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

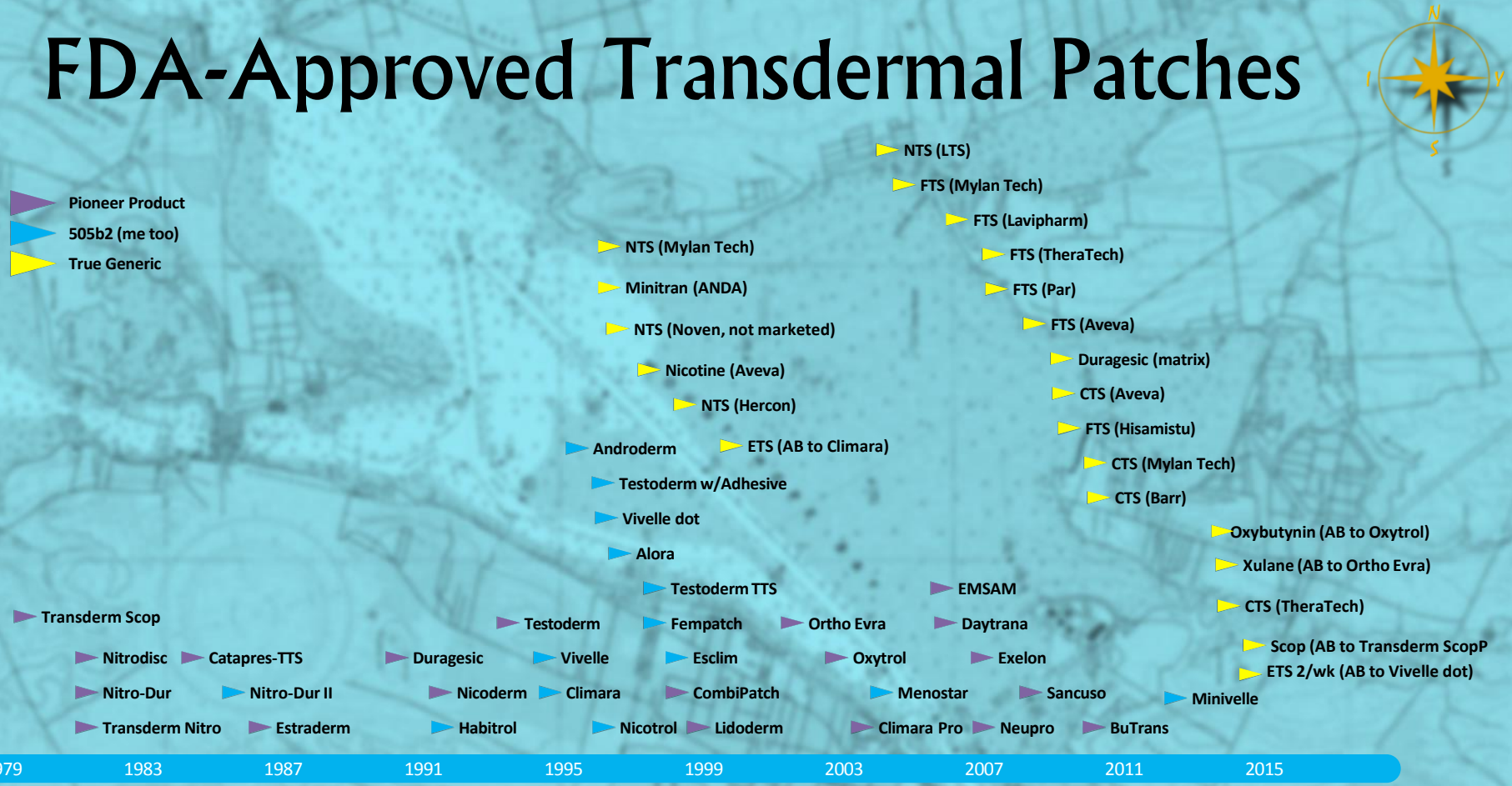
History

- 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

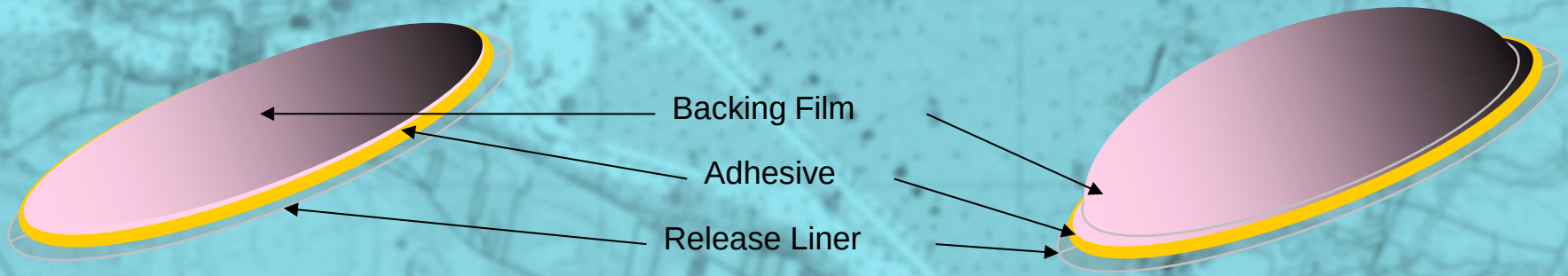
FDA-Approved Transdermal Patches



All Patches Have…

- A removable, disposable protective liner
- A backing film
- An adhesive
- A drug

Patch Anatomy (Matrix vs. Reservoir)



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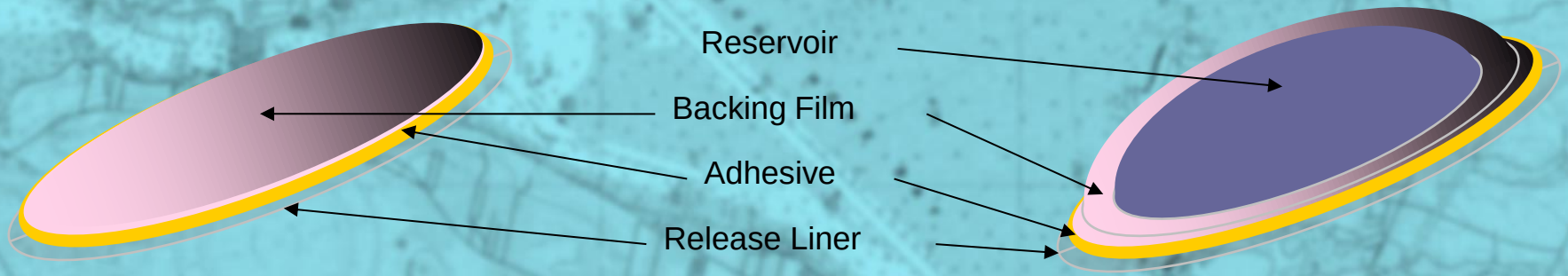
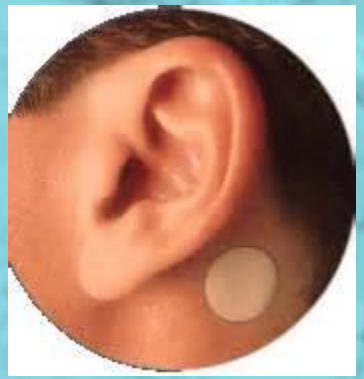
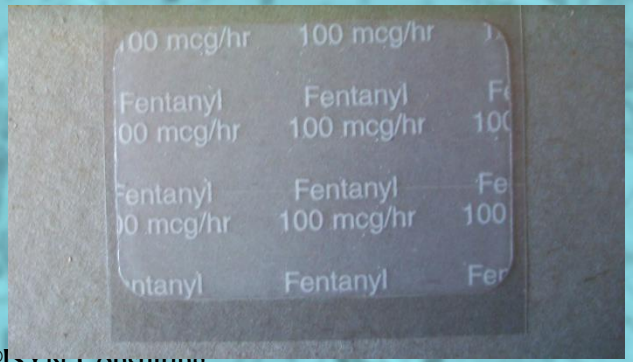


Commercial Patch Examples





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)

- **D**emographics (will patients use the product?)
- **D**isease characteristics (is the product effective?)
- **D**emand (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)*

- **D**elivery rate
- **E**xtent of delivery
- **W**ear
- **S**tability
- **I**rritation
- **E**xcipient compatibility and acceptability

*KJ Miller II, Transdermal product formulation development in Transdermal and Topical Drug Delivery: Principles and Practice, Heather A.E. Benson & Adam C. Watkinson eds. 2011.

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

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

Questions?

ISYN Consulting “I can take you there.”