U.S. FOOD & DRUG ADMINISTRATION

Complex Generic Drug Products (CGDPs) with Complex Formulations Including Nanotechnology Products

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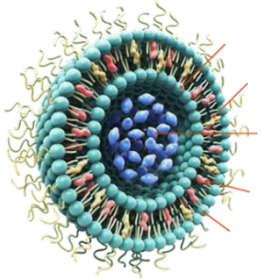
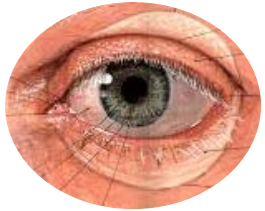




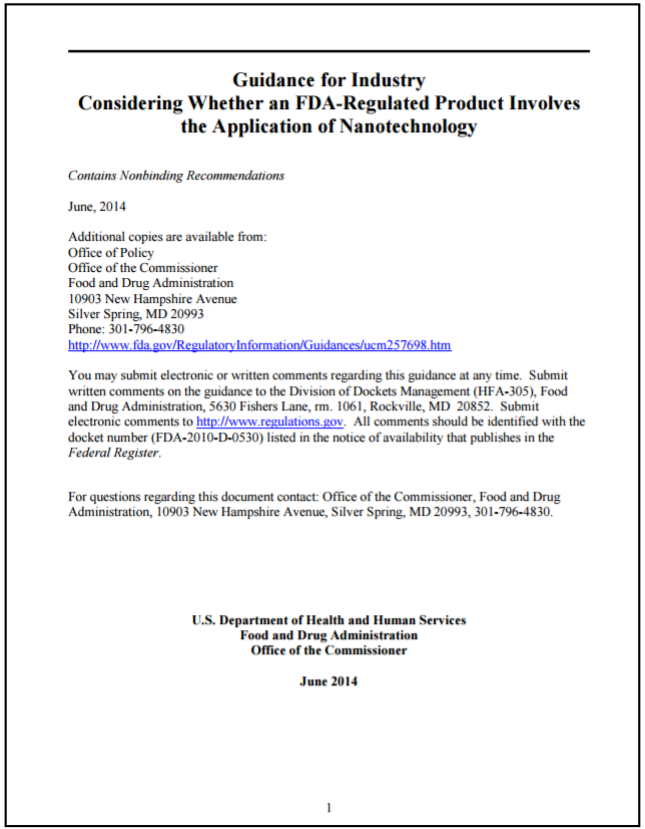
Considerations for the Development of Nanotechnology CGDPs: Topical Ophthalmic Example

1. Characterizing nanotechnology CPGDs
2. Formulation and bioequivalence considerations

1. Characterizing Nanotechnology CPGDs

Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology

- **Points to Consider**
  - Whether a material or end product is engineered to have at least one external dimension, or an internal or surface structure, in the nanoscale range (approximately 1 nm to 100 nm);
  - Whether a material or end product is engineered to exhibit properties or phenomena, including physical or chemical properties or biological effects, that are attributable to its dimension(s), even if these dimensions fall outside the nanoscale range, up to one micrometer (1,000 nm)
- **Key Take-Aways**
  - Regulations and law do not separate nanotechnology products



Guidance for Industry
Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology

Contains Nonbinding Recommendations

June, 2014

Additional copies are available from:
Office of Policy
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Food and Drug Administration
10903 New Hampshire Avenue
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Phone: 301-796-4830
http://www.fda.gov/RegulatoryInformation/Guidances/ucm257698.htm

You may submit electronic or written comments regarding this guidance at any time. Submit written comments on the guidance to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. All comments should be identified with the docket number (FDA-2010-D-0530) listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this document contact: Office of the Commissioner, Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, 301-796-4830.

U.S. Department of Health and Human Services
Food and Drug Administration
Office of the Commissioner

June 2014

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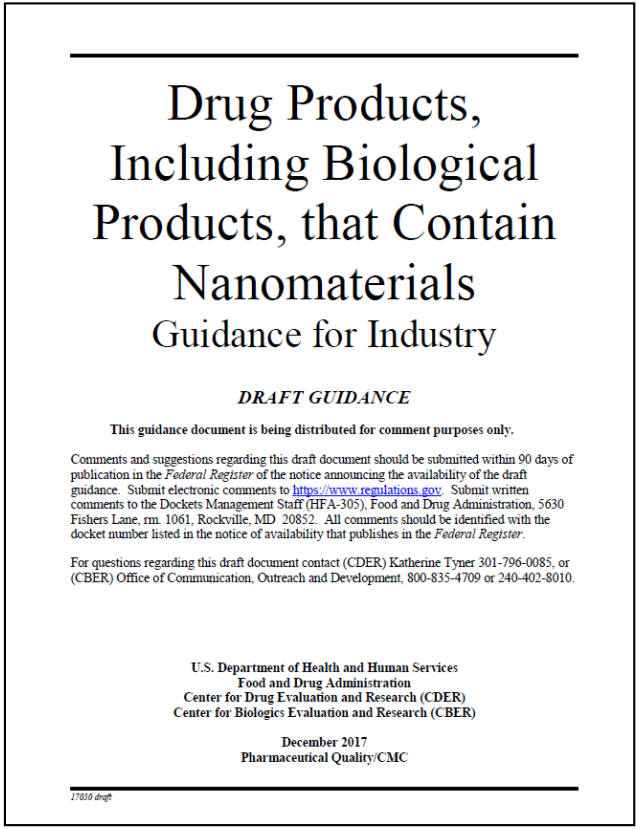
CDER/CBER Nanotechnology Draft Guidance

- **Points to Consider**
  - Adequate characterization of the nanomaterial
  - Understanding of a nanomaterial's intended use and application
  - How the nanomaterial attributes relate to product quality, safety, and efficacy
- **Key Take-Aways**
  - Drug products containing nanomaterials are expected to meet the same standards of safety, efficacy, and quality as other drug products.



Drug Products, Including Biological Products, that Contain Nanomaterials

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 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (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) Katherine Tyner 301-796-0085, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

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

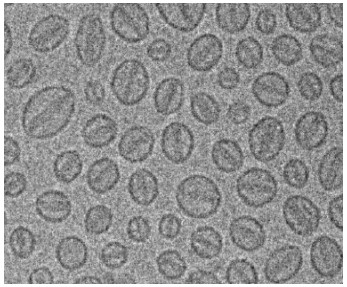
December 2017
Pharmaceutical Quality/CMC

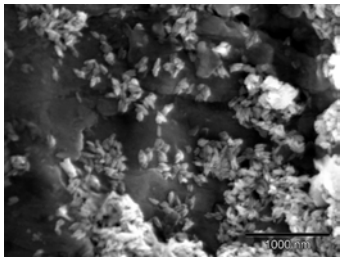
17050 draft

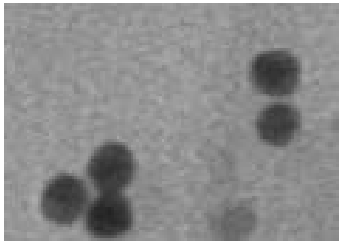
Factors for Nanomaterial Assessment

- Adequacy of characterization of the material structure and its function
- Complexity of the material structure
- Understanding of the mechanism by which the physicochemical properties of the material impact its biological effects
- Understanding the in vivo release mechanism based on the material physicochemical properties
- Predictability of in vivo release based upon established in vitro release methods
- Physical and chemical stability

- Maturity of the nanotechnology (including manufacturing and analytical methods)
- Potential impact of manufacturing changes, including in-process controls and the robustness of the control strategy on critical quality attributes of the drug product
- Physical state of the material upon administration
- Route of administration
- Dissolution, bioavailability, distribution, biodegradation, accumulation and their predictability based on physicochemical parameters and animal studies







Attributes of Nanomaterials

ALWAYS

- **Chemical composition**
- **Average particle size**
- **Particle size distribution**
- **General shape and morphology**
- **Stability, both physical and chemical**

SOMETIMES

- Assay and distribution of any active ingredient
  - Associated with the nanomaterial and free in solution
- Structural attributes that relate to function
- Surface properties
- Coating properties
  - Including how coatings are bound to the nanomaterial

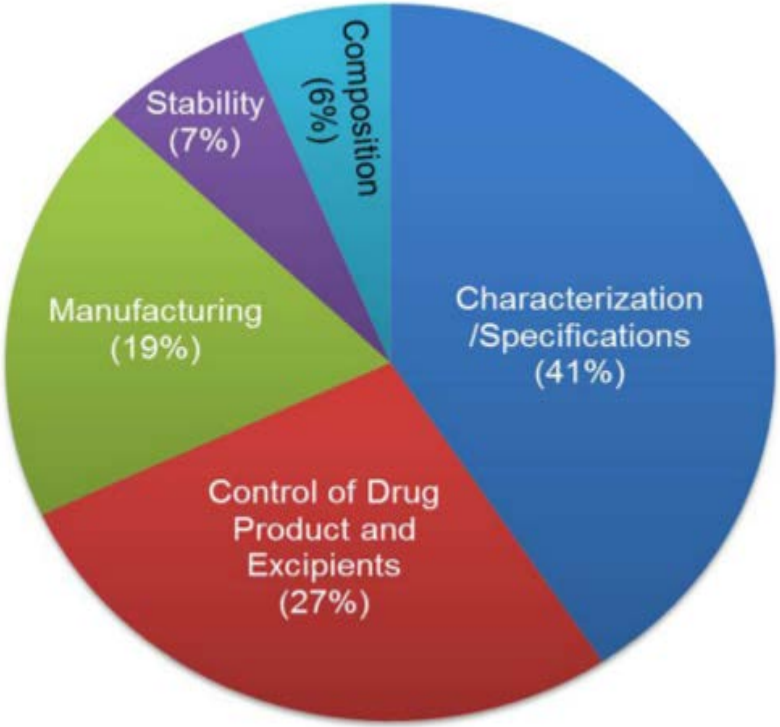
- Porosity
- Particle concentration
- In vitro release
- Crystal form
- Impurities
- Sterility and endotoxin levels

Specific Considerations for Liposomes

Characterization

- Morphology including lamellarity determination
- Surface characteristics
- Net charge
- Drug product viscosity
- Parameters of the contained drug.
- Particle size
- Liposome phase transition temperature
- In vitro release
- Leakage rate of drug from the liposomes throughout shelf life
- Liposome stability

Common Quality Deficiencies



Kapoor M. et al. AAPS J 19(3) 2017

https://www.fda.gov/downloads/drugs/guidances/ucm070570.pdf

2. Formulation and Bioequivalence Considerations

Formulation Requirements for Generic Ophthalmic/Otic Products

21 CFR 314.94(a)(9)(iv) – *Inactive ingredient changes permitted in drug products intended for ophthalmic or otic use.*

Generally, a drug product intended for ophthalmic or otic use shall contain the same inactive ingredients (Q1) and in the same concentration (Q2) as the reference listed drug.

"However, an applicant may seek approval of a drug product that differs from the reference listed drug in **preservative, buffer, or substance to adjust tonicity, or thickening agent** provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product …"

Formulation Q1/Q2 Sameness

- Changes in formulation may affect ocular bioavailability by altering drug retention time and/or permeability of ocular tissues.

- So, despite a similar allowance (to parenteral products) provided for ophthalmic drug products in 21 CFR 314.94(a)(9)(iv), FDA has determined that, as a scientific matter, any qualitative (Q1) or quantitative (Q2) deviations from the reference listed drug (RLD) should be accompanied by an appropriate Bioequivalence study or studies.[1]

1. Guidance for Industry: *ANDA Submissions – Refuse-to-Receive Standards*

Demonstrating Bioequivalence

For more complex products, such as Nanotechnology CGDPs, where ***manufacturing conditions, processing steps, or excipient choice could*** affect the properties of the final product,

"[b]ioavailability may be measured or bioequivalence may be demonstrated by several in vivo and in vitro methods. FDA may require in vivo or in vitro testing, or both, to measure the bioavailability of a drug product or establish the bioequivalence of specific drug products." 21 CFR 320.24(a)

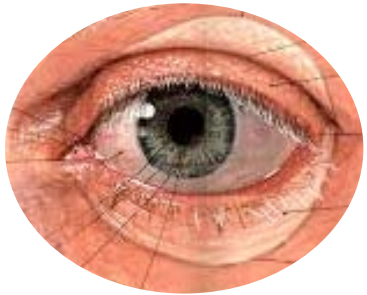
Demonstrating Bioequivalence

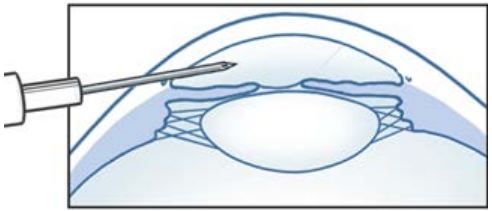
- Study options to demonstrate BE:
  - Comparative in vivo PK studies;
  - Comparative in vivo pharmacodynamic (PD) effect studies;
  - Comparative clinical endpoint studies; and
  - Comparative in vitro studies.
- Each BE option has inherent benefits, risks, and limitations. Not all options may be appropriate for a proposed generic.
- *Ultimately, a BE approach must provide and most accurate, sensitive, and reproducible measure to ensure bioavailability and BE*.

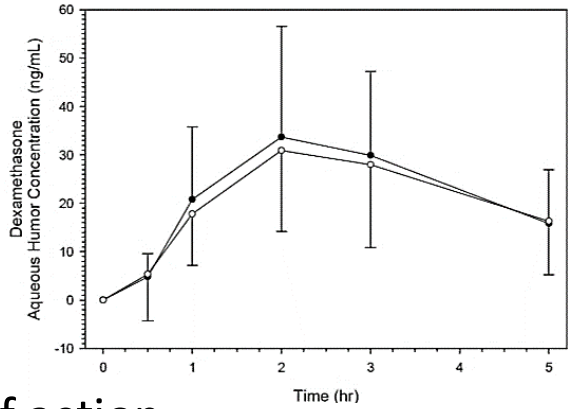
Demonstrating BE of Topical Ophthalmic Products

Local PK: Aqueous humor

Comparative measure of bioequivalent in vivo performance of the generic to RLD.







[2]

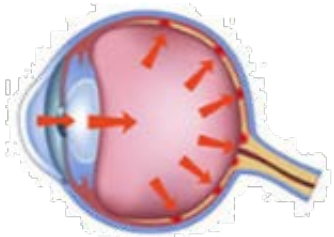
- Compare drug concentration at the local site of action.
- Sparse sampling, single sample per subject, gives rise to the need for large study population and statistical bootstrapping.[3]

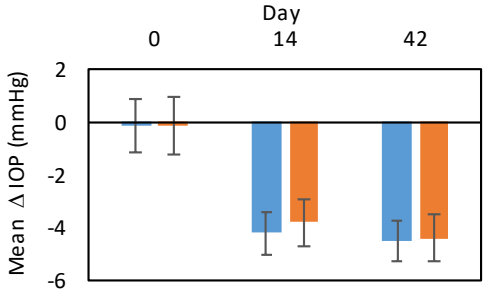
2. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/050818s000clinpharmr.pdf
3. See *Draft Guidance on Loteprednol Etabonate* for aqueous humor PK study recommendations

Demonstrating BE of Topical Ophthalmic Products

Comparative clinical endpoint:

Comparative measure of bioequivalent in vivo performance of the generic to RLD





- Compare a pivotal clinical outcome (e.g., change in intraocular pressure (IOP) over 42 days)[4]
- Endpoint can be semi-qualitative and confounded by patient disease state
- Poor discriminator between similar products and requires large patient population to adequately power the study

4. See *Draft Guidance on Brinzolamide* for IOP comparative clinical study recommendations

In Vitro Characterization to Support BE & Product Quality

For complex products that incorporate nanotechnology, sameness in physicochemical characteristics (i.e., arrangement of matter within the dosage) supports overall product sameness, and thus equivalence

Example of BE Approach Recommendations in Product-Specific Guidance (PSG)

Contains Nonbinding Recommendations

Draft Guidance on Doxorubicin Hydrochloride

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Doxorubicin hydrochloride

Dosage Form; Route: Injectable, liposomal

Recommended Studies: Two studies: in vivo and in vitro

To be eligible for the bioequivalence studies recommended in this guidance, the Test product should meet the following criteria:

- Qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the Reference Listed Drug (RLD)
- Manufactured by an active liposome loading process with an ammonium sulfate gradient
- At least one batch of the Test product should be produced by the commercial scale process and be used in the in vivo bioequivalence study
- Equivalent liposome characteristics including liposome composition, state of encapsulated drug, internal environment of liposome, liposome size distribution, number of lamellar, grafted PEG at the liposome surface, electrical surface potential or charge, and in vitro leakage rates comparable to the Reference Standard (RS).

In Vivo Study:

Type of study: Fasting*
Design: Single-dose, two-way crossover in vivo
Strength: 50 mg/vial or 20 mg/vial
Dose: 50 mg/m2
Subjects: Ovarian cancer patients whose disease has progressed or recurred after platinum-based chemotherapy and who are already receiving or scheduled to start therapy on doxorubicin hydrochloride (liposomal).

Analytes to measure (in appropriate biological fluid): Free doxorubicin and liposome encapsulated doxorubicin.

Bioequivalence based on (90% CI): AUC and Cmax for free doxorubicin and liposome encapsulated doxorubicin.

Two studies (in vivo and in vitro) to demonstrate BE

Formulation (Q1/Q2) and comparative CQA considerations to support BE determination

Recommended in vivo PK BE study:

- Single dose two-way crossover.
- AUC and Cmax for both API associated (encapsulated) and unassociated (free) with the liposome carrier in the biological fluid (e.g., plasma)

https://www.accessdata.fda.gov/drugsatfda_docs/psg/Doxorubicin%20Hydrochloride_draft_Injection%20injec%20lipo_RLD%2050718_RC09-18.pdf

Example of BE Approach Recommendations in Product-Specific Guidance (PSG) (Cont'ed)

In Vitro Study:

1. Type of study: Liposome Size Distribution

   Design: In vitro bioequivalence study on at least three lots of both Test and RS product. At least one lot of the Test product should be produced by the proposed commercial scale manufacturing process.

   Parameters to measure: D10, D50, D90

   Bioequivalence based on (95% upper confidence bound): D50 and SPAN [(i.e. (D90-D10)/D50] using the Population Bioequivalence (PBE) approach. Please refer to the *Guidance on Budesonide* inhalation suspension for additional information regarding PBE.

Dissolution test method and sampling times: The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods Web site, available to the public at the following location: http://www.accessdata.fda.gov/scripts/cder/dissolution/. Conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).

Additional information:

Comparative physicochemical characterization studies should be performed on at least three batches of both the Test and RS products, at least one Test batch should be produced by the commercial scale process and be used in the in vivo bioequivalence study, and should include:

- Liposome composition: Liposome composition including lipid content, free and encapsulated drug, internal and total sulfate and ammonium concentration, histidine concentration, and sucrose concentration should be measured. The drug-to-lipid ratio and the percentage of drug encapsulation can be calculated from liposome composition values.
- State of encapsulated drug: Doxorubicin is largely in the form of a doxorubicin sulfate crystal inside the liposome. The proposed Test product must contain a comparable doxorubicin sulfate crystal inside the liposome, as the RS product.
- Internal environment (volume, pH, sulfate, and ammonium ion concentration): The internal environment of the liposome Test product should be comparable to the RS, including its volume, pH, sulfate, and ammonium concentration maintains the doxorubicin sulfate crystal.
- Liposome morphology and number of lamellae: Liposome morphology and lamellarity should be comparable to the RS as drug loading, drug retention, and the rate of drug release from the liposomes are likely influenced by the degree of lamellarity.
- Lipid bilayer phase transitions: Equivalence in lipid bilayer phase transitions will contribute to demonstrating equivalence in bilayer fluidity and uniformity. The phase transition profile of the liposomal Test product should be comparable to the RS product.

Recommended in vitro BE study:

- Liposome Particle Size.
- BE based on median (D50) and polydispersity (Span)

Dissolution (IVRT) study:
Can discriminate differences in manufacturing and/or formulation

CQA considerations to support BE determination

https://www.accessdata.fda.gov/drugsatfda_docs/psg/Doxorubicin%20Hydrochloride_draft_Injection%20injec%20lipo_RLD%2050718_RC09-18.pdf

Regulatory Utility of Quantitative Methods

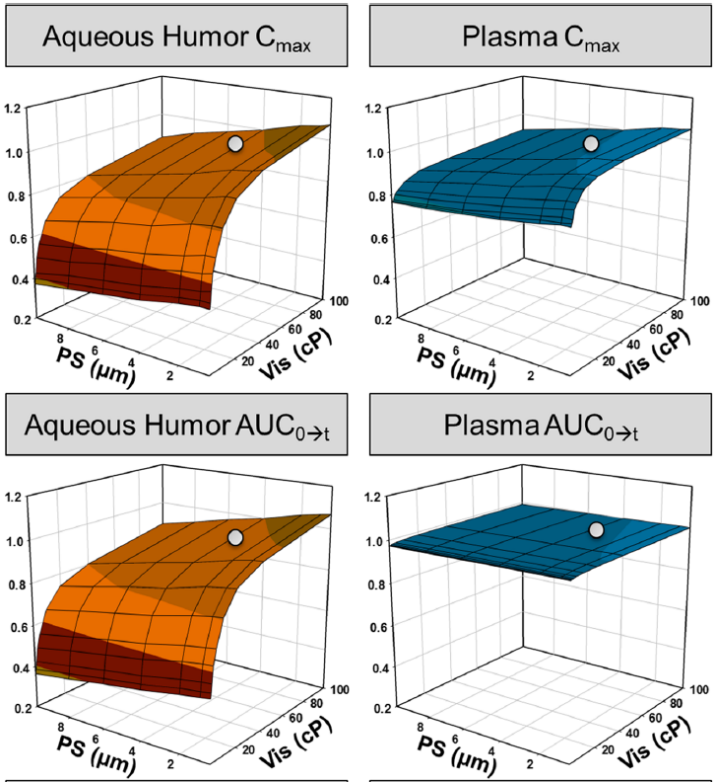
- Mechanistic models of ocular drug absorption, such as Physiologically-Based Pharmacokinetic (PBPK) models, integrate product CQAs and ocular physiology to predict ocular bioavailability
  - Support product development -> gain confidence in formulation selection to conducting local PK, PD, or comparative clinical endpoint BE study
  - Potentially support in vitro only BE approaches in lieu of in vivo studies
  - Guide selection of clinically-relevant in vitro tests for BE
  - Define a safe space for CQAs of ophthalmic products
  - Justify differences in CQAs from the reference-listed drug (RLD)

- BE study design and data analysis
  - Sparse sampling in aqueous humor PK study: model-informed optimal BE design, model-based BE analysis, group-sequential approach
  - Pharmacodynamic endpoints: dose-scale analysis, endpoint sensitivity assessment, alternative study design
  - Clinical endpoints: clinical trial simulation

Zhao et al., Clin Pharmacol Ther. 2018 Nov 10 doi: 10.1002/cpt.1282

CQA Impact on PK - Sensitivity Analysis

- Rabbit ocular PBPK model developed in GastroPlus™ OCAT™ module
- Internally conducted rabbit study with dexamethasone suspension with PK sampling in multiple ocular tissues and plasma for model development
- Model verification with other published PK data:
  - Mean particle size (PS) and PS distribution on ocular absorption
  - Non-linear dose-exposure relationship
  - Formulation viscosity impact of ocular absorption
- Parameter sensitivity analysis in rabbit to assess impact of PS and viscosity on exposure
  - Viscosity is a critical attribute affecting BE
  - Plasma/systemic PK is not reflective of local concentrations
- Regulatory challenge: demonstrate and verify such a relationship in humans to help determine BE and set clinically-relevant specifications



Le Merdy, M. et al., The AAPS Journal 2019 Jul 1; 21(4):65

Developing Reliable Ocular PBPK Models…

Ocular PBPK modeling is a powerful approach that can be used to

- explore relationships between systemic and local drug exposure
- predict in vivo performance of ocular drug products when only product critical quality attributes are available
- conduct risk assessment on the impact of product critical quality attributes on the in vivo drug product performance of reference and test drug products

What would you do if ….

Your Q3 attribute of your Q1/Q2 formulation deviates from the RLD or exhibits greater variability than the RLD?

- Can you establish that the deviation or additional variability will not impact local and/or systemic bioavailability?
- A mechanistic PBPK approach can be used to explore the impact of quality attributes on bioavailability

BE studies with group-sequential designs

- FDA will accept appropriately designed BE studies using a group-sequential approach
  - Possible early termination based on convincing results
  - Potentially fewer subjects
- Protocol must state *a priori* that a group-sequential approach will be used
  - Maintain α of 0.05
  - Minimize loss of power (1 - β)
- The statistical analysis method should be validated via
  - Quantitative analysis such as simulations
  - Literature references

Summary

- Product and process understanding is key for development of drug products containing nanomaterials
  - Potential applicants should ask:
    - What will impact the quality, safety, and efficacy of the product?
    - How do I measure it; In development? In controls and release?
- Parenteral, ophthalmic, and otic products should be formulated Q1/Q2 to the RLD besides in exception excipients (21 CFR 314.94(a)(9)(iii),(iv))

Summary

- In vivo or in vitro testing, or both, may be needed to establish bioequivalence (21 CFR 320.24(a))
  - BE approach (e.g., comparative PK, comparative clinical endpoint, and/or comparative in vitro) must provide an accurate, sensitive, and reproducible measure of BE
- Quantitative methods and modeling is essential for developing complex generic ophthalmic products
  - Identify product critical quality attributes and impact
  - Support alternative approaches for BE assessment and data analysis
  - Critical in ANDA reviews, PSG development, and almost all regulatory activities

In Summary, What would you do When….

You are developing a generic product but the PSG is unavailable:

- Identify the reference listed drug (RLD)
- Review drug label to identify key formulation, PK, and clinical study information
- Identify potential studies to support a demonstration of BE appropriate to the complexity of the dosage form
- Where appropriate, establish Q1/Q2 formulation sameness to RLD
- Identify product critical quality attributes (CQAs)
  - Properties affected by manufacturing process, formulation steps, or excipient grade/source
  - Literature and/or internal studies on product CQAs that affect product quality and/or bioavailability
- Comparative testing of Generic and RLD product CQAs
  - Justification for analytical method(s) used
  - Analytical method development
  - Justification for sameness criteria
- Submit a pre-ANDA meeting request with specific questions to obtain Agency's guidance

Pre-ANDA Meeting

You request a pre-ANDA meeting seeking assistance from FDA by submitting a meeting package including:

- Details about the proposed formulation(s) for the generic product
- A clear outline of the proposed BE approach and any supporting information
- Sufficient preliminary comparative testing information to support analytical methods, equivalence evaluation, and associated questions being raised
- Information to support the feasibility of any novel techniques
- Information about all proposed product packaging configurations
- If modeling involved, should contain a clear presentation of how the model will be used and how the model will be verified

For additional information, please see the draft guidance for industry, Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm578366.pdf

Reference Section

Relevant Guidances

- Agency Nanotechnology Guidance
  - http://www.fda.gov/RegulatoryInformation/Guidances/ucm257698.htm
- CDER/CBER Nanotechnology Guidance
  - https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM588857.pdf
- Liposome Guidance
  - https://www.fda.gov/downloads/drugs/guidances/ucm070570.pdf
- Product-Specific Guidances
  - Doxorubicin (liposome): https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM199635.pdf
  - Loteprednol etabonate (ophthalmic):
  - https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM249244.pdf

Some Characterization Methods

- Dynamic light scattering
- Laser diffraction
- Transmission electron microscopy
- Scanning electron microscopy
- Atomic force microscopy
- Dark field microscopy
- Light microscopy
- Size exclusion chromatography
- Field flow fractionation
- X-ray diffraction
- Mossbauer spectroscopy
- Capillary electrophoresis
- Gel permeation chromatography
- Disc centrifuge measurements
- High performance liquid chromatography
- Analytical Ultra Centrifugation
- Inductively coupled mass spectrometry
- Elemental diffraction analysis
- Gel permeation chromatography
- Dialysis
- Ultrafiltration
- Raman spectroscopy
- Electron paramagnetic resonance
- X-ray absorption near-edge structure
- Electron diffraction
- Small angle x-ray spectroscopy
- Ultraviolet/Visible spectroscopy
- Polarography
- Titration
- Fourier transform infrared spectroscopy
- Thermal gravimetric analysis
- Differential scanning calorimetry
- Gel electrophoresis
- Nuclear magnetic resonance
- Atomic absorption spectroscopy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