Therapeutic Equivalence of Ophthalmic Combination Products in Abbreviated New Drug Product Applications (ANDAs)

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Kimberly Witzmann, Deputy Director

Office of Safety and Clinical Evaluation, OGD, FDA

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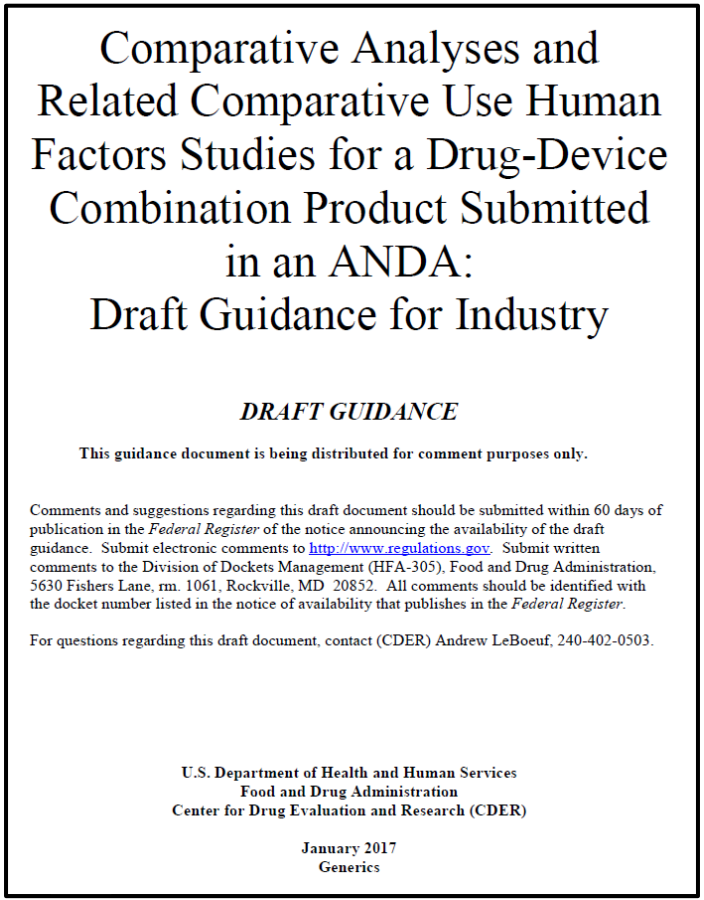
Objectives

- Provide key principles for conducting comparative analyses (CA)
- Describe the impacts of Genus decision for FDA review work
- Review user-interface considerations and features for ophthalmic products
- Discuss examples of user-interface assessment of ophthalmic products in Abbreviated New Drug Applications (ANDAs)

Draft Comparative Analyses Guidance



Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA: Draft Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Andrew LeBoeuf, 240-402-0503.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Generics

Regulatory Framework

- Comparison of the proposed user interface of the generic drug-device combination product to the user interface of the RLD
- All relevant determinations of sameness under section 505(j) are made with respect to the RLD
- When RLD information is unavailable, performing the comparison to the RLD is challenging, but still required
- ANDA applicant-specific questions are addressed in Controlled Correspondences and/or Pre-ANDA product development meetings

Comparative Analyses in ANDAs

- **Therapeutic equivalence**
  > "... can be expected to have the *same clinical effect and safety profile* when administered to patients under the *conditions specified in the labeling*"
- **Same expectations** apply for generic drug-device combination products
  - FDA considers whether end-users can use the generic combination product when it is substituted for the reference listed drug (RLD) without the intervention of the healthcare professional and/or without additional training prior to the use of the generic combination product
- Generic and RLD product do not need to be identical as long as the differences do not preclude approval under an ANDA

General Recommendations

Consider and include all components with which end-users interact when conducting comparative analyses

Physical Comparison

- Visual, auditory, tactile examination of the physical features (size, shape, feedback) of the RLD, compared to those of the delivery device constituent part of the proposed generic combination product

Comparative Task Analysis

- Systematically analyze and compare the sequential activities required for the end-users to use the device and administer the drug product

Labeling Comparison

- Side-by-side, line-by-line comparison of the relevant sections of the prescribing information, instructions for use, and descriptions of the delivery device constituent parts of the generic combination product to its RLD

Assessment of Identified Differences

Consider any identified differences in the context of the *overall risk profile* of the product

- No Differences
- Minor Design Difference
  - If the difference in the user interface of the proposed generic combination product, in comparison to the user interface of the RLD do not affect an external critical design attribute
- Other Design Difference
  - If any aspect of the comparative analyses suggests that difference in the design of the user interface of a proposed combination product as compared to the RLD *may* impact an external critical design attribute that involves administration of the product

Assessment of Identified Differences: Considerations

- Identify and provide adequate justification for **ALL** user interface differences in comparative analyses
- Focus on potential differences in the critical tasks between the RLD and generic drug-device combination product
- Consider context of use

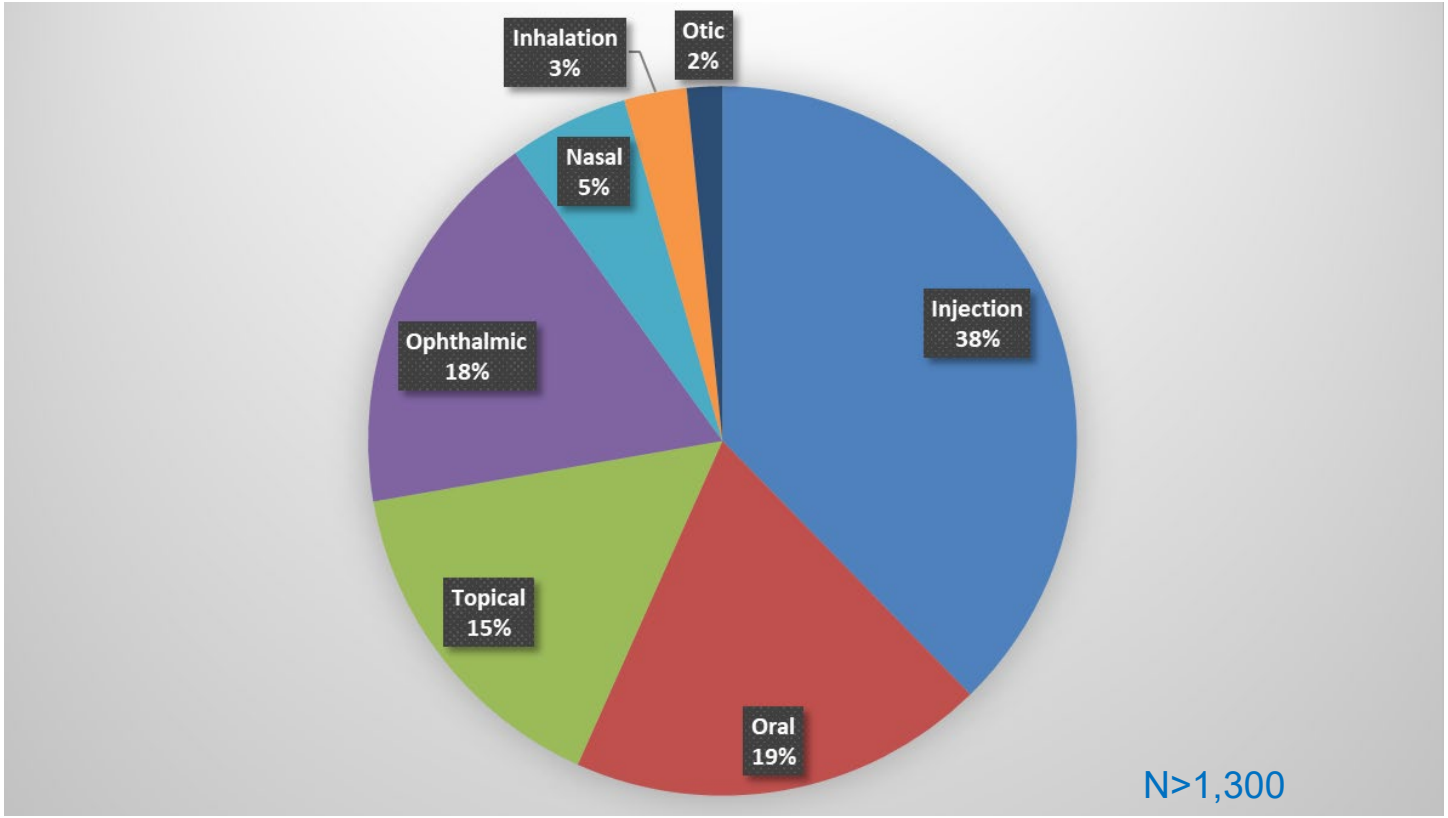
Assessment of Identified Differences: Considerations

Context of use

- Urgency of use: Emergency vs. non-emergency
- Frequency of use: Single use vs. repeated use
- End-user: Patients, caregivers, healthcare professionals
- Environment of use:
  - Clinical: hospital, clinic
  - Nonclinical: home, school, etc.
- Patient population:
  - Dexterity issues (rheumatologic, neuromuscular disorder)
  - Incapacitated (naloxone HCl)

Comparative Analyses and the Genus Experience

Comparative Analyses (CA) by Route of Administration (2018-2025)



Activities post-Genus

- Impacted >100 applications in Tentative Approval (TA) or Complete Response (CR) status
- General Correspondence letters used to update those in TA or CR status of the information needed to evaluate user interface vs. RLD
- ~60 ANDA applications that were in active review status
- These required IR/DRLs requesting Comparative Analyses
- Division of Clinical Review/OGD completed review of submitted CA data on compressed timeline
- Formed a group of reviewers with expertise in ophthalmic products and CA assessments to work on abbreviated timeline, so that GDUFA clocks were not impacted
- Successfully actioned on all ANDAs within the GDUFA clock

Ophthalmic Drug Product Design
User Interface

Ophthalmic User Interface Features

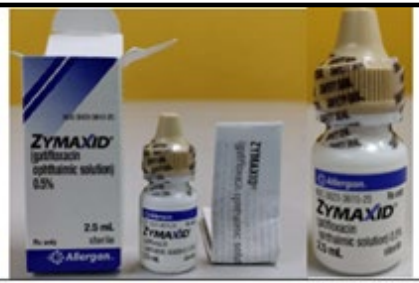
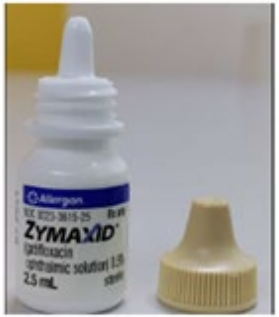
- Often do not include Instructions for Use
- Patient/caregiver administered
- Context of use: chronic and acute use (non-emergency)
- Many tasks are intuitive for users

Ophthalmic User Tasks

1. Remove product from carton
2. Remove/break tamper-evident safety feature
3. Remove Cap
4. Squeeze bottle to deliver prescribed number of drops to affected eye(s)
5. Replace cap

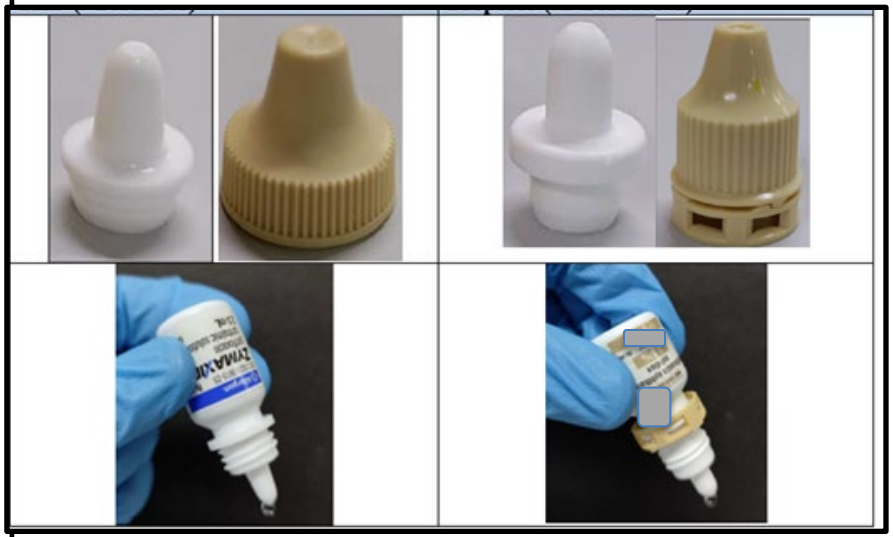
Case Studies: Ophthalmic User Interface Assessment

Example: Tamper-Evident (TE) Differences

RLD	Proposed
	
Nozzle (white) and Cap (tan)	
	

RLD

Proposed



Acceptable

TE Ring User Interface Assessment

- Product does not contain an IFU
- Tasks are self-evident
- Cognitive steps in performing tasks similar
- End-user does not need additional training
- Difference does not impact a critical task

Example: Tamper-Evident Ring

- Brimonidine Tartrate and Timolol Maleate Ophthalmic Solution, 0.2%/0.5%
- Drug Product Review determined that the proposed bottle/cap design was not acceptable "due to a loose tamper-evident ring."
- The difference in the TE feature may impact the safety profile of the proposed product because the quality and functionality of the TE ring cannot be confirmed.
- **Not Acceptable**

RLD

Proposed

2016 Drug Safety Communication

FDA warns consumers about potential risks of using eye drops packaged in bottles with loose safety seals

- Plastic safety seal or tamper-evident ring should stay connected to the bottle neck
- FDA strongly recommends when using tamper-evident rings, the bottle/cap design include a positive-retention mechanism

https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-consumers-about-potential-risks-using-eye-drops-packaged-bottles-loose-safety-seals

Tamper Evident Ring- User Interface

- TE ring security is quality issue and assessed by Drug Product Team in OPQ
- Applicant certifies in writing the ring is secure, and will not pose a safety concern to patients
- For user interface assessment, need confirmation ring is secure
- If quality concerns identified, then user interface impacted, and comparative analyses outcome= inadequate
- Drop size comparison and dose accuracy are not part of Comparative Analyses Review/user interface assessment

Example: Cap Color

RLD label

HOW SUPPLIED: (prednisolone acetate ophthalmic suspension) is supplied in a white, round low-density polyethylene dispenser with a natural low density polyethylene dispensing plug and pink polypropylene cap. Tamper evidence is provided with a shrink band around the closure and neck area of the package.

- Prednisolone Acetate Ophthalmic Suspension USP, 1%
- Consistent with the American Academy of Ophthalmology's (AAO) recommendation for anti-inflammatory steroid drug products, the RLD has a pink cap
- Applicant revised product and "How Supplied" section to reflect pink cap

Before

After

Acceptable

Color Codes for Topical Ocular Medications

- The American Academy of Ophthalmology (AAO) endorses the uniform use of a color-coding system for the caps and labels
- With input from the industry and FDA, the AAO developed a uniform color-coding system
- Help patients distinguish among various medications, thereby minimizing the risk of errors
- Voluntary cooperation and compliance has been very effective

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

Closing Thoughts

- Genus impact means all combination ophthalmic products are expected to provide CAs and address and differences from RLD
- User interface differences from RLD may be acceptable if adequately justified and/or additional data provided
- Opportunities for CC or Pre-ANDA meetings to speak about your specific issue, RLD, etc.

Upcoming Workshop in November

We Are OGD

Ask me why...

"I make sure that the **generic** drug and the **brand** drug work **the same**."

"The first time I was able to buy my son's inhaler as a generic and realized that my out of pocket dropped, I cried and was able to breathe a sigh of relief."

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