

TOPICAL DELIVERY OF ORAL DRUGS

Designing The Path to the Patient



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Abstract:

When technically feasible, topical delivery of drug products, both for local and systemic use, may offer advantages over the oral route. Topical delivery of a drug product which is currently approved as an oral dosage form allows for:

- increased compliance
- avoidance of first pass metabolism by the liver
- delivery of a more even level of the therapeutic agent over time, and
- the possibility of reduced side effects

The presentation will detail the steps to develop a drug from concept to the regulatory submission for marketing approval. To obtain FDA approval of a topically delivered drug, it is critical to involve the Food and Drug Administration (FDA) early in the development process. A strategy should be implemented to involve as much pharmacokinetic and pharmacodynamic data as possible to demonstrate therapeutic equivalence to the oral drug. To support the Investigational New Drug Application (IND), standard irritation and sensitization studies should be performed with the vehicle itself, in animals, and if feasible, normal volunteers. There will be toxicology requirements, but the extent and timing of their implementation can be negotiated with the FDA. The dermatology division at FDA will review dermal aspects of the IND and New Drug Application (NDA), but the primary review will occur at the division which handles the indication under study. Dose ranging studies will usually be required in Phase 2, but a single Phase 3 study could be negotiated.

Key Words: *Topical Drug Delivery, Dermatology, Skin, Pharmacokinetics, Pharmacodynamics*

Introduction:

When technically feasible, topical delivery of drug products for both local and systemic indications offer many advantages over the oral route.

For both the pediatric and adult populations, the advantages include:

- Ease of delivery
- A more cooperative patient
- Enhanced compliance
- Avoidance of first-pass metabolism
- Enhanced efficacy and safety for locally manifested disease

Topical delivery vehicles include creams, lotions, gels, etc. while transdermal drug delivery uses patches, penetration enhancers, etc.

PK Comparisons - Systemic vs Local Drug Delivery



FDA Approval Process

To obtain FDA approval of an orally-approved drug to be delivered either locally or topically:

- Involve the Food and Drug Administration (FDA) early in the development process
- Develop a strategy to involve as much pharmacokinetic and pharmacodynamic data as possible
- Use the toxicology data from the systemic drug to support a reduced toxicology program
- For locally acting drugs, show reduced systemic absorption with equivalent or superior efficacy to the systemic drug

Parameters to Evaluate:

- Drug distribution, over time, in the blood and/or skin, after single or repeat dosing, as measured by the area under the curve
- Maximum drug concentration, in the blood and/or skin, after single or repeat dosing
- Time to achieve maximum drug concentration, in the blood and/or skin, after single or repeat dosing
- Clinical efficacy

Regulatory Strategy to support the Investigational New Drug Application (IND) and NDA Submissions:

- Use as many excipients from the FDA-approved Inactive Ingredient List in the vehicle as possible. Non-approved ingredients will delay the development process.
- Standard irritation and sensitization studies should be performed with the drug product and vehicle in animals/humans.
- Negotiate the timing and implementation of the toxicology requirements.
- The dermatology division at FDA will review dermal aspects of the IND and New Drug Application (NDA).
- For topically applied drugs with systemic therapeutic effects, the primary review will occur at the division which handles the indication under study.
- Dose ranging studies will usually be required in Phase 2.
- Single Phase 3 study could be negotiated.

Conclusions:

Topical drug delivery offers the *advantages* of ease of delivery, a cooperative patient, increased compliance as well as the avoidance of first-pass metabolism. *Disadvantages* are the lack of, or reduced rates of absorption and cosmetic considerations. New drug delivery technology and penetration enhancers may help to obviate some of these objections.

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