Novel Patch Designs & Technologies

(Skinning the Cat Without Reinventing the Wheel)

Ken Miller

ISYN Consulting

American Slang

- "There is more than one way to skin a cat."
  - There is more than one way to solve a problem.
- "Reinventing the wheel"
  - Don't develop a new solution to a problem that's already been solved.

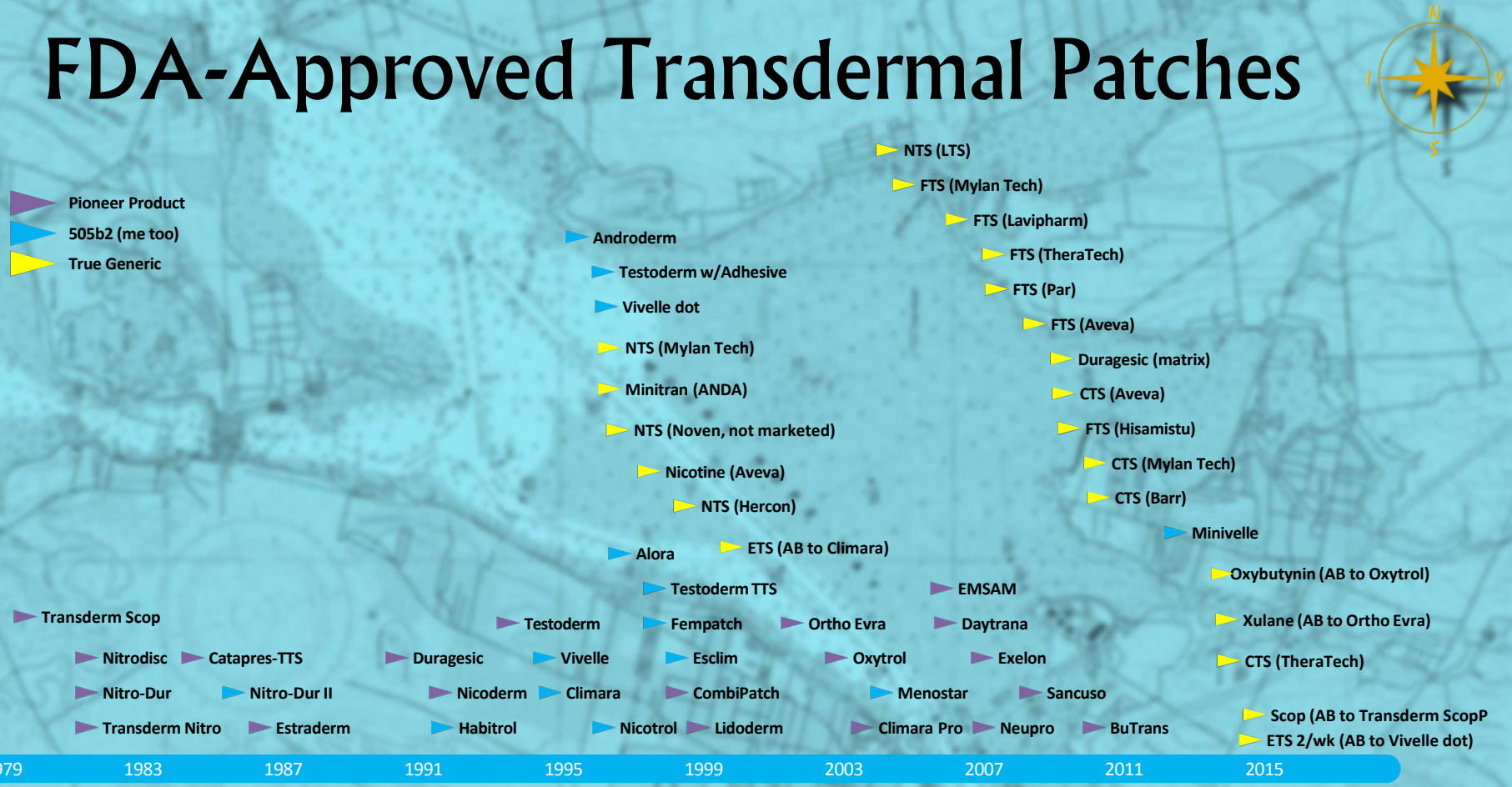
What You're In For

- Novel patch designs and acknowledgement of elegant engineering solutions
- Insight into the commonality of challenges and how solutions transcend industries

History

- The first commercial transdermal patch was Transderm Scop developed by Alza and approved by the FDA on New Year's Eve 1979.
- Alza dominated patch development for the next 20 years with Transderm Nitro, Catapres-TTS, Estraderm, Durogesic, Nicoderm and Testoderm.

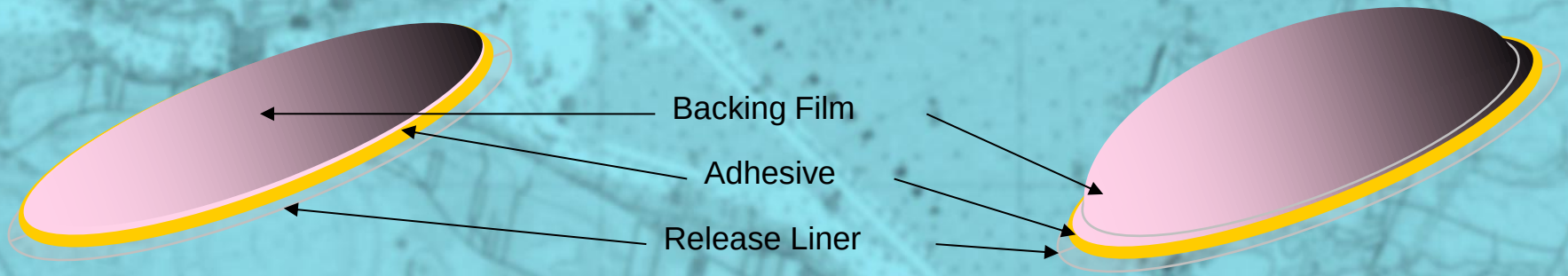
FDA-Approved Transdermal Patches



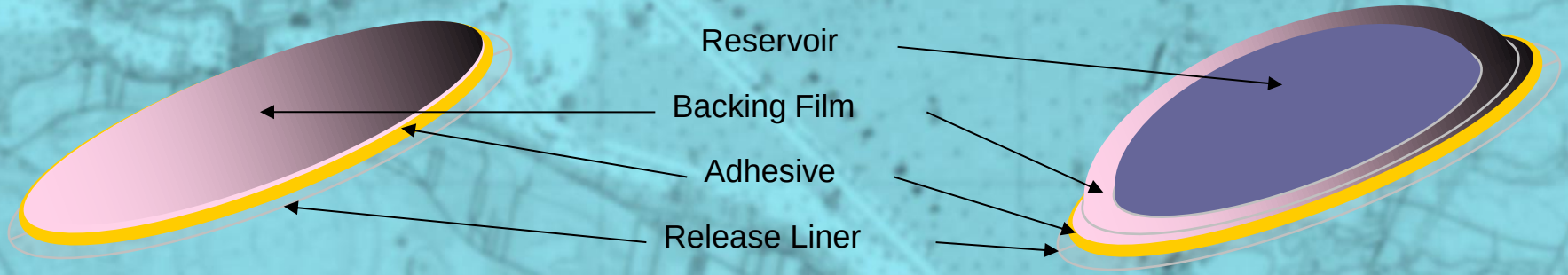
All Patches Have…

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

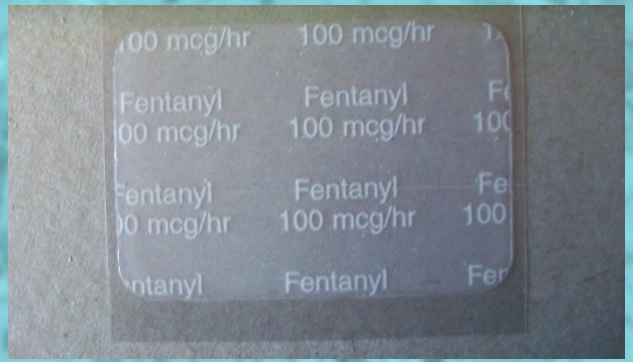
Patch Anatomy (Matrix vs. Reservoir)



Patch Anatomy (Matrix vs. Reservoir)



Commercial Patch Examples



Overcoming Challenges

- Slowing delivery
- Controlling delivery
- Preventing crystallization
- Preventing cold flow
- Preventing oxidation

Challenge #1: Slowing diffusion

- The "rate-controlling" membrane
  - Alza (Transderm Scop, Catapres-TTS, Estraderm, Testoderm, Duragesic)

US Pat 3,996,934: A Zaffaroni (December 14, 1976)

- Filed August 9, 1971
- Claim 1: A medical bandage…wherein one or more…rate controlling membranes are laminated to the surface of the reservoir….

Where Else Have We Seen This?

- Tyvek

Where Else Have We Seen This?

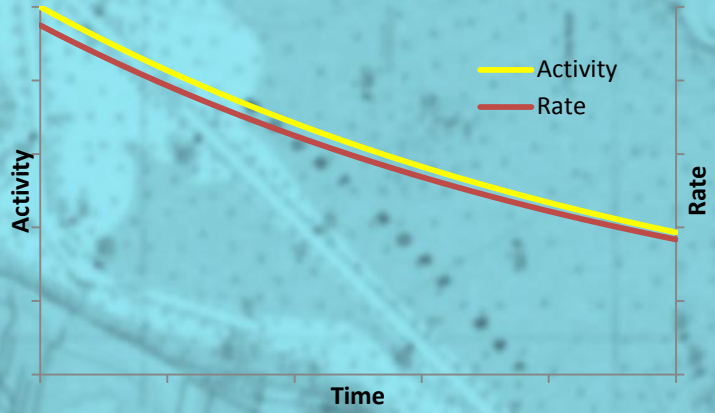
- Air Freshener

Where Else Have We Seen This?

- Salt Shaker

Challenge #2: Steady diffusion

- Fick's 1st law says diffusion from a simple, sub-saturated reservoir is first-order (rate is proportional to thermodynamic activity)



- In other words, if you deliver 10% of the drug, the rate falls by 10%

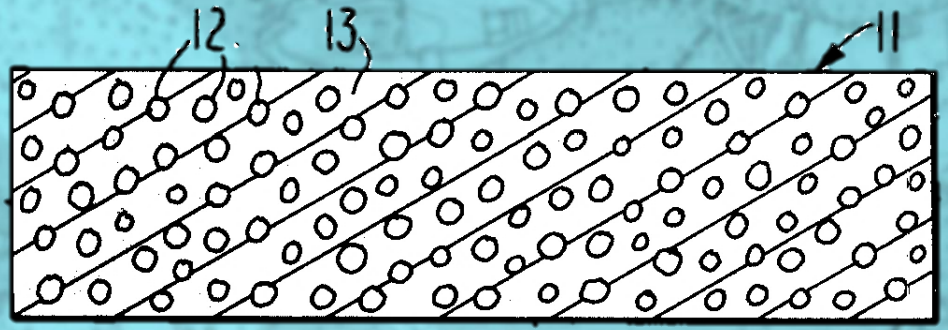
Challenge #2: Steady diffusion

- Conversely, if you want to keep the rate from changing by more than 10%, you can only deliver 10% of the drug in the reservoir.
- The obvious way to avoid this limitation is not to use a simple, sub-saturated reservoir.
- To keep rate constant, thermodynamic activity must be constant

US Pat 4,314,557: S Chandrasakaran (February 9, 1982)

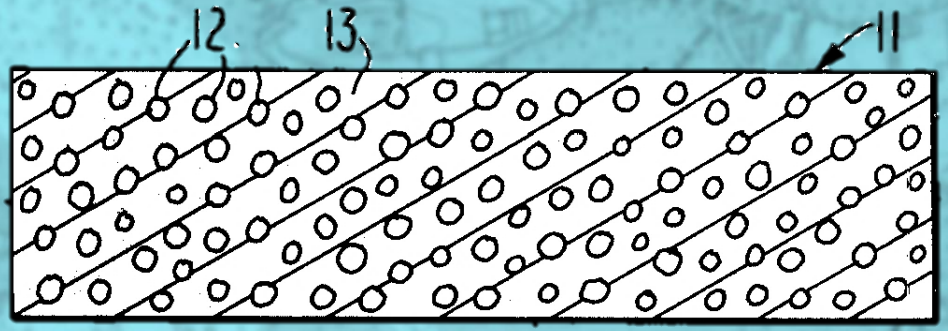
- Filed May 19, 1980
- Claim 1:An active agent dispenser consisting essentially of … a particulate active agent solute phase dispersed in a continuous matrix phase….

US Pat 4,314,557: S Chandrasakaran



11: Solid Flat Body
12: Drug Particles
13: Matrix

US Pat 4,314,557: S Chandrasakaran



- When solid drug particles dissolve into the matrix faster than dissolved drug diffuses through skin, the matrix remains saturated until all drug particles dissolve. (Activity is constant.)

Where Have We Seen This Before?

- Lollipop

Where Have We Seen This Before?

- Toilet Bowl Cleaner

Challenge #3: Crystallization

- Occurs in a super-saturated solution after a **nucleation event.**
- Continues until the solution is no longer super-saturated.
- It's very difficult to tell when a visco-elastic adhesive solution is super-saturated

  …until it crystallizes

Preventing Crystallization

- Two ways to prevent crystallization
  - Avoid super-saturation by reducing concentration or increasing solubility

    (stable, but decreases delivery rate)
  - Avoid nucleation

    (rapid delivery rate, but meta-stable)

Crystal Nucleation

- High-energy interfaces increase the likelihood of nucleation.
  - Backing/Adhesive
  - Membrane /Adhesive
  - Release liner/Adhesive
  - Edges (Air/Adhesive)

Transderm Scop

- Crystals of scopolamine began to occur at the membrane surface.
- Nucleation sites likely created during lamination phase of production.

US Pat 6,238,700: J Dohner et al., (May 29, 2001)

- Filed May 5, 1998
- Claim 1: An improved method for manufacturing …comprising…heating…each individual film or laminate…immediately following formation….
- Creates a meta-stable film *resistant* to spontaneous crystallization

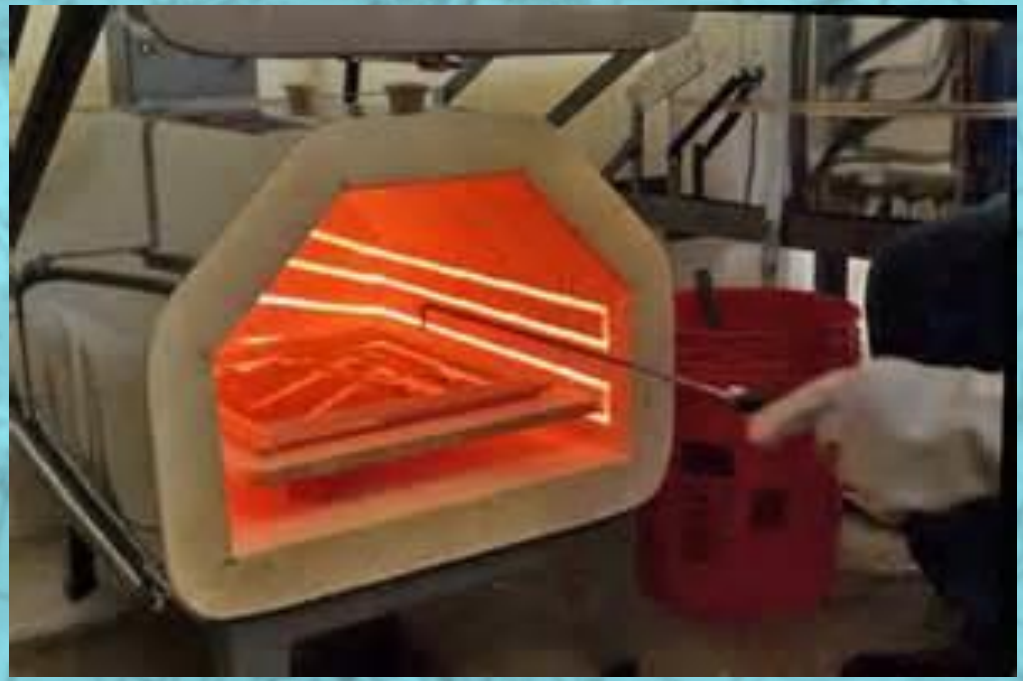
  (but, it's still super-saturated)

Where Have We Seen This Before?

- Metallurgy

Where Have We Seen This Before?

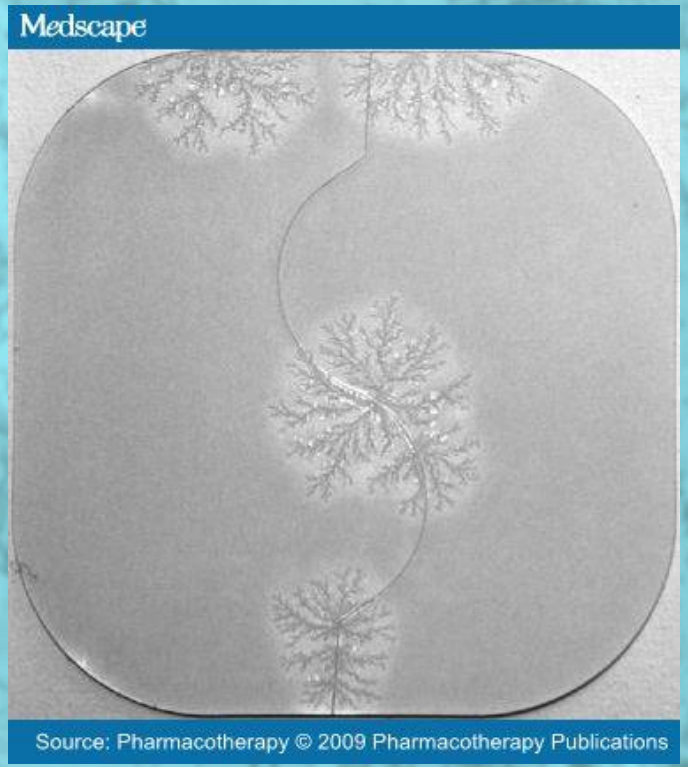
- Glass



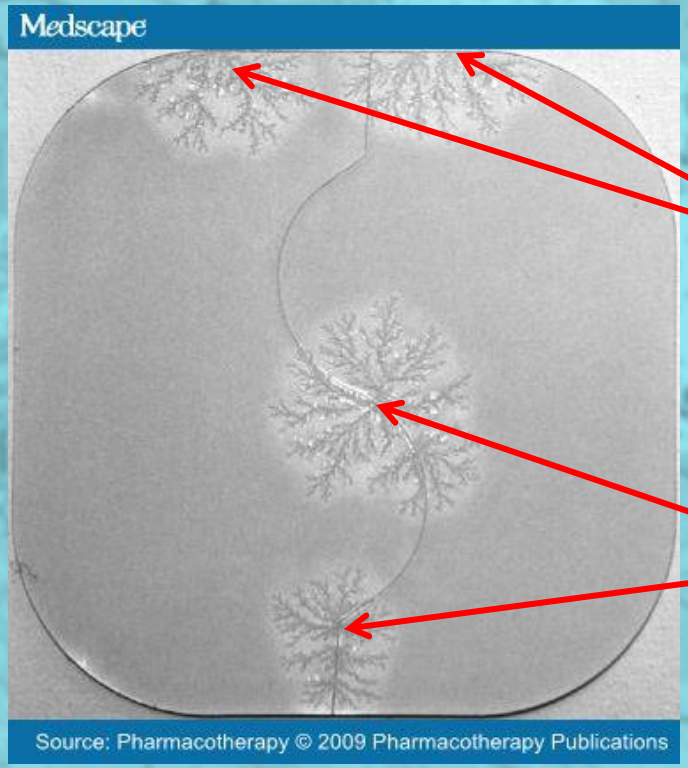
Where Have We Seen This Before?

- Chocolate

What If Heating Once Isn't Enough?



Notice where crystals formed



Edges where release liner, adhesive and backing are cut

Score line (kiss cut) where release liner is cut and adhesive is disturbed

US Pat 8,840,921: I Jasch (September 23, 2014)

- Filed December 22, 2009
- Invention description: …the release liner film and/or the carrier layer are…put through a pair of heatable opposing rollers…. One of both rollers can serve to create peripheral separating edges, particularly to separate individual patches from the layers.
- *Individual patches are cut out using heated dies.*

Where Have We Seen This Before?

- Cutting polystyrene

Where Have We Seen This Before?

- Heat-sealed packaging

Where Have We Seen This Before?

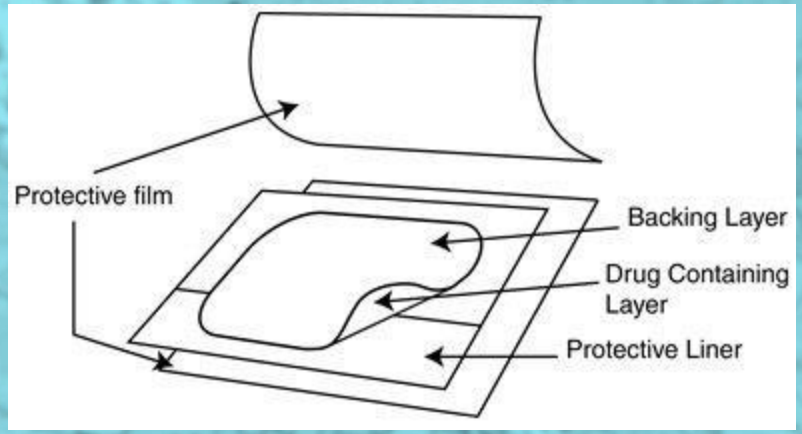
- Surgery

Challenge #3: Cold Flow

- A visco-elastic pressure-sensitive adhesive must flow, but…
- Excessive flow during storage can
  - foul the packaging,
  - foul the release liner
  - reduce potency.

Proven Solutions for Cold Flow

- Minor
  - Release liner inserts (e.g., Mylan FTS)

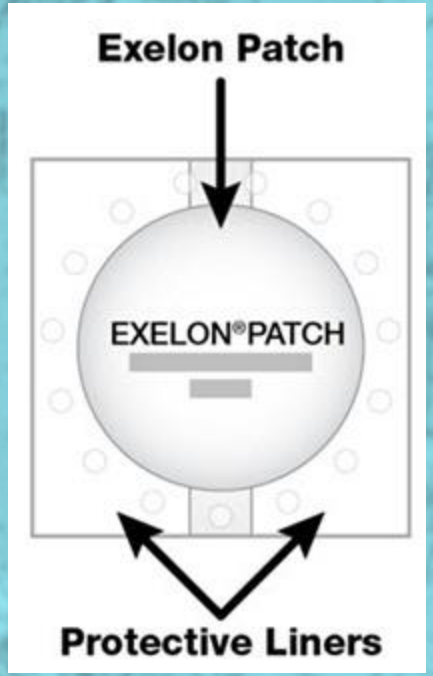


Where Have We Seen This Before?

- Baking

Proven Solutions for Cold Flow

- Moderate to severe
  - Dimples (e.g., Exelon)



Proven Solutions for Cold Flow

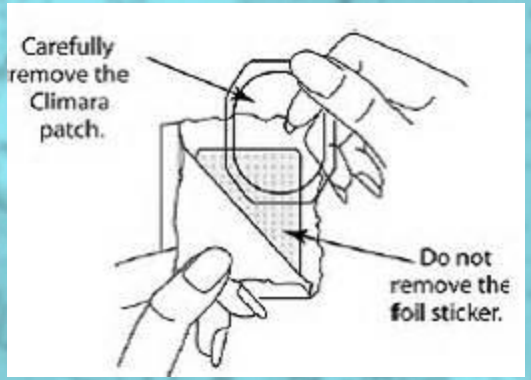
- Moderate to severe
  - Blister package (Patented by Nitto Denko in 2012 [8,146,741])

Challenge #4: Oxidation

- Oxidation of susceptible APIs can occur through
  - Exposure to moisture
  - Direct exposure to oxygen

Protection From Moisture

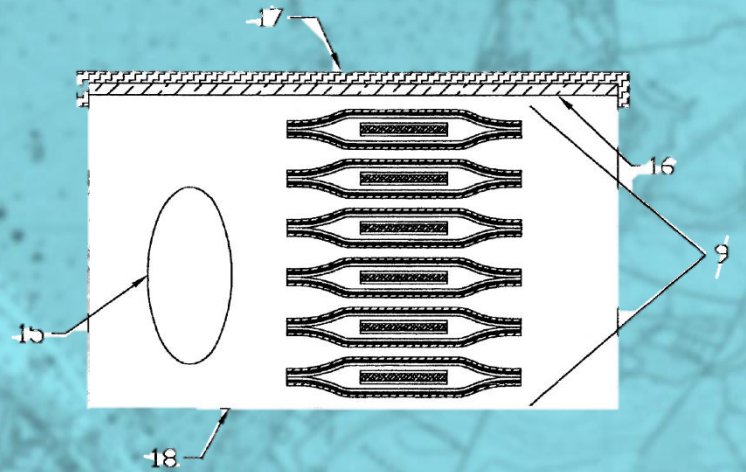
- Dessicant packet inside pouch (e.g., Climara)



Protection From Moisture

- Dessicant in secondary package (Patented by Noven in 2005 [6,905,016])

9 – moisture permeable pouches
15 – dessicant
16 – cover sheet
17 – reusable lid
18 – base sheet



Where Have We Seen This Before?

- Everywhere (baked goods, fresh fruit, electronics)

Protection From O_2 and Moisture

- Heat-sealed release liner (Patented by TheraTech in 1997 [5,662,925])

Where Have We Seen This Before?

- Everywhere (food, household cleansers, cosmetics)

Protection From O_2 and Moisture

- Packaged in dry N_2

Where Have We Seen This Before?

- Food, sporting goods

What's the Message?

- We may think the pharmaceutical industry spends lots of money on innovation…
- But the consumer products industry spends much, much more and…
- They deal with many of the same challenges we do.

It's Not Just Consumer Products

- Transportation
- Heavy industry
- Agriculture
- Arts and crafts

How Do I Know?

- I read the journals.
- I talk to the scientists & engineers.
- And I remind myself that ideas and answers can come from anywhere, so…
- I also watch a lot of cable TV

Questions?

ISYN Consulting “I can take you there.”