



NON-BIOLOGICAL COMPLEX DRUGS : CHALLENGES IN THE ASSESSMENT OF SIMILARITY OR EQUIVALENCE OF OPHTHALMIC EMULSIONS

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lygature Declaration of Interest

Parts of the content of this presentation were developed within the framework of the Non Biological Complex Drugs (NBCD) working group.

The NBCD working group has the mission to ensure that appropriate science-based approval and post-approval standards are created and globally introduced for NBCDs to ensure patient safety and benefit.

Hosted by Lygature (former Top Institute Pharma), a not-for-profit organization based in the Netherlands, the working group consists of experts from industry, academia, and knowledge institutes.

Current partners are the Nanotechnology Characterization Lab, the University of Geneva, Allergan Plc, Teva Pharmaceutical Industries LTD., and Vifor International Inc.



Outline

- > Introduction
- > Non-Biological Complex Drugs (NBCD)
- > Emulsions are complex dosage forms
- > Ophthalmic Emulsions
- > Assessment of Similarity/Equivalence of Ophthalmic Emulsions

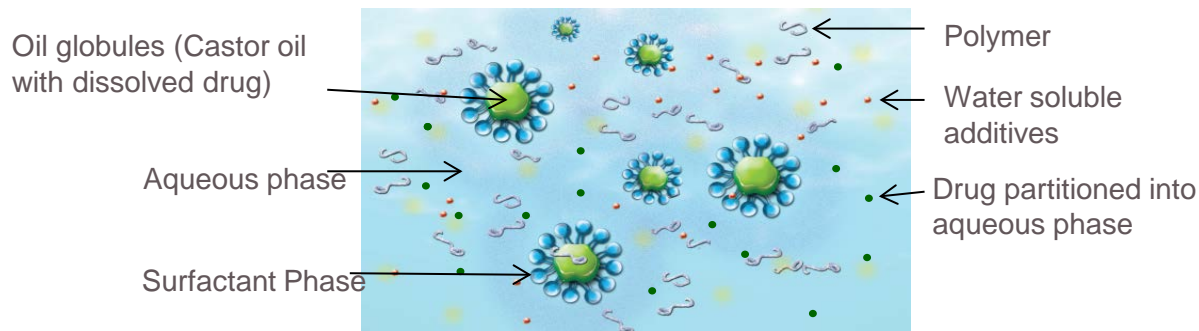
Non Biological Complex Drugs (NBCD)

- > NBCD are different than typical small molecule pharmaceutical agents (Dr. de Vlieger, NBCD Working Group 2015)
 - Consists of a multitude of closely related structures
 - The entire complex is the active pharmaceutical ingredient
 - The properties cannot be fully characterized by physicochemical analysis
 - The well controlled robust manufacturing process is fundamental to reproduce the innovator's product
- > Therefore, with respect to assessment of similarity/equivalence for NBCD, new knowledge & policies need to be created



Emulsions are Complex Dosage Forms

- > Multi-phase systems – contains Oil Phase, Aqueous Phase, Interface consisting of surfactants and other stabilizing polymers, Micellar Structures



- > Drug can be distributed in All Phases – oil, aqueous, surfactant and micellar structures
- > Amount of Drug in each phase is in dynamic equilibrium and can shift based on external environment (Heat, Shear, Chemical interactions , biological interactions, etc)
- > Manufacturing Process is critical to establish:
 - Oil Droplet size
 - Surfactant/Oil Interactions
 - Polymer/Oil/surfactant Interactions
 - Drug Distribution in each of the Phases

Ophthalmic Emulsions (NBCD)

Academia, FDA and Industry have recognized that Ophthalmic emulsions are complex dosage forms because they are locally acting and are multidimensional from a formulations perspective. Some recent references include :

- > Complex Generic Drugs, Robert Lionberger, Ph.D. Center for Drug Evaluation and Research, OGD, FDA (GPhA Fall Technical Meeting, October 29, 2013)
- > Approval of Generic Ophthalmic Suspensions/Emulsions: Current Status and Challenges , Uday Kompella, University of Colorado Denver (FY 2013 Regulatory Science Initiatives Part 15 Public Meeting)
- > The similarity question for biologicals and non-biological complex drugs. Daan J.A. Crommelin et. al. European Journal of Pharmaceutical Sciences, 76 (2015) 10–17

Ophthalmic Emulsions (NBCD)

- > Ophthalmic emulsions are complex systems that are used to deliver poorly soluble drugs to the eye, a complex organ with multiple target tissues
- > These emulsions are locally acting with negligible systemic levels so PK bioequivalence generally not possible
- > Short residence time in the eye (30 sec to 2 min) with complex absorption pathways. Therefore, traditional *in vitro* drug release methods may not be good enough for *in vivo* performance prediction purposes.
- > Manufacturing processes can affect emulsion safety/tolerability and performance by altering drug distribution attributes in the emulsion and hence absorption/distribution kinetics

Assessment of Similarity/Equivalence of Ophthalmic Emulsions

- > Recent FDA draft guidance on ophthalmic emulsions seem to be acknowledging the complexity of ophthalmic emulsions with expectations of additional physico-chemical characterization to show equivalence...
 - ...however, a clear link to *in vivo* performance is still missing
 - ...deficient in details on how robust these characterization methods need to be
- > Further understanding of locally acting ophthalmic emulsions is necessary to create scientifically robust Guidance with respect to assessment of similarity/equivalence of ophthalmic emulsions.
- > Research in the following areas would be a good first step;
 - *In vitro* drug release methods that can be linked to *in vivo* performance
 - Robust emulsion physicochemical characterization methods (e.g., drug distribution, droplet size) that provides meaningful information on impact to *in vivo* performance

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Questions / Discussion

