# Therapeutics Inc.

*The Dermatology CRO*

**Challenges in the Clinical Development of Topical Products**

## Agenda

- TI overview
- Topicals – the category
- Science Requirements
- CMC: Formulation to Manufacturing
- Regulatory Requirements
- Clinical Development Strategy
- Clinical Design and Conduct

## Therapeutics, Inc. - *The Dermatology CRO*

- A Fully Integrated CRO from Concept → FDA Approval
  - Turn-Key Product Development: Program Management, Formulation, CMC, Non-Clinical, Clinical, Regulatory Affairs
  - All Categories: Drugs, Devices, Biologics
  - All Dosage Forms: Topical, Oral, Injectable
  - Dermatology Focus (~85%) / Other (~15%)
- Development Focus
  - Not Discovery; Not Sales & Marketing
- Recent Five Years
  - Filed > 15 IND/IDEs
  - Conducted >90 studies in >10,000 subjects
  - Multiple product approvals
- Headcount: ˜75
- Founded: 1997



## Topicals: The Category

- Health Care Focus
  - Dermatology / Ophthalmology
    - Many 'me-too' products available ; older molecules dominate
    - Orphan indications emerging in dermatology
  - Other (women's health, GI, ENT, etc.)
- Diversity
  - OTC and "Prescription"
- Limited Innovation Has Been The Rule
  - Life cycle management: "proven API" in new dosage form(s) or in combination
  - New Chemical Entities (NCEs) typically borrowed from other health care categories

## Topicals: The Category

- Intellectual Property
  - Composition of Matter, Method of Use, Formulation
  - Majority = Formulation IP
    - Rarely 100% blocking
    - Hatch-Waxman 3/5 yr. exclusivity therefore is always key
- Market
  - Very Competitive Margins, but ….
  - Products Have Modest Annual US Sales ( ≤ $150m)



## Science Requirement

- Dermatology / Ophthalmology
  - Disease indications are diverse and can be complex
    - Many are too small &/or poorly understood (D >O)
  - Cause is rarely well defined (D > O), and limits innovation
  - Smaller markets limits basic science investment
    - Commonality of MOA with larger medical markets drives innovation ( e.g. Restasis for Optho/ Biologics for inflammatory skin diseases)
  - Topical route can provide …
    - A targeted disease pathway ( skin and anterior eye centric diseases )
    - A means to mitigate systemic exposure/toxicity

## CMC: Formulation to Manufacturing

**CMC issues are the leading reason for approval failures in dermatology**

Reasons: TOO NUMEROUS TO COUNT - API, process controls, excipients, method of making (rate of mixing, order/rate of ingredient additions, temperature etc.), stability/specifications, scale limitation to commercial batch size, etc.



## CMC: Formulation to Manufacturing

**CMC issues are the leading reason for approval failures in dermatology**

Solution: START EARLY AND RESPECT THE DOSAGE FORM, create a team (with internal and/or external resources) that knows the category, select phase appropriate reasonable and achievable specifications, use a seasoned and experienced contract manufacturer with a proven track record, etc.

## Regulatory Requirements

- Diverse Skill Set; drugs/devices/biologics
- Robust Regulatory Plan
  - Prior art, guidances, expertise in the category
  - Adequate pre-clinical requirements & robust analytic methods
  - Modify based on learning as program progresses
- Build a Positive and Collaborative Relationship with the FDA
  - Regular interactions with the assigned FDA's PM
  - Meetings are important
    - Obtain Agency guidance in the record as well as rapport and trust
    - Standard meetings Pre-IND, EOP2, etc. but use Type C meetings as/if necessary



## Clinical Development Strategy

- Topicals - Often a Less Complicated Path to Approval
  - Fewer Adverse Events (AEs) and Serious Adverse Events (SAEs)
  - Many products use older "established" API with known safety profiles
- Plan for Generic Competition From Inception
  - Generic Path to Drug Approvals
    - Chemical Equivalence (just solutions), Bioequivalence (just topical steroids), Clinical Equivalence (everything else)
  - IP that enables an FDA Orange Book listing
    - Provides at least some additional protection in addition to facilitating out-licensing

# Clinical Development Strategy

- Develop a Fully Integrated Plan
  - Know the dependencies -- CMC, non-clinical, clinical, regulatory and business requirements
  - Keep it current and indicative of learning/results to date
- Competing Interests
  - Optimal development with unconstrained resources ( $, people, etc. ) is the exception not the rule
  - Anticipate competing interests such that the development plan is optimal for your reality
    - Financing/Partner requirements, FDA requirements, CMC/non-clinical/clinical outcomes, etc.



# Clinical Development Strategy

- Pharmaceutical and Device Development is the Failure Business
  - Even the simplest life cycle management product (e.g. 505(b) 2) can have difficulties
  - Drive clinical studies to early “proof of concept” to support programs advancement or termination to the extent possible
- FDA “Continuing Improvement” Means More Requirements
  - Pediatric Studies, QT/QTc, Carcinogenicity (systemic &/or dermal), etc.

## Clinical Design and Conduct

- Protocol Development
  - Experienced Development Staff
  - Clinical Experts (NOTE: likely not a development expert)
  - FDA feedback
  - Other Resources
    - Publications/Posters
    - FOI/FDA (Summary Basis of Approval, etc.)
    - ClinicalTrials.gov
    - Guidance(s)



## Clinical Design and Conduct

- Endpoints – "softer" than we would like
  - Typically Objective/Subjective Measures
    - "Qualitative" endpoints
      - Examples: degree of redness, scaling, thickness, induration, global composite scores, etc.
    - "Quantitative" endpoints often not readily reproducible
      - Examples: acne lesion or actinic keratoses counts, calculated composite endpoints like PASI (**P**soriasis **A**rea and **S**everity **I**ndex) etc.
- Inclusion/Exclusion Criteria
  - Must reflect the real patient population

## Clinical Design and Conduct

- Clinical Risk Mitigation Strategies
  - Experienced Development Team ( In-house or CRO)
    - Know what you do not know
    - Get help to fill the gaps
  - Experienced Clinical Investigators
    - Critical given the “soft” endpoints
    - Monitor to assure compliance
  - Trial Specific Measures
    - Example – photo review for acne trials with medical monitor oversight



## Clinical Product Development Is Like Raising A Child

**No one knows everything that is best …. it takes a lot of time, effort and money .... there are always dips in the road …. but the rewards can be substantial !**

# Thank-You

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