Development of the Optimal Strategy for Scale-Up and Optimization

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Overview

• Background and history
• Responsibilities of product development
• Market and product criteria
• Development stages
History

• The first commercial transdermal patch was Transderm Scop developed by Alza and approved by the FDA on Dec. 31st, 1979.

• Alza dominated patch development for the next 20 years with Transderm Nitro, Catapres-TTS, Estraderm, Durogesic, Nicoderm and Testoderm.
Patches Through the Years

• Relatively few drugs are suitable for passive transdermal patches
• Some people think this means a limited or uncertain future for patches
• But they are wrong
FDA-Approved Transdermal Patches

- Transderm Scop
- Nitrodisc
- Catapres-TTS
- Nitro-Dur
- Transderm Nitro
- Estraderm
- Testoderm
- Duragesic
- Velle
- CombiPatch
- Nicoderm
- Climara
- Nicotrol
- Lidoderm
- Habitrol
- EMSAM
- Oxytrol
- Exelon
- Menostar
- Sancuso
- Climara Pro
- Neupro
- BuTrans
- Minivelle
- Oxybutynin (AB to Oxytrol)
- Xulane (AB to Ortho Evra)
- Scop (AB to Transderm Scop)
- ETS 2/wk (AB to Vivelle dot)
- Pioneer Product
- 505b2 (me too)
- True Generic

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All Patches Have…

• A removable, disposable protective liner
• A backing film
• An adhesive
• A drug
Patch Anatomy (Matrix vs. Reservoir)

- Backing Film
- Adhesive
- Release Liner
Patch Anatomy (Matrix vs. Reservoir)

- Reservoir
- Backing Film
- Adhesive
- Release Liner

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Commercial Patch Examples
What’s So Special About Patches?

• Many different kinds of raw materials
  – Known pharmaceutical excipients
    • Buffers, acids and bases, antimicrobials, antioxidants, metal oxides, etc.
    • Monograph may or may not be relevant to topical administration
  – Specialty or novel (non-pharmaceutical) excipients
    • Synthetic polymers (adhesives, thickeners, films, coatings, tackifiers), penetration enhancers, crystal inhibitors, etc.
      – It’s up to the developer to assure raw material quality and suitability.
  – Non-polar active ingredients
    • Free acids and free bases often less stable than water-soluble salts.
What’s So Special About Patches?

• Consistently valuable products
  – Convenient, multi-day dosing
  – Unobtrusive, but verifiable compliance
  – Unit dosing
  – Few competitors
  – Product lifespan measured in decades
Product Development

**MUST**
- Create new products according to specific criteria
- Evaluate and manage risk
- Stop when asked (leave questions unanswered)

**MUST NOT**
- Conduct basic or theoretical research
- Expect perfection
Developer’s Role

• Developer’s activities are investments.
• In exchange for salary and expenses, company expects a positive return on investment.
• If efforts are not profitable, company eventually loses ability to support developer.
Market Criteria (3D)

- **Demographics** (will patients use the product?)
- **Disease characteristics** (is the product effective?)
- **Demand** (will the product be profitable?)
Demographics

• Patient population
  – Specific needs
  – Physical limitations
  – Comorbidities

• Geographic distribution (where are they?)
  – Climate
  – Culture
  – Regulatory hurdles
Disease Characteristics

• Ability to treat/cure disease
• Availability of alternate therapies
  – What will compete with product?
• Chronic or acute
  – Treating disease or curing disease?
Demand

• Product profile
  – Wear duration
  – Wear site
  – Basic design (monolith, reservoir, size, shape)

• Value of new product
  – Who will pay for the product?
  – What can they afford?
  – Total number of patients?
Product Criteria (DEWSIE)*

- Delivery rate
- Extent of delivery
- Wear
- Stability
- Irritation
- Excipient compatibility and acceptability


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Delivery Rate

• Is API sufficiently
  – Permeable?
AND
  – Potent?
Extent of Delivery

• How long does therapeutic delivery rate last?
• How efficient is the patch (fraction of total drug delivered during wear)?
Wear

• Does patch remain fully adhered?
  – Partial loss of adhesion will reduce delivery area
  – How does patch lose adhesion?
    • Edges?
    • Center?
    • Tunnels?
Stability

• Ability to retain other critical performance characteristics
  – Chemical stability
    • Potency, related substances, discoloration
  – Physical stability
    • Oozing/cold flow
    • Crystal growth
Irritation

• How do we measure?
  – Erythema (redness)
  – Edema (swelling)
  – Erosions (blisters, fissures, exudate, scabbing, bleeding, etc.)

• Primary irritation or sensitization?
Excipient Compatibility & Acceptability

• Chemically compatible?
• Physically compatible (miscible/soluble)?
• Prior use in patches?
• Relevant monograph?
Timing

• Must consider market criteria early and often (3Ds)
  – Is product still worth pursuing?

• Must achieve all the performance criteria (DEWSIE) by the final stage.
  – Final product must have these properties
  – Pursuit of DEWSIE is the development process
  – Requires asking the right questions at the right time.
Development Stages

- Preformulation
- Formulation/Preclinical
- Scale-up/Pilot
- Pivotal/Launch
Preformulation

• 3Ds
  – Demographics
    • Who are the patients?
    • Where are the patients?
  – Disease
    • Is this disease the best choice for this product?
    • Will a transdermal patch be effective?
  – Demand
    • What alternate therapies will compete?
    • What is the status of the API in my anticipated market?
    • Are there enough patients to justify development?
    • How long should the patch last?
Preformulation

• **DEWSIE**
  – Delivery
    • Is transdermal delivery feasible?
  – Extent
    • How much drug must be delivered per patch?
Formulation/Preclinical

• 3Ds
  – Demand
    • Have any market assumptions changed?
    • Are the excipients too expensive?
    • Is the manufacturing process scalable?
      – Excessive energy input?
      – Custom built equipment?
      – Narrow processing windows?
Formulation/Preclinical

• DEWS-
  – Delivery
    • Target delivery rates achievable?
    • Enhancer(s) needed?
  – Extent of delivery: In vitro flux duration sufficient?
  – Wear: Establish physical test methods
  – Stability
    • Crystallization, Discoloration, Related substances, Loss of potency?
    • Forced degradation (heat, light, oxygen, acid, base)
Formulation/Preclinical

• -IE
  – Irritation: Known irritants?
  – Excipient Compatibility/Acceptability
    • Previously used in patches or banned in target market?
    • Available in bulk?
    • Multiple vendors?
    • (Relevant) quality standards?
Scale-Up/Pilot

• 3Ds
  – Demand
    • What is the proper scale at this stage?
    • What processes are being scaled-up?
    • What processes are being redesigned?
    • Establishing continuous processes?
Scale-Up/Pilot

• **DEWSIE**
  - Delivery: Same as laboratory control formulation?
  - Extent of delivery: Same as laboratory control formulation?
  - Wear
    • Small-scale placebo clinical study
    • Same physical test results as laboratory control formulation?
  - Stability
    • Non-inferior to laboratory control formulation?
    • Evaluate container closure options
  - Irritation
    • Small-scale placebo clinical study
    • Small-scale active animal study
  - Excipients: Evaluate alternate suppliers
Pivotal/Launch

• 3Ds
  – Disease: Active clinical study (is therapy effective?)
  – Demand: Change/refine market projection
    • Maximum batch size (batch frequency)
    • On-going raw material requirements
    • Warehousing, testing & shipping requirements
    • Re-evaluate production costs
    • Assess equipment reliability/institute backup plans
    • Evaluate criticality of dedicated equipment
      – Preventive maintenance
      – Expedited service agreements

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Pivotal/Launch

• DEWSIE
  – Delivery
    • Same in vitro as controls?
    • Active clinical study
  – Extent
    • Same in vitro as controls?
    • Active clinical study
  – Wear
    • Same physical properties as controls?
    • Active clinical study
  – Stability: Evaluate long-term stability results (scale-up/pilot)
  – Irritation: Active clinical study
  – Excipients
    • Supply agreements/change control
    • Bulk pricing
Conclusions

• Two categories to consider
  – Market criteria
  – Performance criteria

• Asking the right questions at the right time leads to faster development and better products