This presentation is subject to change pending the devices we can obtain for session. This would only affect slides 22-24, 26-27. The concepts will remain the same only the devices themselves may need to be changed.

Drug-Device Combination Product Development Simulation

Drug-Device Combination Product 101
Session #5
May 10, 2023
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www.fda.gov

Overview

- Definitions
- Design considerations
- Autoinjectors
- Draft Guidance for comparative analyses (CA)
- Flow chart
- Device for evaluation
- Worksheets

ANDA Drug-Device Regulatory Pathway

- A generic drug product is the same as the reference listed drug (RLD) with respect to the active ingredient(s), conditions of use, route of administration, dosage form, strength, and labeling (with certain permissible differences) and is bioequivalent to the RLD.
- An ANDA may not be submitted if clinical investigations are necessary to establish the safety and effectiveness of the proposed drug product.

Combination Product: 21 CFR 3.2(e)

A combination product has:

1. Components that are physically, chemically, or otherwise combined
2. Components that are packaged together
3. Components that are separately provided but specifically labeled for use together

Types: 9 classifications

1. Convenience Kit or Co-Package

2. Prefilled Drug Delivery Device/ System

3. Device Coated/ Impregnated/ Otherwise Combined with Drug

Sinuva Nasal Implant

Hormonal Vaginal Ring

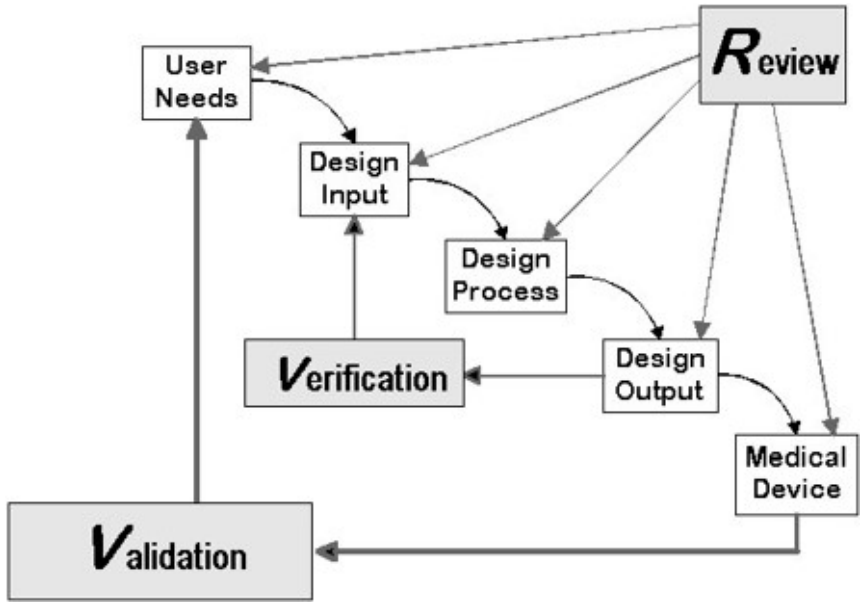
4. Possible Combinations Based on Cross Labeling of Separate Products

https://www.fda.gov/combination-products/about-combination-products/combination-product-definition-combination-product-types

Combination Product

A drug/device combination product is subject to design controls (21 CFR 820) regardless of intended regulatory pathway

- Design inputs/outputs - Requirements for a combination product based on user needs
- Verification – Testing demonstrating device meets the design inputs
- Validation – Testing demonstrating the to be marketed device meets the intended use



https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-guides/design-controls

General Recommendations

1. Identify major design features
2. Use available resources to demonstrate functionality
    a) FDA Guidance documents
    b) FDA recognized consensus standards
3. Confirm the individual components function as intended, do the sum of the parts perform as expected?

Autoinjectors

Definition Autoinjector

CFR 880.6920

- A device that uses a spring-loaded mechanism to drive a hypodermic needle into a patient to a predetermined depth below the skin surface.
- **Another definition**[1]: a device for injecting oneself with a single, preloaded dose of a drug that typically consists of a spring-loaded syringe activated when the device is pushed firmly against the body
  - nonelectrically-powered
  - mechanically-operated
  - method of injecting a drug dose from a cartridge, reservoir, or syringe through a manually-inserted single lumen hypodermic needle

[1] https://www.merriam-webster.com/dictionary/auto-injector

Examples of drugs for use with an autoinjector device

Drug	Route	Indication
Atropine	IM	Nerve agent poisoning
Diazepam	IM	Seizures
Midazolam	IM	Seizures
Epinephrine	IM	Anaphylaxis
Methotrexate	SC	Rheumatoid arthritis
Naloxone	IM	Opioid overdose
Semaglutide	SC	Type 2 diabetes

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7243406/table/table1-030006052092601 9/?report=objectonly

www.fda.gov

Characteristics of an Autoinjector

- Contains a drug cartridge with an embedded needle for subcutaneous (s.c.) or intramuscular (i.m.) injection.
- Can be delivered slowly across a large area (compared to manual i.m. injections) into the muscle, which increases the absorption
- Needle is inside device and not visible to user
- Painless injection
- Power source
  - Spring-loaded
  - Gas powered

General Design Considerations

- Multi-use vs Single-use
- Disposable vs Reusable
- Fixed Dose vs Adjustable variable dose
- 1-step vs. 2-step activation
- Basic safety, quality, and performance
- Environment of use
- Anatomical Location of use
- Intended Population

General Design Considerations-Cont

Consider these in comparison to the reference listed drug

- Size optimization and handling
- Injection speed and duration (time to administer drug ideally 10-15 seconds includes speed, needle insertion, depth, rate of flow)
- Needles
  - Length
  - Needle inner diameter (reduces injection force)
  - Adjustable needle depth settings
- Limited number of tasks
- Modularity of the platform technology (allows customization)

User Interface Design Considerations

- Size and shape of the reference listed drug
- External design attributes and operating principles
  - Dose setting and correction
  - Drug inspection window
  - Color-coded spent indicator
  - Audible/visual/tactile cues
  - Needle extension/safety system
  - Manual/automated injection technology

General Concepts for Mechanism of Action

3 Step Activation:

1. Accelerate the syringe forward, puncturing the injection site
2. Actuate the piston of the syringe, injecting the drug
3. Deploy a shield to cover the needle

Spring-loaded or Gas-powered

Product Quality Considerations

- Need to provide Design Verification testing
- ISO standards such as 11608 can be used during product development
- Provide a ***side-by-side comparison*** of generic and reference listed drug (RLD) performance using the same test methods and conditions to demonstrate comparability
- Need to consider if the device performance will be impacted by the drug product and provide justification why any difference(s) do not impact performance
- During ANDA review, CDER's Office of Pharmaceutical Quality and CDRH will participate in various aspects of device quality/performance review

Product Quality Considerations

- CDRH consult:
  - Device functional performance
  - Biocompatibility of device constituents (non-drug contacting or co-packaged)
  - Sterility of device constituents (Co-packaged)
  - Control Strategy
  - Quality Systems Review

- Verification Testing to determine comparability
  - Delivered volume
  - Activation Force
  - Injection depth
  - Injection time
  - Break-loose and extrusion forces

Special Quality Considerations

- For emergency use the injectors need to have the lowest possible failure rates
- Events occurring within 1/100,000 to 1/1,000,000 detection rate are considered as a remote probability of occurrence.
  - FDA believes the detection of failure to successfully inject in 1/100,000 injection attempts is an appropriate risk management target
- The draft Guidance: *Technical Considerations for Demonstrating Reliability of Emergency-Use Injectors Submitted under a BLA, NDA or ANDA* recommends specifications for successful injection reliability of 99.999% with a 95% level of confidence.

Industry Considerations for Device Selection

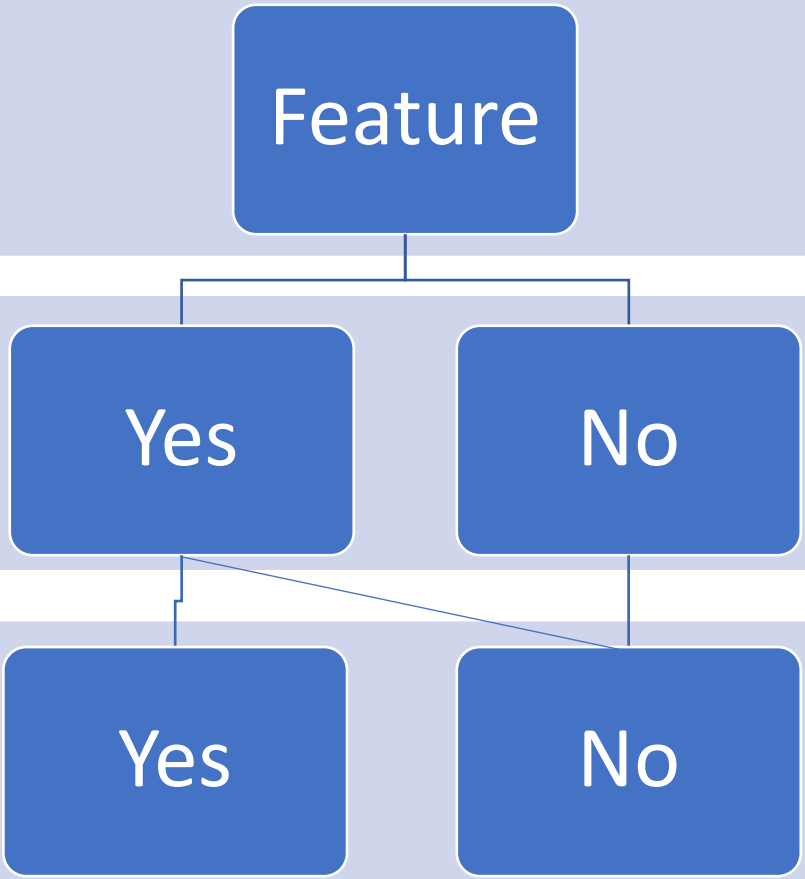
- Suitability
  - Identify design features of the RLD-User Interface that are critical to safe and effective use
  - Are there “unmet needs” / product complaints associated with the RLD?
  - Consider changes to the landscape since the RLD was approved
- Technical Risk, Project Risk, and Regulatory considerations
  - Established device design
  - Will additional information or data (e.g., a comparative human factors study) be needed to support differences in the user interface
  - Changes to the standards or regulations that apply
- Availability
  - Licensing restrictions
  - Drug exclusivities
- Cost

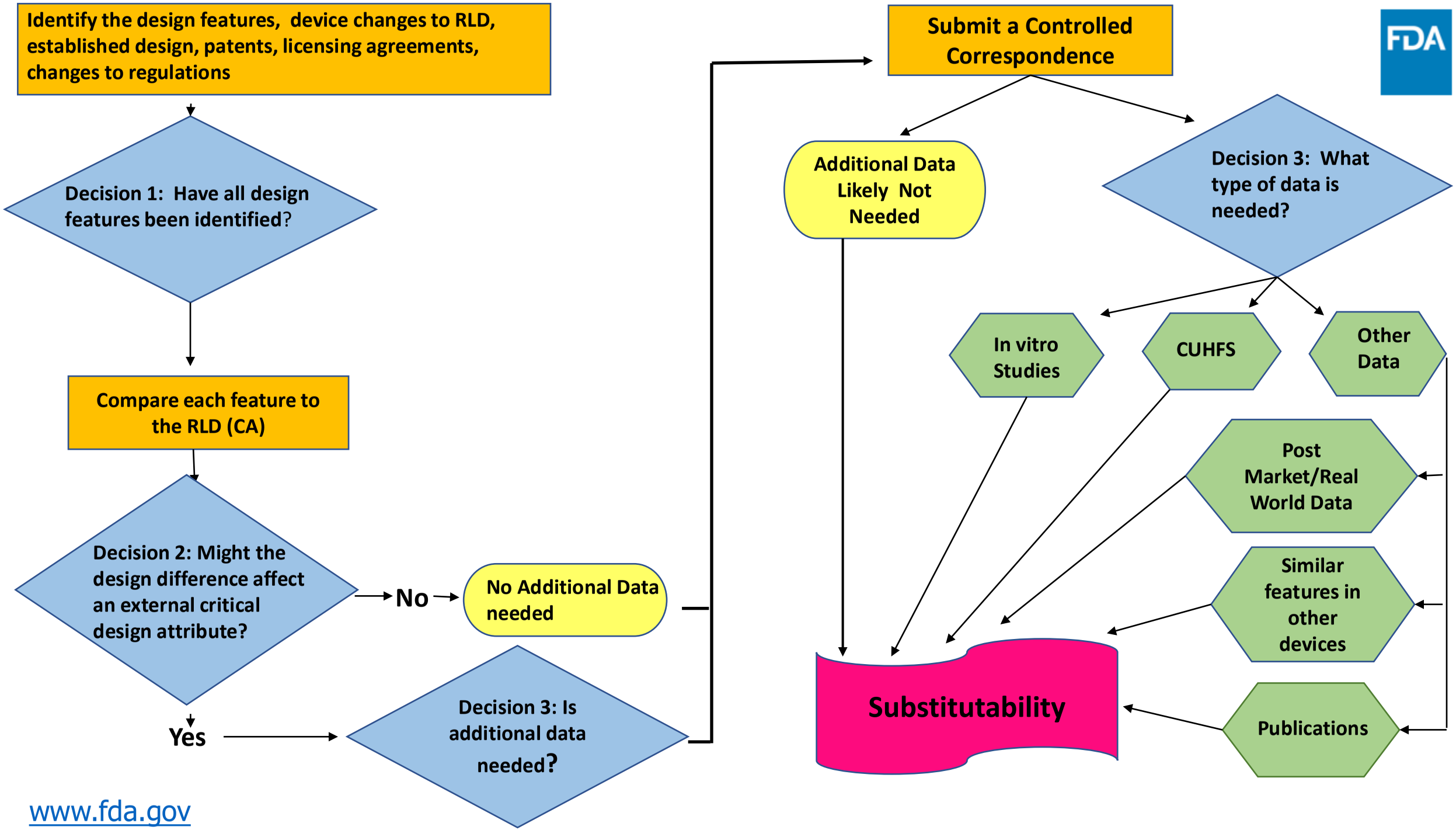
High Level Overview of CA Considerations for Device Selection

External Design Feature (identify each feature)

May Affect an External Critical Design Attribute

Create a Difference in Labeling




Identify the design features, device changes to RLD, established design, patents, licensing agreements, changes to regulations
Decision 1: Have all design features been identified?
Compare each feature to the RLD (CA)
Decision 2: Might the design difference affect an external critical design attribute?
No
No Additional Data needed
Yes
Decision 3: Is additional data needed?
Submit a Controlled Correspondence
Additional Data Likely Not Needed
Decision 3: What type of data is needed?
In vitro Studies
CUHFS
Other Data
Post Market/Real World Data
Similar features in other devices
Publications
Substitutability
FDA

www.fda.gov

Developing a Fictional Generic Referencing RLD "StatDose"

RLD Product


Blue Button
Syringe Cartridges
Safety Catch
Carrying Case
Cartridge Pack
STATdose Pen

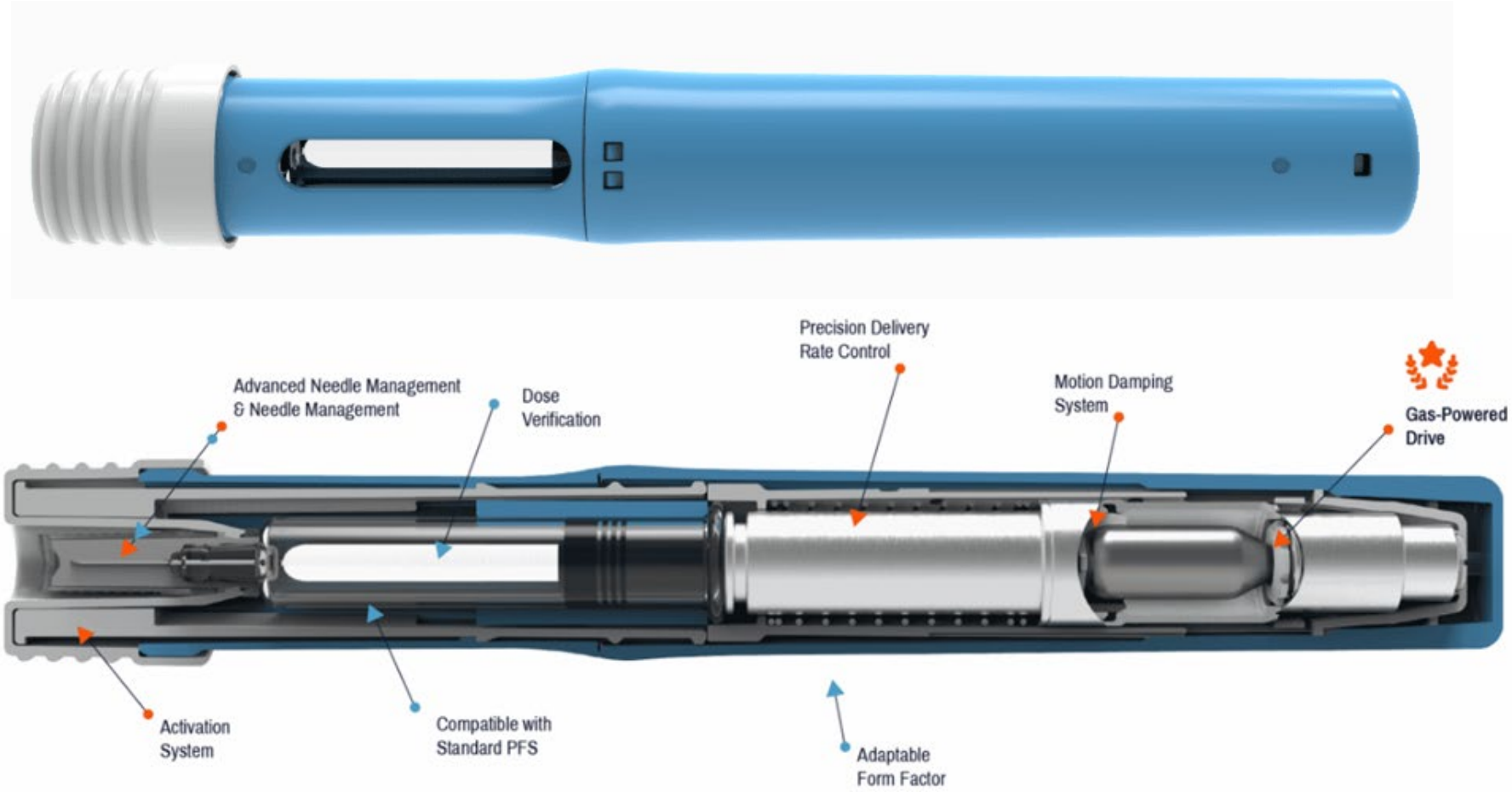
Characteristics of the RLD

- Reusable
- Fixed dose
- Two-piece configuration that requires user to assemble auto-injector
- Two step activation
- Needle Protection System

RLD Product

- Indicated for:
  - Rheumatoid arthritis
  - Migraine
- Intended Use/population:
  - Rheumatoid arthritis:
    - Ages 12 years and older
  - Migraines
    - Age 18 years and older
- Environment of Use
  - Home/Daily life environment (non-healthcare setting)

Proposed Generic Device



Altaviz drug Delivery Platform: altaviz.com/autoinjector

Characteristics of the Proposed Generic Device

- Disposable
- Two-step activation
- Subcutaneous delivery - 27 x 1/2 inch needle
- Needle stick protection system
- Gas powered
- Compatible with standard pre-filled syringe (PFS) cartridges
- Sight window

Design Features

Design Feature	RLD	Proposed Generic

Task Analysis

- **Identify** steps necessary to administer the drug product
  - Include all sub-steps
- **Compare** each step to the RLD
  - Does the design difference create different steps for the user?
    - Does the generic increase the number of steps?
    - Does the generic decrease the number of steps?
  - Audible, visual, or tactile clues
  - Ease of performance (e.g., force to remove cap or activate needle protection system)

Design Differences

Differences	May affect external critical design attribute? Y	N	Minor	Other

Device User Interface Design Differences

1. How would you justify the ***minor design differences*** when submitting your ANDA?

2. How would you support the ***"other" design differences*** identified?

User Task

What are ways to demonstrate that the "*other design* difference to the user interface ***doesn't*** introduce a risk that might impact the clinical effect or safety profile of the generic combination product as compared to the RLD when the generic combination product is substituted for the RLD?

Comparative Analyses: Labeling Comparison

- ANDA *should* include comparisons of all labeling components
  - Prescribing information
  - IFU and other patient materials
  - Carton and container labeling
  - On-device label
- Limited to IFU comparison for Pre-ANDA interactions with FDA for device evaluations

Labeling Comparison: Permissible differences

21 CFR 314.94(a)(8)(iv):

"Comparison of approved and proposed labeling. A side-by-side comparison of the applicant's proposed labeling including, if applicable, any Medication Guide required under part 208 of this chapter with the approved labeling for the reference listed drug with all differences annotated and explained. Labeling (including the container label, package insert, and, if applicable, Medication Guide) proposed for the drug product must be the same as the labeling approved for the reference listed drug, except for ***changes required because of differences approved under a petition filed under § 314.93 or because the drug product and the reference listed drug are produced or distributed by different manufacturers.*** Such differences between the applicant's proposed labeling and labeling approved for the reference listed drug may include differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(5)(F) of the Federal Food, Drug, and Cosmetic Act."

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=314.94

Labeling Changes

Language in the Comparative Analyses Guidance: *Differences that stem from permissible differences in design between the user interface for the proposed generic combination product and its RLD may fall within the scope of permissible differences in labeling for a product approved under an ANDA*

- Do the design differences require changes to the labeling?
  - Different images
  - Change in the user steps
- Are these changes acceptable under 21 CFR 314.94(a)(8)(iv)

Resources

- *Principles of Premarket Pathways for Combination Products:* https://www.fda.gov/media/119958/download
- *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*: https://www.fda.gov/media/102349/download
- *Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products*: https://www.fda.gov/media/76403/download
- *Transdermal and Topical Systems- Product Development and Quality Considerations*: https://www.fda.gov/media/132674/download
- *Requesting FDA Feedback on Combination Products*: https://www.fda.gov/media/133768/download
- *Nasal Spray and Inhalation Solution, Suspension, and Spray Frug Products –Chemistry, Manufacturing, and Controls Documentation:* https://www.fda.gov/files/drugs/published/Nasal-Spray-and-Inhalation-Solution--Suspension--and-Drug-Products.pdf
- *Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Products – Quality Consideration*: https://www.fda.gov/media/70851/download
- *Integration of Dose-Counting Mechanisms into MDI Drug Products*. https://www.fda.gov/media/71073/download
- *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development*: http://www.fda.gov/media/70851/download
- *Technical Considerations for Demonstrating Reliability of Emergency-Use Injectors Submitted under a BLA, NDA or ANDA*: https://www.fda.gov/media/137158/download
- *Glass Syringes for Delivering Drug and Biological Products: Technical Information to Supplement International Organization for Standardization (ISO) Standard 11040-4*: https://www.fda.gov/media/85748/download

Acknowledgements

Thank you to our FDA and Industry Session Planners and Moderators

Tzach Bachar, MS - Director, Regulatory Affairs, Padagis Pharm.
Meenal Chavan, PhD - Chemist, DIMRP III, OLDP, OPQ, CDER, FDA
Jason Flint, PhD -Associate Director of Human Factors, DMEPA-I, OMEPRM, OSE, CDER, FDA
Viral Jogani, MPharm, PhD -GM (R&D) – FR&D, Sun Pharm. Ind. Ltd.
Kristina Lauritsen, PhD -Combination Product Policy Advisor, PJO, OEP, CDER, FDA
Yili Li, PhD- Senior Pharmaceutical Quality Assessor, DLBP I, OLDP, OPQ, CDER, FDA
Michelle Lin, MD -Senior Physician, DCR, OSCE, OGD, CDER, FDA
Claire McDiarmid, MS -Senior Director, Viatris Global Development, Viatris
Ripen Misri, PhD -Director, Co-Development, Apotex Pharm.
Srinivas Naidu, Meng -Senior GM (R&D) – Packaging and Medical Devices, Sun Pharm. Ind. Ltd.
Satyashodhan Patil, BE -Deputy GM (R&D), Device Development (Global Market), Sun Pharm. Ind. Ltd.
Ifeanyi U. Uwemedimo, PhD -Biomedical Engineer/Senior Reviewer, OCP, OCPP, OC, FDA
Kimberly Witzmann, MD -Deputy Director, OSCE, OGD, CDER, FDA
Brandon Wood, BS -Director, Regulatory Affairs, Teva Pharm.

SPECIAL THANK YOU!

Katharine Feibus, MD Team Lead, Team, D/DPT1/ORS/OGD/CDER

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