

Overview of Complex Generics

Regulatory Perspective on Bioequivalence

Xiaohui (Jeff) Jiang, PhD

Deputy Director

Division of Therapeutic Performance

Office of Research and Standards

Office of Generic Drugs

Center for Drug Evaluation and Research, FDA

4th PQRI-FDA Conference on Advancing Product Quality

April 9 -11, 2019



Disclaimer

This presentation reflects the views of the presenter and should not be construed to represent US FDA's views or policies.

Outline



- Regulatory pathways for NDA/ANDA, and equivalence concepts
- Challenges for complex generic drug products
- Bioequivalence and formulation (Q1/Q2) considerations for complex generics

Regulatory Pathways of New Drug Application



- 505(b)(1)
 - “stand-alone” New Drug Application (NDA), usually a New Molecular Entity (NME)
 - Contains full reports of investigations of safety and effectiveness of a proposed drug product
- 505(b)(2)
 - NDA
 - Usually references a listed drug; some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use
- 505(j)
 - Abbreviated NDA (ANDA, i.e., duplicate of a previously approved drug product)
 - Must refer to a listed drug (i.e., a reference listed drug (RLD)), contain information to demonstrate therapeutic equivalence, and may not be submitted if studies are necessary to establish the safety or effectiveness of the proposed drug product

Equivalence Concepts

- **Pharmaceutical Equivalence (PE)**
 - Same active ingredient(s) and
 - Same dosage form and
 - Same route of administration and
 - Same strength and more ...
- **Bioequivalence (BE)**
 - No significant difference in rate and extent of the active ingredient at the site of action
- **Therapeutic Equivalence (TE) of Generic Products**
 - Generics must demonstrate PE and BE to the RLD
 - Generics rely on the safety and efficacy of the RLD
 - TE products can be substituted freely

New Drug Application (NDA) vs. Abbreviated New Drug Application (ANDA)



NDA

1. Chemistry, Manufacturing & Controls (CMC)
2. Testing
3. Labeling
4. Inspection
5. Animal Studies
6. Bioavailability
7. Clinical Studies

ANDA

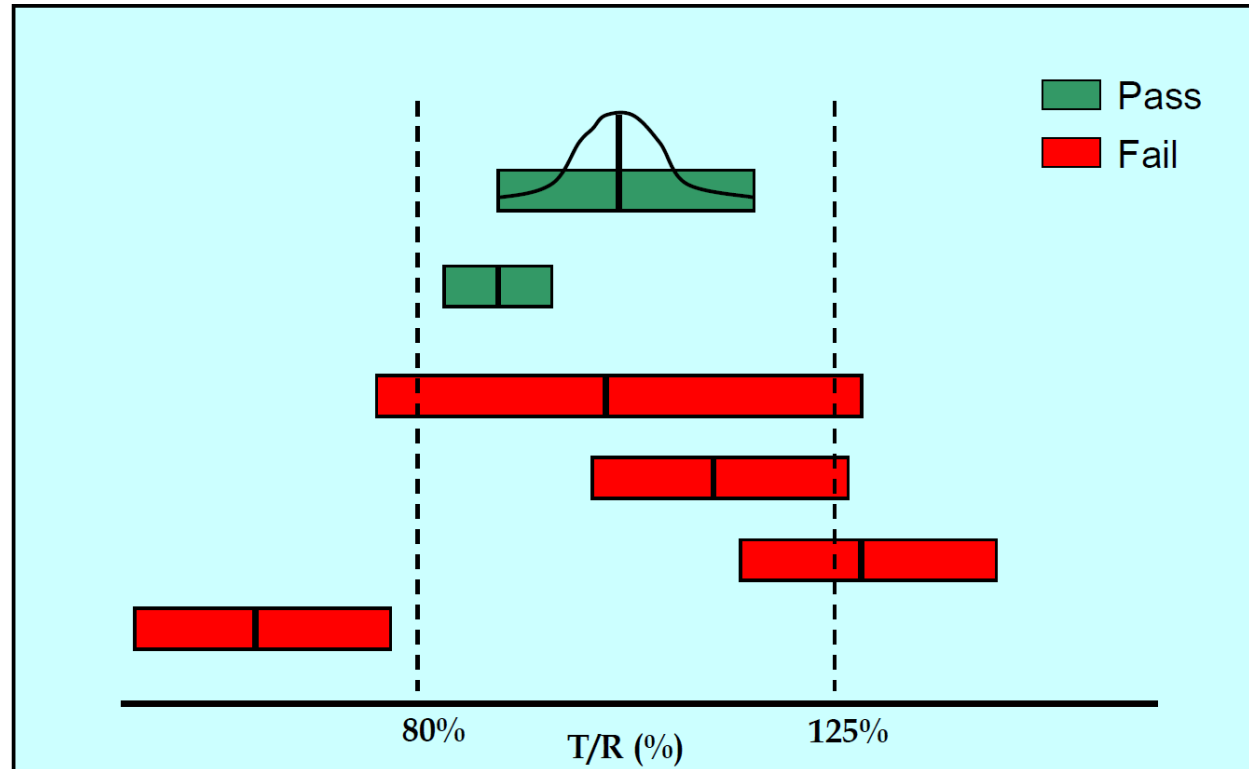
1. Chemistry, Manufacturing & Controls (CMC)
2. Testing
3. Labeling
4. Inspection
5. Bioequivalence

What is Bioequivalence?

- ***Bioequivalence*** is the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study

21 CFR 314.3

An Example of Bioequivalence



AUC and Cmax of T/R: 90% Confidence Intervals (CI) must fit between 80% - 125%

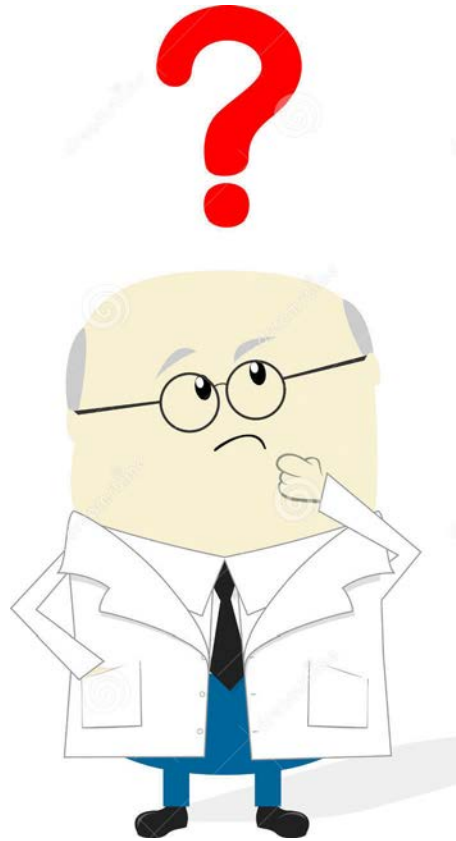
T = average of Test drug product

R = average of Reference drug product

Complex Products under GDUFA II

- Complex active ingredients
 - E.g., Complex mixtures of APIs, polymeric compounds, peptides
- Complex formulations
 - E.g., Liposomes, suspensions, emulsions, gels
- Complex routes of delivery
 - E.g., Locally acting such as ophthalmic, otic, dermatological and inhalational drugs
- Complex dosage forms
 - E.g., Long acting injectables and implantables
- Complex drug-device combinations
 - E.g., Metered Dose Inhalers and transdermals
- Other products where complexity or uncertainty concerning the approval pathway or other alternative approach would benefit from early scientific engagement

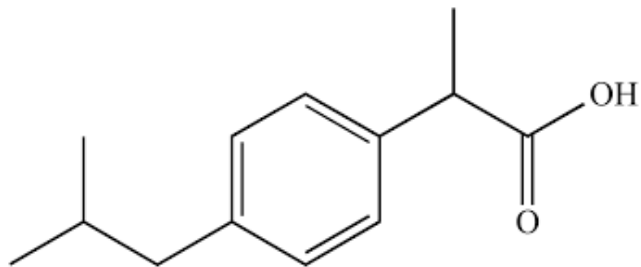
Equivalence Determination “Simple” vs “Complex”



Traditional Approach for Establishing Equivalence of an ANDA



- Active ingredient sameness API characterizations
- Pharmaceutical equivalence Same dosage forms ...
- Bioequivalence PK study ...



Challenges for Complex Generics

- Active ingredient sameness
 - Characterizing mixture of APIs
- Pharmaceutical equivalence
 - Characterizing complex formulation
 - Comparing inactive ingredients if needed*
 - Comparing impurities if needed
- Bioequivalence
 - Locally acting ...
- Same clinical effect and safety profile

How to demonstrate inactive ingredients, impurities and other allowed differences in a proposed drug product do not affect its safety or efficacy???

CFR Requirements on Generic Formulations



Section 314.94 Content and format of an abbreviated applicant

- (a)(9) Chemistry, manufacturing, and controls
 - (ii) Inactive ingredients. Unless otherwise stated in paragraphs (a)(9)(iii) through (a)(9)(v) of this section, an applicant must identify and characterize the inactive ingredients in the proposed drug product and provide information demonstrating that such inactive ingredients do not affect the safety or efficacy of the proposed drug product.
 - (iii)–(v) Specific inactive ingredient requirements for parenteral, ophthalmic, otic, and topical drug products, and differences permitted for such products

Q1/Q2 Requirement for Generic Parenteral Products



21 CFR 314.94 (a)(9)(iii) – *Inactive ingredient changes permitted in drug products intended for parenteral use.*

Generally, a drug product intended for parenteral use must 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 antioxidant 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.

Q1/Q2 Requirement 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 must 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

Q1/Q2 Requirement for Generic Topical Products



21 CFR 314.94 (a)(9)(v) – *Inactive ingredient changes permitted in drug products intended for topical use.*

Generally, a drug product intended for topical use, solutions for aerosolization or nebulization, and nasal solutions shall contain the same inactive ingredients (Q1) as the reference listed drug.

However, an ANDA may include different inactive ingredients 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.

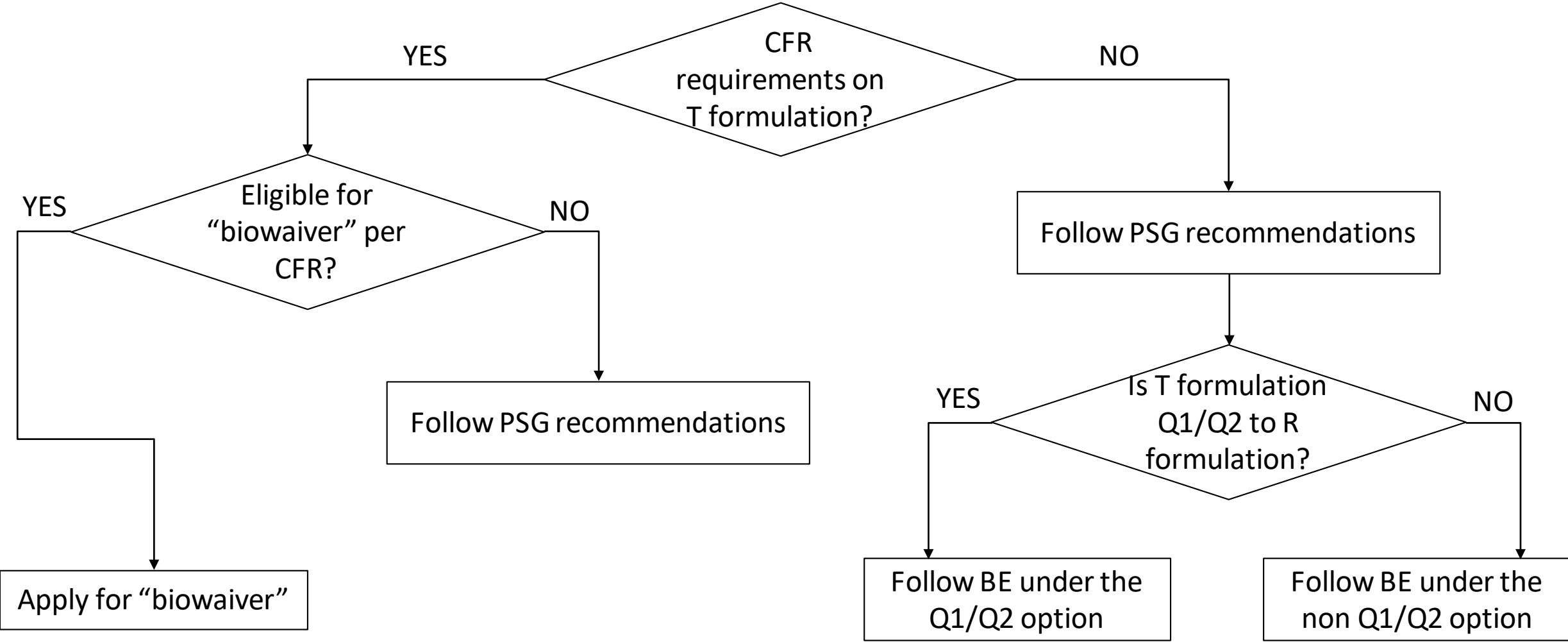
Q1/Q2 Assessments

- Q1: identity of an inactive ingredient. An applicant should provide detailed information on the chemistry and grade of each inactive ingredient, and characterization data, if needed for inactive ingredients.
- Q2: determine the difference (%) of an inactive ingredient in the Test (T) and Reference (R) products (i.e., $[(T-R)/R] \times 100$). The difference should not exceed 5%.

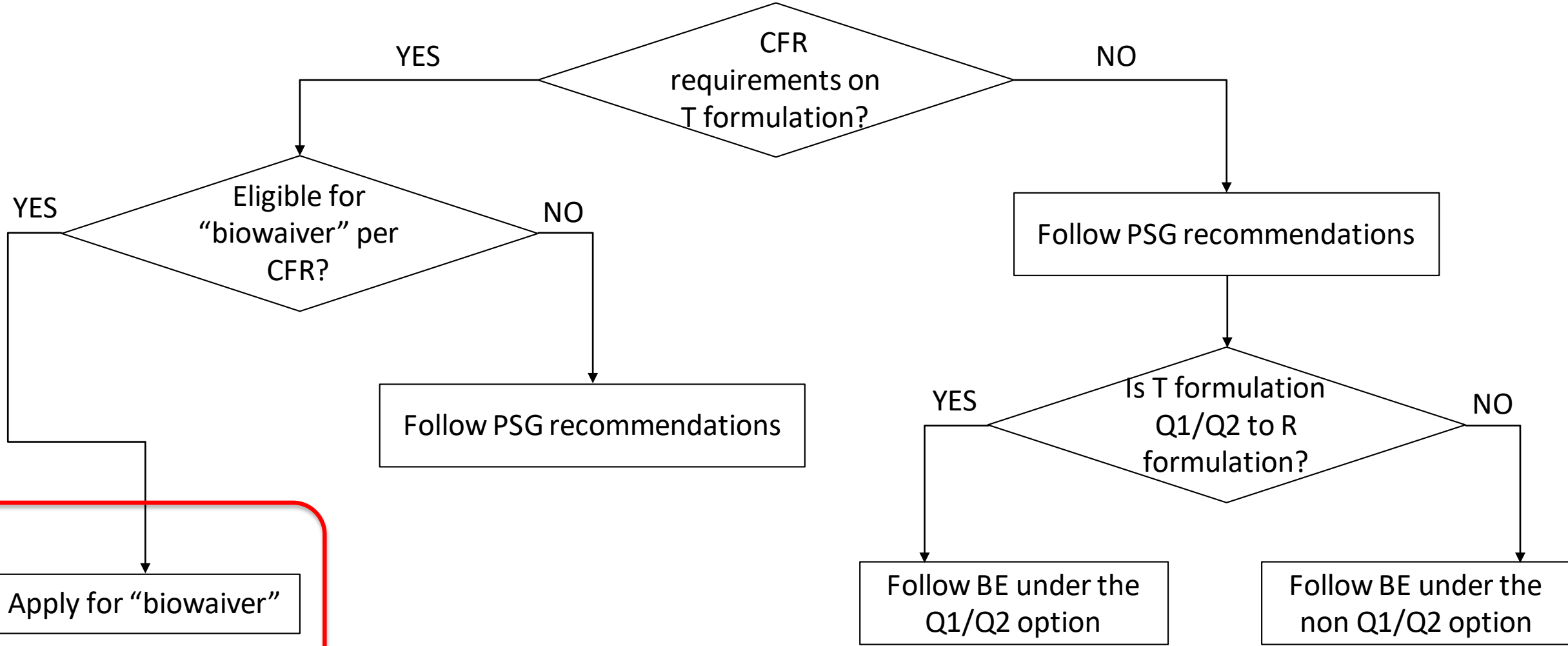
Bioequivalence Approaches

- In vivo PK study or a correlated in vitro study
- In vivo urine study
- In vivo PD study
- In vivo comparative clinical endpoint BE study
- In vitro test acceptable to FDA (usually dissolution rate test)
- Any other approach deemed adequate by FDA to measure bioavailability or establish bioequivalence

Formulation Variations and BE Approaches



Formulation Variations and BE Approaches

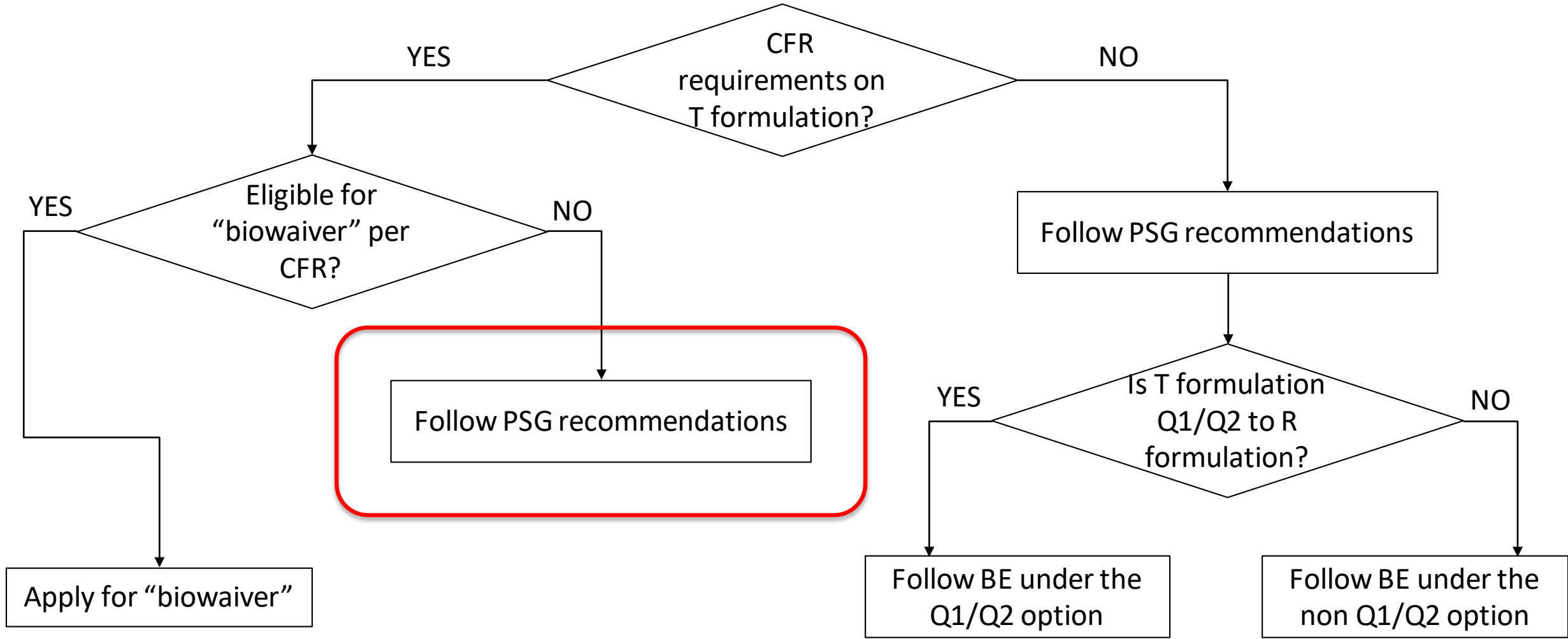


Bioequivalence and Q1/Q2



- Criteria for a “Biowaiver” under 21 CFR 320.22
 - (b)(1) The drug product is a parenteral solution intended solely for administration by injection, or an ophthalmic or otic solution; and contains the same active and inactive ingredients in the same concentration (Q1/Q2) as the RLD product
 - (b)(3) The drug product is a solution for application to the skin, an oral solution, elixir, syrup, tincture, a solution for aerosolization or nebulization, a nasal solution, or similar other solubilized form; ... and contains no inactive ingredient or other change in formulation from the drug product ... that may significantly affect absorption of the active drug ingredient or active moiety for products that are systemically absorbed, or that may significantly affect systemic or local availability for products intended to act locally.

Formulation Variations and BE Approaches



Bioequivalence and Q1/Q2 (continued)



Product specific guidance and FDA general guidance

- Parenteral suspension, emulsion, and liposome*
- Ophthalmic ointment, suspension and emulsion*
- Otic suspension*

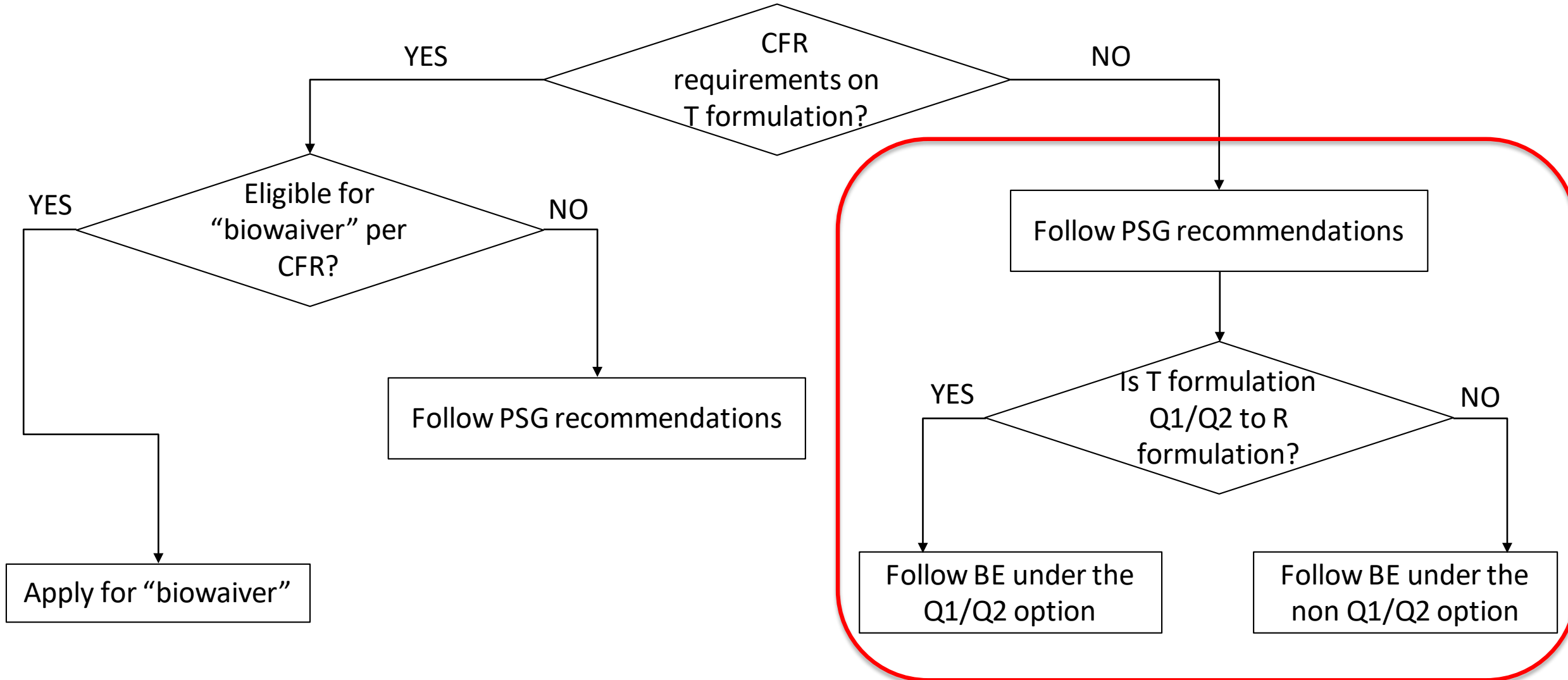
* Those formulation should be Q1/Q2 per 21 CFR 314.94 with permitted differences

In vitro BE option on Q1/Q2 Formulations of Parenteral, Ophthalmic and Otic Products



- Injectable suspension
 - Triamcinolone acetonide
- Ophthalmic suspension
 - Nepafenac, Dexamethasone/tobramycin, Prednisolone acetate, Loteprednol etabonate, Fluorometholone, Dexamethasone, Triamcinolone acetonide
- Ophthalmic ointment
 - Bacitracin, Erythromycin
- Ophthalmic emulsion
 - Cyclosporine, Difluprednate
- Otic suspension
 - Ciprofloxacin, Dexamethasone

Formulation Variations and BE Approaches

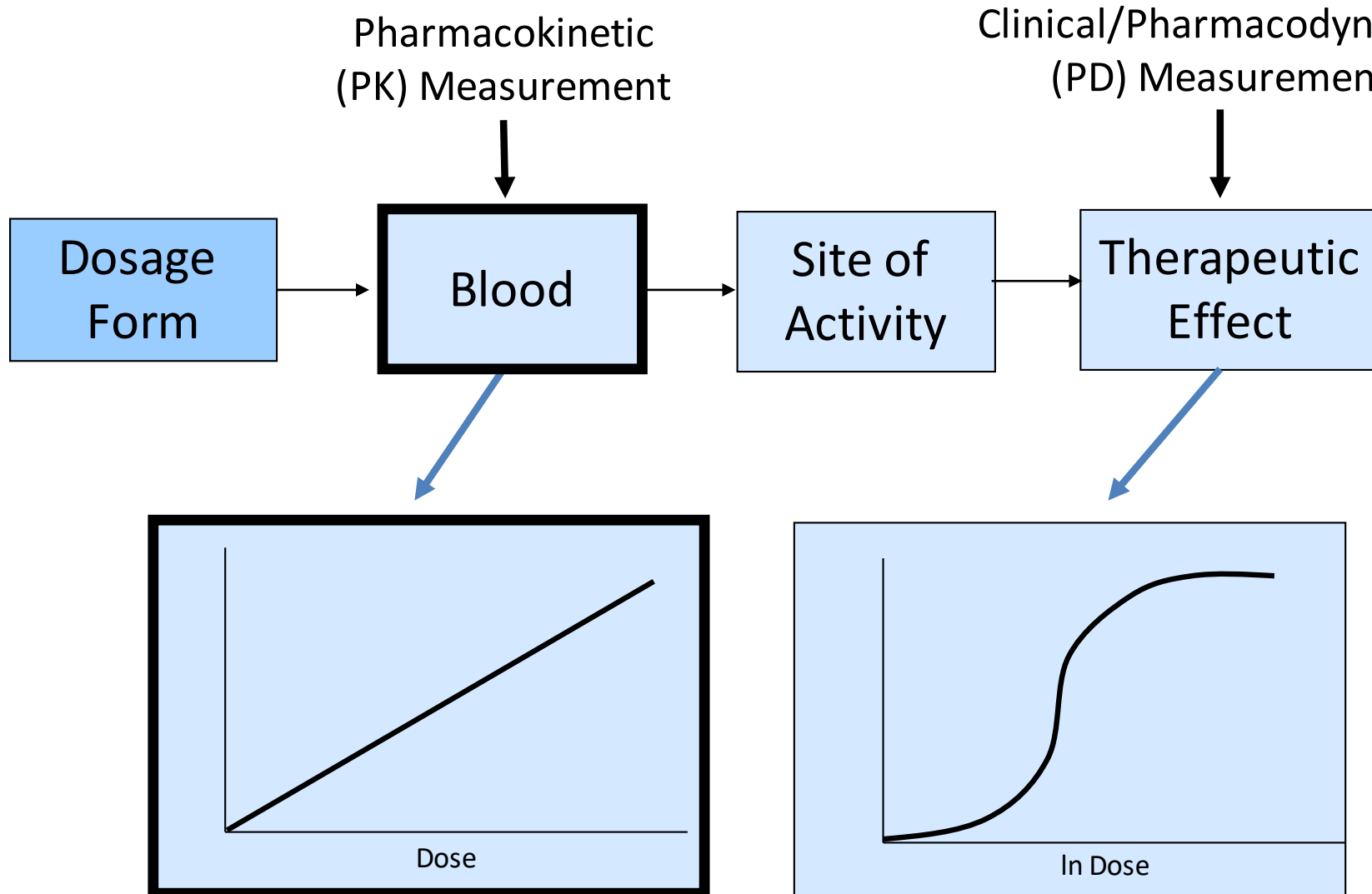


Bioequivalence and Q1/Q2 (continued)



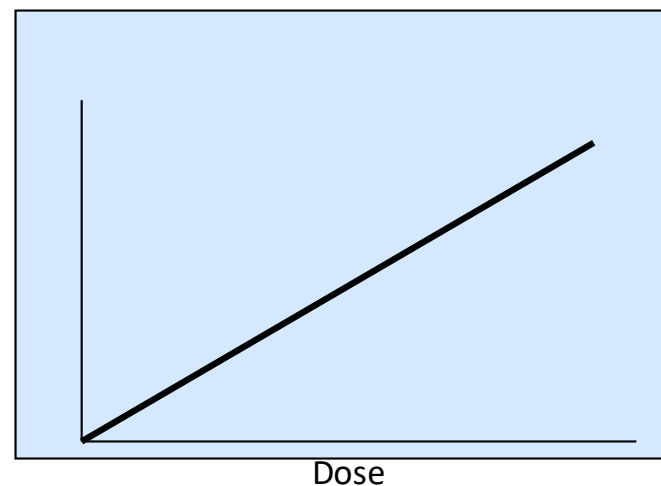
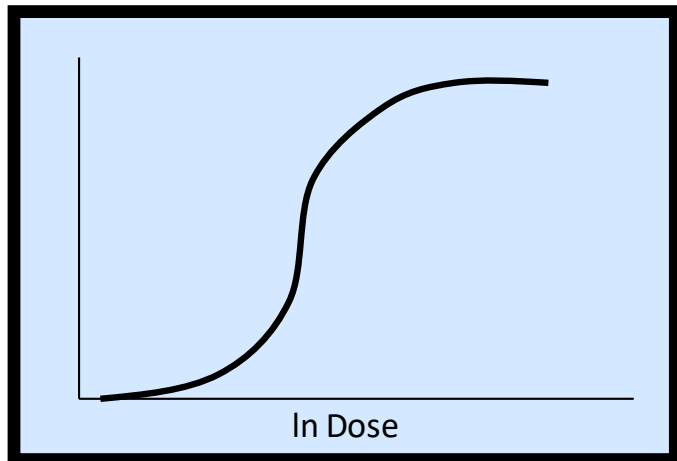
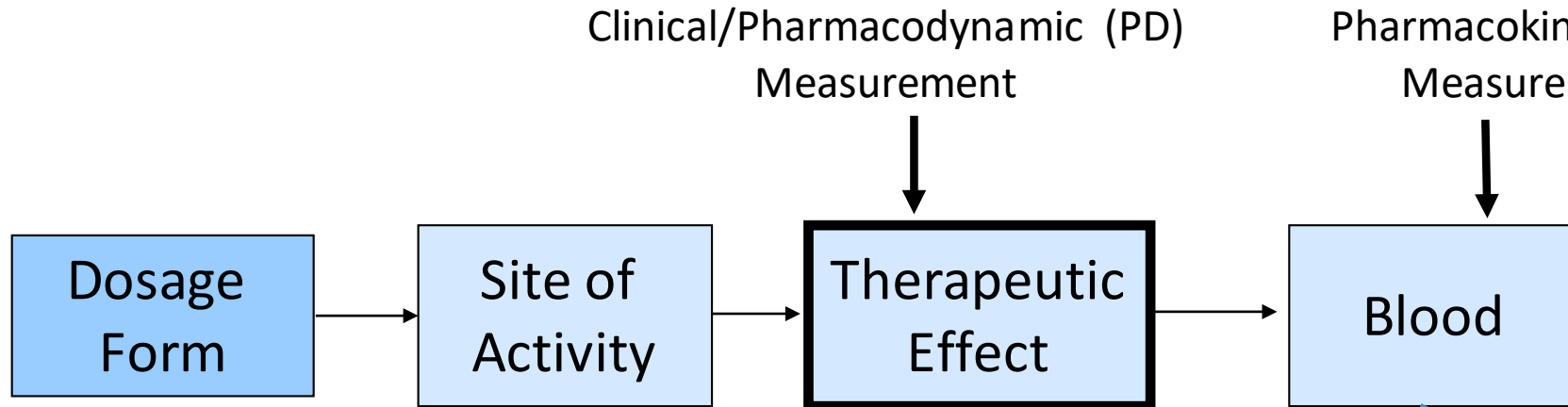
- Product specific guidance and FDA general guidance
- Orally inhaled and nasal drug products (OINDPs)
 - Topical dermatological products

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 (e.g., lung tissue or nose cavity)

Complexity of OINDPs



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



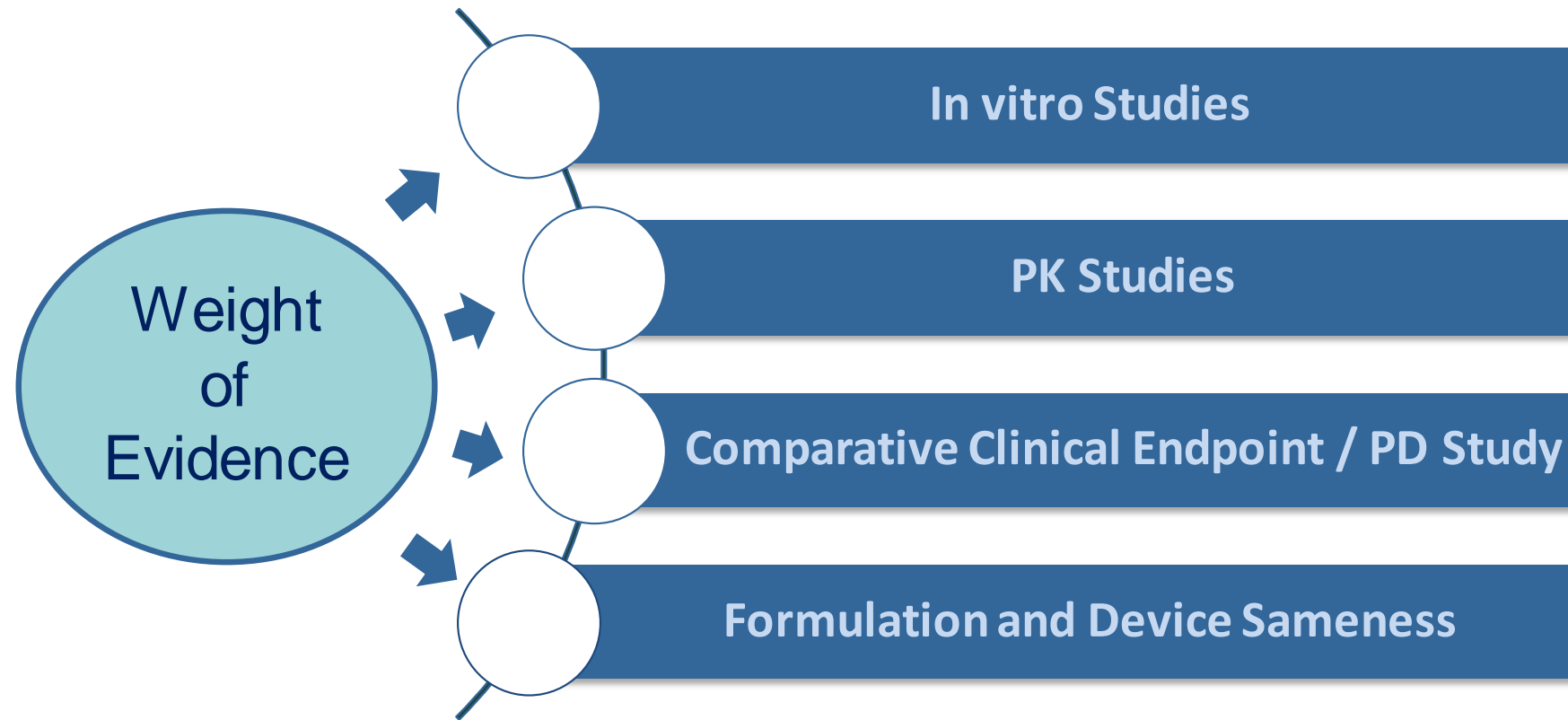
Orally inhaled and nasal drug products (OINDPs)

Challenges in Developing Locally Acting Generic OINDPs



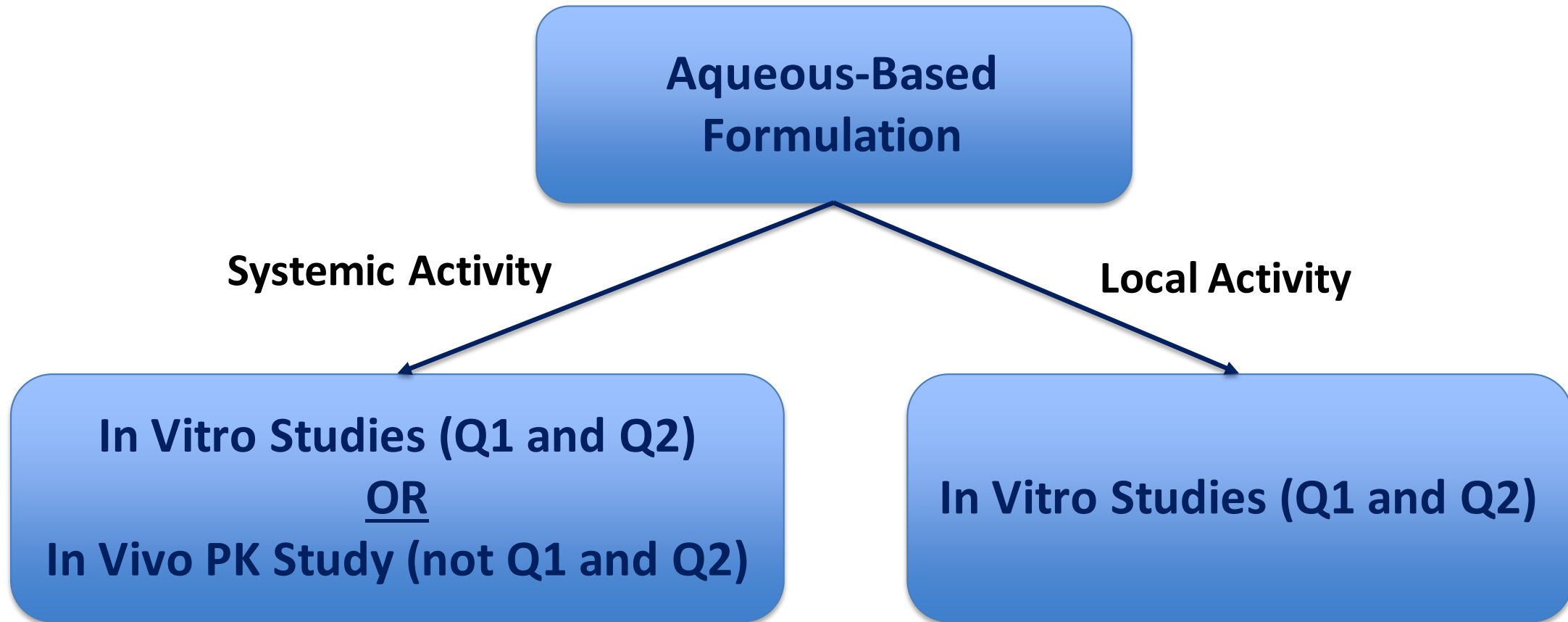
- Device is integral part of the delivered dose
- Several factors influencing drug local and systemic bioavailability
 - Patient-device interactions
 - Device-formulation interactions
 - Regional drug distribution
 - Local dissolution/permeability/clearance
- Drug delivery is local to the site of action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

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 BE Studies for Nasal Solution Products



Current PSGs for OINDPs



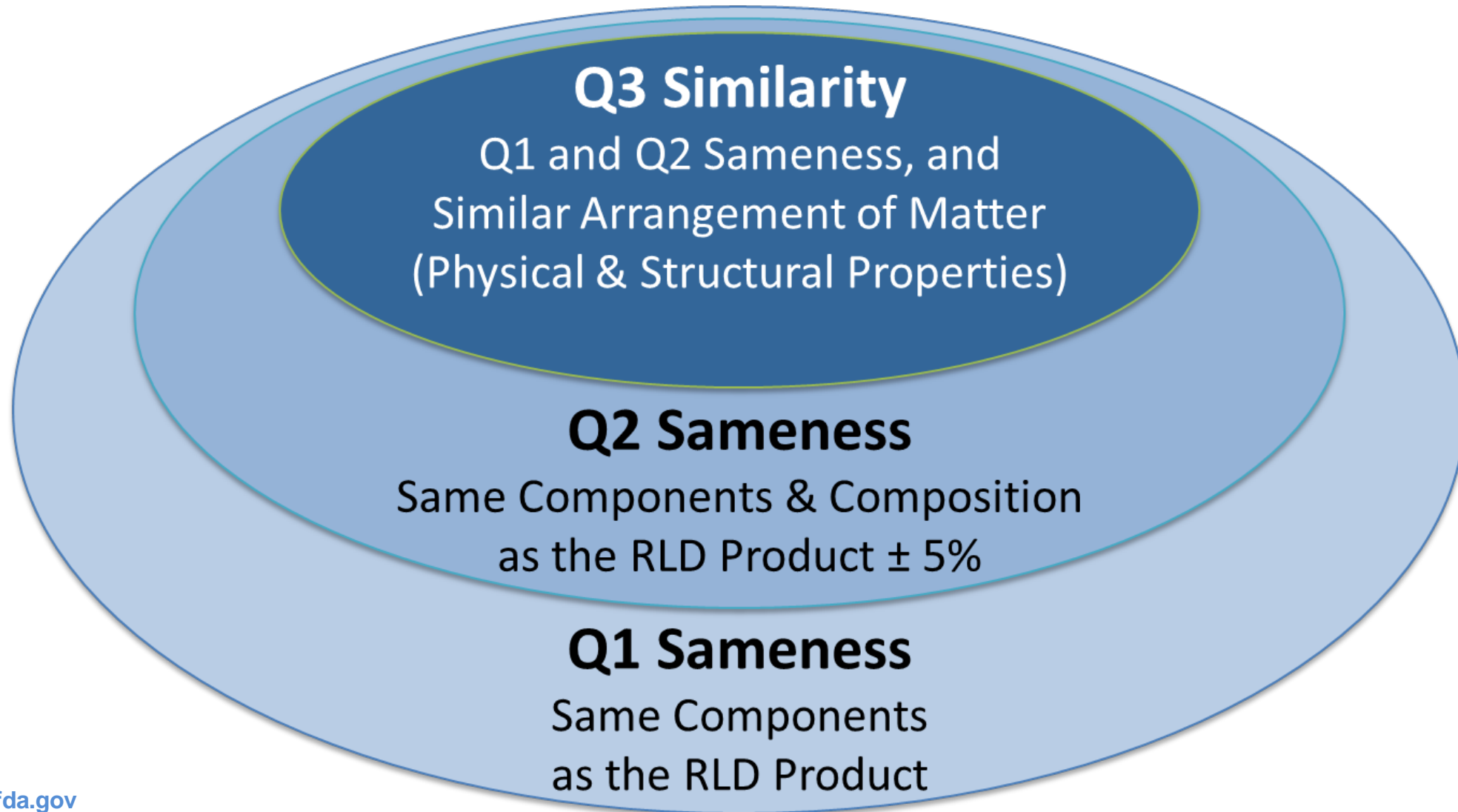
MDIs	DPIs	Nasal Solutions	Nasal Suspensions
<ol style="list-style-type: none"> 1. Fluticasone Propionate 2. Mometasone Furoate 3. Formoterol Fumarate and Mometasone Furoate 4. Ciclesonide 5. Beclomethasone Dipropionate 6. Albuterol Sulfate 7. Levalbuterol Tartrate 8. Budesonide and Formoterol Fumarate Dihydrate 9. Ipratropium Bromide <p>(Q1/Q2 + in vitro + in vivo BE)</p> <p>www.fda.gov</p>	<ol style="list-style-type: none"> 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. Acclidinium Bromide 13. Fluticasone Propionate and Salmeterol Xinafoate <p>(Q1/Q2 + in vitro + in vivo BE)</p>	<ol style="list-style-type: none"> 1. Ketorolac Tromethamine* 2. Olopatadine 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 <p>(Q1/Q2 + in vitro BE, *none Q1/Q2 + in vivo BE)</p>	<ol style="list-style-type: none"> 1. Azelastine Hydrochloride and Fluticasone Propionate 2. Triamcinolone Acetonide 3. Mometasone Furoate Monohydrate 4. Fluticasone Propionate <p>(Q1/Q2 + in vitro + in vivo BE)</p> <p>(Data collected through July 2018)</p>

Topical Dermatological Formulations



- Components, composition, physical and structural properties of a topical product can influence:
 - The drug state(s) and phase(s) of the dosage form
 - The distribution of the drug in the dosage form
 - Drug diffusion within the dosage form
 - Drug partitioning from the dosage form into the skin barrier
 - The structure and chemistry of the skin barrier
 - Drug diffusion within the skin itself
 - Drug delivery & bioavailability at the target site
 - Skin (de)hydration, irritation or damage
 - The metamorphosis of the dosage form on the skin

Q1/Q2/Q3 of Topical Generics



Q1/Q2 Sameness of Topical Generics



- Q1/Q2 Sameness (components and composition)

Mitigates the risk of known failure modes related to:

- Irritation and sensitization
- Formulation interaction with diseased skin
- Stability, solubility, etc. of the drug
- Vehicle contribution to efficacy

Q3 Similarity of Topical Generics

- Q3 Similarity (arrangement of matter)

Mitigates the risk of potential failure modes related to:

- Differences in permitted Q1/Q2 sameness ($\pm 5\%$ tolerances)
- Differences in pH that may sting or irritate diseased skin
- Differences in the polymorphic form of the drug
- Differences in rheology that alter the spreadability, retention, etc.
- Differences in entrapped air and drug amount per dose
- Differences in phase states and diffusion, partitioning, etc.
- Differences in metamorphosis and drying rates

BE and Q1/Q2/Q3 of Topical Generics



- Criteria to Qualify for a Biowaiver for Topical Solutions:
 - **Q1/Q2** sameness
- Criteria to Qualify for an In Vitro-Based BE Option:
 - **Q1/Q2** sameness
 - **Q3** similarity
- BE Options for Non-Q1/Q2/Q3
 - **E.g., In Vivo Comparative Clinical Endpoint** BE studies
 - **E.g., In Vivo Pharmacodynamic (Vasoconstrictor)** BE studies

BE and Q1/Q2 of Oral Drug Products



- Biopharmaceutics classification system (BCS) Class 1 and 3 Biowaiver
- Product specific guidances with in vitro option:
 - Acarbose Oral Tablets (8/2017)
 - Acyclovir Oral Buccal Tablets (9/2015)
 - Barium Sulfate Oral Paste (10/2017)
 - Barium Sulfate for Oral Suspension (2/2018)
 - Fidaxomicin Oral Tablets (8/2016)
 - Miglitol Oral Tablets (6/2015)
 - Sodium Phosphate Dibasic anhydrous & Sodium Phosphate Monobasic Monohydrate Oral Tablets (12/2012)
 - Sucralfate Oral Suspension (10/2017)
 - Vancomycin HCl Oral Capsules (12/2008)
 - Zolpidem Tartrate Oral Spray (4/2013)

Acknowledgement

- Office of Generic Drugs
 - Office of Research and Standards
 - Team of parenteral, ophthalmic, otic and implant products
 - Team of inhalation and nasal products
 - Team of dermal and transdermal products
 - Office of Bioequivalence
 - Office of Generic Drugs Policy
 - Office of Regulatory Operations
 - Division of Filing Review

Questions?





Additional Considerations for Q1/Q2



- Specify the quantitative amount of each ingredient (not “q.s.”)
- Specify each amount to the same number of decimal places
- Specify the nominal amount, not including any overages
- Use matching names of compendial standards if such grade materials are used
- The amount of any inactive ingredient should not exceed the relevant limit in the FDA Inactive Ingredient Database
- Perform comparative characterizations on functional inactive ingredients if recommended by PSG