OPHTHALMIC DRUG-DEVICE COMBINATION PRODUCTS - QUALITY PERSPECTIVE

Poonam Chopra, PhD
Senior Review Chemist, Division of Product Quality Assessment VIII (DPQA VIII)
Office of Product Quality Assessment II (OPQA II), Office of Pharmaceutical Quality (OPQ)
CDER|FDA

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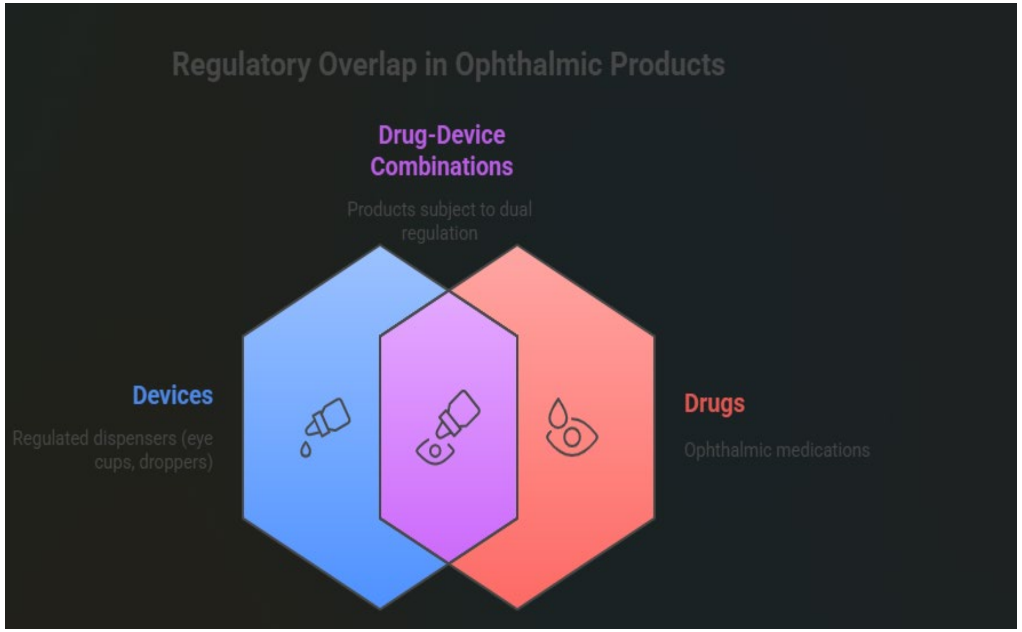
Everyone deserves confidence in their *next* dose of medicine.

Pharmaceutical quality assures the availability, safety, and efficacy of *every* dose.

Outline

- Objective
- Regulatory Framework
- Quality Requirements



Objectives

Discuss various aspects of quality requirements for generic ophthalmic drug-device combination products

ANDA applicants are better equipped to submit quality information

Reduces assessment time and in turn will lead to faster approval of generic ophthalmic drug-device combination drug products

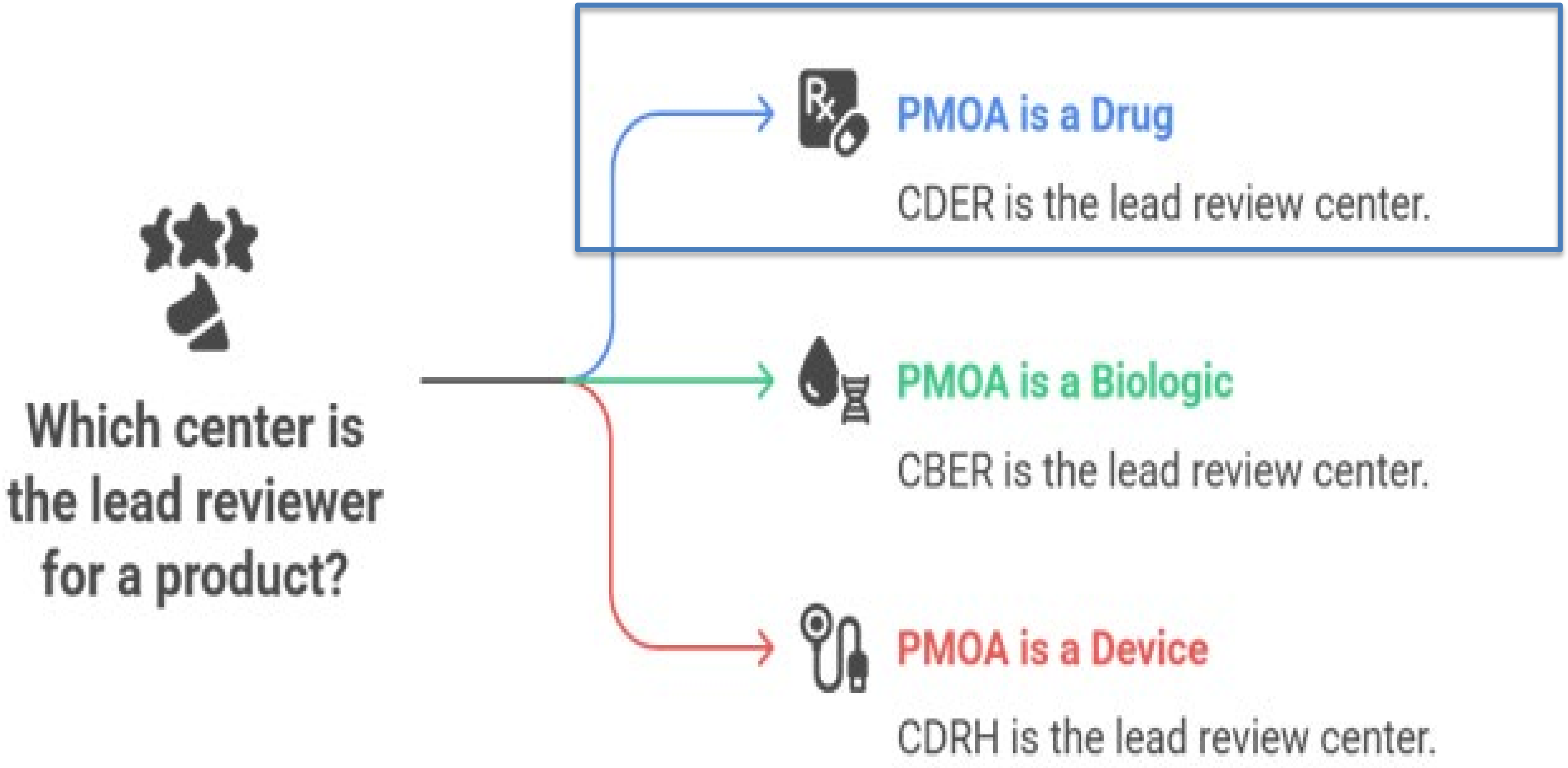
Regulatory Framework for Drug-Led Combination Products

- Drug-Led Combination Products (Drug PMOA): Drug component provides the primary mode of action (PMOA)

  Core Requirements:

  - 21 CFR 314.94(a)(9)(iv) – Q1/Q2 requirement for the drug constituent part
  - USP <771> Ophthalmic Products – Quality Tests
  - 21 CFR 210 and 211 – Current Good Manufacturing Practice (cGMP) for Drugs
  - 21 CFR Part 4 – Regulation of Combination Products
  - 21 CFR Part 820 – Quality System Regulation (typically, assessed during post approval inspection)
    - Generally, Not required to submit detailed QSR documentation as part of initial ANDA submission
    - NO EXEMPTION from QSR requirements

Assessment Assignment based on Primary Mode of Action (PMOA)



Quality Attributes for Ophthalmic Drug-Device Combination Products (Drug PMOA)

- Quality assessment of an ophthalmic drug device combination product can be divided into two parts:
  - CDER/OPQ Assessment:
    - Quality attributes pertaining to drug substance, drug product, microbiology, manufacturing process and facilities.
    - Assessment of Low Risk droptainer, bottles/caps etc.
  - CDRH Assessment (complex and high-risk devices):
    - DP Quality assessor consults for functional attributes → Performance testing
    - Facility assessor consults → Device Quality Systems/Facilities Assessment (21 CFR 820)

Quality Attributes for Ophthalmic Drug-Device Combination Products (Drug PMOA) contd.

http://www.pccarx.com/products/Bottle,-/DROPTAINER,-15-ML-WHITE-OPAQUE/35-2177/DEVICES

https://www.google.com/search?sca_esv=f3abac6c97ce75c7&udm=2&fbs=AIIjpHxU7SXXniUZfeShr2fp4giZjSkgYzz55RrRWAIniWd7tzPwkE1KJWcRvaH01DXIWOFp4UhuzIxwLSKiE1xF1ZWEqjZkRe51b9jK6AN71wXGlgfMAjhu_nxvE2OTRS_qJ8TIbYtQEGwTAxcUtLYkJKqs6wYgmh8dEhSDi7piZRVgyJZhh8u7ig2JpG9aWk9wwgD1_NBTB6UetozDfKxaC98Rbg&q=MDPF+aptar+CCS&sa=X&ved=2ahUKEwjgnIWxlPCPAxX4VvEDHcnMMZsQtKgLegQIFRAB&biw=1920&bih=979&dpr=1#vhid=2dwiPZcSc7AeQM&vssid=mosaic

Multidose Preservative-Free Squeeze Bottles

https://www.google.com/search?q=Novelia+MDPF&safe=active&hl=en&biw=1920&bih=1057&sxsrf=ALeKk01K1RPSIycHOOZSDmwqxoiRKCDduA:1605549203614&tbm=isch&source=iu&ictx=1&fir=QzaModktTHRbzM%252C1BgKTflZxbLjvM%252C_&vet=1&usg=AI4_-kQxwaXe-wH760Yi00sqVdMb7MC8dA&sa=X&ved=2ahUKEwjQgc3v0IftAhWsFlkFHX4wCd0Q9QF6BAgKEBg#imgrc=QzaModktTHRbzM

Simple Device: Bottle/Cap/Droptainer

Complex Device: Multidose Preservative Free

Quality Attributes for Ophthalmic Drug-Device Combination Products (Drug PMOA) contd.

- Drug component
  - Critical Quality Attributes (CQAs)
    - USP<771> OPHTHALMIC PRODUCTS – QUALITY TESTS
    - https://www.youtube.com/watch?v=-x25vGQP1j0&t=15s
    - https://www.youtube.com/watch?v=NLPQXWKoqtc
- Device component
  - Functional Attributes/Performance Testing (CQAs)
    - Container Content (Minimum Fill, USP<755>)
    - Drop size/Weight
    - Sterility (USP<71>)
    - Extractable and Leachables
    - Torque
- FDA Draft Guidance “Quality Considerations for Topical Ophthalmic Drug Products Guidance for Industry”

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/quality-considerations-topical-ophthalmic-drug-products

Quality Attributes for Ophthalmic Drug-Device Combination Products (Drug PMOA) contd.

- **Drop Size/Weight Study (for multidose containers):**
  - For all topical ophthalmic drug products, FDA recommends that the **drop size** in a multidose CCS be between 20 and 70 microliters.
  - *For ANDAs, the drop size (one-time study) in a multidose CCS should be between 20 and 70 microliters and within ±10% of the drop size for the reference listed drug (RLD).*
  - *For any deviations from the RLD, the generic (ANDA) applicant should provide a justification to demonstrate that there will be a similar number of delivered doses as the RLD.*
  - Drop volume/drop weight should be measured and included in the ANDA submission.
  - Testing conditions, such as **the number of drops** in the container and its **holding angle during dosing**, should be included in the ANDA submission.

Additional CQAs for Ophthalmic Drug-Device Combination Products (Assessed by CDER/OPQ)

1. Device Description Documentation

- Description of device constituent design, including any novel features and/or functionalities.
- Drawings /diagrams of the device
- Describe the principles of operation of your device

2. AAO Recommended Color Codes for Caps and Labels

- For a uniform color-coding system, FDA recommends that manufacturers follow the American Academy of Ophthalmology's (AAO) Color Codes for Topical Ocular Medications.
- Drug products that do not fall into any of the listed classes should have a white cap (even if the RLD cap color is not white).

The American Academy of Ophthalmology recommends to the FDA and the pharmaceutical industry that a uniform color-coding system for the caps and labels of all topical ocular medications be established. No other topical medications should carry the same color.

The recommended color codes are:

Class	Color	Pantone Number
Adrenergic agonist combinations	Light Green	373C
Adrenergic agonists	Purple	2583
Anti-infectives	Tan	467
Anti-inflammatory, non-steroidal	Gray	4
Anti-inflammatory, steroids	Pink	197
Anti-inflammatory, immunomodulators	Olive Green	5763C
Beta-blocker combinations	Dark Blue	281
Beta-blockers	Yellow	Yellow C
Carbonic anhydrase inhibitors	Orange	1585
Cytotoxic	Black	6
Miotics	Dark Green	348
Mydriatics and cycloplegics	Red	1797
Prostaglandin analogues	Turquoise	326

http://www.aao.org/about/policies/color-codes-topical-ocular-medications

Additional CQAs for Ophthalmic Drug-Device Combination Products (Assessed by CDER/OPQ)

3. <u>Tamper-Resistant Packaging</u>

- 21 CFR 200.50 (a)(3) Ophthalmic preparations and dispensers, the containers of ophthalmic preparations shall be **<u>sterile</u>** at the time of filling and closing.

- The container or individual carton shall be so **<u>sealed that the contents cannot be used without destroying the seal.</u>** The packaging and labelling of ophthalmic preparations that are over-the-counter drugs shall also comply with 211.132 of this chapter on tamper-resistant packaging requirements.

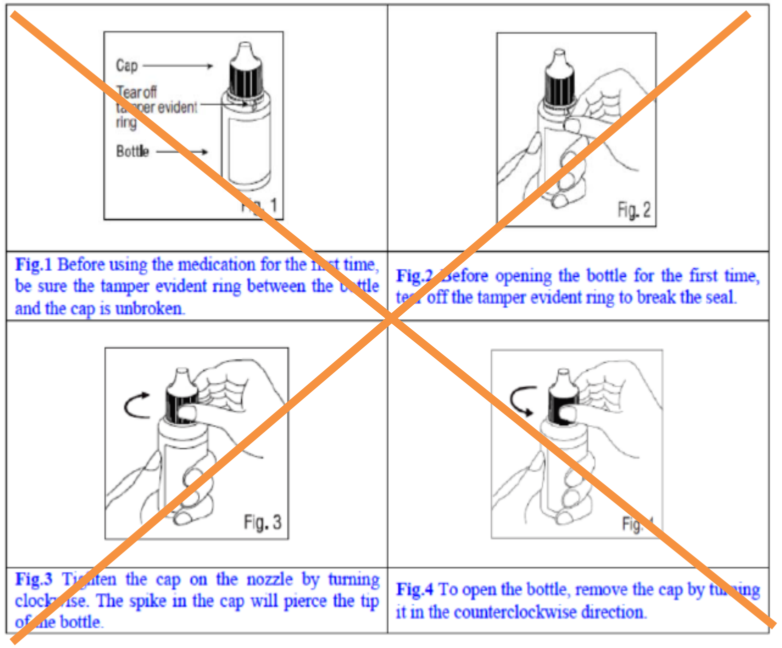
- - USP <659>-Tamper-Evident: A packaging system that may not be accessed without obvious destruction of the seal or some portion of the packaging system.

http://www.pharmtech.com/ophthalmic-drug-packaging-safety-risks-and-patient-acceptability-issues

Additional CQAs for Ophthalmic Drug-Device Combination Products (Assessed by CDER/OPQ)

4. Tip Activation Mechanism

- If container closure tip is sealed until the first opening by the patient (Activation):



Spike design using two-step process is not acceptable. The 2-step activation involves twisting in one direction to puncture the tip and the opposite direction to remove cap.

INSTRUCTIONS FOR USE:

1. Before using the medication for the first time, be sure the tamper evident ring between the bottle and the cap is unbroken (Fig. 1).

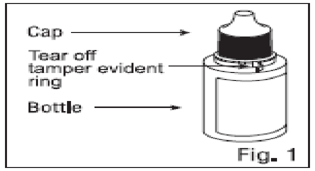


Fig. 1

2. Before opening the bottle for the first time, tear off the tamper evident ring to break the seal (Fig. 2).

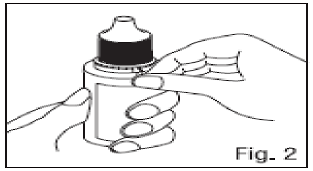


Fig. 2

3. To open the bottle, remove the cap by turning it in the counterclockwise direction (Fig. 3).

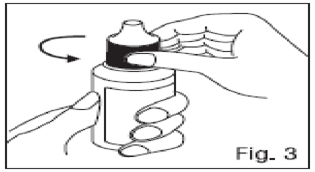


Fig. 3

Single-step activation process involving simple intuitive twisting without removal of cap is acceptable.

Summary

- **Drug-Led Generic Ophthalmic Combination Products (Drug PMOA):**
  - The drug constituent part must comply with 21 CFR 314.94(a)(9)(iv) and 21 CFR Parts 210 and 211
  - Ensure all critical quality attributes of the drug and device constituent parts are evaluated and included in the submission (e.g., USP <771> and FDA Draft Guidance “Quality Considerations for Topical Ophthalmic Drug Products Guidance for Industry”)
  - The device constituent part must comply with 21 CFR Part 4 and Part 820, but detailed QSR documentation is not required for initial ANDA submission, though there is no exemption from QSR requirements
  - Ensure complete documentation in the submission (e.g., Form FDA 356h reflecting combination product status and include device facility information)

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