Complex Drug-Device Generic Combination Products

October 9-10
Sheraton Silver Spring, MD

Combination Drug-Device Products as Complex Generic Drugs – Summary of Presentations and Horizon Scanning for Future Scientific Research

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DIA

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Quick Recap of Two-day Syllabus

October 9, 2018

Day 1 Session 1 – Regulatory Expectations

Day 1 Session 2 – Inhalation, Nasal, and Auto-Injector Products

October 10, 2018

Day 2 Session 3 – Quality Considerations

Day 2 Session 4A – Long-Acting Implants

Day 2 Session 4B – Transdermal Products

Generic Drug-Device Combination Products May be Complex

- Complex products, in terms of generic drug development, are products where there may be greater challenges to concluding therapeutic equivalence of a product.
- Some combination drug-device products fall within this category either due to how these products are applied or used (site of action complexity) or due to the presence of the device component (physical complexity).

Perspectives – Therapeutic Equivalence Considerations

- Manufacturer Perspective – Challenges to overcome in developing the product
  - Patent/design considerations
  - Technology considerations
  - Manufacturing/Facilities considerations
- FDA Perspective - Therapeutic equivalence considerations for the device portion of the combination product are multi-factorial
  - Design/Engineering Considerations
  - Use/Human Factor Considerations
  - Risk evaluation for differences in design, robustness, critical use steps
- User Perspective – Can I use this and get an equivalent therapeutic effect?

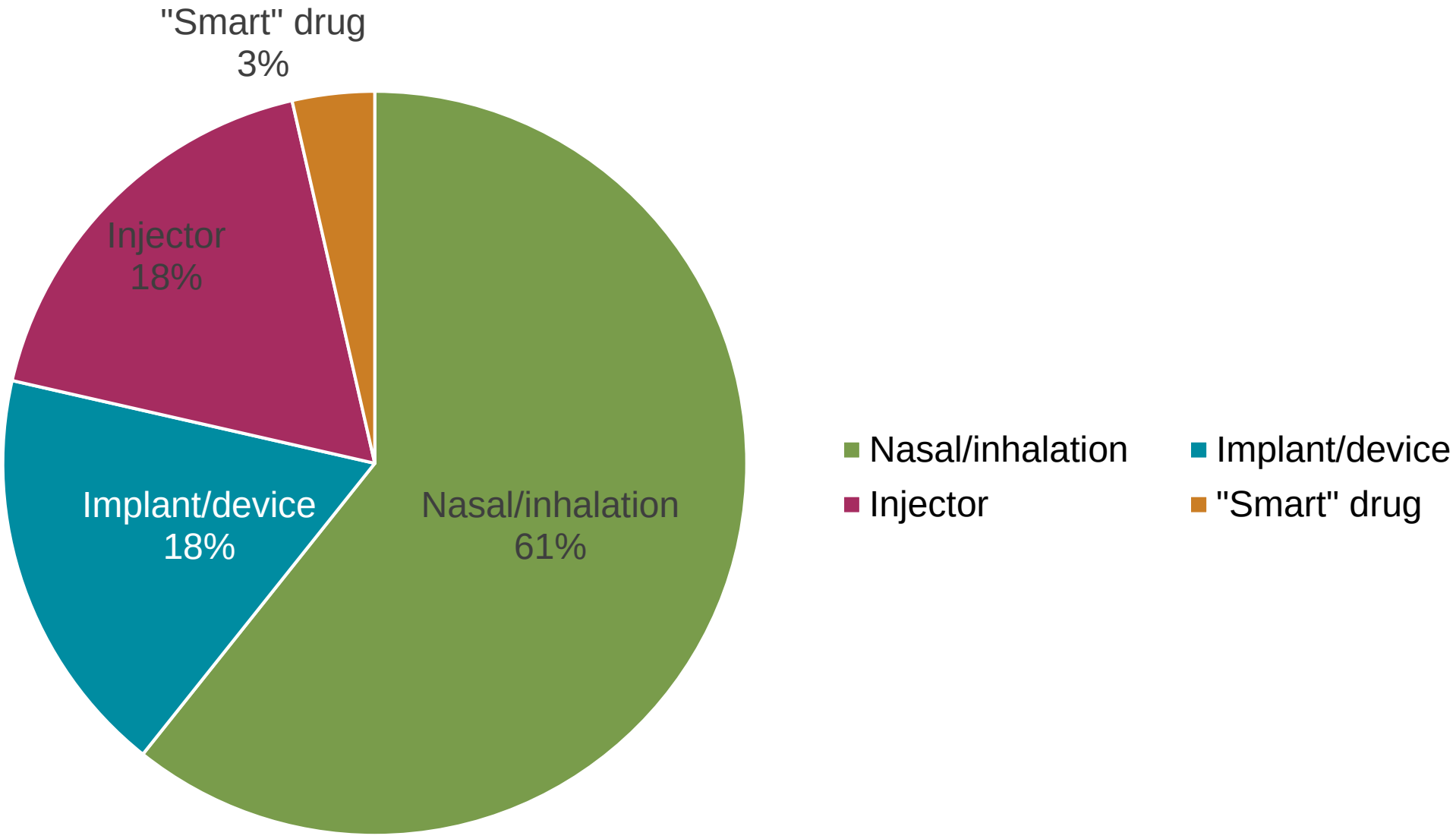
Device Functions in Combination Products

- Drug Delivery
  - Physical Application of the Drug - e.g. syringe/needle, pump spray, dermal patch, implant matrix
  - Drug Dosage Confirmation - Markings on the syringe, Dose counter, Dose tracking
- Drug Modification - Light activation of pro-drug, Laser-activated polymerization

Questions to Consider

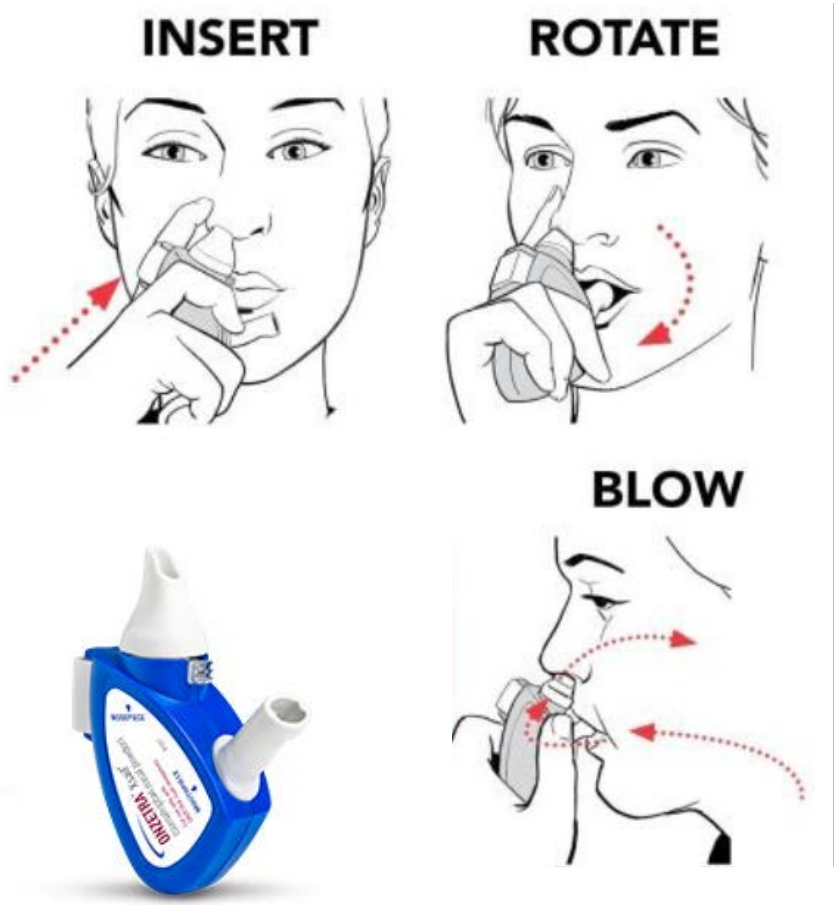
- Who is using the device?
  - Professional (e.g. physician)
  - Patient?
- Does the device deliver the drug to/at the site of action at the same rate/concentration?
- How does the device compare to the RLD device?
- What are the risks (safety or effectiveness) associated with any observed differences with the device?

NDA Drug Products with Device Components 2015-2017 (N=28)



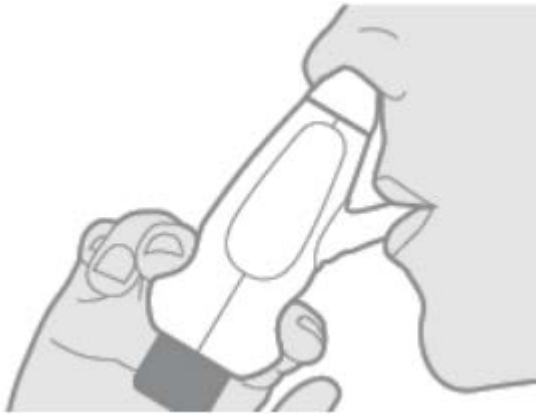
ONZETRA XSAIL

- New approach for the acute treatment of migraine
- Approved: 01/27/2016 (NDA 206099)
- API: Sumatriptan nasal powder
- Dosage Form/Route: nasal powder
- **Complexity**: ONZETRA Xsail is supplied as a disposable nosepiece containing a capsule and a reusable delivery device body. The patient blows forcefully through the mouthpiece to deliver the sumatriptan powder into the nasal cavity.



XHANCE

- New approach to nasal spray
- Approved: 09/18/2017 (NDA 209022)
- API: Fluticasone propionate
- Dosage Form/Route: nasal spray
- **Complexity**: XHANCE is delivered into the nose by actuating the pump spray into one nostril while simultaneously blowing (exhaling) into the mouthpiece of the device.



STIOLTO RESPIMAT

- New approach to inhalation spray
- Approved: 05/21/2015 (NDA 206756)
- API: Tiotropium bromide and olodaterol
- Dosage Form/Route: inhalation spray
- **Complexity**: Respimat is a new inhalation drug delivery device and commonly referred to as "Soft Mist Inhaler"

Research Underway to Address Inhaled Combination Products

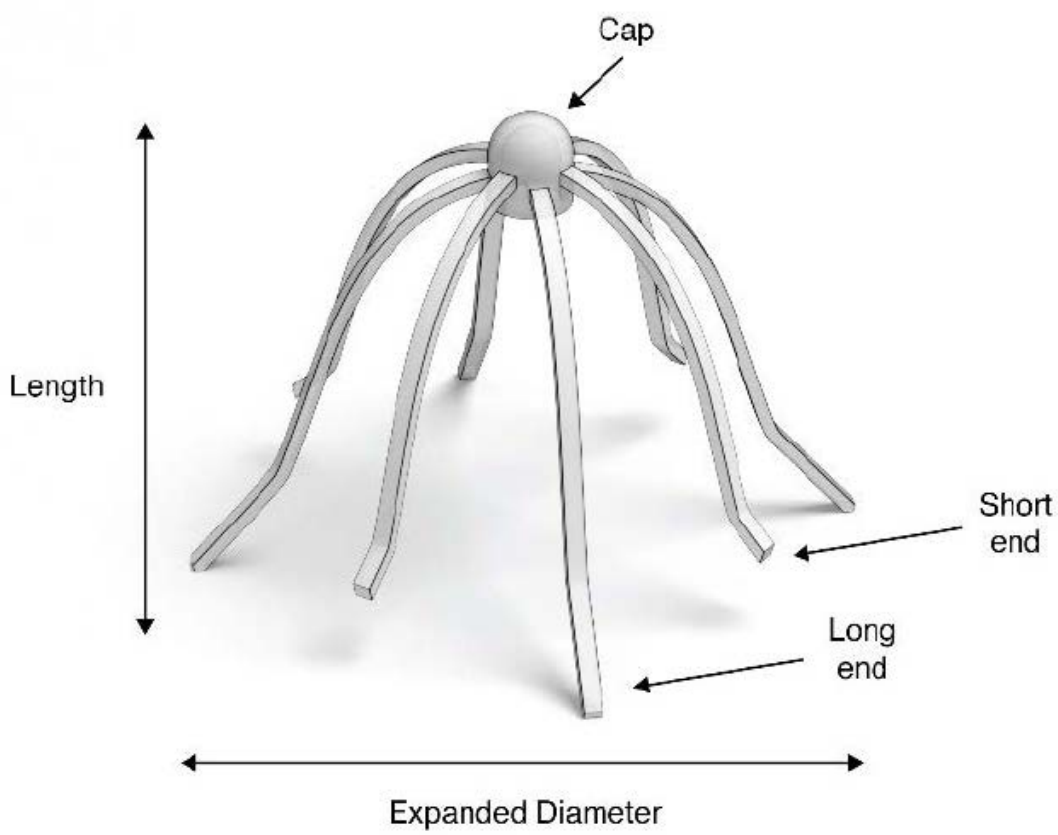
- Ongoing research by FDA into realistic nasal and respiratory models may have application for some of these devices.
- “Soft mist inhalers” such as the one mentioned present research opportunities for FDA:
  - aerodynamic particle size distribution with an impactor
  - spray velocity and plume geometry
  - regional drug deposition (mouth-throat)
  - computational fluid dynamics modeling

Patient Perception/Human Factors

- FDA has ongoing research on patient perception of inhaler resistance with different devices, which has broad application across this product range.
- A new FDA contract has been awarded to evaluate human factors as related to device design for these inhalers (evaluate the impact of identified differences in the user-interface on the substitutability of generic drug-device combination products).

SINUVA

- New Approach to Treating Nasal Polyp Disease
- Approved: 12/08/2017 (NDA 209310)
- API: Mometasone furoate
- Dosage Form/Route: Implant; implantation
- **Sinus Implant**: corticosteroid-eluting implant indicated for the treatment of nasal polyps in patients ≥ 18 years of age who have had ethmoid sinus surgery
- **Complexity**: Complex dosage form (i.e., extended release implant); drug-device combination



Ongoing research into drug release from polymeric substrates

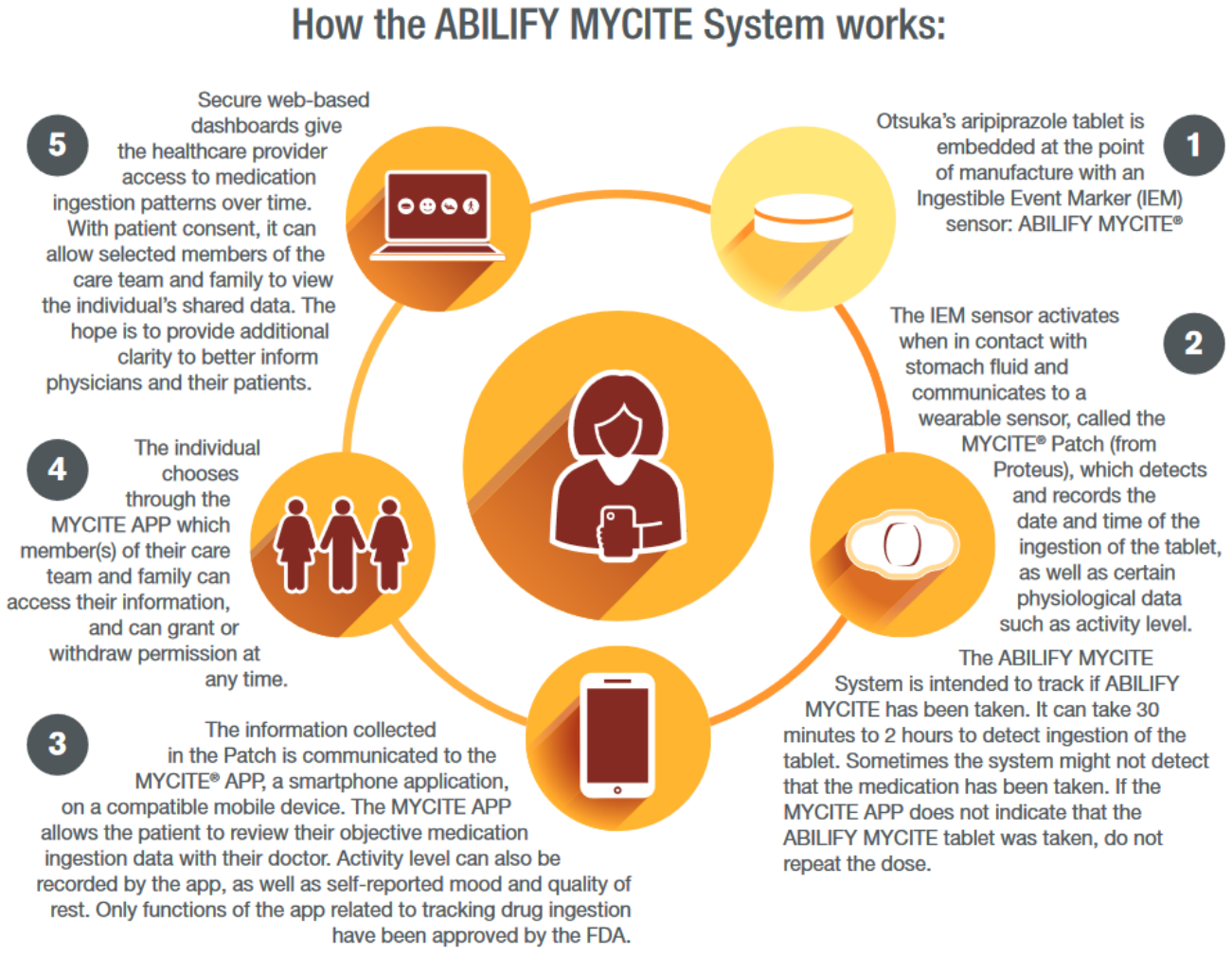
- FDA/ORS has ongoing and completed research projects investigating the nature of drug release from long-acting polymeric substrates such as poly-(DL-lactide-co-glycolide) [PLGA] implants.
- This research may have application to new similar polymeric substrate products such as Sinuva.
- A generic formulation of such a product would need to demonstrate bioequivalence, e.g., comparative drug release and comparative substrate dissolution characteristics.

ESKATA

- New Product to treat raised seborrheic keratoses
- Approved: 12/2017 (NDA 209305)
- API: Hydrogen peroxide, 40% (w/w)
- Dosage Form/Route: Topical solution delivered through pen
- For Topical Use, to be administered by a healthcare provider
- **Complexity**: Drug-device combination; Topical application of caustic solution

Smart Pill ABILIFY MYCITE

- First digital ingestion tracking system approved (NDA 207202) in the U.S.
- Approved: 11/13/2017
- API: ARIPIPRAZOLE
- Dosage Form/Route: TABLET;ORAL
- **Indication:** Treatment of adults with schizophrenia; bipolar I disorder; major depressive disorder
- **Complexity:** Drug-device combination



Research Vehicles for Understanding Drug/Device Interaction

- Grants
- Contracts
- FDA laboratories
  - CDER
  - CDRH
- Partnering with stakeholders
- Review of incoming submissions

Future User Interface Developments

- A wider range of ways to interact with patients is emerging
  - Apps, displays, voice recognition, wireless interface with other device
- The claims that appear in the RLD label about these interfaces will impact ANDA development and evaluation
- FDA should learn from the experience across all products to identify the critical attributes of these interfaces that effect generic drug substitution

Conclusions

- More and more products are being developed to address healthcare needs that are combination drug-device products
- Some of these products are “complex” in nature and relatively difficult to develop a generic product due to a variety of factors
- FDA scientists respond to this challenge by investigating drug and device parameters that allow for a determination of therapeutic bioequivalence and ANDA approvals to allow generic competition and drug accessibility for the American public.

Future challenges

- New drug products approved continue to present challenges to FDA's generic drug research program.
- FDA's scientists work to solve these in concert with our academic partners and provide answers to industry.
- FDA and academic partners disseminate information from this research program in the form of publications, product specific and general guidance documents.
- In addition, we meet with interested and invested industry in pre-ANDA meetings and respond to controlled correspondence to diligently answer questions about product development.

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