Current Product-Specific Guidances and Common Questions in pre-ANDA Communications for Orally Inhaled and Nasal Drug Products

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Outline

- Overview on orally inhaled and nasal drug products (OINDPs)
- Bioequivalence recommendations for OINDPs
- Role of product-specific guidances (PSGs)
- Common questions in pre-ANDA communications, and information to be submitted to facilitate the FDA assessment

Orally Inhaled and Nasal Drug Products (OINDPs)

- Drug-device combination products
- Treatment of diseases of respiratory tract
  - Asthma, chronic obstructive pulmonary disease (COPD), rhinitis
- Complex products*
  - Formulations, routes of delivery, dosage forms

* As per GDUFA II Commitment Letter: https://www.fda.gov/downloads/forindustry/userfees/genericdruguserfees/ucm525234.pdf

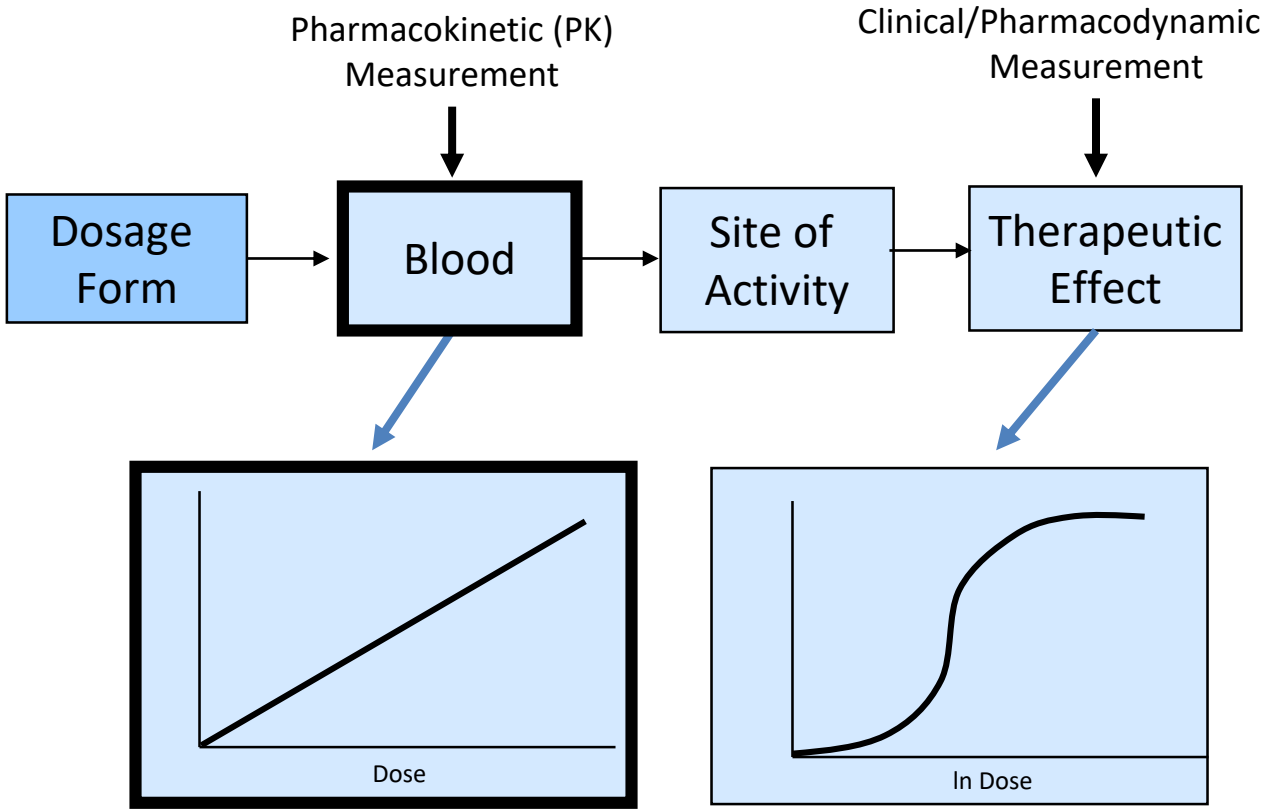
Complexity of OINDPs

Drug State	Site of Action	Dosage Form	Route
Solution	Systemic	Aqueous Spray	Nasal
	Local	Aerosol Metered	Nasal
			Inhalation
		Aqueous Spray	Nasal
			Inhalation
Suspension	Local	Aqueous Spray	Nasal
		Aerosol Metered	Inhalation
Solid blend	Systemic	Powder	Nasal
			Inhalation
	Local	Powder	Inhalation

Challenges in Developing Locally Acting Generic OINDPs

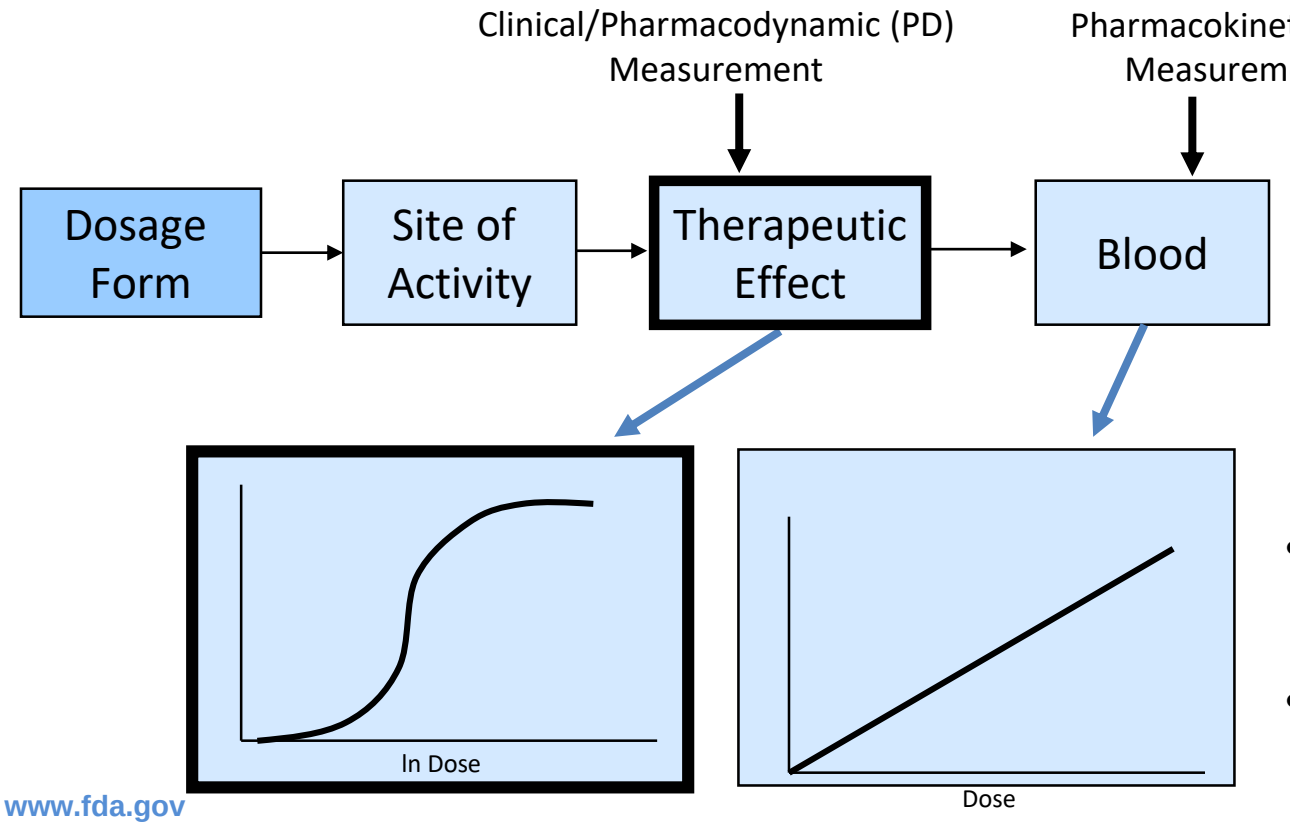
- Device is integral part of the delivered dose
- Several factors influencing drug local and systemic bioavailability
  - Patient-device interactions
  - Device-formulation interactions
  - Regional drug distribution
  - Local dissolution/permeability/clearance
- Drug delivery is local to the site of action (e.g., lung tissue or nasal cavity), not systemic
  - Intended target effect does not rely primarily on systemic absorption
  - Challenges to measuring local effect

BE for Systemically Acting Drugs



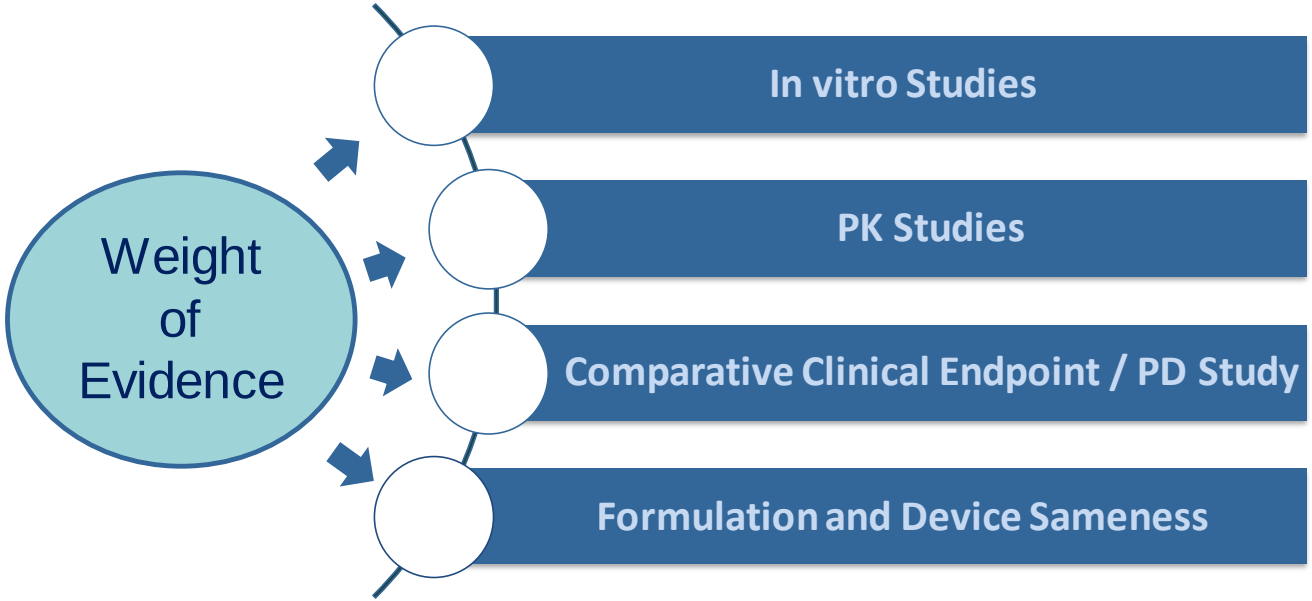
- Delivered to the bloodstream for distribution to site(s) of action in the body
- BE determined with PK studies
  - Relatively short studies
  - Relatively small number of subjects

BE for Locally Acting Drugs



- Not intended to be absorbed into the bloodstream to deliver its effect
- Delivered directly to sites of action (lung or nose)

Weight of Evidence Approach for Establishing Bioequivalence



- Currently recommended for locally acting dry powder inhaler (DPI), metered dose inhaler (MDI) and nasal suspension spray products

Recommended In Vitro BE Studies for DPI, MDI and Nasal Suspension Products

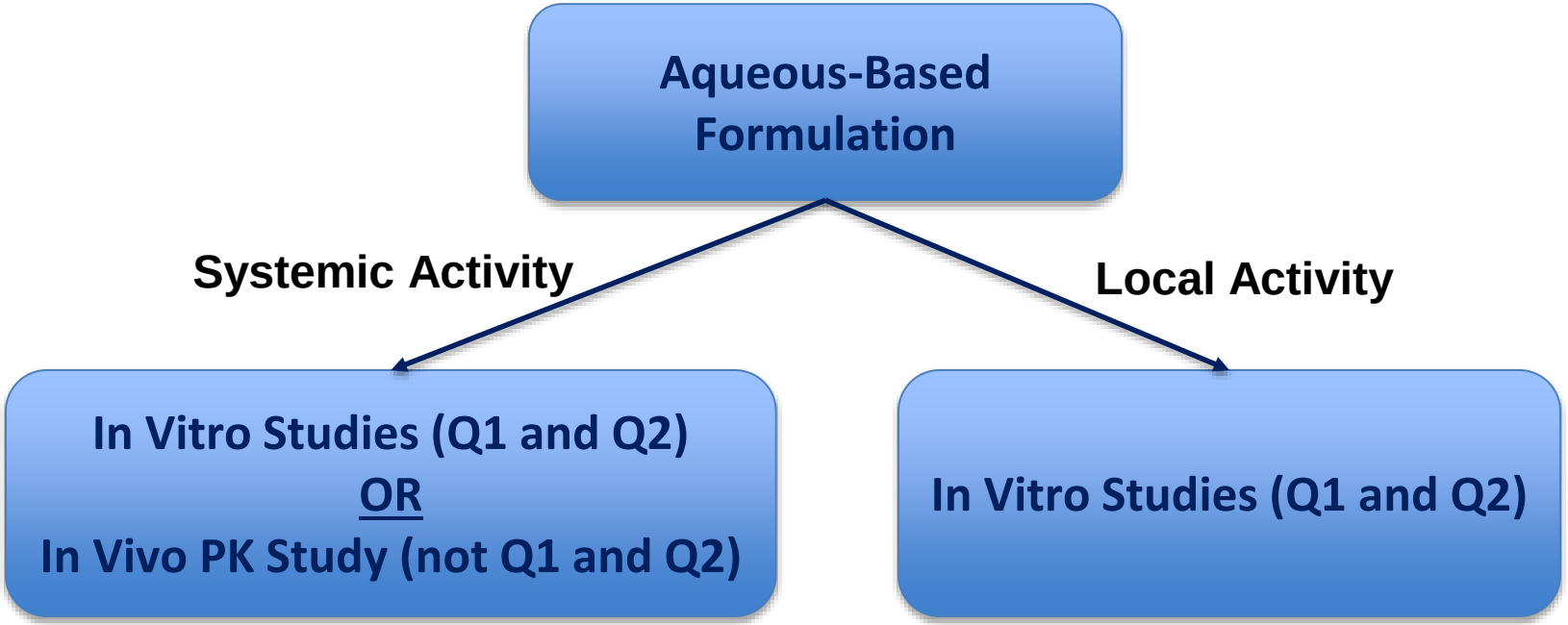
DPIs	MDIs	Nasal Suspensions
- Single Actuation Content (SAC) at beginning (B), middle (M) and end (E) lifestages and using 3 flow rates - Aerodynamic Particle Size Distribution (APSD) at B and E lifestages and using 3 flow rates	- SAC at B, M and E lifestages - APSD at B and E lifestages - Spray Pattern at B lifestage and 2 distances from actuator mouthpiece - Plume Geometry at B lifestage - Priming and Repriming (if required by the R product)	- SAC at B and E lifestages - Droplet Size Distribution by Laser Diffraction at B and E lifestages and 2 distances from actuator orifice - Drug in Small Particles/Droplets at B lifestage - Spray Pattern at B lifestage and 2 distances from actuator orifice - Plume Geometry at B lifestage - Priming and Repriming (if required by the R product)

- Conducted with all strengths, at least 3 batches of test (T) and reference (R) products, with no fewer than 10 units from each batch

Recommended In Vivo BE Studies for DPI, MDI and Nasal Suspension Products

In Vivo BE Studies	DPIs	MDIs	Nasal Suspensions
Comparative Pharmacokinetic (PK)	- Fasting, single-dose, two-way crossover, minimum number of inhalations, healthy subjects, all strengths, endpoint: AUC and Cmax		
Comparative Clinical Endpoint (EP) or Pharmacodynamic (PD)	- Multiple-dose or single-dose (based on the drug mechanism of action), randomized, placebo-controlled, parallel group or crossover, placebo run-in period followed by the treatment period of placebo, T and R, patients with asthma or chronic obstructive pulmonary disease (COPD), lowest strength, endpoint: FEV1 - Bronchoprovocation or bronchodilatation dose-response PD study (short acting beta agonists, SABAs), endpoint: PC20 (or PD20) or FEV1		- Multiple-dose, randomized, double-blind, placebo-controlled, parallel group, placebo run-in period, three-arm, patients with seasonal allergic rhinitis, endpoint: TNSS

Recommended BE Studies for Nasal Solution Products



Pre-ANDA Communications with FDA for Complex Products Under GDUFA II

- General Guidances
  - *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA* (Jan 2017)
    https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm536959.pdf
- Product-Specific Guidances (PSGs)
  - https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm
- Controlled Correspondences
  - *Controlled Correspondence Related to Generic Drug Development* (Nov 2017):
    https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm583436.pdf
- Pre-ANDA Meetings
  - *Formal meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* (Oct 2017):
    https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm578366.pdf

PSGs for Generic Products

- Roles
  - To facilitate generic drug product availability
  - To assist generic pharmaceutical industry
  - To identify the most appropriate methodology to support ANDA
- Guiding Principles
  - 21 CFR 320.24
  - Different types of evidence may be used to establish BE for pharmaceutically equivalent drug products
  - Selection for BE method depends upon
    - Purpose of study
    - Analytical methods available
    - Nature of the drug product
  - Use the most accurate, sensitive, and reproducible approach available

https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm

PSGs Website

- > **60%** of all MDI and DPI products have PSGs
- > **55%** of all nasal products have PSGs

Current PSGs for OINDPs

MDIs	DPIs	Nasal Solutions	Nasal Suspensions
1. Fluticasone Propionate 2. Mometasone Furoate 3. Formoterol Fumarate and Mometasone Furoate 4. Ciclesonide 5. Beclomethasone Dipropionate 6. Albuterol Sulfate 7. Levalbuterol Tartrate 8. Budesonide and Formoterol Fumarate Dihydrate 9. Ipratropium Bromide	1. Mometasone Furoate 2. Fluticasone Propionate 3. Salmeterol Xinafoate 4. Tiotropium Bromide 5. Glycopyrrolate 6. Budesonide 7. Umeclidinium Bromide 8. Indacaterol Maleate 9. Fluticasone Furoate 10. Fluticasone Furoate and Vilanterol Trifenatate 11. Formoterol Fumarate 12. Aclidinium Bromide 13. Fluticasone Propionate and Salmeterol Xinafoate	1. Ketorolac Tromethamine 2. Oloppatadine Hydrochloride 3. Azelastine Hydrochloride 4. Cyanocobalamin 5. Tetracaine Hydrochloride and Oxymetazoline Hydrochloride 6. Naloxone Hydrochloride 7. Nicotine 8. Zolmitriptan 9. Sumatriptan 10. Fentanyl 11. Calcitonin-Salmon 12. Ciclesonide 13. Beclomethasone Dipropionate	1. Azelastine Hydrochloride and Fluticasone Propionate 2. Triamcinolone Acetonide 3. Mometasone Furoate Monohydrate 4. Fluticasone Propionate

(Data collected through July 2018)

Types of Common Questions Received in Pre-ANDA Communications for OINDPs

- Formulation evaluation (Q1 and Q2), inactive ingredients
- Device evaluation (comparative analyses)
- BE-related questions:
  - Patient population for comparative clinical study
  - Clinical protocol review
  - Degree of blinding
  - Guidance clarification
  - Alternative BE approaches
- Other (chemistry, packaging, filing, stability)

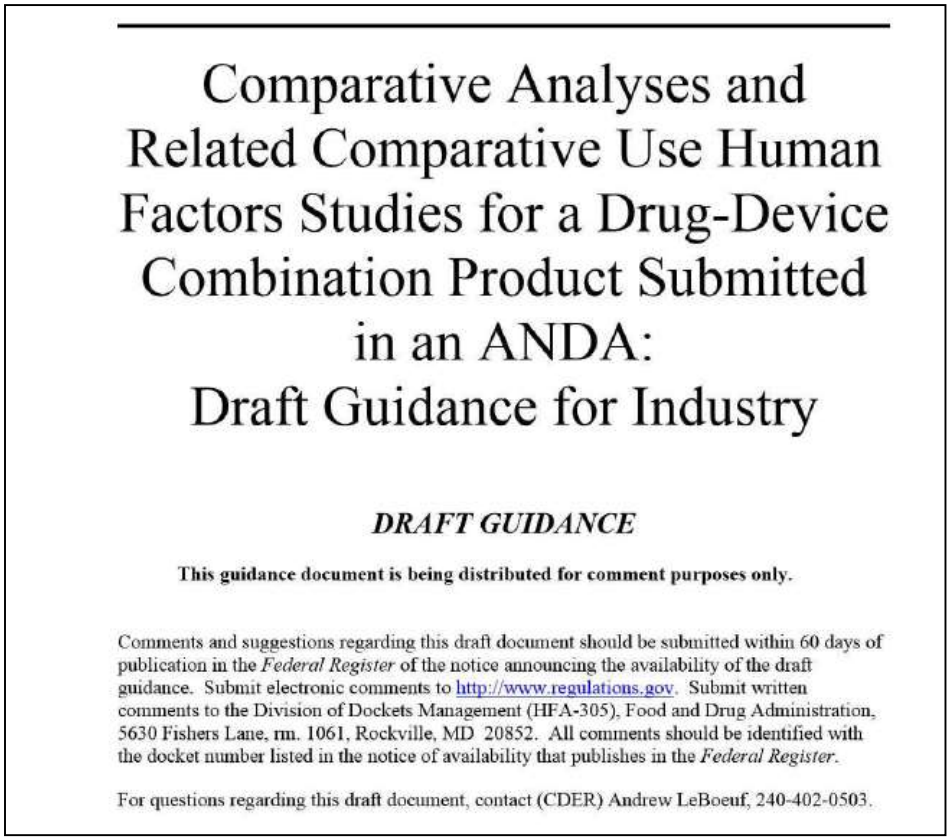
Are the proposed T formulations Q1 and Q2 the same as the R formulation ?

- FDA assessment process
  - Q1 means the T formulation uses the same excipients as the R formulation
  - Q2 means that the concentration of excipients used in the T formulation are within +/- 5% of those used in the R formulation
- Information to submit to facilitate the assessment
  - Up to 3 proposed T formulations per each strength per control
  - Complete information about all excipients (e.g., complete names, grades, hydrate or anhydrous)
  - Concentration (e.g., %w/w, %w/v) of excipients inside the container (e.g., canister, bottle, blister, capsule, reservoir)

Is the proposed T device acceptable for an ANDA submission ?

- FDA assessment process
  - Comparative (threshold) analyses as per the FDA guidance, "*Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*" (Jan 2017)
    - Labeling comparison
    - Comparative task analysis
    - Physical comparison of the delivery device constituent part
- Information to submit to facilitate the assessment
  - Samples of T and R devices
  - Comparative (threshold) analyses
  - Specific question(s) based on the outcomes of comparative analyses

Guidance for Complex Drug-Device Combination Products – User Interface



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.

Posted in Jan 2017

Is the proposed BE clinical study protocol acceptable?

- BE clinical study protocols are not pre-reviewed
  - Acceptability is determined during the scientific review of the ANDA
- To submit a request related to BE clinical protocol evaluation
  - For a specific question not covered by the PSG, submit a controlled correspondence requesting FDA to comment on the specific question
  - For evaluation of a BE study design that deviates from that recommended in the PSG, submit a controlled correspondence requesting FDA to evaluate the alternative approach
  - For multiple questions or complex issues, submit a pre-ANDA meeting package

Refer to the FDA Guidance "Controlled Correspondence Related to Generic Drug Development" (Nov 2017)
https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm583436.pdf

Is the T product eligible for "biowaiver" of in vivo studies ?

- FDA assessment process
  - In general, in vivo bioavailability or bioequivalence of complex OINDPs may not be self-evident, so that a request to simply "waive" in vivo studies based on 21 CFR 320.22 may not be applicable
  - Product-specific
  - Case-by-case manner
  - Ultimately determined at the time of ANDA submission
- Information to submit to facilitate the assessment
  - Alternative BE approach
    - Rationale and justification for the proposal
    - Preliminary data, if available

Is this Acceptable?

- Examples
  - Is the ANDA acceptable for filing?
  - Is the ANDA acceptable for review?
  - Will the ANDA be approved?
- These types of vague, non-specific questions cannot be adequately addressed through pre-ANDA communications
  - Scientific review of ANDA is time- and resource-intensive
  - Acceptability for filing and approvability depend on many factors, which may not be apparent until after the data has been reviewed
  - Requires involvement of multiple disciplines within the OGD
  - Requires involvement of other offices or centers within the Agency
- Ask specific, detailed questions about a complex situation or issue for your generic development program

Conclusions

- OINDPs are complex drug-device combination products
- Product-specific guidances (PSGs)
  - Facilitate generic drug product availability
  - Assist generic pharmaceutical industry
  - Use the most accurate, sensitive, and reproducible approach available
  - Identify the current thinking methodology to support ANDA
- Questions submitted in pre-ANDA communications
  - Clearly defined
  - Focus on complex situations or issues for the development program
  - Supported by scientific rationale, clear and concise justification
  - Supported by preliminary data, if available

Thank You!

- Acknowledgments
  - Kimberly Witzmann, M.D.
  - Sharad Mangal, Ph.D.
  - Bryan Newman, Ph.D.
  - Kamrun Nahar, Ph.D.
  - Renish Delvadia, Ph.D.
  - Markham Luke, M.D., Ph.D.
  - Lei K. Zhang, Ph.D.
  - Robert Lionberger, Ph.D.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