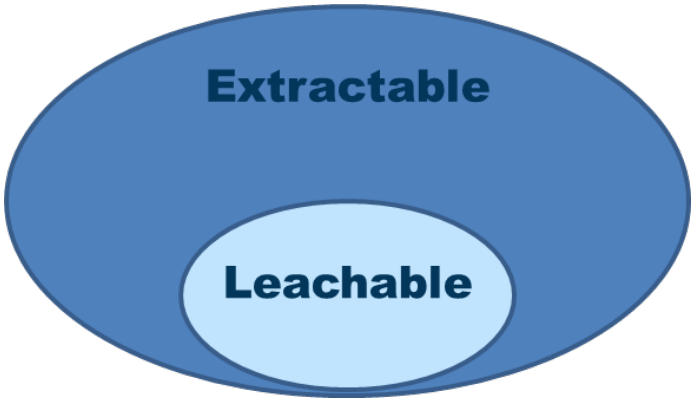
- Three registration batches on stability
  - Effective June 2014
- Statistical approach defined in the Budesonide Inhalation Suspension Draft Guidance (September 2012)
- Chi2 Ratio for cascade impaction (CI)
  - FDA will look at the whole CI profile
  - No equivalence criterion on this ratio yet
- Don’t forget CMC characterization studies (applies to NDAs too)
  - Leachables

Leachables Studies

- Delivery device in contact with drug product
- Leachables profile is drug product specific
  - ✓ Responsibility of the pharmaceutical companies
- Leachables assessment can be performed based on extractables information and methods
- Performed during stability studies

Knowledge of leachables and their toxicity can determine which extractables are to be put under routine control





Bridging to Regulated Markets

- Container Closure System Needs
  - Routine testing controls from Supplier
  - Materials that meet regulated market expectations
    - Extractables and leachables
  - Manufacture to ISO or GMP standards
  - Reference DMF (US) market or MAA (EU)

- Formulation
  - Compatibility with closure
  - API and excipients

Patient Experience (ANDA Route)

- Device sameness—US Expectation
- For Dry Powder Inhalers
  - Shape, size, dose counter, resistance, external operation
  - Internal operation can be different as long as it doesn affect patient experience
- Thought process extends to nasal sprays and other device platforms

Advair Package Insert

Alternate US Pathways

- 505(b)(1) New Drug Application (NDA)
  - Full clinical, toxicology and CMC
- 505(b)(2)
  - New drug approval without conducting the full complement of safety and efficacy trials
  - Stability and CMC package required
  - Examples
    - Benzodiazepines delivered as nasal sprays
    - Albuterol sulfate branded generic (ProAir)

Diazepam

Similars

- Branded generic
  - Formulations may differ
  - Example: preservative free formulations
- Must follow Brazil Technical Standard No. 001/2013 for registration
- Potential future pathway for Similar to become a Reference

Budecort AQ
32 and 64 µg
Reference

Noex
32 and 64 µg
Similar

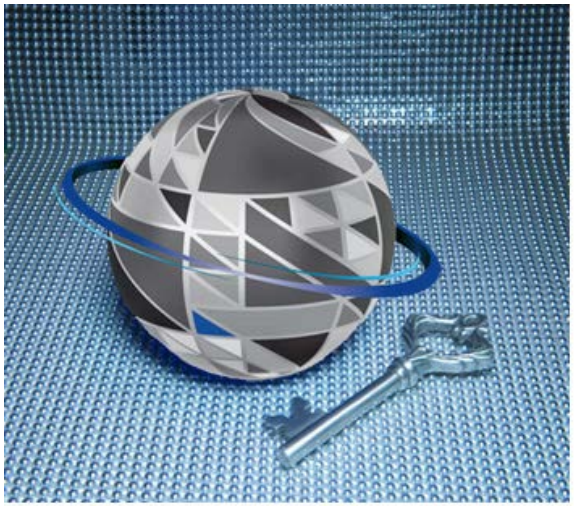
Noex
50 and 100µg
Reference

Future

- Affordable healthcare
  - US OTC Switch
- Growing regulations in China
- FDA presence in India
  - FDASIA monitoring exports
    - Safety, drug shortages…
  - Expansion to other countries?

Summary: Select the Right Closure

- Regulatory requirements
- Market demands
- Keys to success
  - Quality agreement with Supplier
  - Routine controls
  - Ability to scale manufacture
  - Domestic production
  - Strong relationship with regulatory bodies



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