Public Hearing Comment Regarding Devices Proposed for a New Use with and Approved, Marketed Drug

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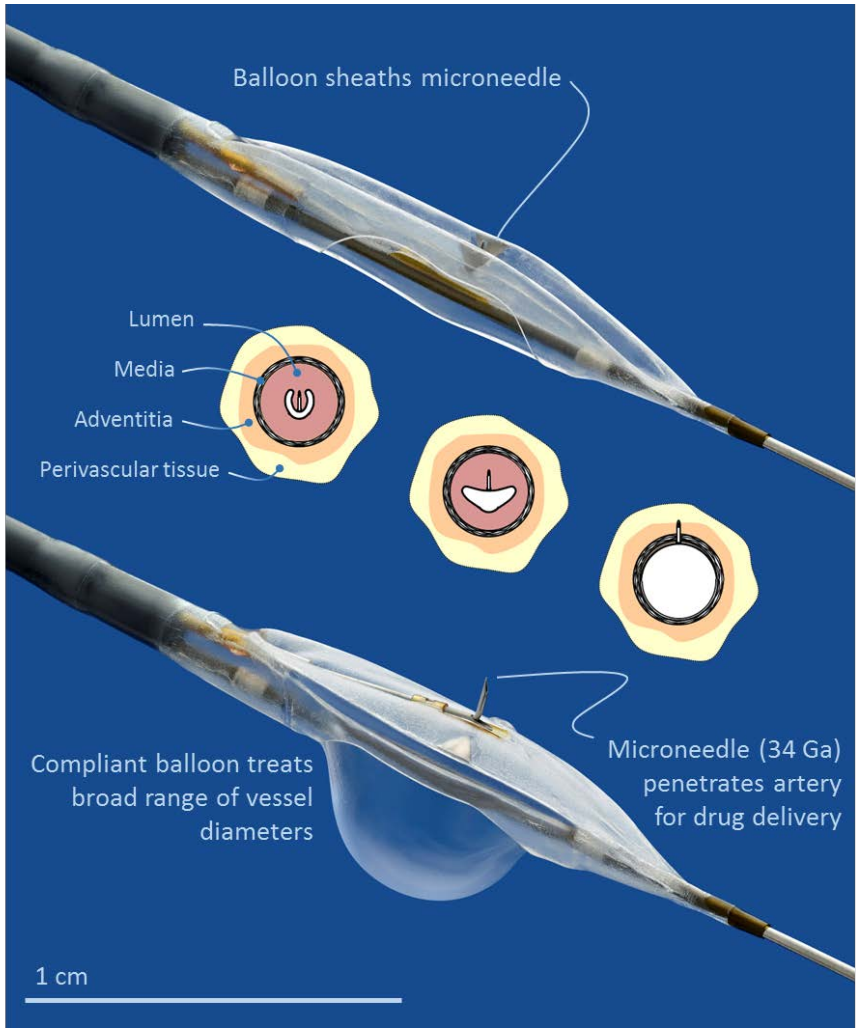
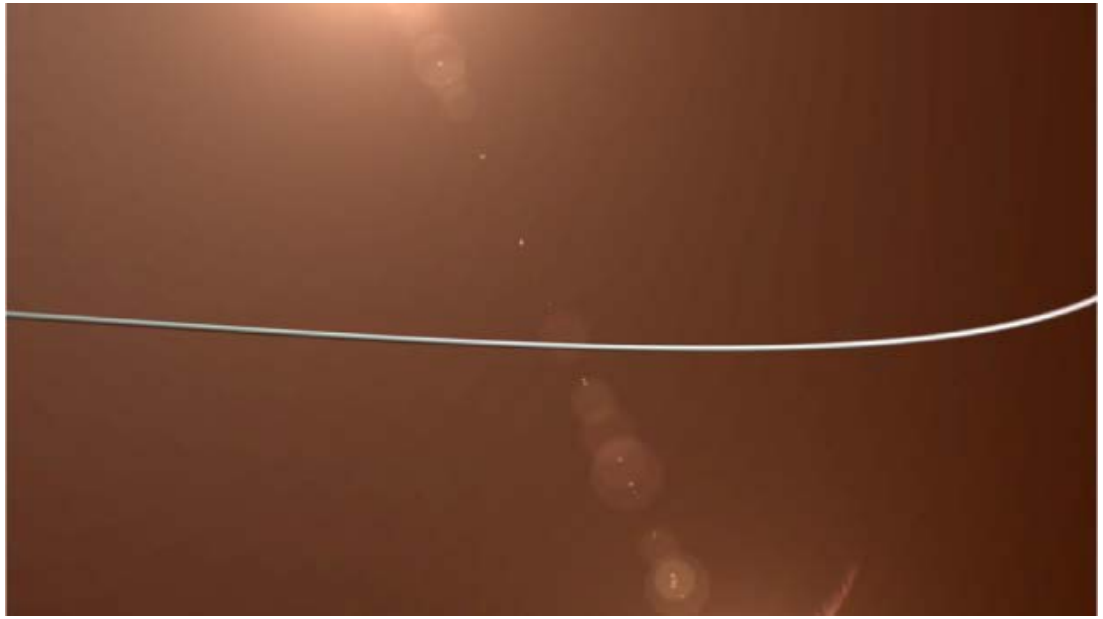
Introduction

- Wish to congratulate the Agency on confronting an issue that is important to medicine and development of novel therapies using known therapeutic agents
- Clearly, the DRD process is intended to address the need for greater clarity and promote consistent expectations
- In this presentation:
  - Provide background/case study example of where DRD would clearly apply
  - Comment on how to establish risk profile (Class II or Class III DRD)
  - Comment on application of evidence burden (substantial evidence or reasonable assurance)
  - Comment on user confusion and medication error/use error factor
  - Comment on identification of generic drugs within DRD labeling
  - Comment on DRD proposal as it relates to CDRH regulatory science priorities

Background/Case Study:
Bullfrog® Micro-Infusion of Dexamethasone





Background/Case Study: Bullfrog® Micro-Infusion of Dexamethasone

- The device is 510(k) cleared
  - Intended use: In selective areas of peripheral and coronary vessels, the Bullfrog Micro-Infusion Device is intended for the infusion of diagnostic and therapeutic agents into the vessel wall and perivascular area, or intraluminally.
- Clinical trials with legally marketed drugs (such as dexamethasone) delivered by this route have been completed or are under way
- Generic drug manufacturers lack interest in labeling updates or changes
  - As a group: Any new liability weighs against limited upside
  - Individually: No one generic manufacturer would step up because of the reality of immediate substitution
- The DRD process is directly applicable to this technology

Response to Question 1 (slide 1 of 2): DRDs Are Not Inherently Class III

Q1: Are there public health, scientific, regulatory, or legal issues that should be considered with respect to this potential approach for DRDs? If so, are there ways to address those issues?

- DRDs would not likely be substantially equivalent (NSE) to legally marketed predicate devices (since drug aspect would be new and raise different questions of safety or effectiveness)
- Thus, DRD proposal suggests PMA route would generally be the appropriate device marketing application
- However, PMA should only be for Class III:
  - support or sustain human life
  - substantial importance in preventing impairment of human health
  - present a potential, unreasonable risk of injury

Response to Question 1 (slide 2 of 2): DRDs Are Not Inherently Class III

Q1: Are there public health, scientific, regulatory, or legal issues that should be considered with respect to this potential approach for DRDs? If so, are there ways to address those issues?

- Nothing inherent to DRDs leads to automatic Class III
- The known safety and risk profile of the drug should be considered
- DRDs should be classified based on risk:
  - Class III DRDs (high risk), which require general controls and a PMA
  - Class II DRDs (moderate to high risk), which require general and special controls, and traditional or de novo 510(k)
  - Class I DRDs (low to moderate risk), which require general controls

Response to Question 2 (slide 1 of 4): Standards of Evidence Should Be Appropriate

Q2: Is each of the factors and submission considerations described above appropriate? If not, why not? What modifications would you propose and why? Are there additional factors or submission considerations that the Agency should take into account? Please provide examples to illustrate your view.

- In the DRD proposal, the standard of evidence for demonstrating S&E is Substantial Evidence of safety and effectiveness (the NDA standard, since this is the standard that applies to new uses of drugs) rather than Reasonable Assurance of safety and effectiveness (the device standard)
- While these standards have the same intent, they appear to be implemented differently
- At a minimum, the quantity of clinical evidence required is not equivalent
  - "Substantial evidence" requires two adequate and well controlled clinical trials, with relevant exceptions such as with label expansions
  - "Reasonable assurance" has no such requirement, and can often be determined with real-world evidence or non-randomized trials in comparison to performance goals
- Distinctly different types of endpoint data are allowed by the two standards
  - "Substantial evidence" requires clinical outcome measures (feel/function/survival)
  - "Reasonable assurance" does not require clinical outcome measures, but rather often relies on physical or mechanical endpoints

Response to Question 2 (slide 2 of 4): Standards of Evidence Should Be Appropriate

Q2: Is each of the factors and submission considerations described above appropriate? If not, why not? What modifications would you propose and why? Are there additional factors or submission considerations that the Agency should take into account? Please provide examples to illustrate your view.

- In some cases of drug/device combo products with device PMOA, the intent of the drug is to preserve the device outcome, e.g.
  - Preserving device functionality (coated pacemaker leads, drug-eluting stents)
  - Preserving the result created by the device (drug-coated angioplasty balloons)
- This is not limited to device/drug combination products; in some cases the drug can be unlinked from the device to accomplish the same effect while allowing more patient-specific treatment
- Primary approval outcomes for device/drug combos (e.g. primary arterial patency) have not been linked to standard “substantial evidence” outcomes (feel, function, survival)
- This should be preserved whether the device and drug are combined or separate
- In other applications where the drug provides therapeutic effect independent of other procedural (i.e. surgical) benefit, then drug endpoints may more easily apply (e.g. better delivery of a chemotherapeutic for head/neck cancer patient)

Response to Question 2 (slide 3 of 4): Standards of Evidence Should Be Appropriate

Q2: Is each of the factors and submission considerations described above appropriate? If not, why not? What modifications would you propose and why? Are there additional factors or submission considerations that the Agency should take into account? Please provide examples to illustrate your view.

- The DRD process is about unlocking innovation by device innovators taking older drugs with a long history of safe use, and incrementally changing them
- In regulating DRDs, CDRH should have the flexibility to determine validity of endpoints and use the “reasonable assurance” standard
- At the very least, products with similar medical intent should be afforded the same standard of evidence, including what type of endpoints need to be demonstrated

Response to Question 2 (slide 4 of 4): Standards of Evidence Should Be Appropriate

Q2: Is each of the factors and submission considerations described above appropriate? If not, why not? What modifications would you propose and why? Are there additional factors or submission considerations that the Agency should take into account? Please provide examples to illustrate your view.

Other factors:

- If the evidence standard of "substantial evidence of safety and effectiveness" prevails, will the following drug regulations also apply to DRDs?
  - Breakthrough designation
  - Fast-track approval
  - Priority review
  - Exclusivity provisions
    - What happens when a DRD includes IP for a new indication of an old drug?
    - Would Orange Book references change?

Response to Question 4: User Confusion, Medication Error/Use Errors

Q4: With respect to the user confusion and medication error/use error factor, are there other issues that DRD sponsors should address or that FDA should consider, to ensure that the DRD labeling provides adequate directions for the new use with the approved, marketed drug, without approval of conforming labeling changes for the approved, marketed drug? What issues should be considered with respect to promotional activities by the DRD sponsor and/or by any sponsors for the drug being referenced?

- The same level of detail should be provided as exists within the current drug labeling
- This should include supplemental information for each section of the drug labeling where different or new information is available related to the new use, e.g.:
  - Indications and usage
  - Contraindications
  - Warnings and precautions
  - Dosage and administration
  - Adverse reactions
  - Clinical pharmacology

Response to Question 6: Multiple Versions of the Drug/Generics

Q6: When multiple versions of the drug, including generics, are marketed, what challenges exist in identifying which versions of the drug can be used with the DRD? How can DRD sponsors make this information clear to health care providers, pharmacists, and patients?

- For DRDs that depend on an injectable solution, we are confident that generics all keep to the same solution
- As all ANDAs that reference a single NDA call out the generic name of the drug, the DRD sponsor should simply be able to reference the generic name as well
- If there are specific excipients that should be excluded from the DRD labeling, they should be called out in the Dosage Forms and Strengths section of the Drug Supplemental Label

Application of CDRH Regulatory Science Priorities

- The following CDRH Regulatory Science Priorities (2017) should be considered when drafting DRD rules
  - Leverage “Big Data” for regulatory decision-making
  - Leverage real-world evidence and employ evidence synthesis across multiple domains in regulatory decision-making
  - Develop methods and tools to improve and streamline clinical trial design
- The appropriate standards of evidence (reasonable assurance vs. substantial evidence) should incorporate the guidance offered by these priorities

Summary

- DRDs can be a valuable tool in advancing medicine without unnecessary or cumbersome regulatory barriers
- De Novo 510(k) should be considered with Class II DRDs
- Standards of evidence should be appropriate, and should allow for “reasonable assurance of S&E” standard to be applied
- CDRH Regulatory Science Priorities should be strongly considered during the DRD policy