



In Vivo Armamentarium & Integrated Assessment for Locally Applied Products

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Agenda

1	Does Clinical Bioequivalence Comes First?
2	Introduction
3	Regulatory Frameworks: FDA and EMA Decision Trees
4	In Vitro & Transitions to In Vivo
5	In Vivo – Decision Process, FDA vs EMA
6	In Vivo – VasoConstriction Assay, Transdermal Patches & Clinical End Point Study
7	Emerging Techniques – Iontophoresis, Microdialysis, Microperfusion, Microneedles, Tape Stripping
8	Nasal Sprays
9	Bioanalytical Considerations
10	Summary



Topical Applications Pre-Conclusion





Is Clinical BE Trial the Universal Default?

ARE IN VITRO AND PHARMACODYNAMIC METHODS THE EXCEPTIONS & NOT THE RULE?

- ▶ Every topical and transdermal generic can be approved for bioequivalence using a comparative clinical endpoint BE (CCEPBE) study — this pathway is always available
- ▶ The appropriate BE pathway depends on dosage form, site of action, systemic exposure, formulation complexity, and the current PSG
- ▶ In vitro (IVRT/IVPT) and pharmacodynamic (vasoconstrictor assay, VCA) pathways are alternatives FDA/EMA permit only when specific scientific criteria are met — they are not a wholesale replacement for clinical data as the reference standard
- ▶ Only a small, specific set of products has ever been approved for BE using IVRT or IVPT instead of a clinical trial — acyclovir ointment/cream is the classic IVRT example
- ▶ The reasons regulators created these alternatives are practical (cost, time, feasibility) — not a judgment that clinical trials are unnecessary or obsolete
- ▶ Rule of thumb for this talk: start from “what would the clinical trial look like” — then ask whether a validated alternative genuinely applies to your product



**“Let's evaluate
What is- & What is not- Appropriate”**

Introduction



Topical Products – *Treatment of Skin*

A PRACTICAL DECISION FRAMEWORK

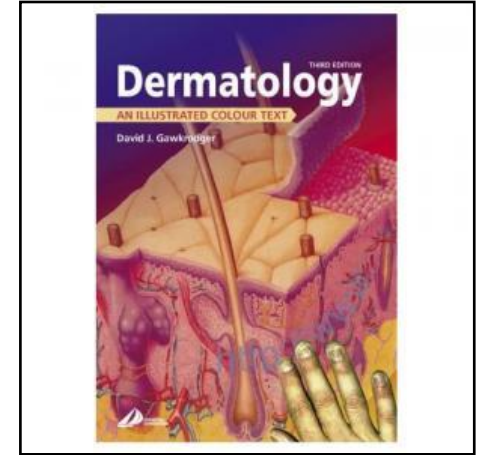
▶ Locally Acting Dermatologic Agents:

- ▶ *Salicylic acid creams or ointments used for warts and acne.*
- ▶ *Tretinoin creams used for acne and photoaging*
- ▶ *Petroleum jelly or zinc oxide ointments used for diaper rash and dry skin.*
- ▶ *Antifungals (clotrimazole or ketoconazole) creams used for athlete's foot and ringworm*
- ▶ *Corticosteroid (Hydrocortisone) creams used for eczema and insect bite inflammation*
- ▶ *Anesthetic (lidocaine or benzocaine) gels used for pain or minor burns*
- ▶ *Antiparasitic (Permethrin) lotions used for scabies or head lice*
- ▶ *Minoxidil topical solutions used for hair loss*

▶ Cosmetics

▶ Treat Un-Desired Skin Exposure (Toxic Compounds)

- ▶ *Corticosteroids (Prednisone & Prednisolone) for flare-ups, rashes, contact dermatitis (poison ivy), or immunobullous conditions*
- ▶ *Sunscreens*
- ▶ *Tretinoin for sun burns*
- ▶ *Calamine lotion for itching and blisters*



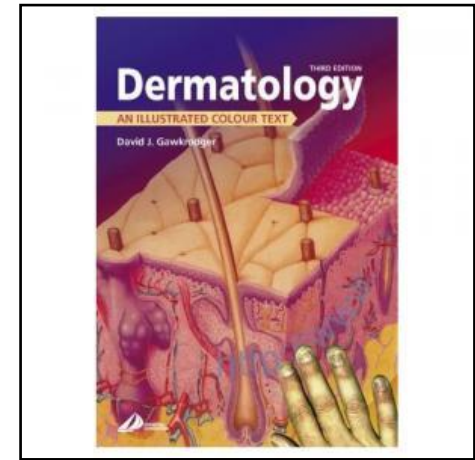


Topical Products – *Treatment of Skin*

A PRACTICAL DECISION FRAMEWORK

▶ Systemically Acting Dermatologic Agents (*Admin. Topically or Orally*):

- ▶ Isotretinoin (Accutane) for acne
- ▶ Acitretin (Soriatane) for severe plaque psoriasis and congenital ichthyosis
- ▶ Bexarotene (Targretin) for cutaneous T-cell lymphoma
- ▶ Scopolamine patch for motion sickness
- ▶ Dupilumab (Dupixent) inhibit IL-4 & IL-13 to treat moderate-to-severe atopic dermatitis (eczema)
- ▶ Secukinumab (Cosentyx) & Ixekizumab (Taltz) inhibit IL-17 to treat moderate-to-severe plaque psoriasis
- ▶ Adalimumab (Humira) & Etanercept (Enbrel) inhibit TNF-alpha to treat for severe psoriasis and hidradenitis suppurativa
- ▶ Immunosuppressants Methotrexate & Cyclosporine for severe plaque psoriasis and severe atopic dermatitis
- ▶ Azathioprine & Mycophenolate Mofetil for severe autoimmune blistering skin conditions like lupus
- ▶ Janus kinase (JAK) inhibitors Upadacitinib (Rinvoq) & Abrocitinib (Cibinqo) for severe atopic dermatitis and alopecia areata
- ▶ Phosphodiesterase-4 (PDE-4) inhibitor Apremilast (Otezla) for underlying inflammatory cycles in plaque psoriasis
- ▶ Antibiotics (Doxycycline, Minocycline, Sarecycline) are antibacterial/antimicrobial agents for moderate-to-severe acne and rosacea
- ▶ Antifungals (Terbinafine, Fluconazole, Itraconazole) for severe tinea capitis (scalp ringworm) or onychomycosis (fungal nail infections)

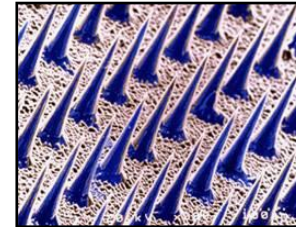




Topical Products - *Formulation Designs*

A PRACTICAL DECISION FRAMEWORK

- ▶ Liquids and Semi-Solids
 - ▶ *Solutions, Gels, Emollients,*
 - ▶ *Creams, Ointments*
- ▶ Trans-Dermal Delivery Systems
 - ▶ *Patches*
 - ▶ *Semi-solids*
- ▶ Cutaneous Injections
- ▶ Mechanical Systems
 - ▶ *Microneedles*
 - ▶ *Iontophoresis*



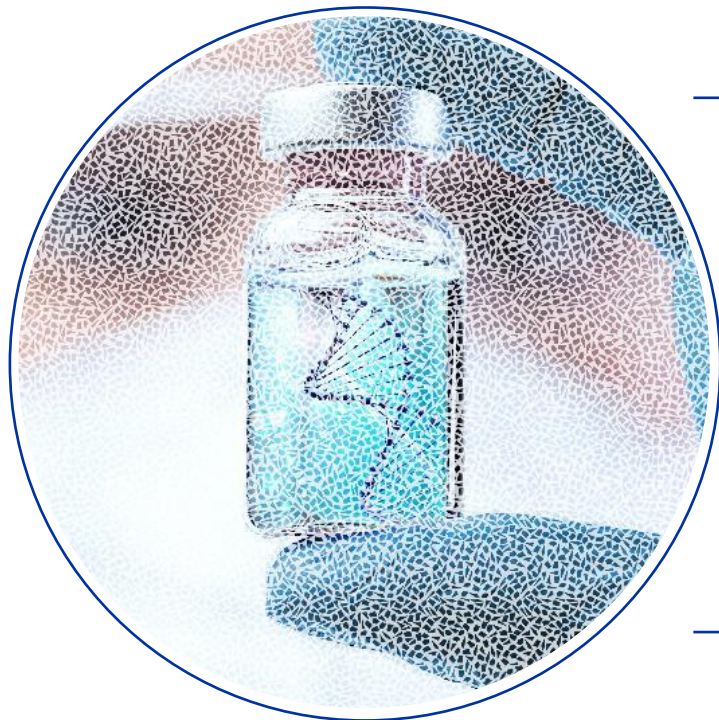
Microneedles



Topical Products – *Study Types*

A PRACTICAL DECISION FRAMEWORK

- ▶ BA/BE
 - ▶ *PK for Dermatologics*
 - ▶ *Blood Levels for Transdermals*
 - ▶ *Vasoconstriction for Corticosteroids*
- ▶ Safety
 - ▶ *Safety (Irritation and Sensitization)*
 - ▶ *Photo-Toxicity*
 - ▶ *QTc*
 - ▶ *Chronic Exposure Issues*
- ▶ Efficacy
 - ▶ *First in Humans*
 - ▶ *Phase II – Phase IV*
- ▶ Performance/Claims Substantiation
 - ▶ *Cosmetics*
 - ▶ Fine-Line Wrinkles
 - ▶ Moisturization
 - ▶ Skin Lightening
 - ▶ Dry Skin
 - ▶ *SPF Testing*



Regulatory Frameworks: FDA and EMA Decision Trees



Determine Therapeutic equivalence of Topical Products

A PRACTICAL DECISION FRAMEWORK

Prove Efficacy and Safety Profile of the test and reference products is sufficiently comparable

Prove any Clinically relevant difference between products can be reliably excluded

Demonstration of therapeutic equivalence is a stepwise approach*

*EMA/CHMP/QWP/708282/2018 Corr.1 — Guideline on quality and equivalence of locally applied, locally acting cutaneous products (adopted 9 Sept 2024, effective 2 April 2025)



EMA's Stepwise Approach: The Same Philosophy

IN VITRO IS A BRIDGE; PD/CLINICAL REMAINS THE FALLBACK OF RECORD

- ▶ Step 1 — Pharmaceutical equivalence: same Q1/Q2 composition and Q3
physicochemical/structural characterization vs. the reference product
- ▶ Step 2 — Permeation kinetics: IVPT, TS or IVRT
as a bridge for simple formulations
- ▶ Step 3 — Pharmacodynamic or clinical study: required whenever Steps 1–2 cannot establish equivalence, or whenever the drug's site of action lies deeper than the skin
can bridge via PK
- ▶ Corticosteroids - Vasoconstriction is explicitly recognized (Annex IV) as the accepted PD method
mirroring FDA's VC pathway
- ▶ **When Permeation kinetics (Step 2) fails & no validated PD model exists (Step 3-N/A)**
EMA's guidance recommends reformulating the product rather than defaulting to a weaker in vitro claim
Clinical/PD evidence is not optional when the bridge doesn't hold (EMA, Section 5.4)

IVRT = in vitro skin permeation, TS = in vivo stratum corneum tape stripping, IVPT = in vitro release test



FDA's Four BE Approaches for Topical Products

PSGS OFTEN NAME MORE THAN ONE ACCEPTABLE OPTION

Comparative Clinical Endpoint BE study	CCEPBE	the universal default*
Characterization-based BE approach	Q3 + IVRT Q3 + IVRT & IVPT Q3 + IVRT & in vivo PK	Depends on formulations**
Vasoconstrictor	VCA	Topical Corticosteroids***
Waiver of in vivo BE studies	For simple, well-characterized formulations meeting strict sameness criteria	Follow PSGs

Example: FDA's PSGs for psoriasis products alone allow corticosteroids to use a waiver, VC study, characterization-based approach, OR a CCEPBE study — the applicant chooses the best-fit route, clinical remains available throughout

*FDA: Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA; May 2026

**FDA: Physicochemical and Structural (Q3) Characterization of Topical Drug Products Submitted in ANDAs; March 2026

**FDA: In Vitro Release Test Studies for Topical Drug Products Submitted in ANDAs Oct 2022

**FDA: In Vitro Permeation Test Studies for Topical Drug Products Submitted in ANDAs Oct 2022

***FDA: Topical Dermatologic Corticosteroids: In Vivo Bioequivalence Guidance for Industry; July 2026



**In Vitro
Q1, Q2, Q3, IVRT & IVPT
& Where it Transitions to
In Vivo**





Characterization

A PRACTICAL DECISION FRAMEWORK

- ▶ Q1 - Qualitative Composition
- ▶ Q2 - Quantitative Composition
- ▶ Q3 – Physicochemical properties

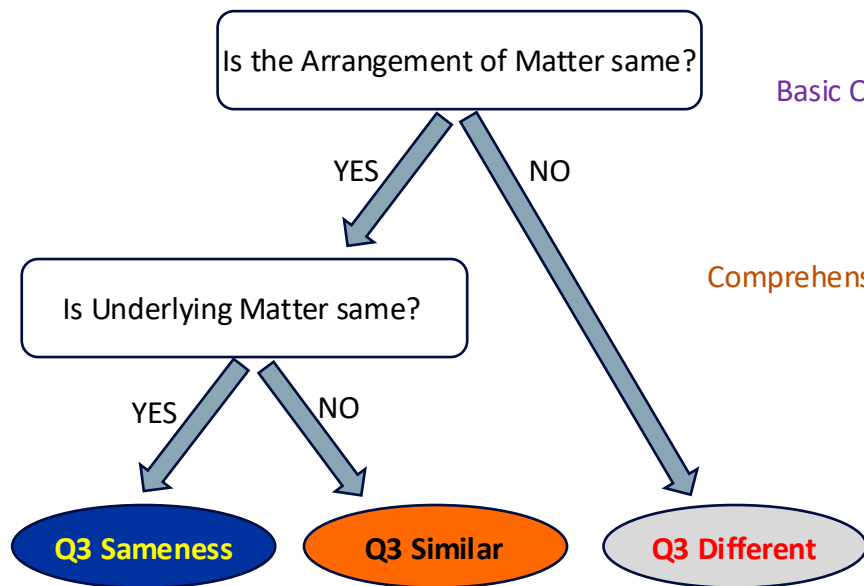
	Simple Formulation	Complex Formulation
Characterization of Excipient	Easy	Difficult
If Excipient Enhances Drug Permeability	Does not Enhance	Enhances



Characterization Based BE

A PRACTICAL DECISION FRAMEWORK

► Q1/Q2 match + Q3 match – in case of a Simple Solution



Basic Q3

- 1. Characterization of appearance and texture
- 2. Characterization of phase states
- 3. Characterization of structural organization of matter

Comprehensive Q3

- 4. Characterization of polymorphic form of the active ingredient
- 5. Characterization of rheological behavior
- 6. Characterization of water activity and/or drying rate
- 7. Characterization of pH and buffering
- 8. Characterization of oleaginous components
- 9. Characterization of specific gravity
- 10. Characterization of metamorphosis-related changes



The “No Significant Difference” (NSD) Standard

NOT EVERY FORMULATION DIFFERENCE FORCES A CLINICAL TRIAL

- ▶ USP Excipients between Test and Ref — allows for minor grade differences, but same function and level
- ▶ NSD expands eligibility for the characterization-based BE approach
a product doesn't have to be a perfect Q1/Q2 match to skip straight to a clinical trial
- ▶ Q1 (qualitative sameness) / Q2 (quantitative sameness)
but also recognizes certain excipient differences as scientifically inconsequential
- ▶ Comparative Q3 characterization data needed
across ≥ 3 batches of test and reference product to support the substitution
- ▶ NSD keeps more products inside the “characterization + IVRT/IVPT” lane
reserving clinical trials for differences that could plausibly change local or systemic availability

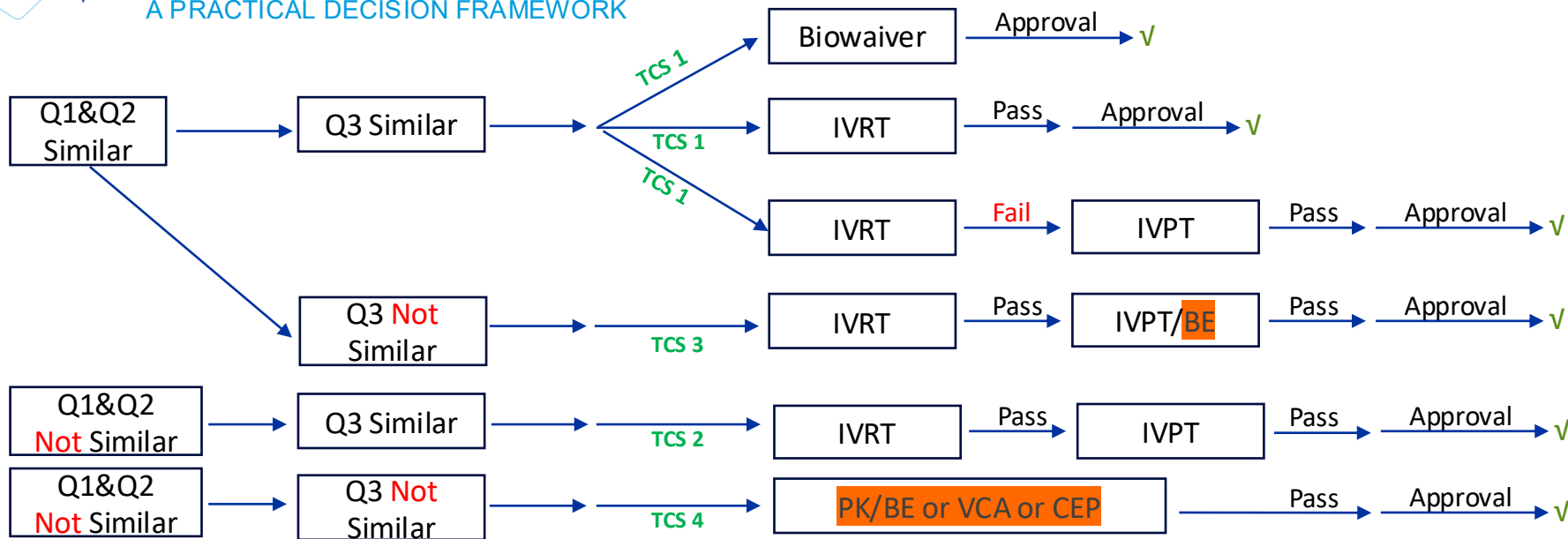
*FDA: ANDA Submissions – Refuse-to-Receive Standards, December 2016



In Vitro, In Vivo — or Both?

A PRACTICAL DECISION FRAMEWORK

TCS = Topical Drug Classification



- ▶ Systemic safety concerns (potent/toxic actives) → in vitro preferred wherever a validated model exists, to limit human exposure
- ▶ When a clinical endpoint would require an impractically large or slow trial (e.g., acyclovir's ~5,000-patient problem) → regulators increasingly accept a well-validated in vitro (IVRT/IVPT) pathway instead
- ▶ IVPT or TS (Tape Stripping) – drugs w/o skin permeation, i.e. on surface (but not for buccal, rectal or vaginal)



IVRT: A Manufacturing and Formulation Tool First

BIOEQUIVALENCE USE IS THE EXCEPTION, NOT THE ORIGINAL PURPOSE

- ▶ IVRT's original purpose:*
- ▶ *QC procedure to characterize the dosage form*
- ▶ *assure lot-to-lot bioavailability equivalence*
- ▶ *support minor reformulations*
- ▶ *study release/permeation during product development*
- ▶ The original 1987 workshop report explicitly did NOT contemplate IVRT as an alternative for approving generics based on in vitro bioequivalence
- ▶ Current BE applications:**
- ▶ *A small number of PSGs use IVRT to demonstrate BE outright (acyclovir being the best-known case)*
- ▶ *most PSGs that include IVRT pair it with additional data (Q3 characterization, IVPT, or PK)*
- ▶ Bottom line: treat IVRT as your formulation/manufacturing monitoring tool by default
- ▶ *its use as a stand-alone BE tool is the exception you must specifically justify*

*SUPAC-SS, May 1997

**"In Vitro Release Test (IVRT) and In Vitro Permeation Test (IVPT) Methods: Best Practices and Scientific Considerations for ANDA Submissions", August 18–20, 2021

**FDA: In Vitro Release Test Studies for Topical Drug Products Submitted in ANDAs Oct 2022



IVPT: A Formulation Tool, a Situational BE Alternative

WHAT IVPT CAN — AND CANNOT — TELL A REVIEWER

- ▶ Primary use: formulation development
 - ▶ *screening vehicles, penetration enhancers, and prototype formulations for percutaneous delivery before a clinical program begins*
- ▶ Secondary use: an FDA-accepted BE alternative for only a limited, growing set of PSGs
 - ▶ *not a universal substitute for clinical or IVRT data*
- ▶ IVPT measures percutaneous absorption kinetics only (permeation rate and extent)*
- ▶ Critical limitation: IVPT does NOT demonstrate in vivo metabolism, route of excretion, efficacy, or safety
- ▶ Practical value when PK is infeasible: when in vivo blood levels fall below the bioanalytical LLOQ, IVPT can be purpose-designed to measure percutaneous absorption directly, rather than relying on unquantifiable in vivo data**
- ▶ So: IVPT tells you drug got into/through skin at a certain rate — it does not tell you the drug worked, was safe, or how the body handled it afterward

*FDA and AAPS Report of the Workshop on Principles and Practices of In Vitro Percutaneous Penetration Studies: Relevance to Bioavailability and Bioequivalence; June 1987, Pharmaceutical Research 4(3)

**FDA: In Vitro Permeation Test Studies for Topical Drug Products Submitted in ANDAs Oct 2022



IVPT “Coming of Age”? — The Honest History

IN VITRO–IN VIVO CORRELATION HAS IMPROVED, BUT UNEVENLY

- ▶ “Human skin is notorious for its high level of barrier variability”¹
 - ▶ *still a live challenge for IVPT reproducibility today*
- ▶ In Vitro does not correlate to In Vivo Absorption²
 - ▶ *historical interlaboratory variability - poor agreement in the data*
 - ▶ *harmonized best practices & validated methods - a large improvement, but on a much smaller, more curated data set*
- ▶ Absorption ≠ Efficacy: “in vitro absorption does not correlate to in vivo efficacy” was the norm
 - ▶ *IVPT was found to be substantially more sensitive and less variable than the VC assay for assessing clobetasol bioavailability*³
 - ▶ *IVPT comparison to VC and/or TS across many corticosteroid formulations indicated that IVPT is a suitable surrogate test for BA/BE*⁴
- ▶ IVPT is a maturing method
 - ▶ *with real, product-specific validation gaps — not a settled, drop-in replacement for in vivo evidence*⁵

¹FDA and AAPS Report of the Workshop on Principles and Practices of In Vitro Percutaneous Penetration Studies: Relevance to Bioavailability and Bioequivalence; June 1987, Pharmaceutical Research 4(3)

²P.A. Lehman, S.G. Raney, T.J. Franz: Percutaneous Absorption in Man: In vitro-in vivo Correlation. Skin Pharmacol Physiol (2011) 24 (4): 224–230

³P Lehman, Franz T: Assessing topical bioavailability and bioequivalence: A comparison of the in vitro permeation test and the vasoconstrictor assay. Pharm Res 31(12):3529-3537, 2014

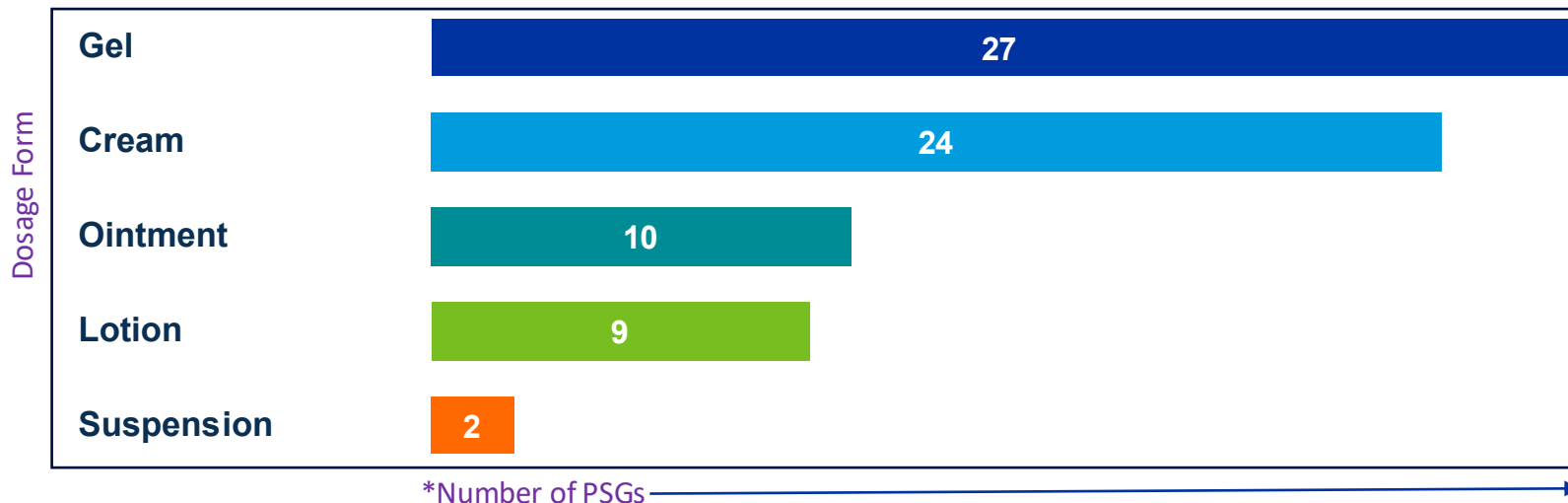
⁴Lehman PA, Franz TJ. Cutaneous Bioavailability of Corticosteroids from Topical Formulations: a Retrospective Analysis of Data from In Vitro Permeation Testing (IVPT) and In Vivo Assessments. Pharm Res. 2026 Jun;43(6):2055-2068

⁵FDA: In Vitro Permeation Test Studies for Topical Drug Products Submitted in ANDAs Oct 2022



PSG Snapshot: Characterization-Based BE by Dosage Form

PRODUCT-SPECIFIC GUIDANCES USING A CHARACTERIZATION-BASED APPROACH



► Real examples from current PSGs:

- *Doxepin hydrochloride cream requires – Q1, Q2, Q3, IVRT, IVPT (May 2026)*
- *By contrast, several antifungal creams (e.g., ketoconazole, luliconazole) - Q1, Q2, Q3, IVRT OR CEP (Oct 2026) – skips IVPT*



In-Vivo Decision Process

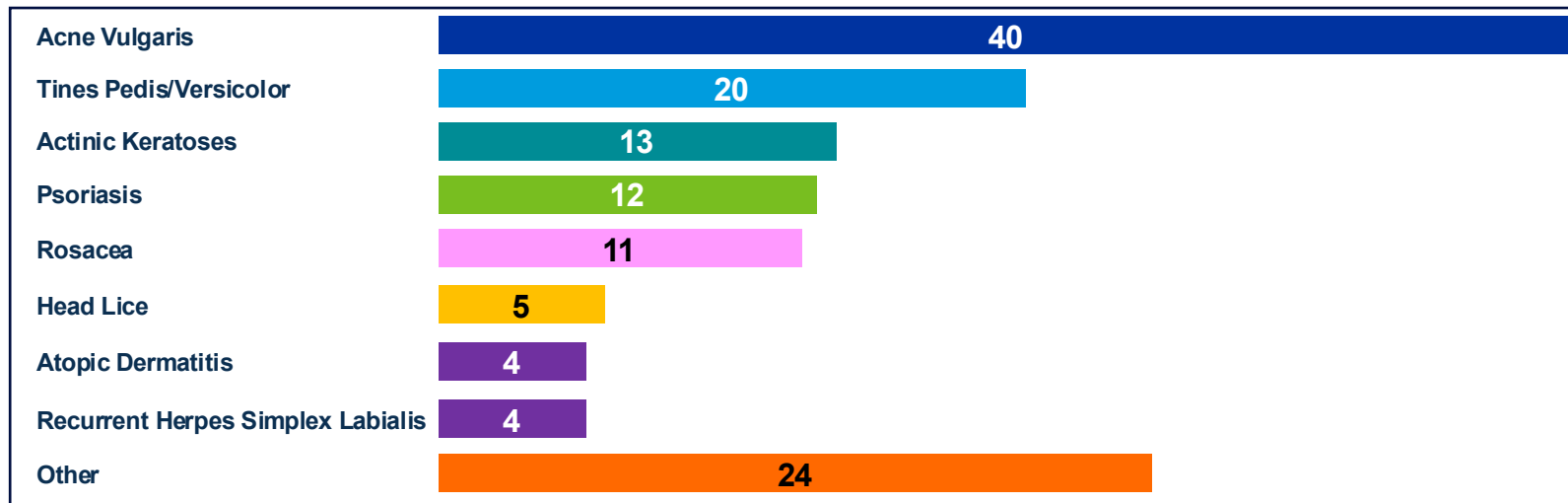




PSG Snapshot: CCEPBE studies for Topical products

IN VITRO AND PHARMACODYNAMIC METHODS ARE THE EXCEPTIONS, NOT THE RULE

Indications



*Number of PSGs



Clinical & Application Challenges to PK/BE Studies for Topicals

IN VITRO AND PHARMACODYNAMIC METHODS ARE THE EXCEPTIONS, NOT THE RULE

▶ Healthy Volunteer Recruitment

- ▶ *History of skin reaction, Baseline abnormalities/pre-existing, Compliance & Exposure to sunlight/cosmetics/soaps*

▶ Application & Dosing

- ▶ *positioning, application pressure and time, consistency (more challenging for cream/gel/solution)*
- ▶ *site election, skin inspection, hair removal if needed*
- ▶ *duration of dose, number of doses, removal of dose*
- ▶ *prevention of un-Intentional removal/detachment*

▶ Blinding

▶ Environmental Control (Humidity and Temperature)

- ▶ *travel, exercise, excessive sweating*

▶ PK sampling

- ▶ *Accuracy is required*

▶ Safety

- ▶ *Local (Application Site) or Systemic Adverse Events*



Regulatory Strategy for Approval of Topical Applications

CREAMS, GELS, LOTIONS, SOLUTIONS (KEY DIFFERENCES- EMA VS FDA)

	EMA	FDA
Regulatory strategy	Stepwise, totality-of-evidence approach	In-vivo PD-driven BE approach
BE pathway	Q1/Q2/Q3 → IVRT → IVPT/SC sampling → PD/clinical endpoint, as needed	Pilot → ED50/Emax → pivotal vasoconstrictor BE
In-vitro evidence	IVRT and IVPT explicitly integrated into equivalence assessment	In-vitro data are supportive; vasoconstrictor PD is the core approach in this guidance
Tape stripping	Explicitly recognized as an equivalence method	Not a principal method in this guidance
Vasoconstrictor assay	One of several approaches for corticosteroid equivalence	Primary in-vivo BE method
Pilot study	Used mainly to optimize dose/application duration	Used to establish dose–duration response and ED50/Emax
Study design & controls	Test + Reference + Vehicle + Untreated controls	Test + Reference + D1/D2 calibrators + Untreated controls
Statistics / sample size	Minimum 12 subjects for corticosteroid vasoconstrictor assay; conventional equivalence analysis	Pivotal study powered for adequate detectors; specialized AUEC/PD analysis
Overall flexibility	More flexible; alternative approaches may avoid clinical endpoint studies	More prescriptive for the corticosteroid in-vivo PD pathway

Controlled Correspondence with EMA is the best option



Cost and Time: The Real Trade-offs

IN VITRO AND PHARMACODYNAMIC METHODS ARE THE EXCEPTIONS, NOT THE RULE

Vasoconstrictor (VC) Assay

COST
Cheapest & Fastest

TIME
Weeks to ~2 months

Clinical BE Trial (CCEPBE)

COST
~\$200K–\$400K

TIME
~3–4 months

IVPT Study

COST
**Often cheaper \$
than clinical**

TIME
**~6–12 months
(slower)**

IVPT's appeal is dollar cost, not speed — a sponsor choosing IVPT to “go faster” is often mistaken; it typically takes longer than the clinical trial it replaces*

**cost and duration range are assumptions from past experience; actual timelines may vary with method readiness, recruitment, product, and regulatory feedback*



In Vivo VCA, Patches, CEP





Human Dermal VC Study Designs

TOPICAL CORTICOSTEROIDS: IN VIVO BIOEQUIVALENCE - 1

Implementation Roadmap

Phase 1

Q1/Q2/Q3 Formulation development,
Initial IVRT release testing



Phase 2

Pilot HSBA study to establish ED-50 and select D1 / D2 durations (DRF)



Phase 3

Pivotal In-vivo BE study in healthy responder subjects (Dose & Durations from PL)



Phase 4

Statistical 90% CI validation
ANDA regulatory filing submission

HSBA = Human Skin Blanching Assay

DRF = Dose Range Finding



Human Dermal VC Study Designs

TOPICAL CORTICOSTEROIDS: IN VIVO BIOEQUIVALENCE - 2

Study Protocol Comparison

Parameter	Pilot Dose-Response Study	Pivotal In Vivo BE Study
Primary Objective	Determine ED 50 & dose durations	Demonstrate T vs R bioequivalence
Sample Size	12 – 24 Healthy Volunteers	40 – 80 Validated Responders
Dose Durations	Multiple intervals (0.25 to 6 hours)	Fixed dose (D1 & D2) durations
Primary Metric	Emax model dose response curve	AUEC 90% Confidence Interval



0



1



2



3



4



Transdermal Patches: In Vivo PK Is the Default

SYSTEMIC ABSORPTION IS MEASURABLE — SO PK LEADS

- ▶ Because transdermal delivery systems are designed for systemic absorption, blood levels are typically quantifiable
 - ▶ *In vivo PK bioequivalence study the natural first-choice method*
 - ▶ *PK confirms exposure, disposition and systemic bioequivalence*
- ▶ Unlike most locally-acting topicals, where systemic levels are low and PK alone cannot support a BE claim
- ▶ Adhesion and Irritation/Sensitization (I/S) studies are companions to the PK study, not substitutes
 - ▶ *PK helps understand the absorption and distribution of the active pharmaceutical ingredient (API)*
 - ▶ *Adhesion confirms performance and retention*
 - ▶ *I/S confirms tolerability, skin/system immune reaction*
- ▶ Safety driven Study Designs
 - ▶ *Single or Multi dose for PK depending on the patch dose application*
 - ▶ *Test & Ref as ½ patches to avoid overdosing*
 - ▶ *I/S studies can we with/without drug (placebo)*
 - ▶ *For potent actives (e.g., fentanyl, nicotine, methylphenidate, testosterone patches) use placebo patches*
- ▶ IVPT has a role here too
 - ▶ *chiefly in formulation development, and as a way to characterize absorption when PK sampling alone would be underpowered near LLOQ*
- ▶ Rule of thumb: for a transdermal patch, plan the in vivo PK study first; treat adhesion, I/S, and any in vitro permeation work as supporting evidence around it

Product	Indication
Scopolamine	Motion sickness
Nicotine	Smoking cessation
Norelgestromin	Contraception
Rotigotine	Parkinson's disease
Lidocaine/Tetracaine	Pain relief



FDA: Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA; May 2026

FDA: Assessing Adhesion With Transdermal and Topical Delivery Systems for ANDAs, July 2026

FDA: Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs, July 2026



Human Dermal TDS Study Designs

TRANSDERMAL PATCHES - WHY IRRITATION AND SENSITIZATION MATTER

TDS design, application site & skin prep. can influence skin response - and potentially drug delivery



- ✓ Skin conditions (sweat/hair), Skin reactions can alter skin permeability and/or TDS adhesion(A)
- ✓ Adhesive removal can physically damage the stratum corneum (SC) and contribute to irritation(I)
- ✓ Physical activity, Clothing friction, Patch displacement/detachment/manipulation affect irritation/sensitization(S)
- ✓ For wear periods ≥ 24 hours, exposure to routine bathing/showering should be considered in study conduct
- ✓ Be aware of delay/progression of skin response; calls for trained investigators & assessors of A/I/S
- ✓ Irritation and sensitization can affect patient comfort and compliance

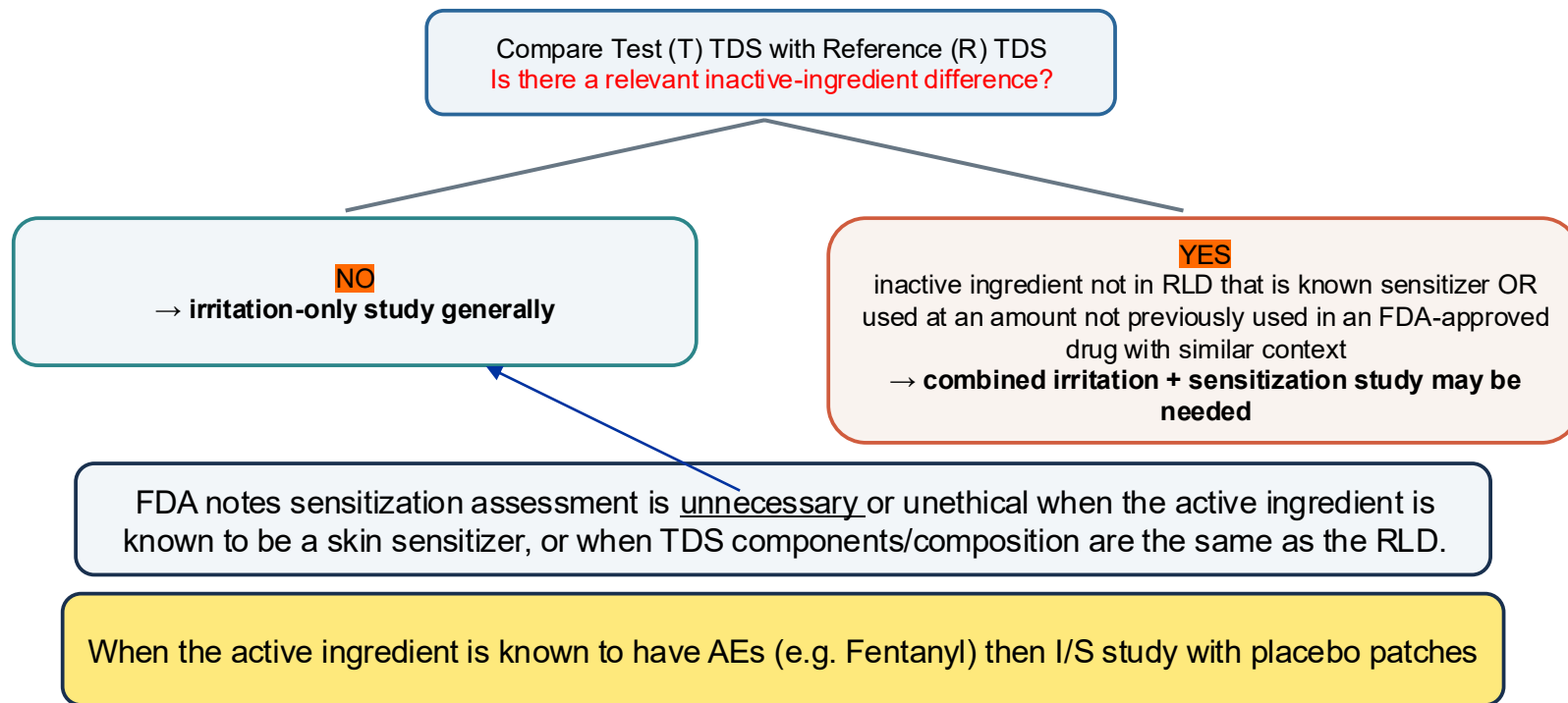
Regulatory objective: Demonstrate that the proposed generic TDS does not have a clinically meaningful worse irritation/sensitization profile than the reference, when applicable



Human Dermal TDS Study Designs

DECISION TREE: IRRITATION VS SENSITIZATION

The need for sensitization testing depends on formulation & inactive ingredient differences (2026 FDA guidance*)



*FDA: Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs, July 2026



Human Dermal TDS Study Designs

COMBINED IRRITATION + SENSITIZATION STUDY

Fitzpatrick Scale



Type I

Light, pale white,
freckled skin color
—
Blue eye color

Reaction to sun:
always burns, never tans.



Type II

White, peach, fair
skin color
—
Blue, green, hazel eye
color

Reaction to sun:
skin will usually burn in
the sun and tans with
difficulty.



Type III

White to light brown,
olive skin tone
—
Dark blue, hazel,
brown eye color

Reaction to sun:
skin will sometimes burn
and will tan gradually



Type IV

Olive, light to moderate
brown skin tone
—
Light brown eye color

Reaction to sun:
skin rarely burns and tans
easily.



Type V

Brown, dark brown
skin tone
—
Dark brown eye color

Reaction to sun:
very rarely burns and tans
very easily.



Type VI

Very dark brown to
black skin tone
—
Dark brown eye color

Reaction to sun:
never burns, tans very
easily, deeply pigmented.

One study integrates a 21-day induction with a post-rest challenge



Day 1

Start induction



Days 1–21

Repeated TDS wear /
removal / replacement



14–17 days

Rest period



Challenge

48 h on naïve skin



30 min / 24 / 48 / 72 h

Post-removal assessments



4–8 weeks

Rechallenge
if potential sensitization

Irritation: Minimum 40* evaluable participants

Irritation + Sensitization study: Minimum 200* evaluable participants

Challenge T and R simultaneously at contralateral sites on the same anatomical site.

Challenge TDS is applied to a naïve skin site for 48 hours.

If a potential sensitization reaction is observed, FDA recommends a rechallenge 4–8 weeks later.

*FDA guidance



Human Dermal TDS Study Designs

IRRITATION + SENSITIZATION STUDY (KEY DIFFERENCE EMA VS FDA)

	EMA	FDA
Treatment Arms	T + R + Placebo	T + R
Induction	21 days; two application schedules	21 days; based on RLD wear period
Sample size	No fixed minimum	40 irritation / 200 irritation + sensitization
Primary endpoint	Mean Irritation Score (MIS) + cumulative irritation	Mean Irritation Score (MIS)
Statistics	Equivalence	Non-inferiority
Acceptance criterion	90% CI: 0.80–1.25	NI margin: 0.20 MIS
Sensitization	Generally expected unless justified	Risk-based
Challenge	48 h; 0.5/24/48/72 h assessments	48 h; 0.5/24/48/72 h assessments
Rechallenge	Not routinely specified	4–8 weeks, when indicated

Adhesion, Irritation & Sensitization Scoring Differs between FDA and EMA

FDA: Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs, July 2026

EMA: Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms, Nov 2014



Clinical End Point Studies (CEP)

SYSTEMIC ABSORPTION IS NOT EASILY MEASURABLE — DETERMINING EFFICACY IS KEY

- ▶ Utilized when a pharmacokinetic study alone cannot reliably establish bioequivalence
- ▶ Locally acting products - minimal systemic absorption & low plasma levels
 - ▶ *Topical products (cream, gel, ointment)*
 - ▶ *Inhaled corticosteroids*
 - ▶ *Ophthalmic products*
 - ▶ *Rectal, Vaginal or Buccal products*
- ▶ Systemically acting products that are topically dosed
 - ▶ *Metered-dose inhalers*
 - ▶ *Nasal spray*



Clinical End Point Studies (CEP)

SYSTEMIC ABSORPTION IS NOT EASILY MEASURABLE — DETERMINING EFFICACY IN KEY

▶ Study Design

- ▶ *Randomized Parallel-arm studies - Test/Reference/Placebo*
- ▶ *Compare Test and Reference products to establish BE*
- ▶ *Compare Test and Reference separately to placebo - assay sensitivity*

▶ Analysis Population

- ▶ *Normal Process*
 - ▶ *Intent-to-Treat (ITT), randomized subjects by treatment*
- ▶ *Other Uncommon Processes*
 - ▶ *Modified Intent-to-Treat (MITT)*
 - ▶ *randomized subjects by at least one dose of products*
 - ▶ *Per Protocol (PP)*
 - ▶ *sub population of IIT, subjects that met the protocol*
 - ▶ *Pharmacokinetics (PK)*
 - ▶ *sub population of IIT, subjects that had PK sampling*
 - ▶ *Safety*
 - ▶ *all subjects based on treatment received*

▶ Clinical Endpoints

- ▶ *Continuous*
 - ▶ *lesion counts (mean percent reduction from baseline)*
 - ▶ *average scales over several assessments*
- ▶ *Binary*
 - ▶ *cure/no cure*
 - ▶ *success/failure*

▶ Criteria to establish Bioequivalence (Types of Hypothesis Testing)

- ▶ *Equivalence*
- ▶ *Superiority*



CEP Assessments

TOPICALS, NASAL SPRAYS, SUPPOSITORIES

Product Type	CEP Assessments
Topical steroids	Skin-blanching by "Chromameter"
Topical antibiotics	Inflammatory lesions or bacteria counts
Topical NSAID (nonsteroidal anti-inflammatory drug)	Summary pain scores
Nasal spray	Total nasal symptom scores
Inhaler	Forced expiratory volume (FEV)
Dermal patch	Adhesion, irritation, and sensitization
Vaginal cream	Cytology and total symptom scores
Suppository	Symptom summary scores



Case Study: Acyclovir — Why FDA Sought an Alternative

A CLINICAL ENDPOINT THAT NEEDED THOUSANDS OF PATIENTS

- ▶ Acyclovir ointment/cream treats recurrent herpes labialis; the clinical endpoint is time-to-healing (duration of episode) vs. placebo
- ▶ FDA's own estimate: discriminating a clinically meaningful ~half-day improvement in healing time over placebo would require on the order of 3,000–6,000 subjects*
- ▶ That scale makes a CCEPBE trial impractical for a routine generic filing — this, not a general preference for in vitro data, this is why FDA created an in vitro alternative here
- ▶ Result: an established IVRT-based option (*draft guidance, 2012/2016*) — a synthetic-membrane release test comparing test vs. RLD — became an accepted BE route for this specific product
- ▶ IVPT was added later as a further alternative in the same guidance, not as IVRT's replacement — both remain options alongside the original clinical pathway (*Oct 2022*)

*Raney et al. / FDA Regulatory Science Program (2015–2018)

Sam G. Raney et al., *Pharmacokinetics-Based Approaches for Bioequivalence Evaluation of Topical Dermatological Drug Products*, June 2015, *Clinical Pharmacokinetics* 54(11):1095-1106

Sam G. Raney et al., *A New Paradigm for Topical Generic Drug Products: Impact on Therapeutic Access*, February 2020, *Journal of the American Academy of Dermatology* 82(6)

Sam G. Raney et al., *Cutaneous Pharmacokinetic Approaches to Compare Bioavailability and/or Bioequivalence for Topical Drug Products*, July 2022, *Dermatologic Clinics* 40(3)



Case Study: Tretinoin — Clinical BE Still Works

DR. K.M. SPEAR'S 400-SUBJECT STUDY REFRAMED WHAT WAS “IMPOSSIBLE”

- ▶ Tretinoin generic approval faced a similar claim: a clinical acne endpoint trial would need an impractically large number of subjects
- ▶ Dr. K.M. Spear found a way to design and run a clinical BE study with only ~480 subjects* — and secured the first generic approval** of Tretinoin on that basis
- ▶ This is the direct counterpoint to acyclovir: “too many subjects for a clinical trial” is a product-specific engineering problem, not a universal rule that clinical BE is infeasible for topicals
- ▶ Good clinical trial design — endpoint choice, population, duration — can sometimes shrink the “impossible” trial to a feasible one, without ever leaving the in vivo clinical pathway
- ▶ Takeaway: don't reach for IVRT/IVPT by default — first ask whether a smarter clinical design solves the problem

*Bioequivalence Study of Generic Tretinoin 0.1% Microsphere Gel, 0.1% Retin-A Micro® and Placebo (ClinicalTrials.gov ID NCT01135069)

**FDA: 75265 Tretinoin Approval - September 21, 1997 (ANDA 75-213)

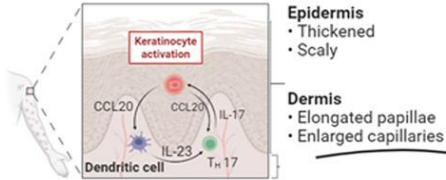


Emerging Techniques

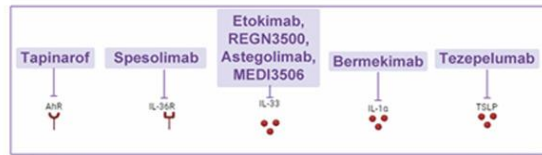


Emerging Techniques:

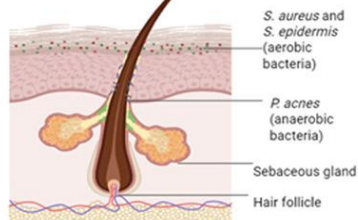
Psoriasis



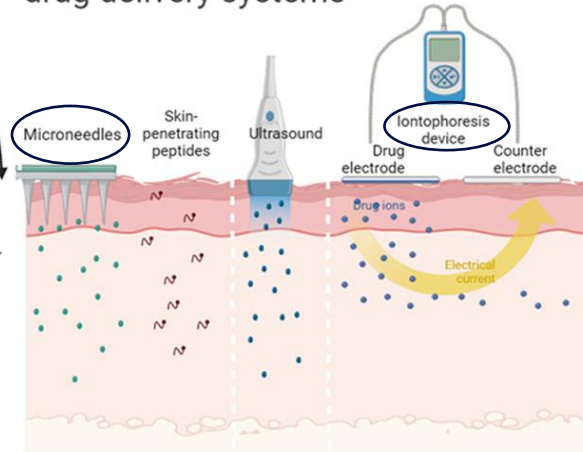
Atopic dermatitis



Acne vulgaris



Techniques for transdermal drug delivery systems





Emerging Techniques:

IONTOPHORESIS

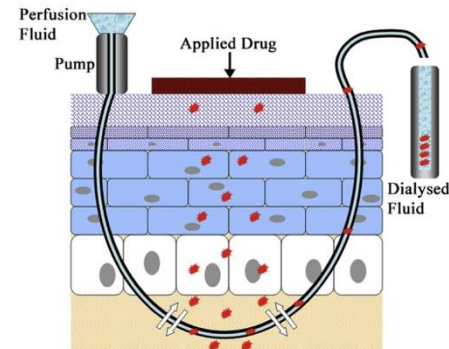
▶ Iontophoresis

- ▶ *Non-invasive technique*
- ▶ *The system applies a constant, low-voltage direct current to actively move charged or hydrophilic molecules across the skin barrier (SC) via electro repulsion (ER) and electro osmosis (EO)*
- ▶ *Its ability to enhance drug penetration through the skin's barrier, particularly the stratum corneum (SC), addresses a critical limitation in traditional topical treatments*
- ▶ *It bypasses first-pass metabolism and increases local absorption rates significantly compared to passive topical application*
- ▶ *Iontophoresis-assisted transdermal drug delivery has proven to be a transformative approach for the management of inflammatory dermatoses, such as AD, psoriasis, and acne vulgaris*
- ▶ **Approvals:**
 - ▶ *LidoSite: The first FDA-approved iontophoretic local anesthetic patch combining lidocaine hydrochloride (10%) & epinephrine (0.1%) for dermal local anesthesia*
 - ▶ *Ionsys (Fentanyl): A patient-activated, needle-free transdermal system - for the short-term management (acute postoperative pain) in adult patients in a hospital setting*
 - ▶ *Lidocaine/Epinephrine formulations: Various low-voltage patch & solution systems designed to drive charged anesthetic molecules into superficial tissues prior to minor dermatological procedures*



Emerging Techniques

MICRODIALYSIS



► Microdialysis

- *real-time, continuous monitoring/sampling of the extracellular concentration of drug/metabolite in the dermis and hypodermis*
- *a linear probe with a semipermeable membrane is implanted into the dermis or hypodermis with the help of a guide needle*
- *Insertion of the probe and guide needle is a minimally invasive procedure that requires small skin punctures and provokes minor tissue trauma that generally resolves to baseline after 60–90 minutes*
- *probe functions as an artificial vessel with an inlet and outlet tube that is perfused with a physiological solution, which equilibrates with the interstitial fluid (ISF), allowing passive diffusion of substances smaller than the cut-off value of the membrane*
- *The perfusate is typically isotonic saline or Ringer's lactate solution and is pumped at a very slow flow rate (1–5 $\mu\text{l}/\text{min}$). If the drug is lipophilic, solvents may have to be added to the solution to allow better solubility*
- *perfusate is typically analyzed using HPLC-MS*
- *absorption profile of the drug (the C_{max} , T_{max} , absorption constant, AUC, and lag time) can be determined from the plot of free drug/metabolite concentration in the dermis or hypodermis as a function of time*
- *E.g. used the dermal microdialysis technique to derive the AUC for topical ketoprofen*



Emerging Techniques

MICROPERFUSION



► Microperfusion

- ▶ *A variant of microdialysis is open-flow microperfusion, which uses probes with macroscopic openings rather than porous membranes*
- ▶ *Allows open exchange with the interstitial fluid, with fewer limitations due to molecular size, drug protein-binding, and drug lipophilicity*
- ▶ *Open Flow Microperfusion (OFM) is an in-vivo sampling and testing technique*
- ▶ *Instead of just creating a hole, a microperfusion device continuously circulates a physiological fluid through a specialized probe embedded in target tissue (like the skin, brain, or fat)*
- ▶ *Fluid is gently pushed in and pulled out. The fluid mixes directly with the surrounding interstitial fluid (ISF), allowing one to extract and analyze exactly what medications or biomarkers are present in the tissue without altering the sample*
- ▶ *Clinical verification studies have successfully demonstrated that **Dermal Open Flow Microperfusion (dOFM)** can accurately reproduce bioequivalence results (such as with acyclovir and lidocaine/prilocaine creams) and differentiate between inequivalent formulations*
- ▶ *Regulatory bodies view these cutaneous pharmacokinetic methods as promising tools, but applicants wishing to use them for official generic approvals **must still consult agencies** via pre-ANDA product development meetings*



Emerging Techniques

MICRONEEDLES



► Microneedles

- *Are tiny needles fabricated from silicon, metal, or dissolving polymers for drug delivery*
- *They are long enough to breach the dead outer layer of skin but short enough to avoid hitting deep nerves or blood vessels, making them virtually painless*
- *They are used as "painless syringes" in wearable transdermal patches to deliver medications or vaccines*
- *They can be solid, hollow (to allow fluid flow), coated with a drug, or entirely made of a dissolving material that melts inside the skin*
- *Numerous drug-loaded or dissolving microneedle systems are in clinical trials for vaccines, small molecules, and biologics*
- *None have achieved final marketing authorization for systemic or local therapeutic delivery*
- *Aesthetic Devices: The FDA has cleared and legally authorized mechanical microneedling devices (such as motorized pens and rollers) strictly for aesthetic uses like improving facial wrinkles and acne scars*
- *The FDA classifies therapeutic microneedle products as complex combination products (drug plus device), requiring extensive safety, sterility, and bioequivalence data before any commercial rollout*



Emerging Techniques: Still Investigational

TAPE STRIPPING

▶ Tape Stripping

- ▶ *Tape stripping involves the sequential application and removal of adhesive tape on the skin to peel off microscopic layers of the stratum corneum (SC - the outermost skin layer) just after removing the applied drug from multiple sites at sequentially increasing time intervals from the time of application and the SC is collected*
- ▶ *Quantify the amount of SC and drug/metabolite removed include weighing the tape strips before and after stripping, various assays of proteins in corneocytes*
- ▶ *Total epidermal water loss measurements are made using Fick's first law*
- ▶ *Graph the concentration of the drug/metabolite as a function of its relative depth into the SC, yielding the following parameters after curve fitting to an appropriate solution of Fick's second law*
- ▶ *Usable only when the active is quantifiable in the stratum corneum (SC) and does not fully permeate through it – antibiotics, antiseptics, antimicrobials treating skin infection (but not for buccal, rectal or vaginal)*
- ▶ *The DPK (dermatopharmacokinetic) method assumes that (i) the SC is the rate-limiting barrier to topical absorption and (ii) drug levels in the SC are directly related to drug levels in the underlying epidermis*
- ▶ *The FDA released draft guidance (June 1998) on the dermatopharmacokinetic (DPK) approach using tape stripping to assess the bioequivalence of topical dermatological products*
- ▶ *The FDA officially withdrew the draft guidance (May 2002)*
- ▶ *Reproducibility concerns: Two independent laboratories got contradictory results when testing tretinoin gel products*



Nasal Spray





Types of Intranasal Drug Products

1

Nasal Sprays

Pump-actuated aqueous solutions or suspensions — the most common intranasal dosage form

2

Nasal Aerosols

Propellant-driven, deliver non-aqueous formulations as fine dry particles

3

Nasal Powders

Breath-actuated, solid drug ($\pm$ excipients) delivered as a dry powder

4

Nasal Gels / Ointments

Semisolid formulations for more localized, prolonged mucosal contact

5

Nasal Implants*

Physician-placed, bioabsorbable polymer matrices for sustained, extended release



Tiered Approach for Approval

NEITHER APPROACH WINS ON EVERY DIMENSION

► In Vitro (IVRT / IVPT / Device Testing)

1. Single Actuation Content (SAC)
2. Droplet Size Distribution
3. Drug in Small Particles (DISP)
4. Spray Pattern
5. Plume Geometry
6. Drug Particle Size Distribution (DPSD)
7. Priming and Repriming
8. Dissolution

FDA – tiered approach

Test = Ref – 1-8 In vitro assays

Test ≠ Ref – 1-6 In vitro assays + PK + CEP

FDA – Population Bioequivalence (PBE)

► In Vivo (PK / PD & Clinical Endpoint)

- Directly measures the outcome regulators care about
- Captures real physiological and behavioral variability
- Accepted “gold standard” fallback when no in vitro model exists
- Slower, costlier; requires human subjects
- Assay sensitivity (LLOQ) can limit feasibility for low-exposure products

EMA - tiered approach

case by case basis, accepts In-vitro with justification

EMA - Average Bioequivalence (ABE)



Intranasal In Vivo Studies

A FASTER CLOCK THAN CLINICAL-ENDPOINT PROGRAMS

- ▶ Single- or multiple-dose PK studies in healthy volunteers are logistically simple
- ▶ The timeline depends on bioanalytical method readiness, recruitment, regulatory feedback, product complexity, and study design
- ▶ Nasal absorption/clearance is rapid, so PK sampling windows are short (hours, not weeks)
- ▶ Typical program: protocol + bioanalytical method (4–6 wk) → dosing & PK sampling (2–4 wk) → analysis & report (6–8 wk)
- ▶ Contrast with clinical-endpoint studies (allergic rhinitis, migraine) which need seasonal recruitment and can run well beyond 6 months
- ▶ Speed makes PK-based approaches attractive when a validated systemic or local PK endpoint exists



Intranasal BE: Weight-of-Evidence by Product Type

WHEN IN VITRO ALONE IS ENOUGH — AND WHEN IN VIVO IS ADDED

Product Type	Approach
Locally-acting solution sprays	Q1/Q2 sameness + device comparison + in vitro studies (often sufficient alone)
Locally-acting suspension sprays	Weight-of-evidence: formulation/device similarity + in vitro (incl. particle size) + PK + clinical endpoint where needed
Systemically-acting sprays	Either formulation/device match + in vitro, OR a PK study without full formulation matching
Nasal powders	In vitro (particle size, single-actuation content) PLUS a fasted PK bioequivalence study

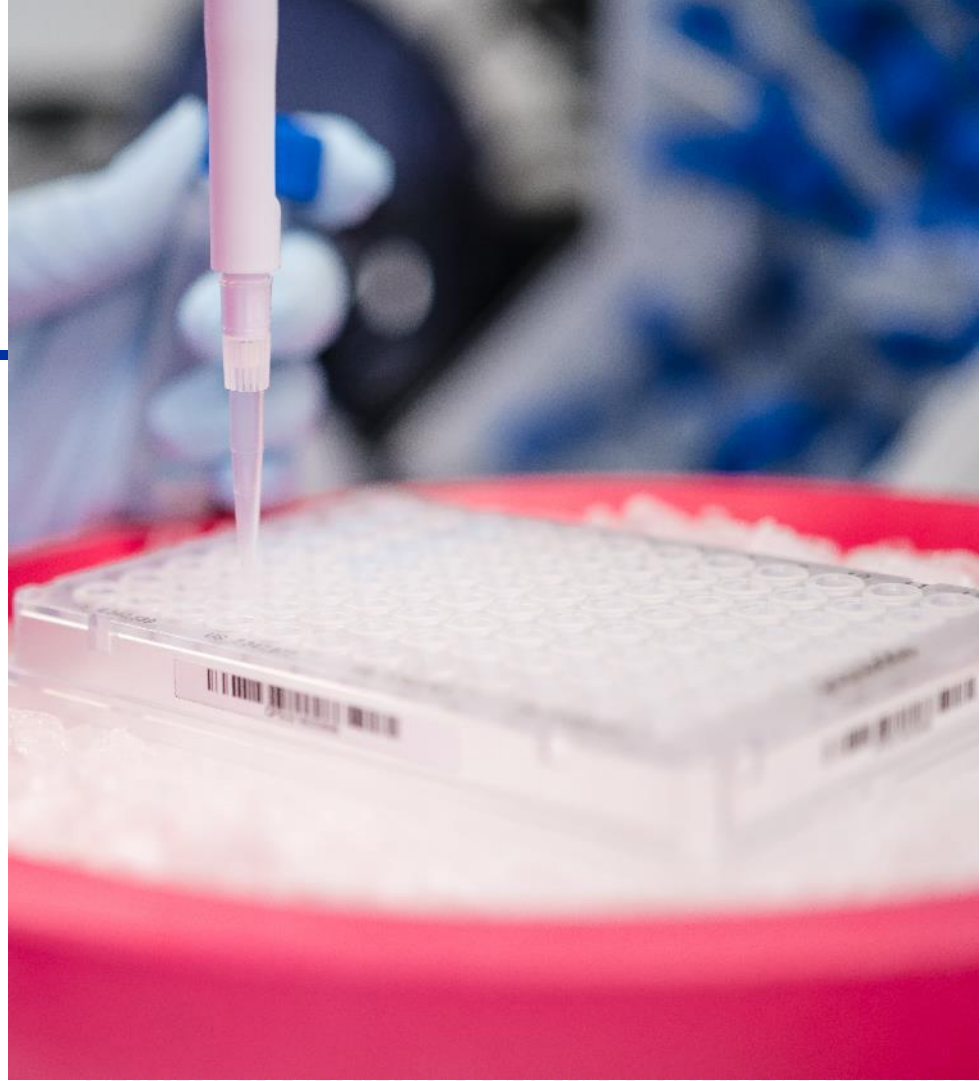
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European Medicines Agency (EMA) Guideline on Pharmaceutical Quality of Inhalation and Nasal Products (EMA/CPMP/QWP/49488/2003)

Davit, B. et. al., BCS Bioequivalence: similarities and differences among EMA, FDA, and WHO requirements, May 2016, AAPS J 18 (3)

GurJai Pal Singh, Relevance of distinctions and parallels between the US and EU guidelines for determination of comparative effectiveness and safety of the orally inhaled drug products, 2024, European Journal of Pharmaceutical Sciences 201(106872)

Bioanalytical Considerations





Bioanalytical Challenges driven by Clinical Dosing/Application

VARIABILITY FROM CLINICAL REQUIRES ATTENTION & AWARENESS

▶ In case of Transdermal Products

- ▶ *Low systemic bioavailability through skin*
- ▶ *Slow and prolonged absorption*
- ▶ *Low plasma concentrations*
- ▶ *Patch Application, Duration, Adhesion affect requirement*

▶ In case of Other Topical Products

- ▶ *Exact dose variable in case of cream/gel/solution*
- ▶ *Variable skin absorption*
- ▶ *Washing/rubbing of application site*
- ▶ *Differences in application technique*
- ▶ *Potentially very low systemic exposure*
- ▶ *Greater inter- and intra- subject variability*

▶ In case of Nasal Products

- ▶ *Nasal mucosa can produce rapid uptake*
- ▶ *Peak may occur within minutes*
- ▶ *Part of the dose remains in the nasal cavity or is swallowed*
- ▶ *Drug deposited in the nasopharynx can be swallowed and absorbed GI*
- ▶ *Spray technique, head position, nasal anatomy, congestion, and mucociliary clearance vary*
- ▶ *Plasma exposure may be low, particularly for peptides or poorly absorbed drugs*
- ▶ *Some compounds are unstable in plasma or whole blood*
- ▶ *Drug may undergo local nasal metabolism or first-pass metabolism after swallowing*



Bioanalytical Requirements – Meet the Need

METHOD SENSITIVITY AND REPRODUCIBILITY

- ▶ Develop a highly sensitive LC-MS/MS method
- ▶ Target an LLOQ substantially below the expected exposure - than simply the minimum validation requirement
- ▶ LLOQ must demonstrate acceptable accuracy, precision and selectivity
- ▶ The calibration range should be driven by anticipated PK - not simply by a standard generic range
- ▶ Optimize extraction efficiency
- ▶ Use a Stable-Isotope-Labelled IS
- ▶ Checking selectivity using multiple individual plasma lots
- ▶ Low-end performance should be challenged with individual plasma lots
- ▶ Evaluate IS-normalized matrix factor, not just absolute recovery
- ▶ Plasma phospholipids and endogenous components can cause ion suppression/enhancement in LC-MS/MS
- ▶ Check carryover in different systems, optimize needle wash, injection volume, wash solvent & injection sequence
- ▶ Preferably use High sensitivity mass spec like Sciex 7500+

LLOQs needed for Nasal Spray

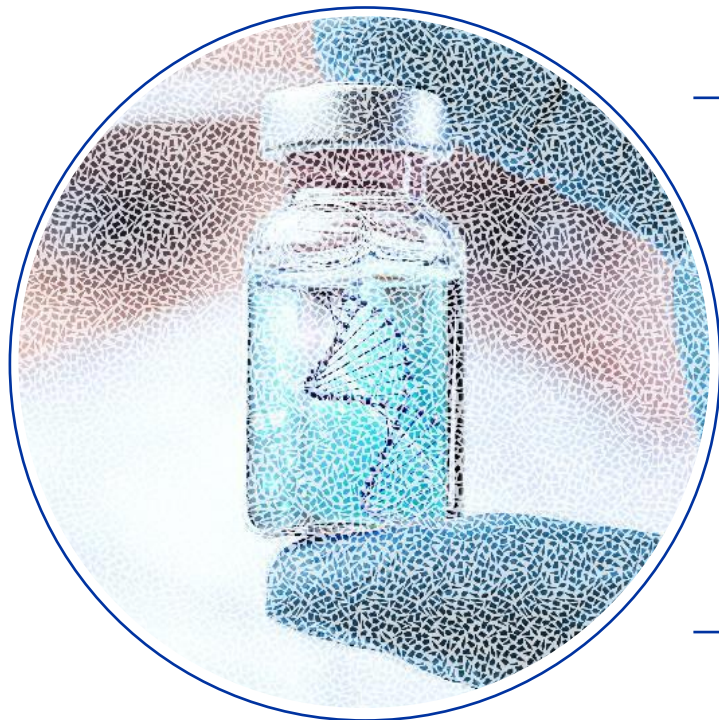
- ▶ Formoterol – 0.1 pg/mL
- ▶ Mometasone Furoate – 0.3 pg/mL
- ▶ Fluticasone – 0.1 pg/mL
- ▶ Vilanterol – 0.2 pg/mL
- ▶ Umeclidinium – 0.5 pg/mL



LLOQ and Assay Limitations

WHY BIOANALYTICAL SENSITIVITY CAN MAKE OR BREAK A PK STUDY

- ▶ **LLOQ (Lower Limit of Quantification)**
 - ▶ *the lowest analyte concentration a validated assay can measure with acceptable accuracy and precision*
- ▶ **Locally-acting Topicals, Transdermals, and Intranasals are designed to minimize systemic absorption**
 - ▶ *concentrations often sit near, at, or below LLOQ – target 5% of C_{max}*
- ▶ **BLQ (Below Limit of Quantification) samples, i.e. below LLOQ**
 - ▶ *Non-Compartmental Analysis (NCA) – most common; Compartmental and Population PK Modeling*
 - ▶ *Must be handled as per Statistical Analysis Plan (SAP) and pre-specified rules*
 - ▶ *e.g., excluded/missing, or set to Zero or LLOQ/2 or M3 or M4 Methods with NONMEM*
 - ▶ *the choice can materially shift C_{max} /AUC and the BE conclusion*
- ▶ **Consequences of a high LLOQ (assay not sensitive enough)**
 - ▶ *missed real exposure differences, underestimated $T^{1/2}$, false conclusions of bioequivalence, or an infeasible PK study altogether*
- ▶ **Mitigations**
 - ▶ *highly sensitive LC-MS/MS methods*
 - ▶ *larger sample volumes*
 - ▶ *longer/denser sampling near T_{max}*
- ▶ **Fall back to VCA, IVRT/IVPT, CEP when PK simply isn't sensitive enough**



Summary



Matching the Study to the Dosage Form

GENERAL APPROACH ACROSS TOPICAL, TRANSDERMAL & INTRANASAL PRODUCTS

Dosage Form / Class	Typical BE Pathway	Example
Topical corticosteroids	Vasoconstrictor Assay (VCA) — pharmacodynamic endpoint	Hydrocortisone Lotion/Ointment Betamethasone Lotion/Creams
Non-complex topical solutions (Q1/Q2 match)	In vitro release only (IVRT), or biowaiver	Clotrimazole solution - CEP waiver if Inactive ingredients are similar to RLD Clotrimazole cream – In Vitro or CEP
Complex topical semisolid (creams/gels/ointments)	IVRT ± IVPT, or clinical endpoint if in vitro insufficient	Acyclovir ointment-In Vitro or CEP Tretinoin gel-In Vitro or CEP Tretinoin Solution- CEP waiver if Inactive ingredients are similar to RLD Clindamycin phosphate lotion-In Vitro or CEP Benzoyl peroxide+Tretinoin (Cream)-Only CEP Leuprolide Acetate powder-In Vitro or PK/BE study
Transdermal delivery systems (patches)	PK (systemic BE) + Adhesion + Irritation/Sensitization	Fentanyl, nicotine, methylphenidate patches
Locally-acting nasal sprays (solution)	Q1/Q2, SAC, APSD, Realistic APSD, Dissolution, PK/BE OR Q1/Q2, SAC, APSD, PK/BE, CEP	Fluticasone nasal spray
Locally-acting nasal sprays (suspension)	Weight-of-evidence: formulation + in vitro + PK ± clinical endpoint	Mometasone nasal spray Fluticasone furoate



Key Takeaways

THE RULE OF THUMB, CORRECTED

- ▶ Let science pick the tool-PD marker (VCA) when one exists, In Vitro (IVRT/IVPT) when a validated model exists, In Vivo when it doesn't
- ▶ IVRT/IVPT tell different things & are increasingly required together-does not address metabolism, excretion, efficacy or safety
- ▶ Cost and speed cut differently than assumed
 - ▶ VC is fastest; a clinical BE/PK trial is often faster than IVRT (4m)/IVPT (6–12m), even where IVPT costs less
- ▶ The clinical BE trial may be the universal always available default for topical and transdermals
 - ▶ Limitations due to sample size, BA, etc.
- ▶ CEP – has an impact on both time and cost – but is sometimes the only pathway
- ▶ A transdermal BE package usually means PK + Adhesion + Irritation/Sensitization-each answering a different question
- ▶ Ethical & practical constraints (AE risk, 5,000-patient trials, LLOQ limits)-push to In Vitro alternatives wherever possible
- ▶ Intranasal BE is genuinely product-type-specific-always confirm the current PSG rather than assuming one playbook fits all
- ▶ Before reaching for a shortcut, ask - is there a smarter clinical design that keeps you in vivo?
- ▶ Bottom line: match the study to the question you actually need answered — not the study that is easiest to run



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