Noven Pharmaceuticals, Inc.

Innovations in Passive Transdermal Drug Delivery:

High Doses in a Small Patch

A Releasing Technology Workshop
CRS 2006 Annual Meeting
July 23, 2006

Presenters

- **Juan A. Mantelle**
  - **Vice President of R&D and Chief Technical Officer**
    - ***Transdermal State of the Art***
- **David Kanios**
  - **Director - Research & Development**
    - ***DOT Matrix™ Technology for Developing Transdermal Drug Delivery Systems***
- **Christopher W. McDaniel, Ph.D., MBA**
  - **Director - New Technology Assessment**
    - ***Transdermal Product Development Considerations: Passive and Active Transdermal Delivery Systems***
- **Pavan Handa**
  - **Vice President - Business Development**
    - ***NOVEN - Bringing Transdermal Product Innovations to Market***

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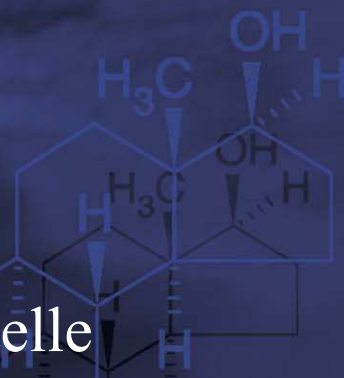
Transdermal State of the Art: Passive Systems



Juan A. Mantelle
Vice President – Research & Development
and Chief Technical Officer

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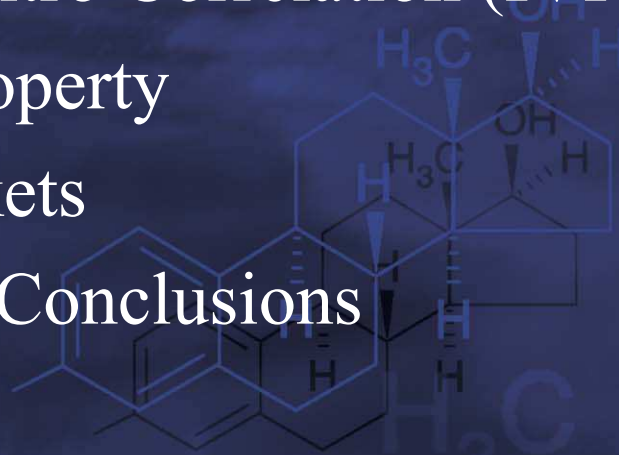
Transdermal State of the Art: Passive Systems

- OUTLINE
  - Background on Noven
  - Why transdermals? Which type?
  - Dot Matrix™ Technology: What is it?
  - In Vivo – In Vitro Correlation (IVIVC)
  - Intellectual Property
  - Potential Markets
  - Summary and Conclusions



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Who We Are – Background on Noven

World's Leading Transdermal Technology

- **Founded: 1987**
- **HQ: Miami, Florida**
- **Employees: 500**
- **HQ/Manufacturing: 200,000 sq/ft**
  - **Annual capacity of 650+ million patches for general and controlled substances**
- **$120+ million plus HT business through JV**
- **Vivelle-Dot - #1 Transdermal ET product**
- **Daytrana™ transdermal patch approved by FDA for treatment of ADHD**
- **Profits, cash, no long-term debt**
- **Stock - Nasdaq: NOVN**

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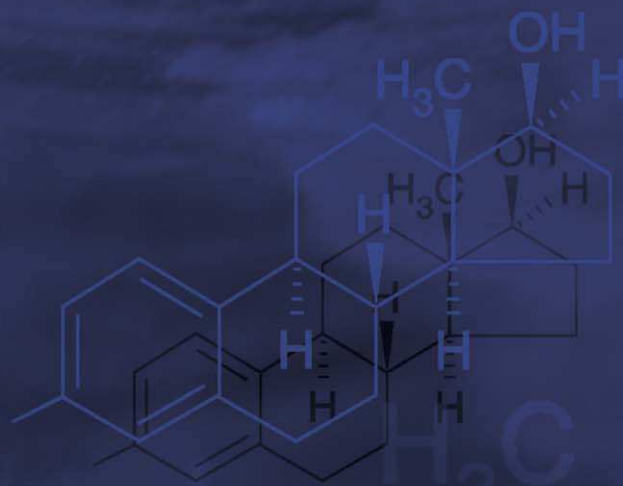
Why Transdermals?
Which Type?



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Why Transdermals?

Benefits of Patches vs. Pills

As compared to pills, patches:

- Eliminate first pass metabolism
- Provide steady delivery/blood levels
- Increase compliance/convenience
- Reduce systemic drug interactions
- Can minimize abuse/diversion
- Permit dose discontinuation via removal
- Provides product life cycle extension opportunities at lower cost with lower risks

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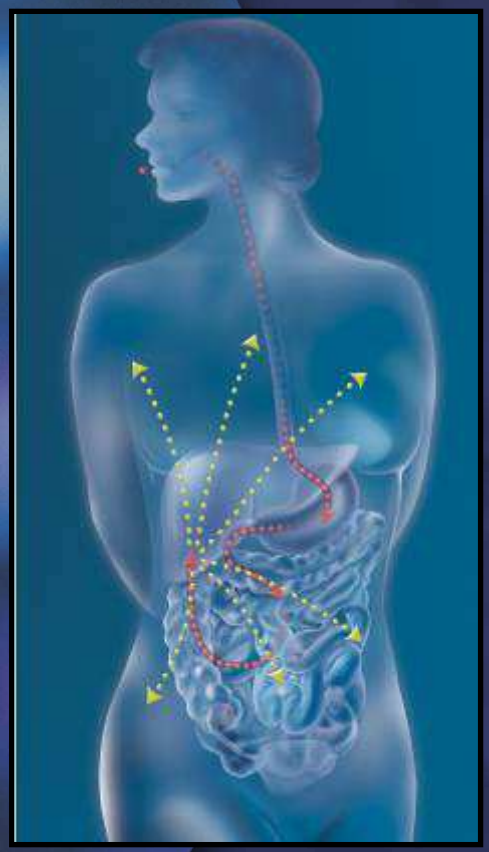
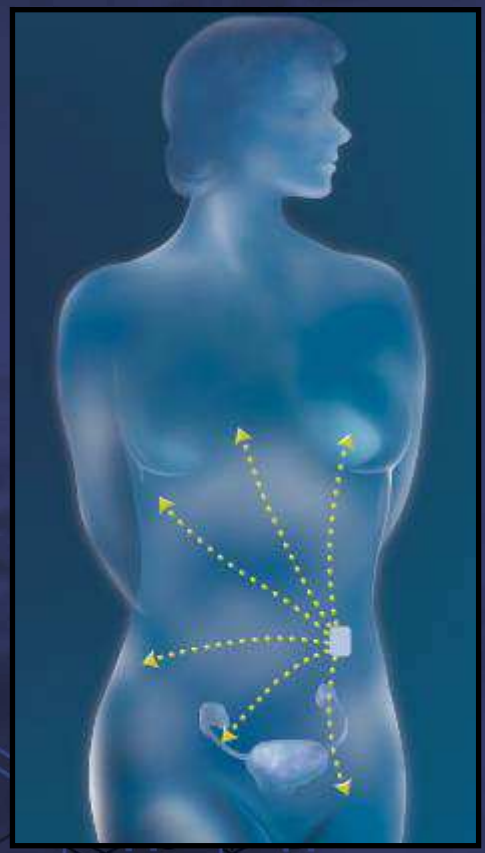
Transdermal vs Oral Delivery

Oral delivery



Transdermal delivery



Patch History & Hurdles

The Patch Design Dilemma

- Patients demand patches with the following attributes:
  - Comfortable (non-irritating)
  - Adherent (stay put)
  - Reproducible blood levels
  - Small (discreet)

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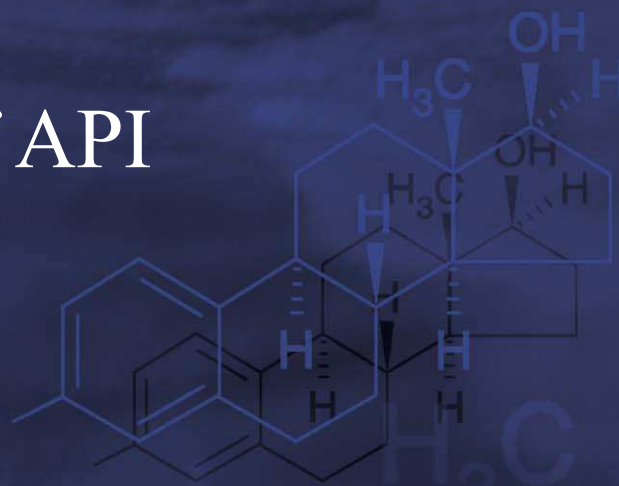
Limitations to Permeation

1. Stratum Corneum
2. Molecular Weight of the API
3. Melting Point / Volatility of API
4. Hydrophilic / Hydrophobic properties
5. Doses
6. Solubility of API



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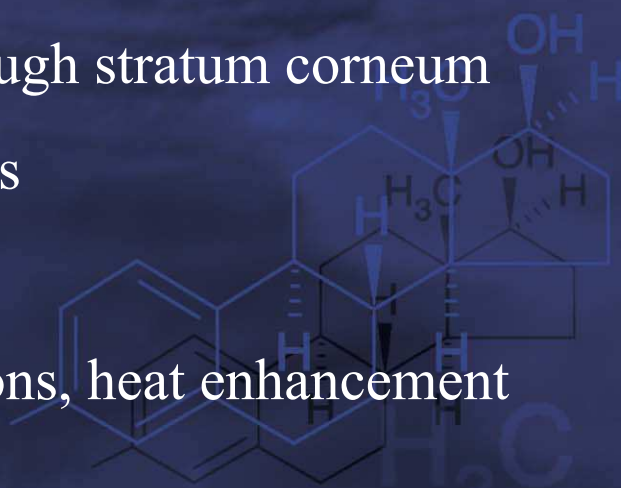
Optimization of Passive Transdermal Delivery

- Maximize thermodynamic driving force (solubilization to quasi-saturation)
- PRO-DRUG Formulation (i.e., NETA vs. NET)
  - Lower melting point
  - Enhanced lipophilicity
- GRAS listed chemical enhancement
  - Enable channeling through stratum corneum
  - Avoid irritant molecules
- Mechanical Enhancement
  - Micro needles/projections, heat enhancement



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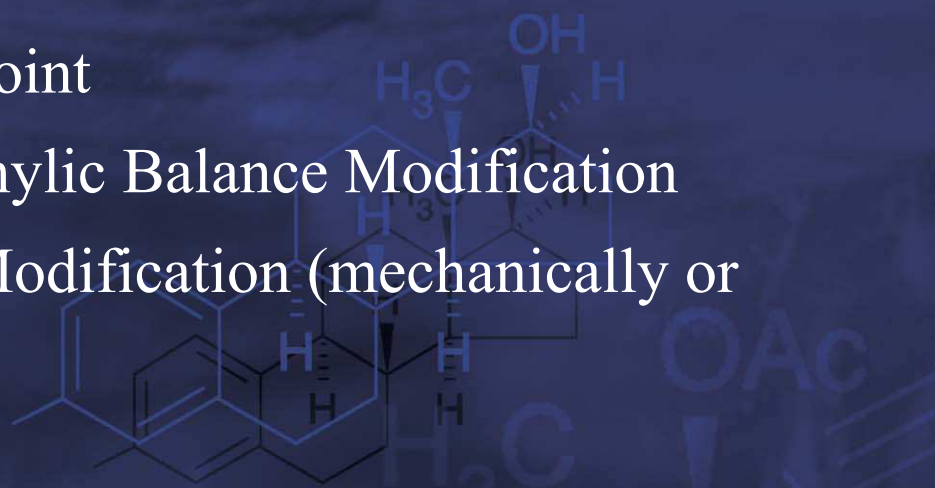
Summary

Barriers to transdermal delivery can be overcome in many cases by techniques such as:

1. Polymer Composition Selection
2. Solubilization
3. Esterification or Pro-Drug formation
4. Effective Concentration Enhancement
5. Lower of Melting Point
6. Hydrophylic/Lipophylic Balance Modification
7. Stratum Corneum Modification (mechanically or chemically)



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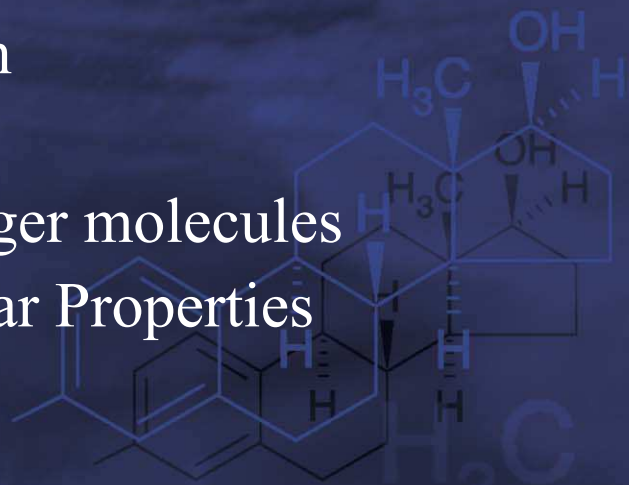
Which Type of Transdermal Best Suits My Application ?

- Reservoir Systems
  - Volatile API
  - Expensive API – higher yields
- Traditional Drug – in – Adhesive Systems
  - Inexpensive API
  - Low doses / smaller molecules
- Dot - Matrix™ System
  - Expensive API
  - Higher doses / larger molecules
  - Customizable Wear Properties



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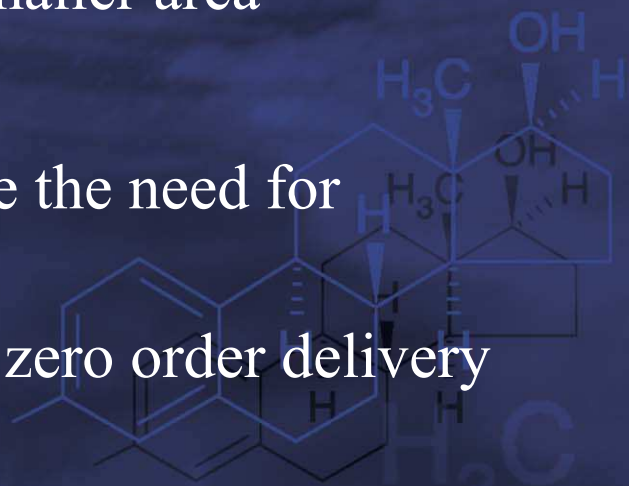
DOT Matrix™ Technology

Patented through 2014

- New class of highly-efficient passive transdermal systems
- 33 U.S. patents issued or allowed
- Advantages over reservoir and the traditional drug-in-adhesive patches
  - More drug through smaller area
  - Excellent adhesion
  - Minimize or eliminate the need for irritating enhancers
  - Reproducible pseudo zero order delivery



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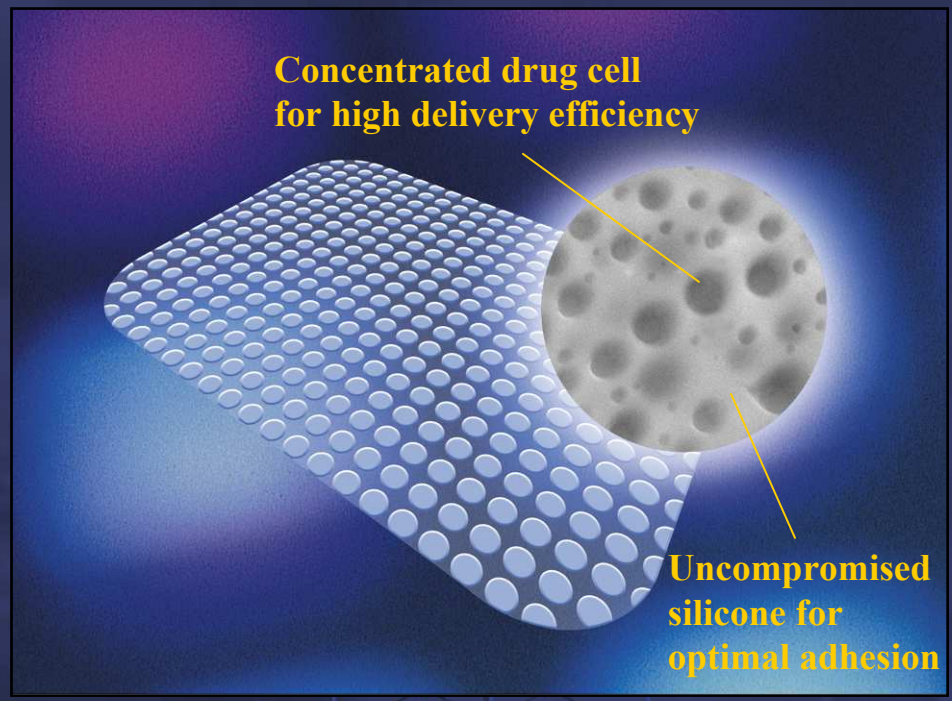
DOT Matrix Technology

How it works

- Drug is solubilized in acrylic in very high concentrations
- Drug/acrylic then mixed with silicone adhesive
- Forms concentrated drug cells in uncompromised silicone adhesive
- Concentration gradient between drug and skin causes highly efficient diffusion
- Precise content ratios control rate of delivery



Circular image is the surface of the drug/adhesive layer of a DOT Matrix patch photographed with a scanning electron microscope.

In Vivo- In Vitro Correlation: The Vivelle- Dot Story

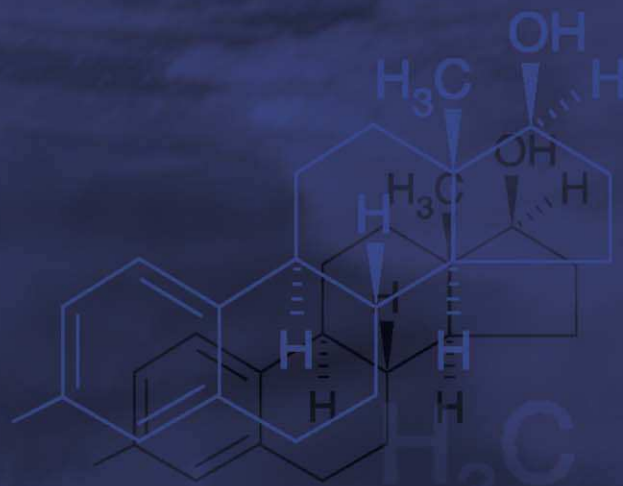


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Figure #1 - In Vitro Human Cadaver Skin Permeation Study Summary.
Averages For Five Different Skin Donors

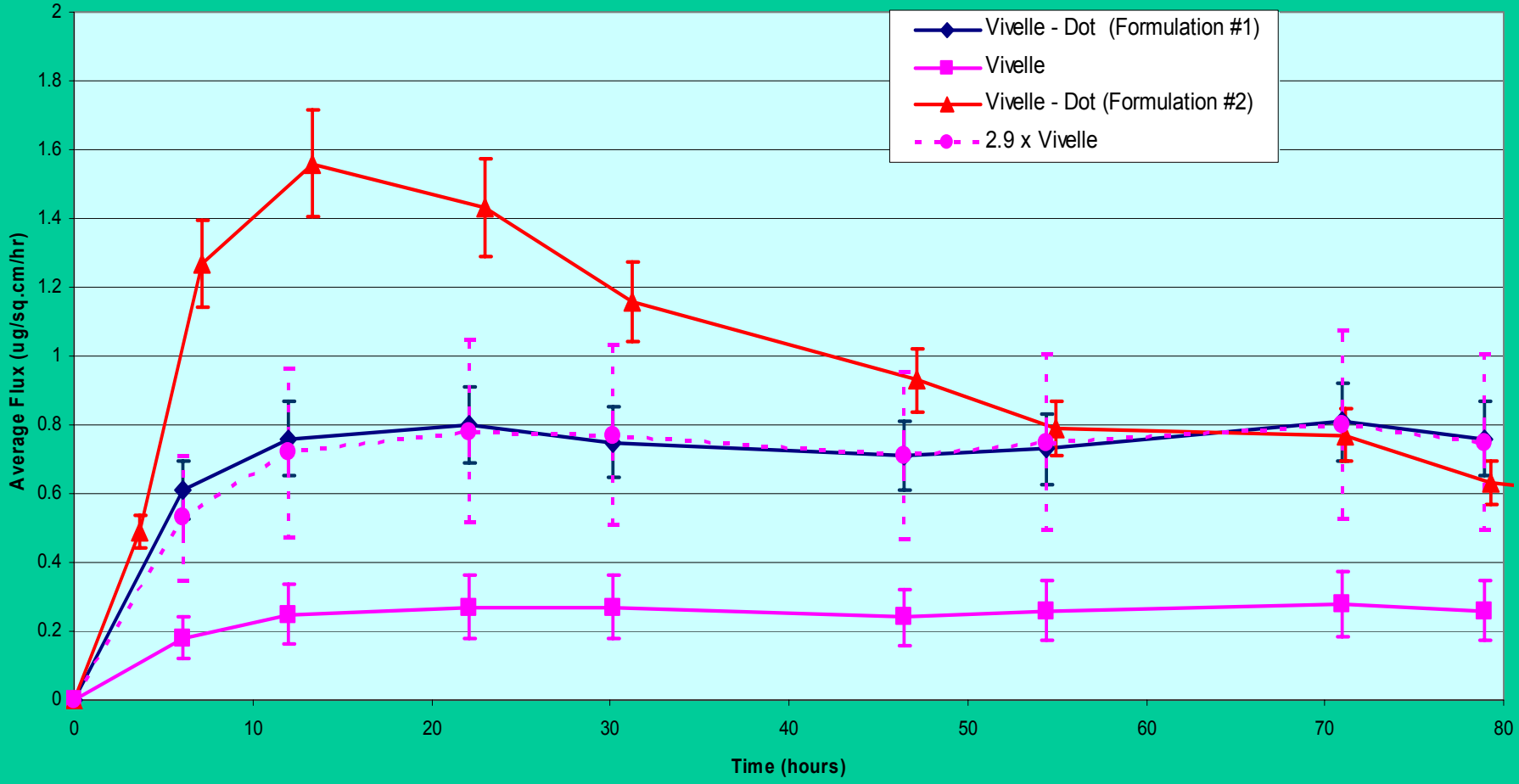
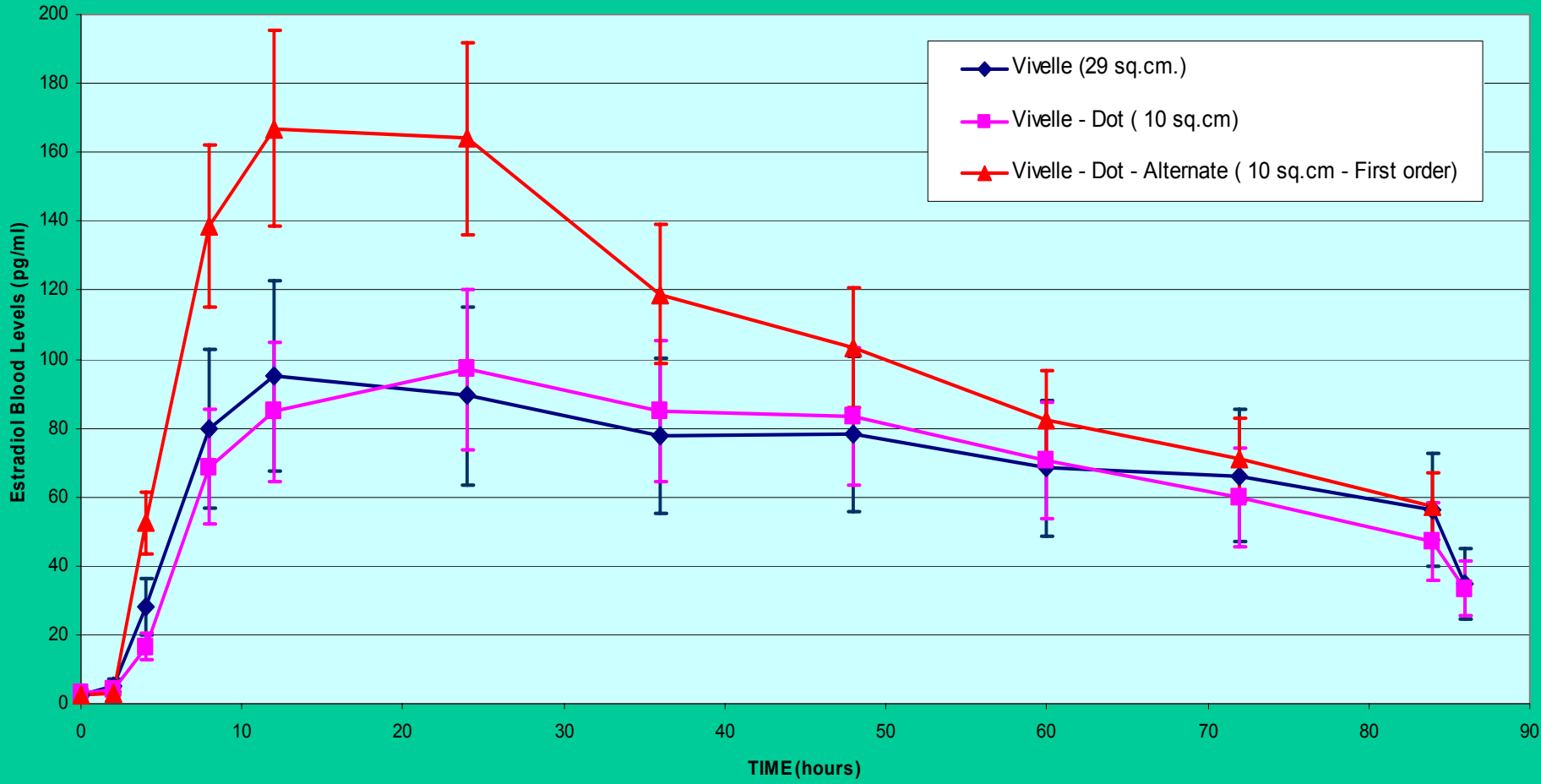


Figure #2 - In Vivo Comparison of Vivelle with Two Vivelle- Dot Potential Formulations on Human Volunteers (n=12)



Less Drug, Smaller Area, Same Effect

Based on Label Claim for 0.05 mg/day Dose

Product	Patch Size	Estradiol Content	% Depletion
Vivelle-Dot	**5.0 cm^2**	**0.8 mg**	**22.4%**
Vivelle	14.5 cm^2	4.3 mg	4.0%
Climara***	12.5 cm^2	3.9 mg	9.0%
Estraderm	18.0 cm^{2*}	4.0 mg	4.4%
Mylan***	23.7 cm^{2**}	1.9 mg	18.0%
Alora	18.0 cm^2	1.5 mg	11.6%
Esclim	22.0 cm^2	10.0 mg	1.8%

* Active area is 10.0 cm^2.
** Active area is 15.5 cm^2.
*** 7-day patch; others are 3.5-day.

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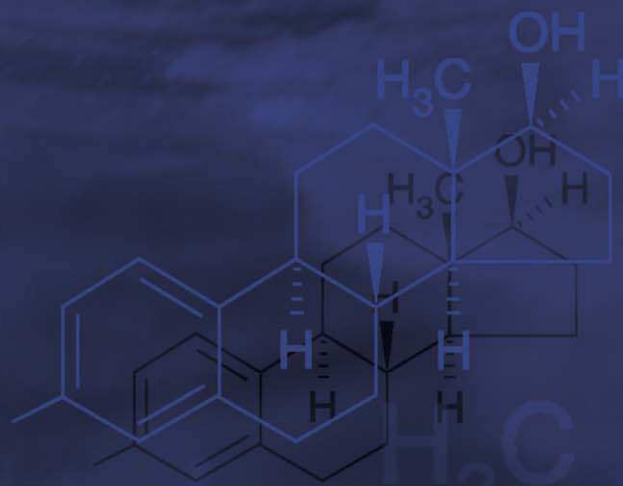
INTELLECTUAL PROPERTY



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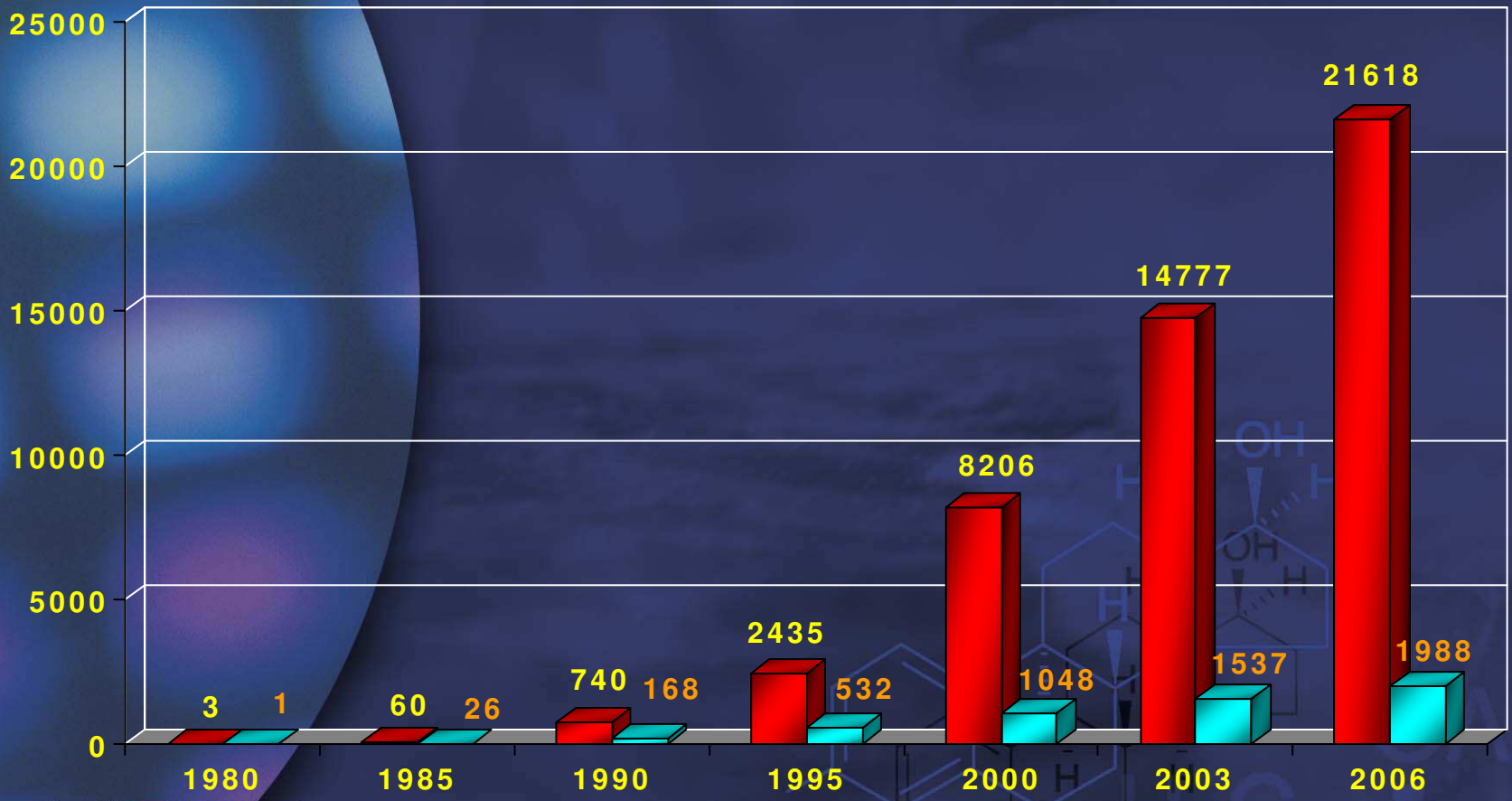
U.S. Patents Incorporating the Word "Transdermal" in the Specification or Claims



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Who Are These Transdermal Patents Assigned To ? – The "Expected" List

- Alza -249
- Lohman – 147
- Ciba Geigy - 139
- 3M – 121
- Cygnus – 85
- Dow Corning – 45
- Noven – 33
- Monsanto -31
- Theratech -29
- Merrell Dow - 25
- Key - 23
- J & J - 19
- Hexal – 13
- Berlex - 12
- Lectec – 11
- Hercon -10
- Bertek – 9
- Lavipharm – 9
- National Starch – 8
- Watson -7

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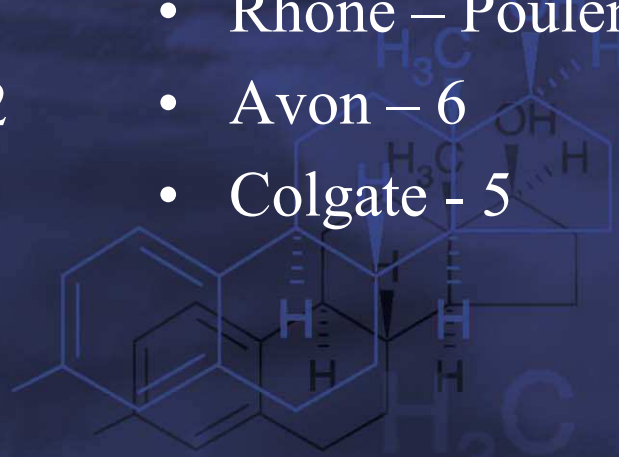
Who Are These Transdermal Patents Assigned To ? – The "Unexpected" List

- Merck – 636
- Schering – 583
- Pfizer – 328
- GD Searle – 271
- Sanofi – 212
- American Home - 194
- Procter & Gamble – 192
- Aventis – 192
- GSK – 165
- Syntex -155
- Upjohn -119
- Warner Lambert – 114
- Novartis – 87
- Elan - 78
- Rhone – Poulenc – 53
- Avon – 6
- Colgate - 5



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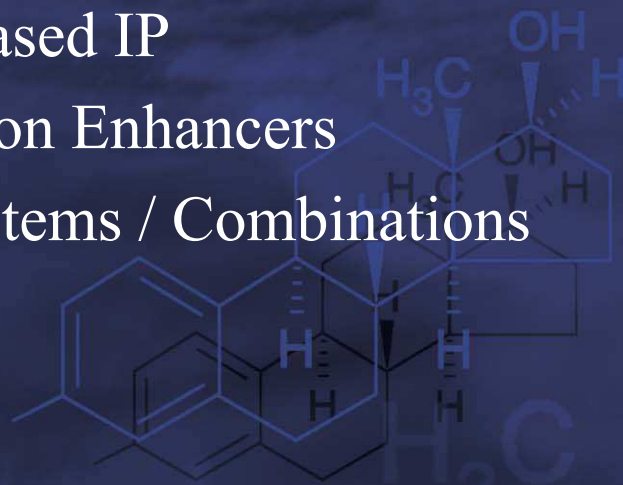
Future IP Strategies

- "Picture" Claims
  - Narrow composition windows
  - New methods of manufacturing
- Expiring Patents
  - Making older technology new again.
- New Chemical Entities
- Pharmacokinetic – based IP
- Novel Skin Permeation Enhancers
- Novel Polymeric Systems / Combinations



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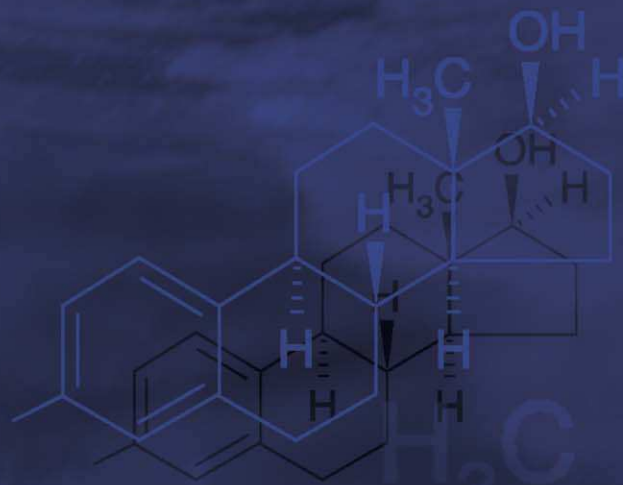
Potential Markets and Opportunities



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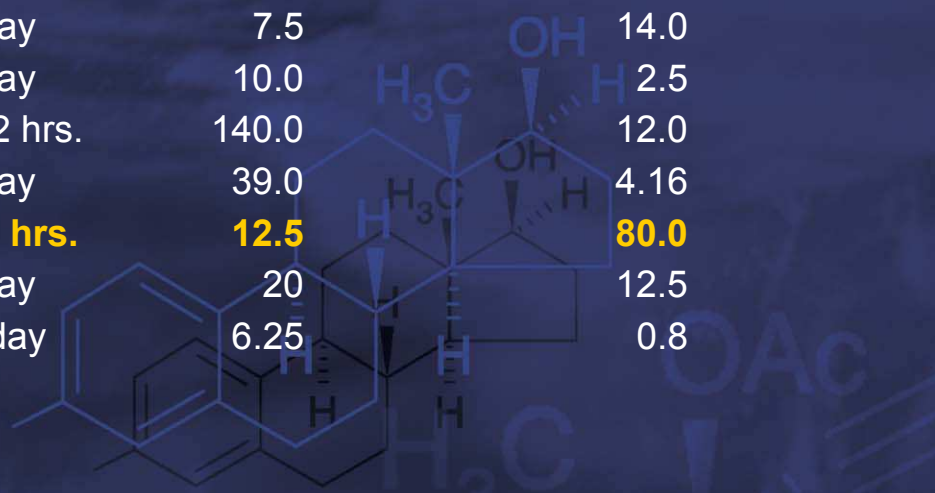
Properties of Commercialized Transdermals

	Drug	Molecular Weight	Daily TD Dose	Smallest Patch Size (cm^2)	In-Vivo Permeation Rate ($\mu g/cm^2/hr$)
1.	Scopolamine	303.35	0.33 mg/day	2.5	5.5
2.	Nitroglycerin	227.09	1.6 mg/16 hrs.	5.0	20.0
3.	Clonidine	230.10	0.1 mg/day	3.5	1.19
4.	**Estradiol**	**272.38**	**0.1 mg/day**	**10.0**	**.42**
5.	**NETA**	**340.45**	**0.14 mg/day**	**9.0**	**0.65**
6.	Ethinyl Estradiol	296.40	0.02 mg/day	20.0	0.042
7.	Norelgestromin	327.47	0.15 mg/day	20.0	0.31
8.	Nicotine	162.23	7.0 mg/day	7.0	42.0
9.	Testosterone	288.42	2.5 mg/day	7.5	14.0
10.	Fentanyl	336.50	0.6 mg/day	10.0	2.5
11.	Lidocaine	234.34	21.33 mg/12 hrs.	140.0	12.0
12.	Oxybutynin	357.49	3.9 mg/day	39.0	4.16
13.	**Methylphenidate**	**233.31**	**12.0 mg/12 hrs.**	**12.5**	**80.0**
14.	Selegiline	187.28	6.0 mg/day	20	12.5
15.	Buprenorphine	467.64	0.12 mg/day	6.25	0.8



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Examples of Noven's transdermal drug development opportunities

Depression
Buspirone
Bupropion

Urinary Incontinence
*Tolterodine
Oxybutynin

Allergies
Azelastine

Obesity
Phentermine
Methamphetamine

Hypertension
Enalapril
Clonidine
*Ramipril
Timolol

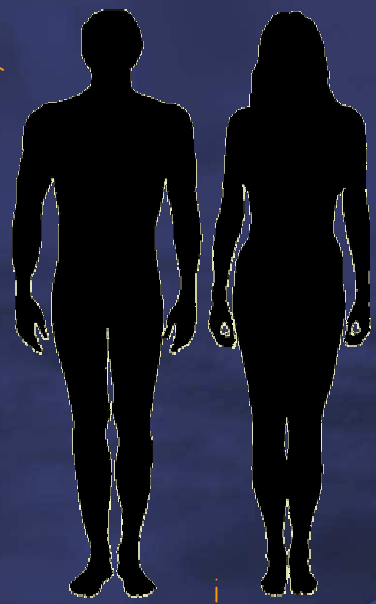
Nausea
*Granisetron

Parkinson's
*Ropinirole
Pergolide
*Pramipexole
*Rotigotine

Anxiety
Alprazolam

Alzheimers
Tacrine
Memantine

ADHD
Methylphenidate
Amphetamine



Birth Control
Estrogen/Progestin
Combinations (various)

Motion Sickness
Scopolamine

Epilepsy
Clonazepam

Pain
Buprenorphine (Chronic)
Fentanyl (Chronic)
Sufentanyl (Chronic)
Levorphanol (chronic)
Various NSAIDs (Arthritic)
*Triptans (Migraine)
Lidocaine

Male Hypogonadism/ Female Sexual Dysfunction
Testosterone

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*** Under patent protection by originator**

Potential Patch Markets

Therapy	Year 2003	Year 2005	Year 2007
Angina pectoris	$1.2 billion	$1.5 billion	$1.8 billion
Arthritis	$8.5 billion	$12.5 billion	$16.0 billion
Attention deficit hyperactivity disorder	$1.3 billion	$1.5 billion	$1.7 billion
Contraception, prevention of pregnancy	$5.6 billion	$7.0 billion	$8.6 billion
Dermatologicals	$5.2 billion	$6.5 billion	$7.8 billion
Erectile dysfunction	$2.2 billion	$3.0 billion	$3.7 billion
Estrogen replacement therapy	$3.8 billion	$4.5 billion	$5.1 billion
Female sexual arousal disorder	$1.1 billion	$1.5 billion	$1.9 billion
Hypertension	$18.0 billion	$19.3 billion	$24.6 billion
Male testosterone replacement therapy	$0.6 billion	$1.0 billion	$1.3 billion
Pain * (only selected conditions)	$7.2 billion	$9.8 billion	$12.6 billion
Parkinson's disease	$1.9 billion	$2.5 billion	$3.0 billion
Smoking cessation	$0.8 billion	$1.2 billion	$1.5 billion
TOTAL	**$ 57.4 billion**	**$ 63.9 billion**	**$ 72.0 billion**

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* Source: 2004 Transdermal Drug Delivery Report by Jain PharmaBiotech.

Summary and Conclusions

- Transdermal Drug Delivery Systems provide low cost / reduced risk opportunities for product life cycle extension.
- Predictive models work very well but are NOT flawless.
- Intellectual Property examination and "navigation" have become two of the more critical aspects of new transdermal product development.
- As a "novel" technology, the upside potential for transdermal delivery of new molecules in almost all therapeutic categories is still very significant.
- Dot Matrix™ Technology is uniquely suited to provide access to larger molecules and larger doses as can be seen by the Daytrana™ experience.

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DOT Matrix™ Technology For Developing Transdermal Drug Delivery Systems

David Kanios
Director - Research & Development

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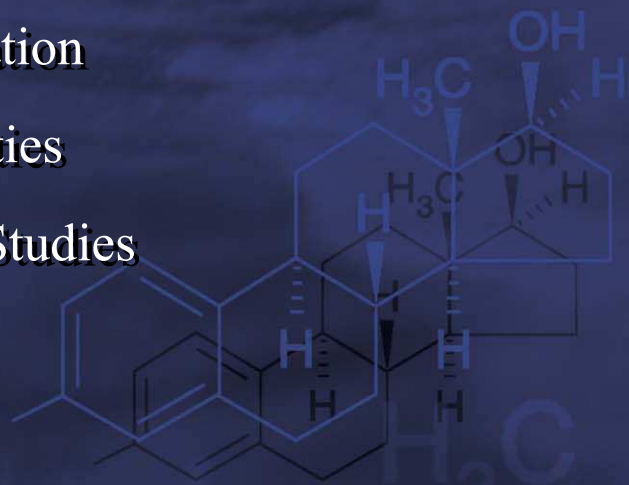
OVERVIEW

- Transdermal Drug Delivery Systems (TDDSs)
- Adhesives
- Additives
- Films
- Packaging Materials
- Stability Properties
- In-Vitro Permeation
- Physical Properties
- Research Case Studies
- Conclusion



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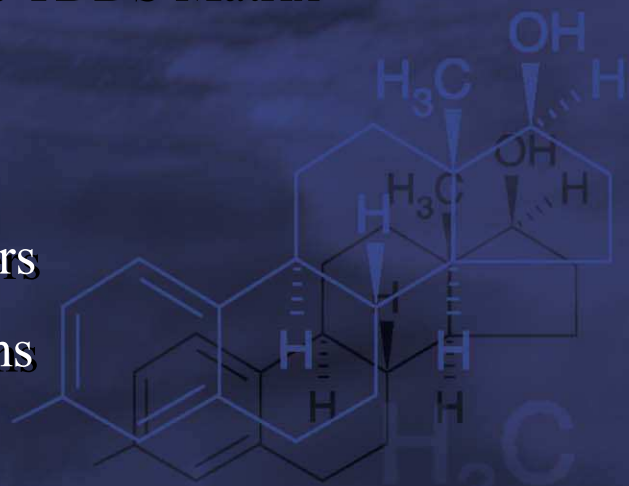
TRANSDERMAL DRUG DELIVERY SYSTEMS

- DOT Matrix™ Technology
  - Silicone / Acrylic Pressure Sensitive Adhesive Blend
  - Reduced Size
  - Enhanced Wear
  - Passive Drug Delivery
- Drug-In-Adhesive TDDS Matrix
  - Adhesives
  - Additives
  - Release Liners
  - Backing Films
  - Drug(s)



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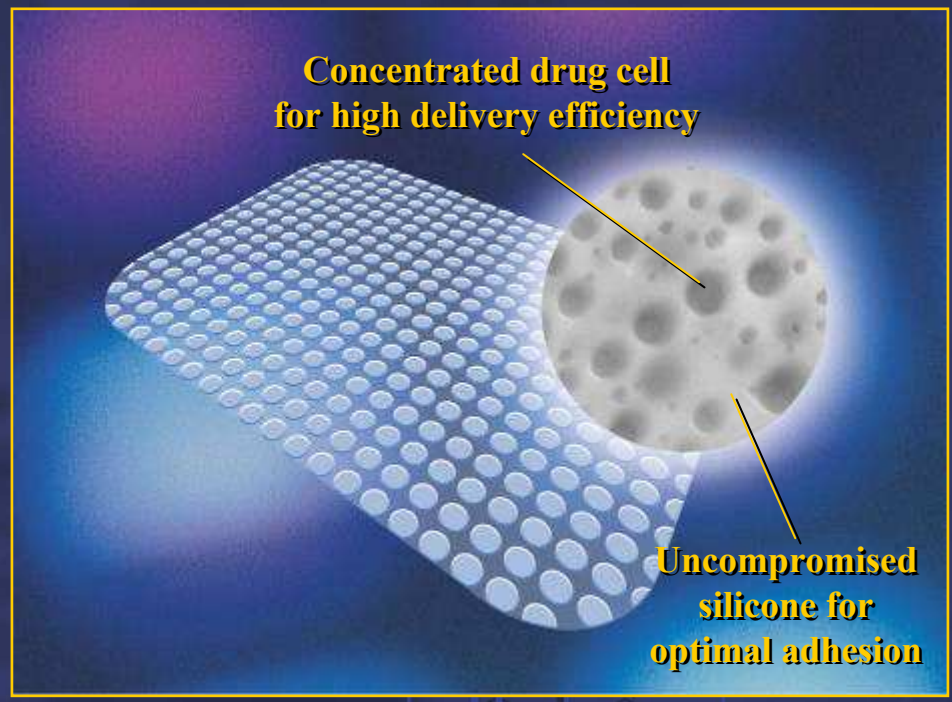
DOT Matrix™ Technology

How It Works

- Drug solubilized in acrylic in very high concentrations
- Drug/acrylic mixed with silicone adhesive
- Concentrated drug cells formed in silicone "sea"
- Concentration gradient causes highly efficient diffusion
- Precise content ratios control rate of delivery



Circular image is electron microscope view of the surface of a DOT Matrix™ patch.

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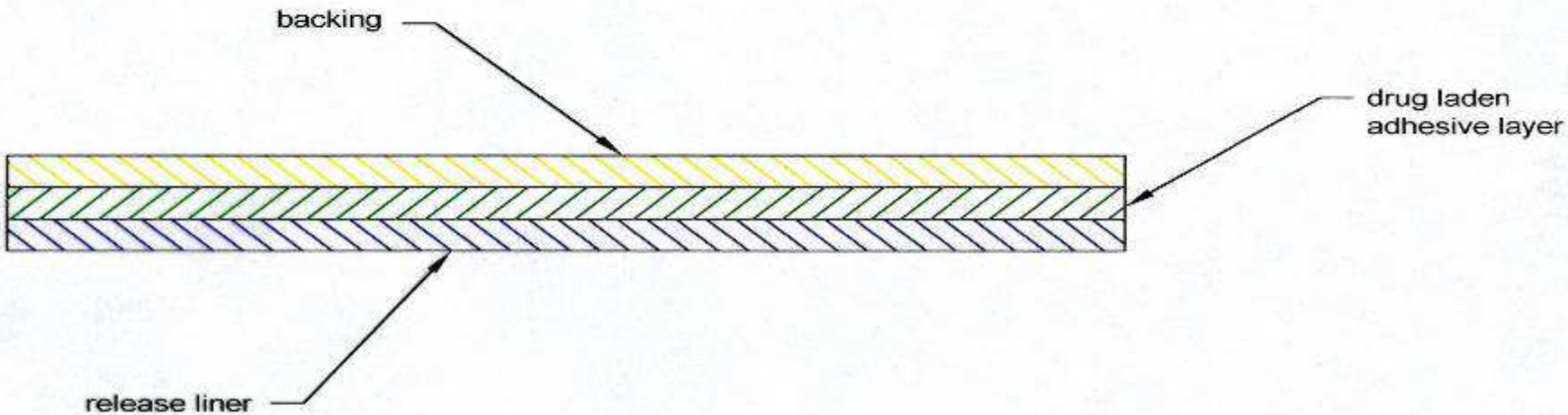
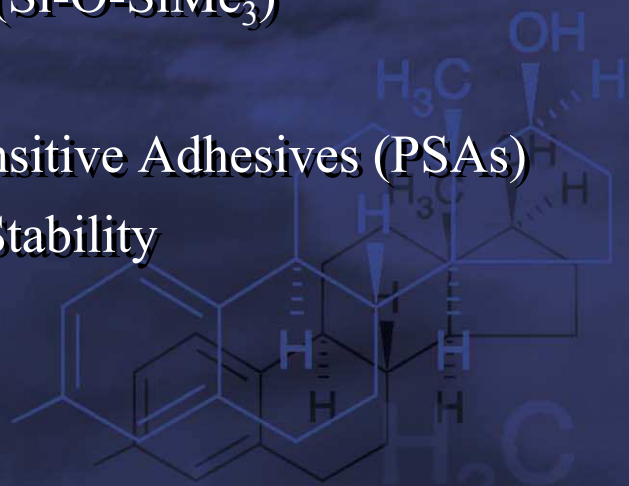
Illustration 1: Drug-in-Adhesive Transdermal System



ADHESIVES

- Acrylic Pressure Sensitive Adhesives (PSAs)
  - Functional PSAs
  - Reactive PSAs
  - Non-Functional/Non-Reactive PSAs
  - Drug Solubility
- Silicone Pressure Sensitive Adhesives (PSAs)
  - Silanol (Si-OH)
  - SiOH Silylated (Si-O-$SiMe_3$)
  - Wear Properties
- Blended Pressure Sensitive Adhesives (PSAs)
- Drug Compatibility/Stability



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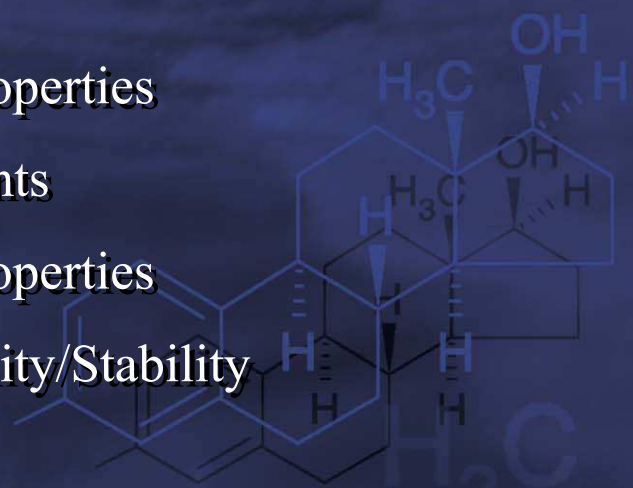
ADDITIVES

- Co-Solvents
  - Solubility
  - Physical Properties
- Plasticizers
  - Physical Properties
- Polymers
  - Solubility
  - Physical Properties
- Natural Ingredients
  - Physical Properties
- Drug Compatibility/Stability



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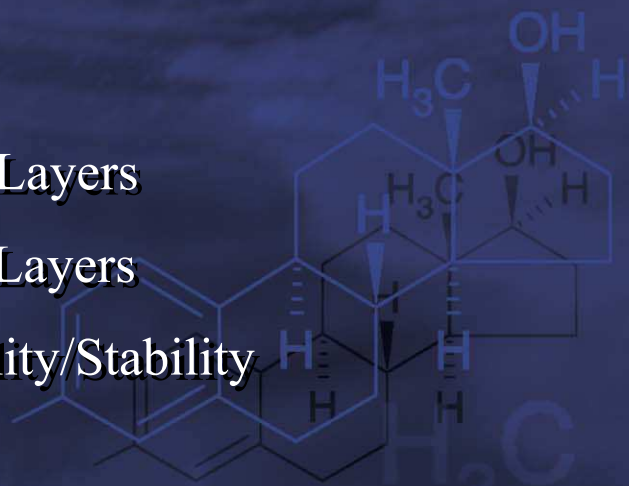
FILMS

- Release Liner Films
  - Thermoplastic
  - Release Agents
    - Silicone
    - Fluorocarbon
    - Neat
- Backing Films
  - Neat Films
  - Composite Layers
  - Functional Layers
- Drug Compatibility/Stability



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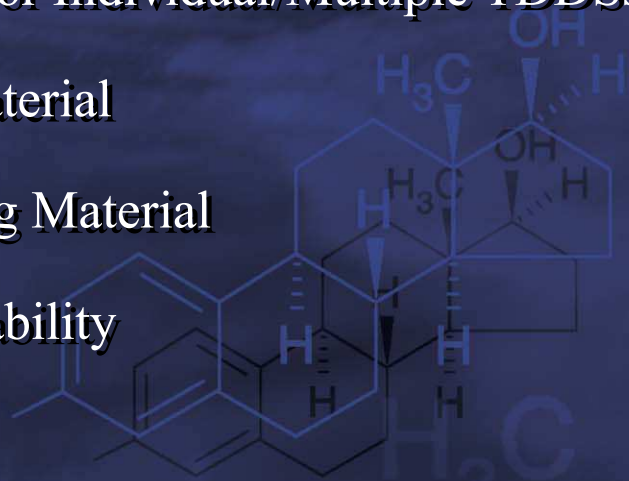
PACKAGING MATERIALS

- Primary Packaging for Individual TDDSs
  - Pouchstock
    - Paper/Foil/Seal Layer
    - Plastic/Foil/Seal Layer
    - Plastic/Seal Layer
- Secondary Packaging for Individual/Multiple TDDSs
  - Thermoplastic Material
  - Primary Packaging Material
- Drug Compatibility/Stability



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STABILITY PROPERTIES

- Formal Stability Testing
  - ICH Storage Conditions
  - TDDS Analytical Analysis
  - TDDS Physical Properties
- Informal Stability Testing
  - Developmental/Investigative
  - Packaged/Unpackaged TDDSs/Laminate
  - Extreme Stressed Storage Conditions
  - Analytical Analysis
    - Related Substances at Extremes
    - Physical Properties at Extremes

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IN-VITRO PERMEATION

- Developmental/Investigative Qualitative Tool
- Modified Franz Flux Cell
- Isotonic Saline Receiver Solution
- Human Cadaver Skin
- In-Vitro Permeation Control
- Sampling Regimen
- HPLC Analysis for Drug Concentration at Sample Points
- Graphical Representation of HPLC Analysis
  - Average Cumulative Permeation (ug/cm^2)
  - Average Flux ($ug/cm^2/hr$)

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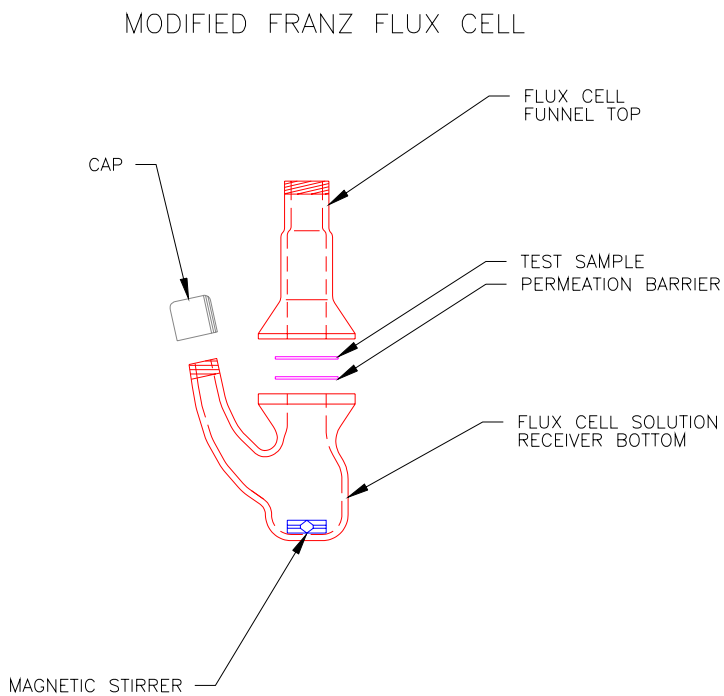
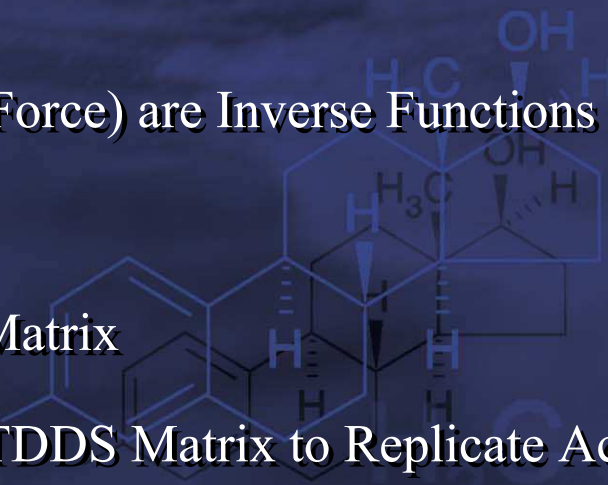
Illustration 2



PHYSICAL PROPERTIES

- Shear Testing
  - Modified Test Method PSTC-7
  - Function of Time
- Peel Testing
  - Modified Test Method PSTC-2
  - Function of Force
- Shear (Time) and Peel (Force) are Inverse Functions
- Placebo Wear Studies
  - Sans Drug TDDS Matrix
  - Modified Placebo TDDS Matrix to Replicate Active TDDS Matrix Physical Properties



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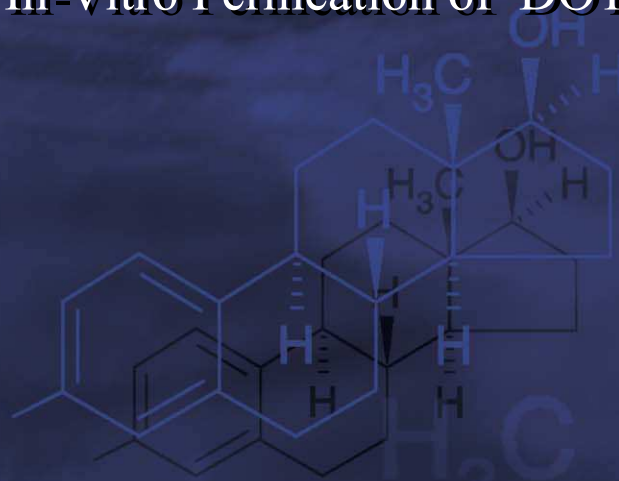
RESEARCH CASE STUDIES

- Research Case Study I
  - Comparison of Hormone Multi-Polymer and DOT Matrix™ TDDSs
- Research Case Study II
  - DOT Matrix™ Technology of Methylphenidate TDDSs
- Research Case Study III
  - Backing Film Influence on In-Vitro Permeation of DOT Matrix™ TDDSs



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RESEARCH CASE STUDY I

- Comparison of Hormone Multi-Polymer and DOT Matrix™ TDDSs
  - Estradiol Multi-Polymer TDDS (Vivelle®)
  - Estradiol DOT Matrix™ TDDS (Vivelle-Dot™)
  - Estradiol/Northindrone Acetate DOT Matrix™ TDDS (Combipatch®)
  - Components
  - In-Vitro Permeation
  - Results

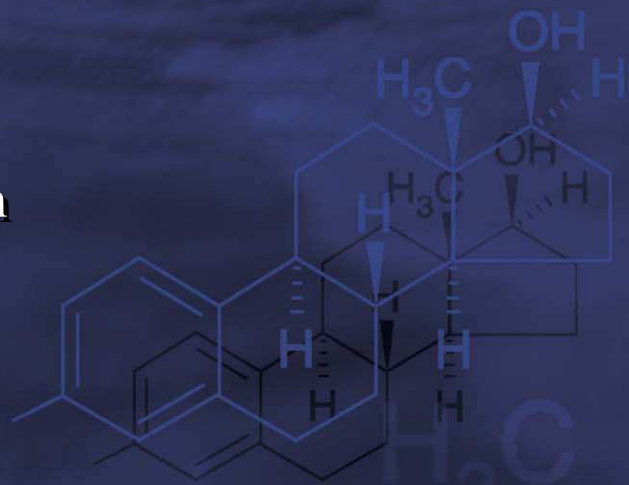

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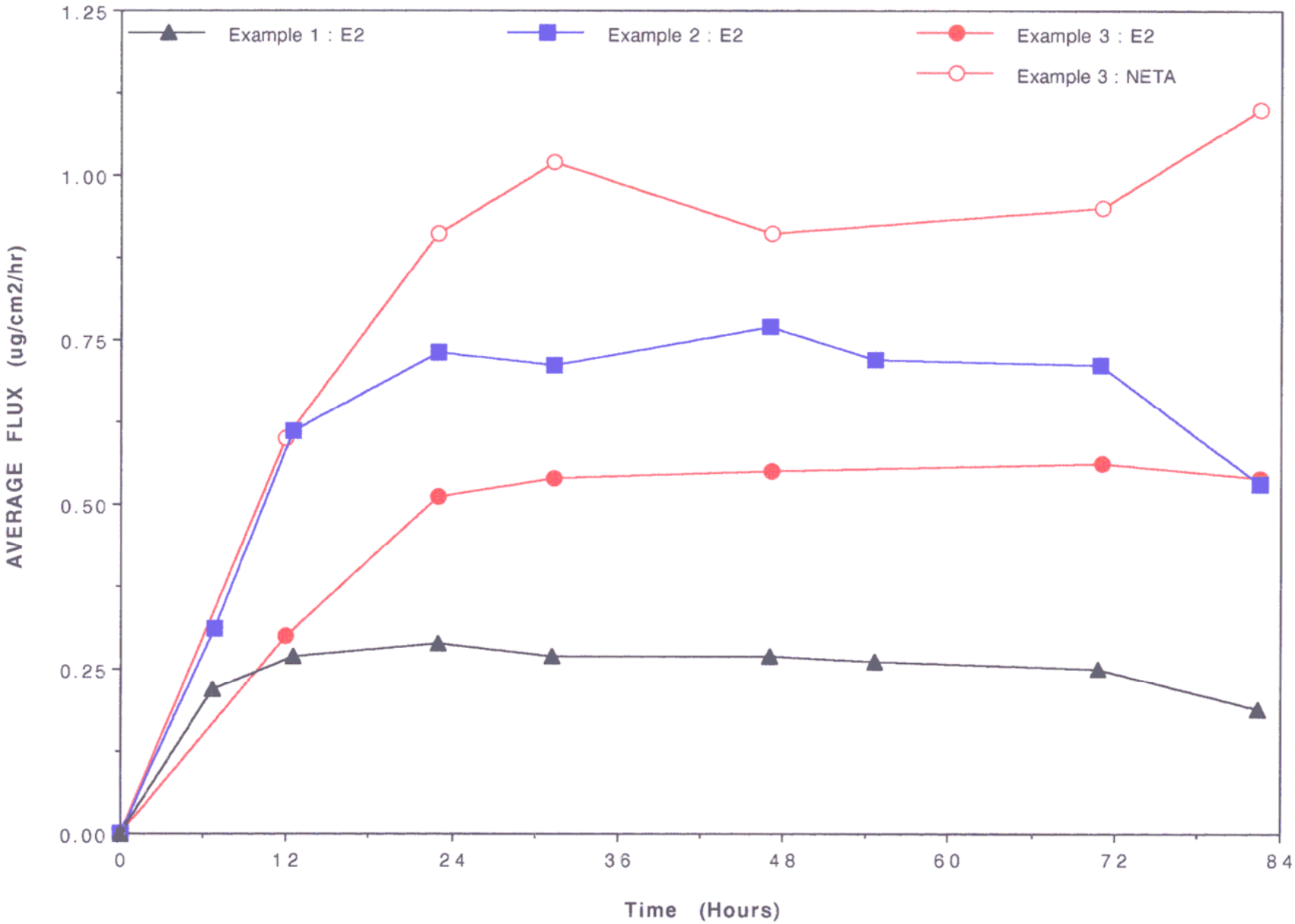
Table 1: Active Matrix Example Components

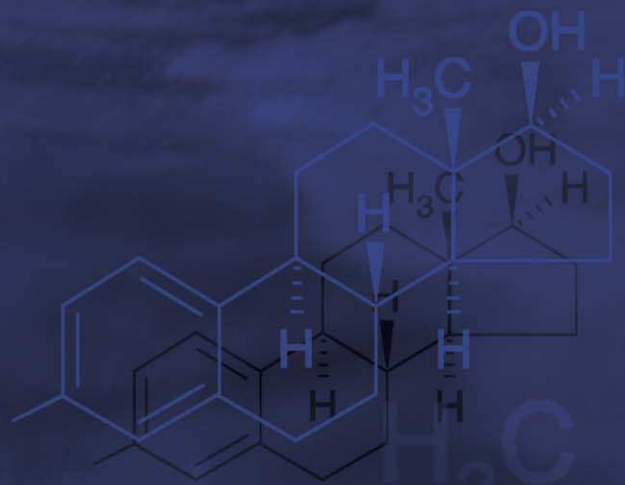
Ingredient	Example 1	Example 2	Example 3
PSA Neat	◆ Copolymer COOH, XL	◆ Copolymer OH, unXL ◆ Silicone	◆ Copolymer OH, XL ◆ Silicone
PSA Blend	◆ A-B-A Rubber		
Elastometric Polymer	◆ Polyisobutylene		
Thermoplastic Polymer	◆ Ethylene Vinyl Acetate	◆ Polyvinylpyrolidone	◆ Polyvinylpyrrolidone
Plasticizer/ Co-Solvents	◆ Dihydric Alcohol ◆ Phospholipid ◆ Monosaturated Fatty Acid ◆ Petroleum Oil	◆ Dihydric Alcohol ◆ Unsaturated Alcohol	◆ Dihydric Alcohol ◆ Monosaturated Fatty Acid
Natural	◆ Colloidal Clay		
Drug	◆ 17-β Estradiol	◆ 17-β Estradiol	◆ 17-β Estradiol ◆ Norethindrone Acetate

FIGURE 1 : In-Vitro Flux Data for Active Matrix Examples
Samples Fluxed @ 32.2C; n=5



RESEARCH CASE STUDY I

- Results : Research Case Study I
  - Simplified Formulary Utilizing DOT Matrix™ Technology
  - Size Reduction for TDDSs Utilizing DOT Matrix™ Technology



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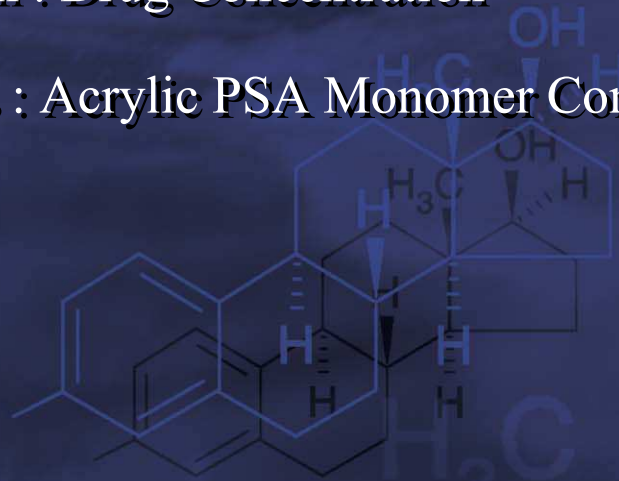
RESEARCH CASE STUDY II

- DOT Matrix™ Technology of Methylphenidate TDDSs
  - In-Vitro Permeation : Acrylic PSA Functionality
  - Stability Properties : Acrylic PSA Functionality
  - In-Vitro Permeation : Effect of Acrylic PSA to Silicone PSA Ratios
  - In-Vitro Permeation : Drug Concentration
  - Physical Properties : Acrylic PSA Monomer Composition
  - Results



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RESEARCH CASE STUDY II

Acrylic PSA Functionality

Ingredients	Formulations		
	1A	1B	1C
MPB	20	20	20
Silicone PSA	60	60	60
PSA1 (AA)	20		
PSA2 (NF/NR)		20	
PSA3 (OH)			20
All formulations are based on Dry Weight Percent			

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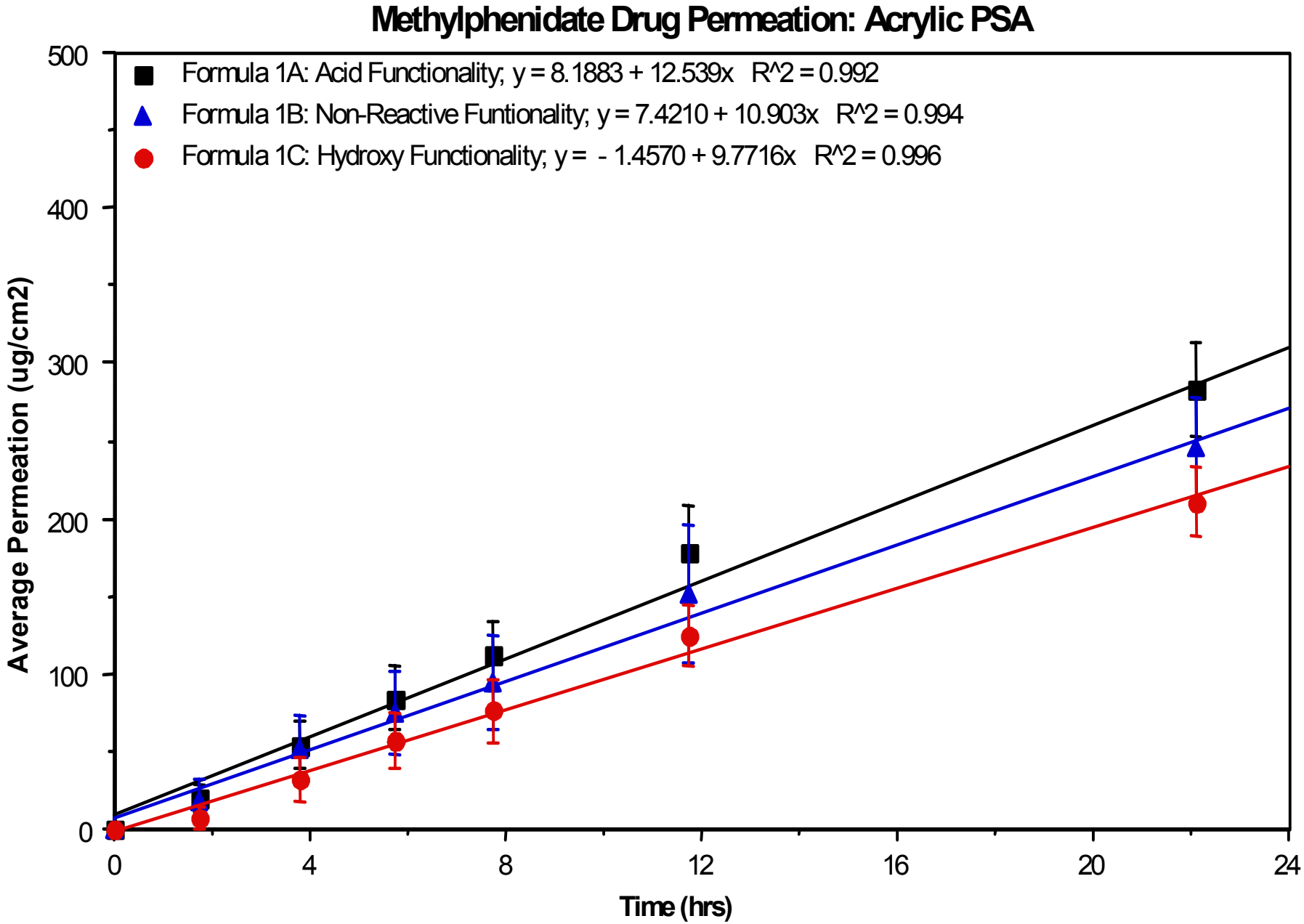
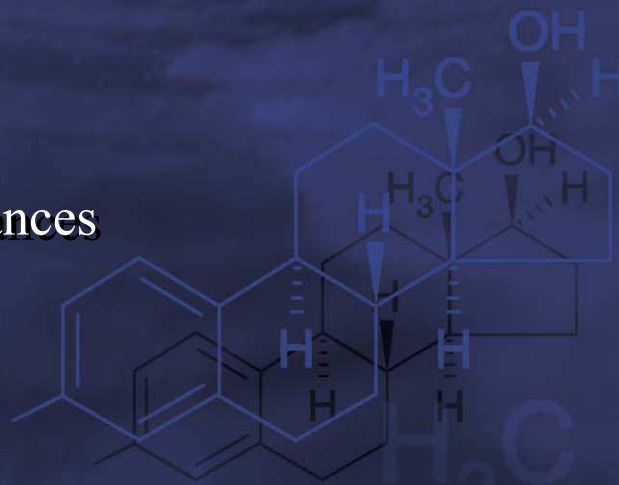
FIGURE 1


Methylphenidate Drug Permeation: Acrylic PSA
Formula 1A: Acid Functionality; y = 8.1883 + 12.539x R^2 = 0.992
Formula 1B: Non-Reactive Funtionality; y = 7.4210 + 10.903x R^2 = 0.994
Formula 1C: Hydroxy Functionality; y = - 1.4570 + 9.7716x R^2 = 0.996
Average Permeation (ug/cm2)
Time (hrs)
0
100
200
300
400
500
0
4
8
12
16
20
24

RESEARCH CASE STUDY II

- Stability Properties
  - Units Die-Cut from Active Laminates from the Acrylic PSA Functionality In-Vitro Permeation Study
  - TDDS Units Packaged in Tri-Layered Pouchstock
  - Accelerated Aging of Packaged TDDSs
  - TDDSs Analysis
    - HPLC
    - Related Substances



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RESARCH CASE STUDY II

Stability Properties

Ingredients	Formulations	
	1A	1B
MPB	20	20
Silicone PSA	60	60
PSA1 (AA)	20	
PSA2 (NR/NF)		20
All formulations in Dry Weight Percent		

Degradants	Formulations	
	1A	1B
% RS1	41.0	0.52
% RS2	22.6	6.23
% RS3	9.6	2.44
% RS4	3.7	1.65
Total %	76.9	10.84
%RS = %PA/%Drug		

RESEARCH CASE STUDY II

Effect of Acrylic/Silicone PSA Ratios

Ingredients	Formulations				
	2A	2B	2C	2D	2E
MPB	20	20	20	20	20
Silicone PSA	20	30	40	50	60
Acrylic PSA 2	60	50	40	30	20

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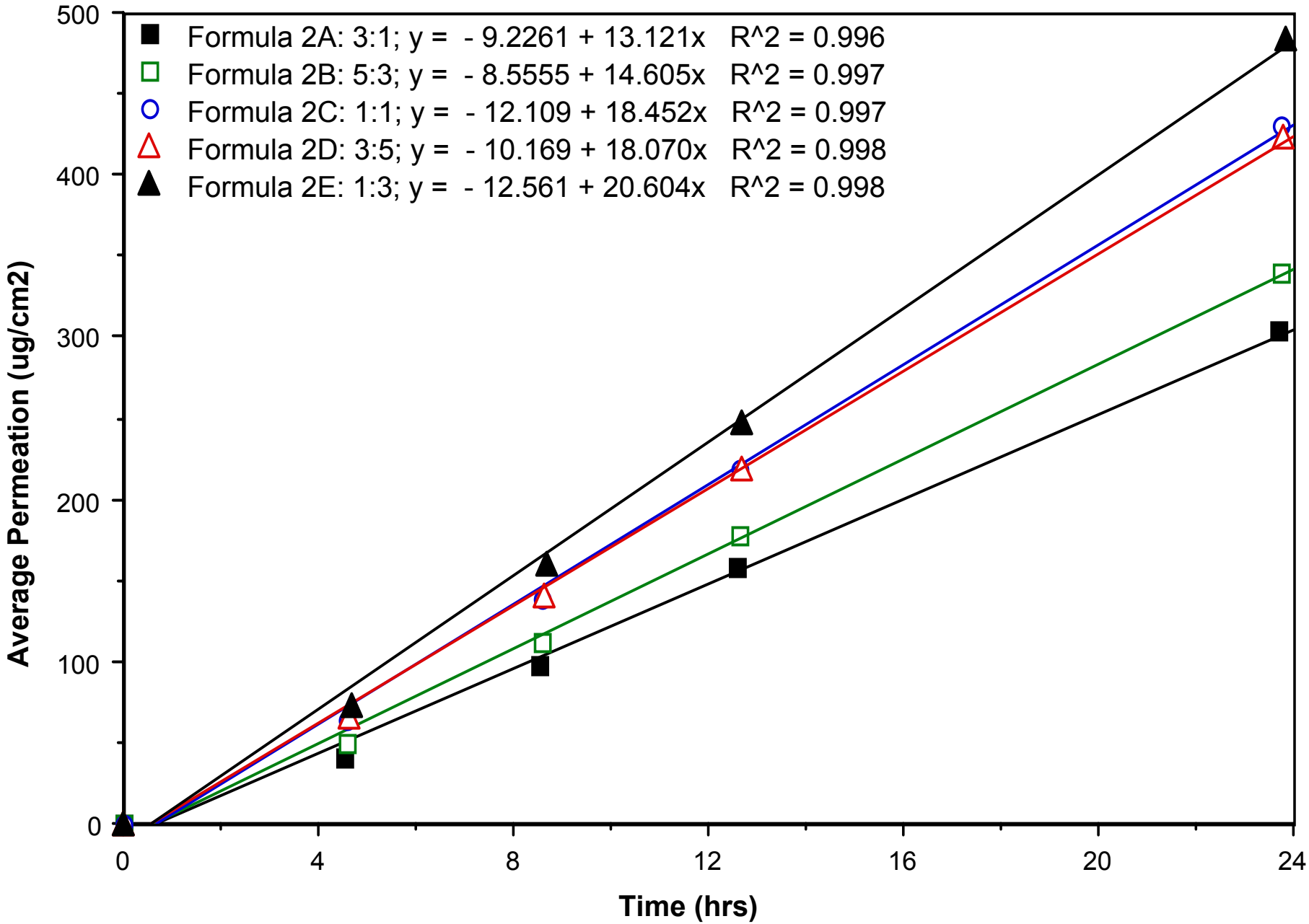
FIGURE 2

Methylphenidate Drug Permeation: Acrylic/Silicone PSA Ratios



RESEARCH CASE STUDY II

Drug Concentration

Ingredient	Formulation		
	3A	3B	3C
MPB	10	20	30
Silicone PSA	85	75	65
Acrylic PSA 2	5	5	5

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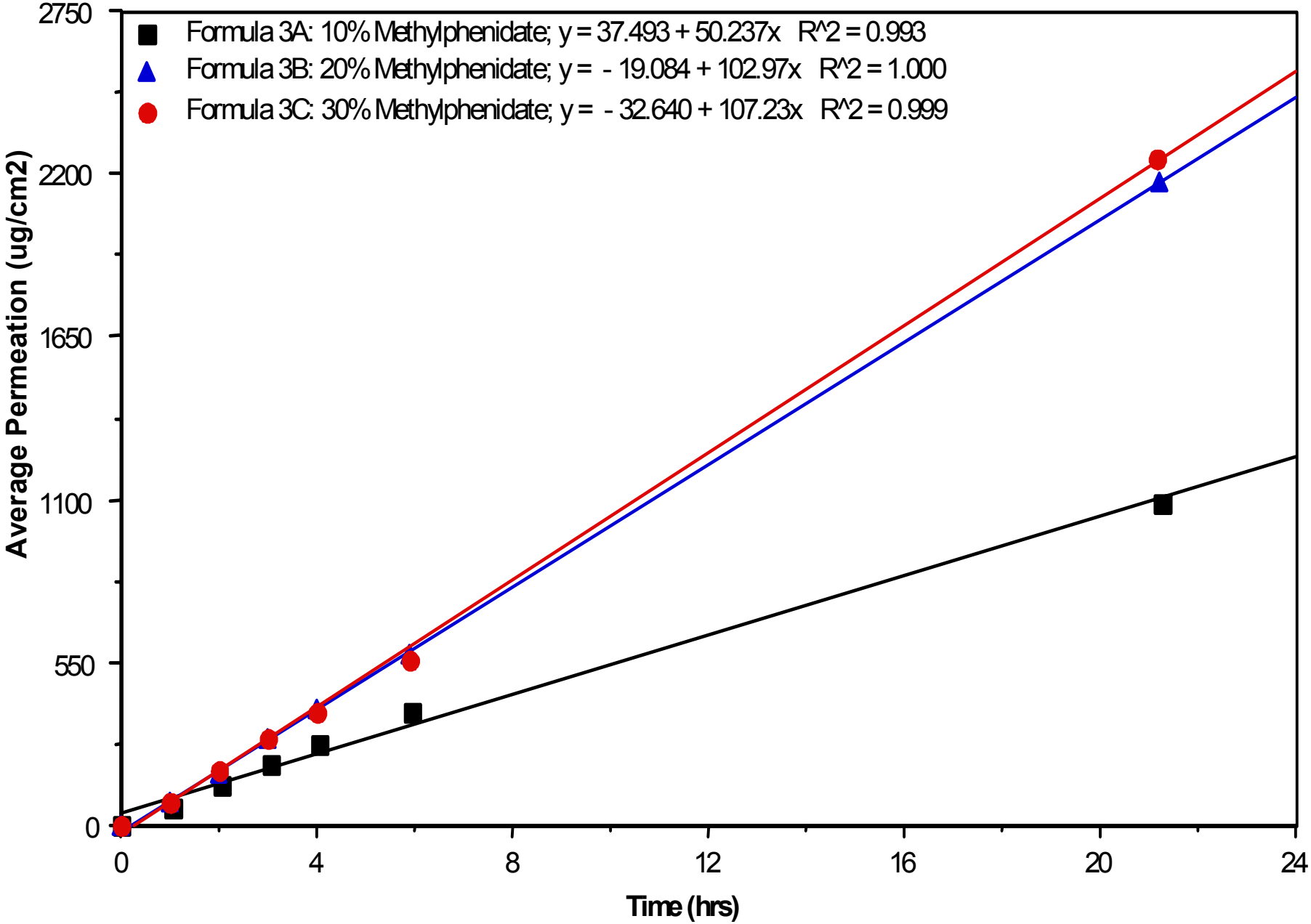
FIGURE 3

Methylphenidate Drug Permeation: Maximum Drug Loading



RESEARCH CASE STUDY II

Physical Properties

Ingredients	Formulations		
	1B	1D	1E
MPB	20	20	20
Silicone PSA	40	40	40
PSA4 (NF/NR: 70/30)	40		
PSA2 (NF/NR: 50/50)		40	
PSA5 (NF/NR: 20/80)			40
Shear Results (min.)	1	4	20
All formulations are based on Dry Weight Percent			

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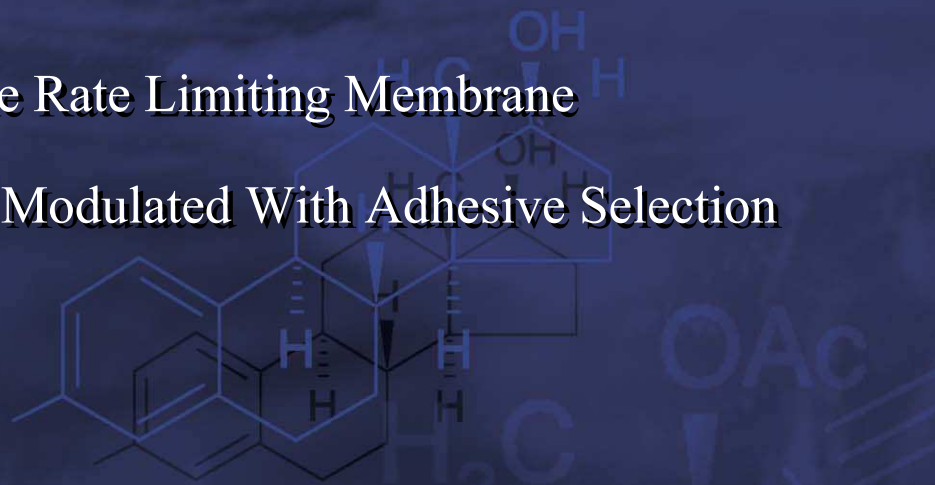
RESEARCH CASE STUDY II

- Results : Research Case Study II
  - Acrylic PSA Functionality Influences In-Vitro Permeation
  - Acrylic PSA Functionality Influences Stability Properties of TDDSs
  - Acrylic PSA to Silicone PSA Ratio Influences In-Vitro Permeation
  - Skin can become the Rate Limiting Membrane
  - Physical Properties Modulated With Adhesive Selection



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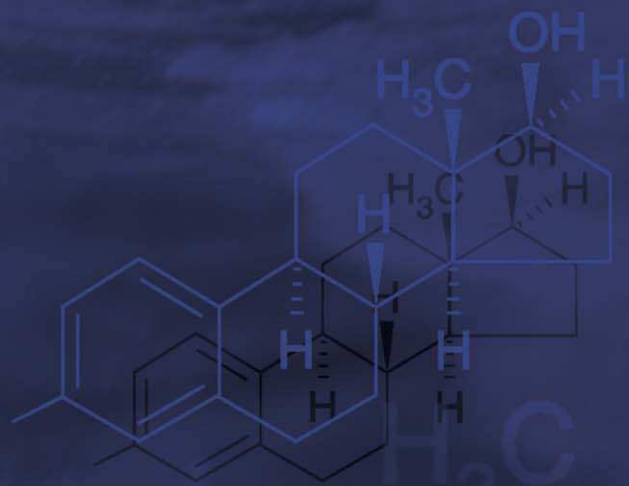
RESEARCH CASE STUDY III

- Backing Film Influence on In-Vitro Permeation of DOT Matrix™ TDDSs
  - In-Vitro Permeation : Effect of Acrylic Monomer Ratio
  - In-Vitro Permeation : Effect of Acrylic Monomer Functionality
  - Results



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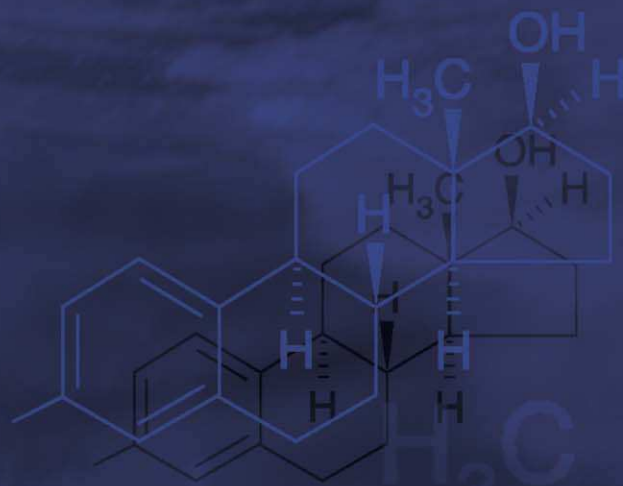
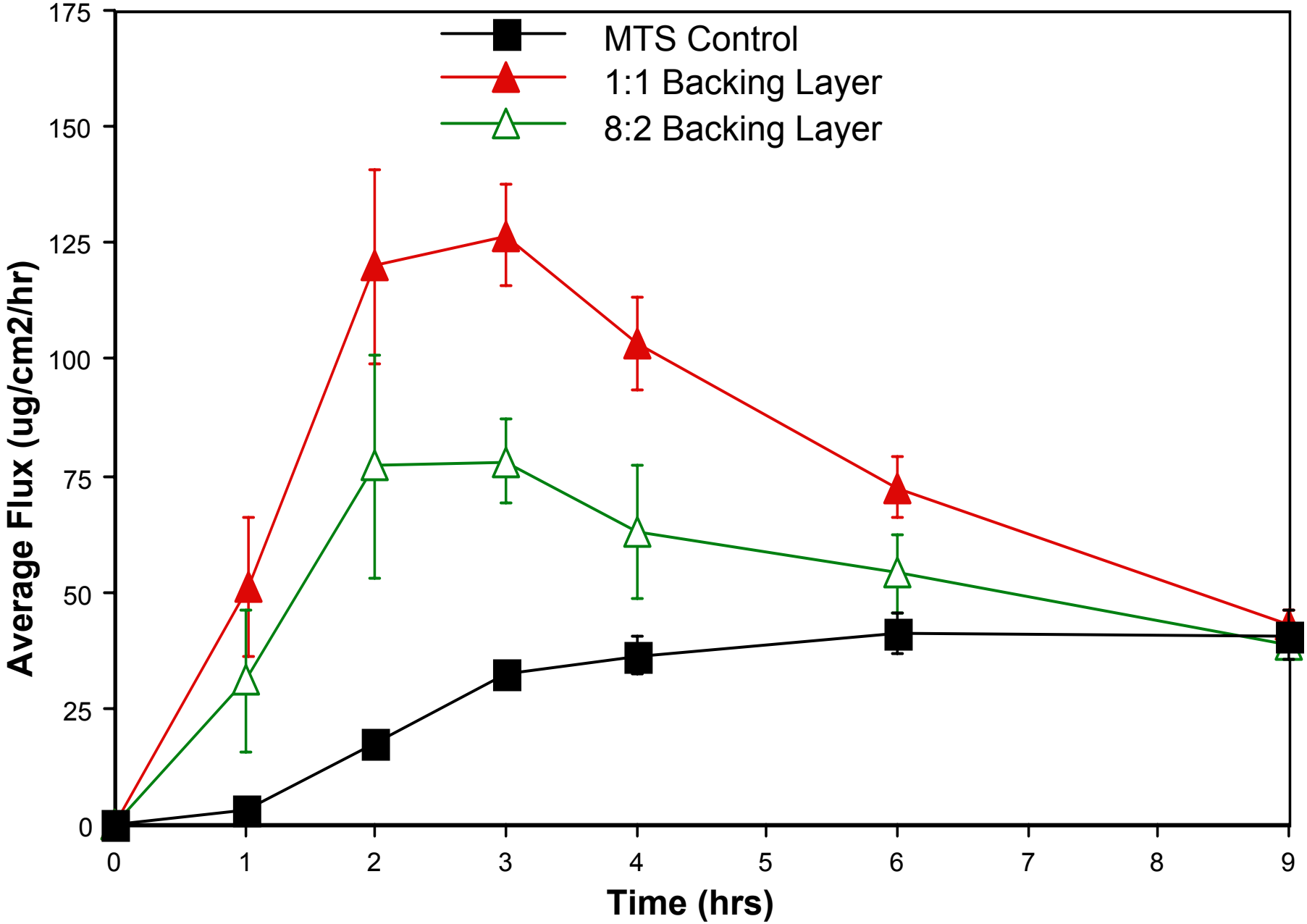
RESEARCH CASE STUDY III

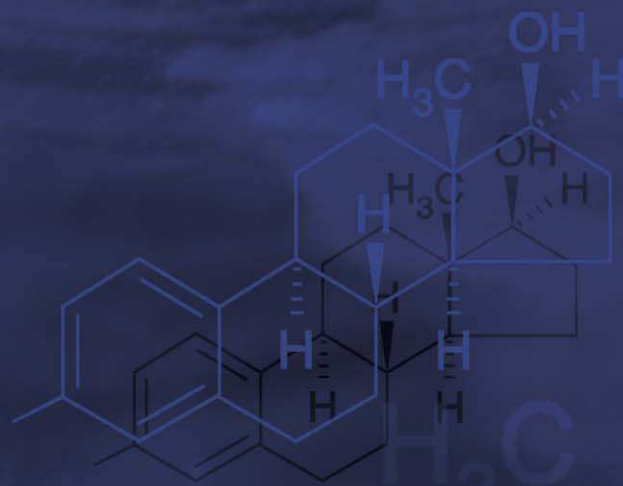
- In-Vitro Permeation : Effect of Acrylic Monomer Ratio
  - Low Molecular Weight Amine (R050) at 20% Concentration
  - Silicone to Acrylic PSA Ratio at 15:1
  - Acrylic Backing Comprised of High T_g and Low T_g Monomers




MTS Control
1:1 Backing Layer
8:2 Backing Layer
Average Flux (ug/cm2/hr)
Time (hrs)
0
25
50
75
100
125
150
175
0
1
2
3
4
5
6
7
8
9

RESEARCH CASE STUDY III

- In-Vitro Permeation : Effect of Acrylic Monomer Functionality
  - Low Molecular Weight Amine (R050) at 20% Concentration
  - Silicone to Acrylic PSA Ratio at 15:1
  - Acrylic Backing Comprised of High T_g and Low T_g Monomers
  - Functional Acrylic Monomer (COOH) at 0% to 8% Concentration



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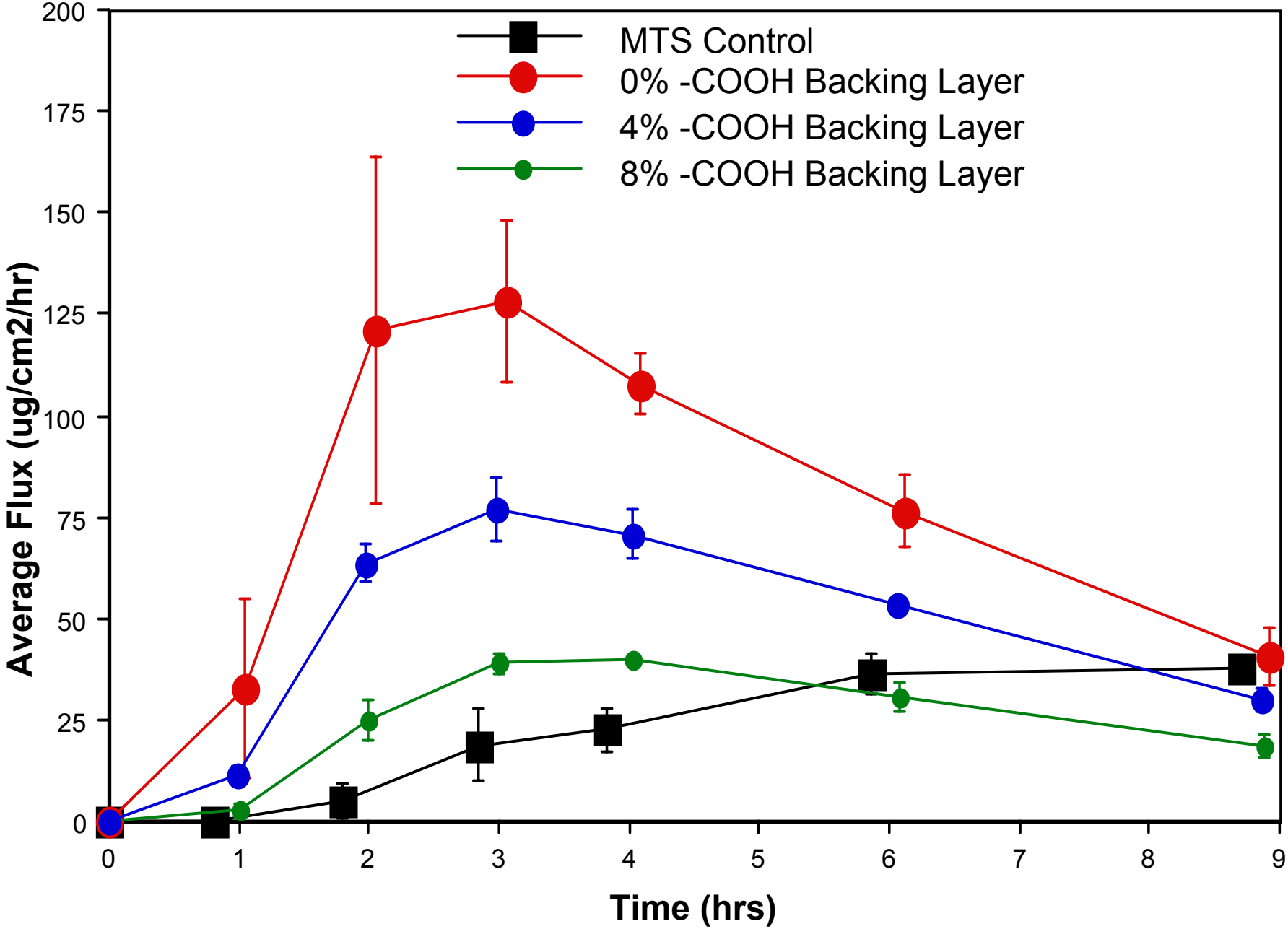
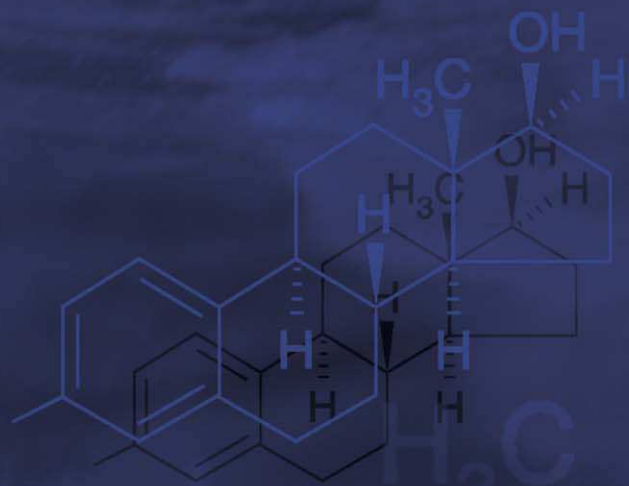

MTS Control
0% -COOH Backing Layer
4% -COOH Backing Layer
8% -COOH Backing Layer
Average Flux (ug/cm2/hr)
Time (hrs)
0
25
50
75
100
125
150
175
200
0
1
2
3
4
5
6
7
8
9

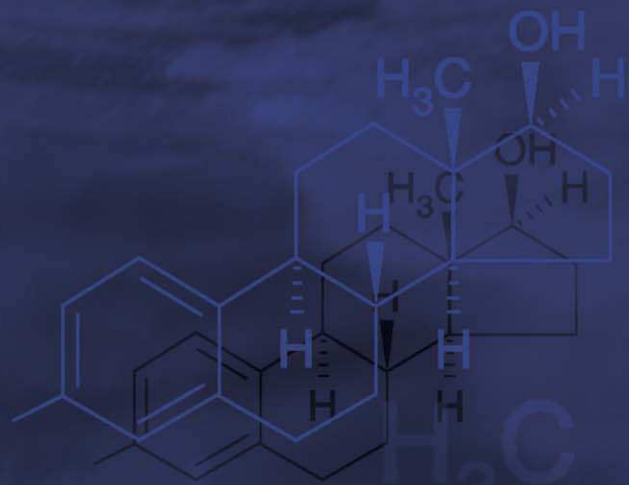
RESEARCH CASE STUDY III

- Results : Research Case Study III
  - Acrylic Monomer Ratio Influences In-Vitro Permeation
  - Acrylic Monomer Functionality Influences In-Vitro Permeation



CONCLUSION

- Complex TDDS Formulary Problems Simplified with the use of DOT Matrix™ Technology
- TDDS Permeation Modulated with the Proper Selection of Materials
- TDDS Adhesion Modulated with the Proper Selection of Materials
- Drug Stability Decreases Safety Concerns for the Patient with Proper Selection of Materials



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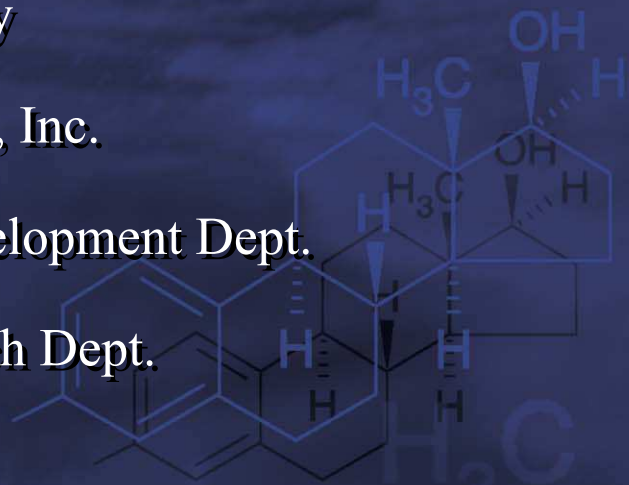
ACKNOWLEDGMENTS

- 3M™
- BASF
- Cytec
- Dow Corning Corporation
- National Starch and Adhesives
- Rohm & Haas Company
- Noven Pharmaceuticals, Inc.
  - Research and Development Dept.
  - Analytical Research Dept.



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Transdermal Product Development Considerations:

Passive and Active Transdermal Delivery Systems

Christopher W. McDaniel, Ph.D., MBA
Director, New Technology Assessment

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Transdermal Product Development

From Transderm Scōp® to Daytrana™:

Product development and regulatory requirements have undergone extensive changes over the years.

- Advances in materials
- Advances in technologies
- Advances in understanding how drugs penetrate the skin
- Clinical experience

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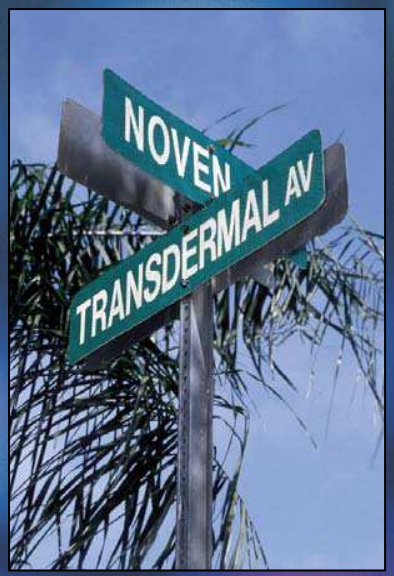
Active Transport Transdermal Technologies

Patch and Device Technologies



- Electric Field Force Assisted
  - Novosis AG's SmartPatch®
- Microneedles
  - NanoPass' MicroPyramid™
  - Alza's Macroflux®
  - BioValve Technology's Micro-Trans™

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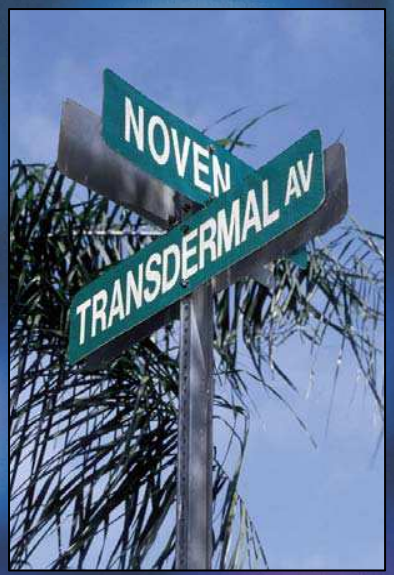
Active Transport Transdermal Technologies

Patch and Device Technologies



- Thermal Assisted
  - ZARS' CHADD Technology
- Microporation
  - Altea Therapeutics' Passport™ System
  - TransPharma Medical's ViaDerm™ System

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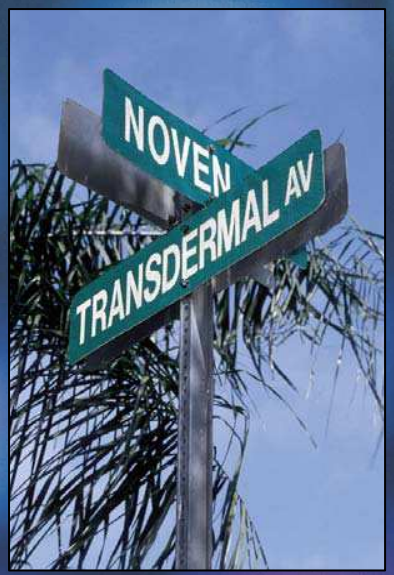
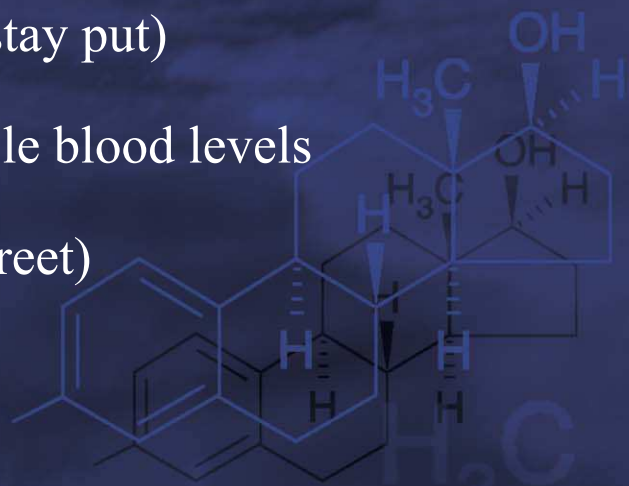
Active Transport Transdermal Technologies



- Active Transdermal Technologies Continue to Use Patch Technology
  - Many of the same requirements as passive transdermal patches
    - Comfortable (non-irritating)
    - Adherent (stay put)
    - Reproducible blood levels
    - Small (discreet)



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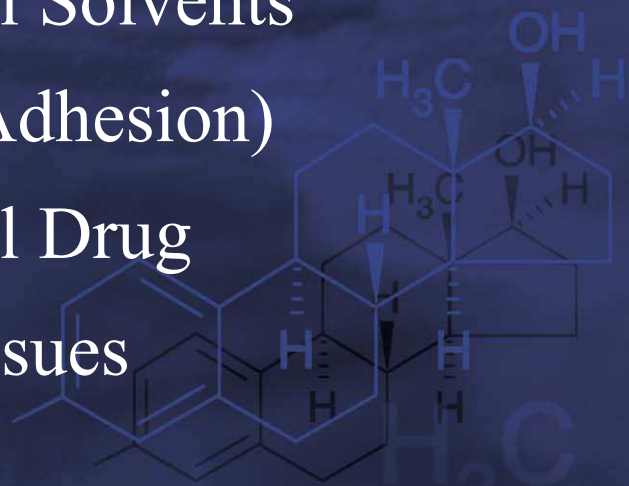
Transdermal Development Considerations

- Irritation
- Sensitization
- Toxicity
- Residual Monomers
- Residual Solvents
- Wear (Adhesion)
- Residual Drug
- Other Issues



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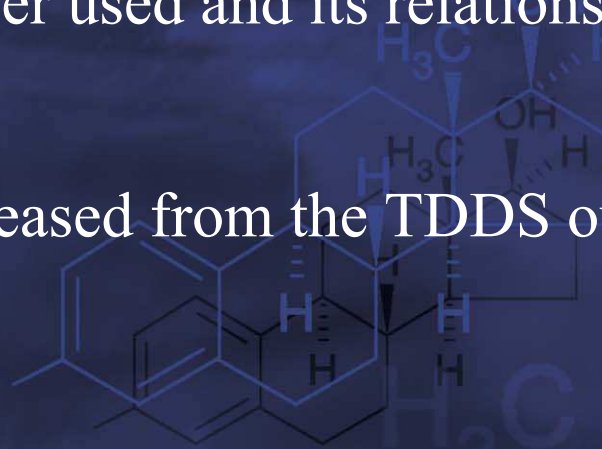
EMEA Development Considerations

- Type of TDDS, matrix or reservoir
- Description of TDDS including material, function, dimensions, compatibility
- Description of development manufacturing process
- Description of excipients in PSA
- Description of penetration enhancer used and its relationship with drug absorption
- Drug load versus total amount released from the TDDS over the intended use period



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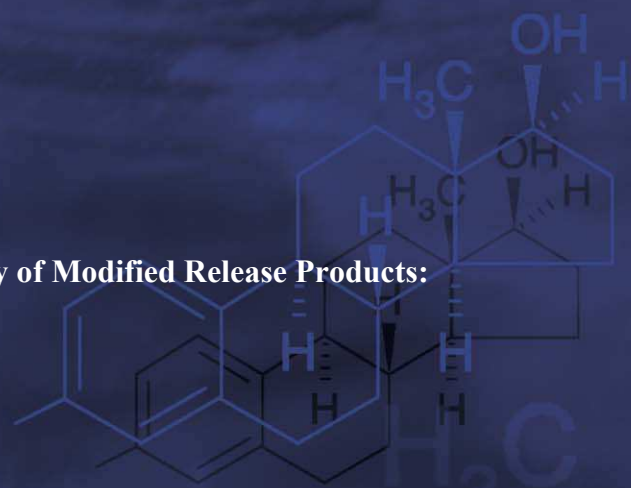
EMEA Development Considerations (cont.)

- Adhesive properties of TDDS covering intended period of use including information on local tolerance (irritation) and waterproofness if relevant
- Residual solvents
- Proportionality of different strengths if relevant
- Occlusion
- Dissolution
- Content uniformity

CPMP: Note for Guidance on Quality of Modified Release Products:

A: Oral Dosage Forms

B: Transdermal Dosage Forms



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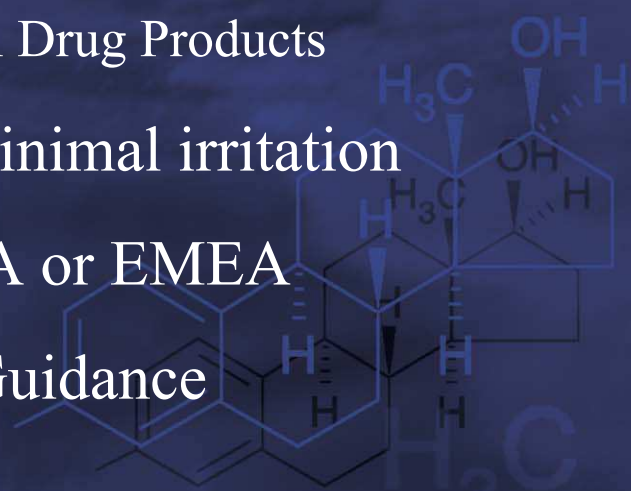
Product Irritation Studies

- Irritation one of the primary AEs reported for transdermal products
- Drug irritation vs. product irritation
- Withdrawn!
  - USFDA Guidance for Industry: Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products
- Present need to demonstrate minimal irritation
- Propose irritation study to FDA or EMEA
- Possibly use study outline in Guidance



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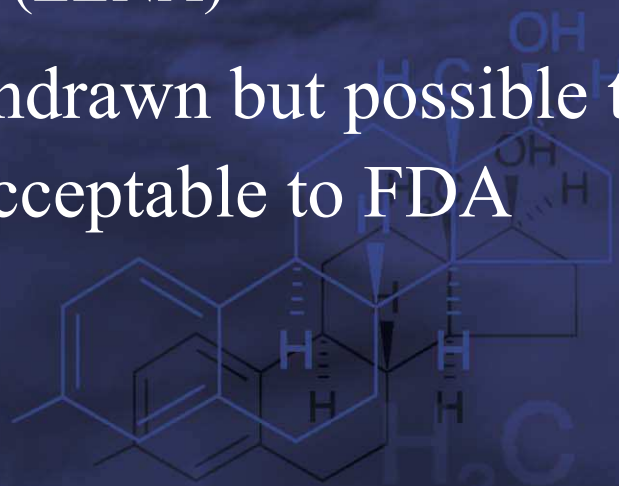
Skin Sensitization Studies

- Dermal sensitization is a leading concern for possible AEs for regulatory agencies
- Use of preliminary indicators for sensitization
  - Guinea pig study
  - Local Lymph Node Assay (LLNA)
- Guidance for generics withdrawn but possible to use the same study design if acceptable to FDA



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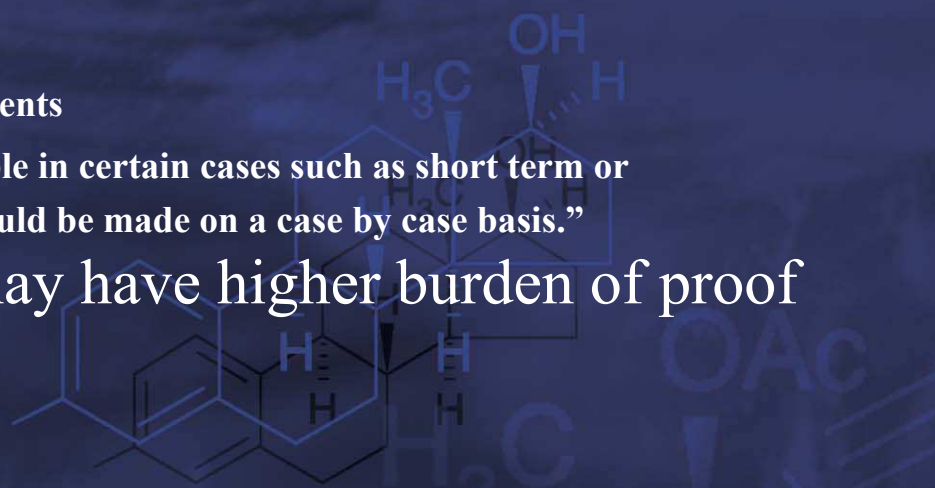
Transdermal Product Component Toxicity

- If possible, use components on GRAS list
- FDA asking to review –
  - DMF of adhesives
    - Residual monomer content
    - Polymerization initiators
  - Explain why components are safe
  - Residual solvent content
- ICH Guidelines

  Q3C(R3): Impurities: Guideline for Residual Solvents

  "Higher levels of residual solvents may be acceptable in certain cases such as short term or topical application. Justification of these levels should be made on a case by case basis."
- Active transport technologies may have higher burden of proof required



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Transdermal Product Adhesion

- FDA requesting wear studies – protocols, data
- Possible to use criteria outlined in the withdrawn Guidance
  - **5-point scale**

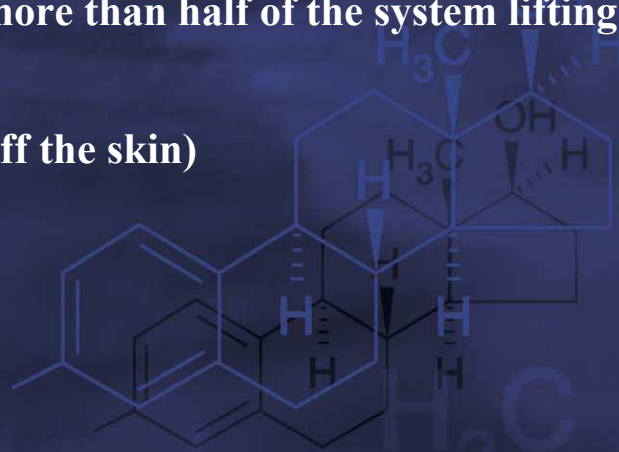
0 = ≥ 90% adhered (essentially no lift off of skin)

1 = ≥ 75% to < 90% (some edges only lifting off skin)

2 = ≥ 50% to < 75% (less than half of the system lifting off skin)

3 = < 50% adhered but not detached (more than half of the system lifting off skin without falling off)

4 = patch detached (patch completely off the skin)



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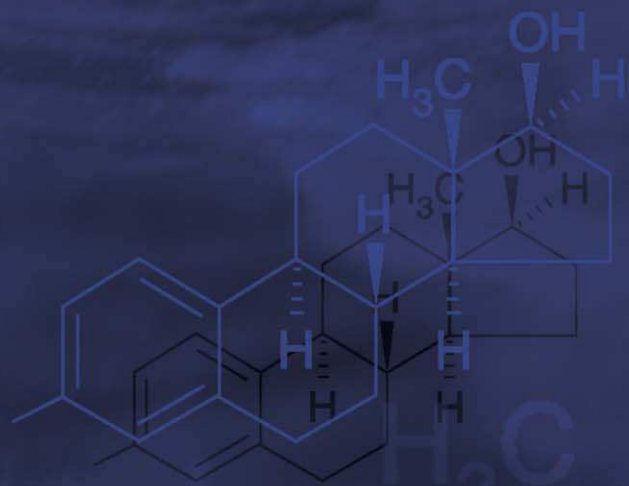
Transdermal Product Adhesion

- The product works only if it stays in place the duration of the intended wear time
  - **Efficacy**
  - **Safety**
  - **Compliance**



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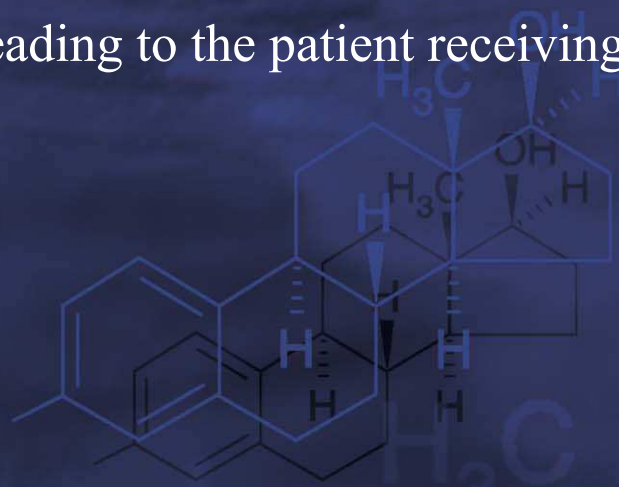
Adhesion, A Case in Point: Fentanyl

- July 2005 FDA Alert for Healthcare Professionals
  - **Fentanyl Transdermal System (marketed as Duragesic)**
- July 2005 FDA Public Health Advisory
  - **Safety Warnings Regarding the Use of Fentanyl Transdermal (Skin) Patches**
- In some cases, poor adhesion led patients to try to improve adhesion by methods that compromised the patch leading to the patient receiving an overdose



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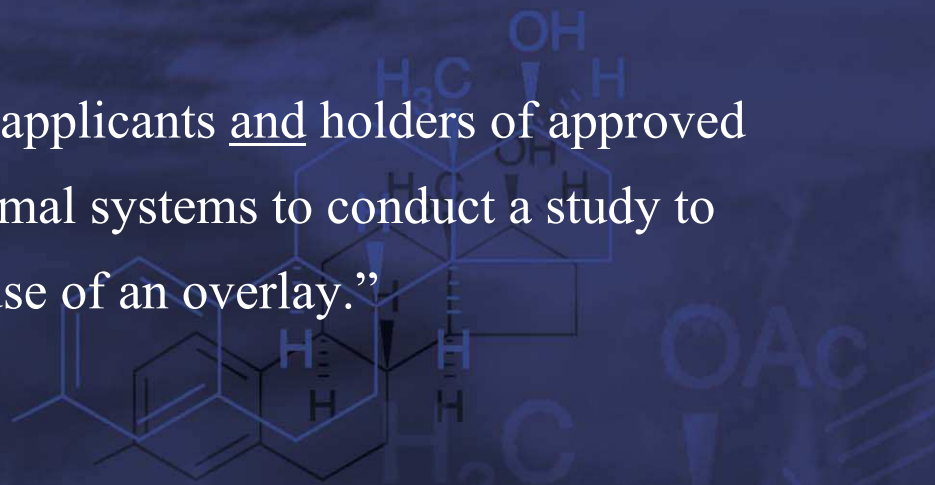
Adhesion, A Case in Point: Fentanyl (cont.)

- Citizen Petition from Mylan Laboratories (March 2006, Docket # 2006P.0123
  - "…the patch may have problems "sticking" to the skin."
  - "…patients have taken this problem in their own hands by using some type of overlay to help the patch stick to the skin."
  - "The use of an unapproved and untested overlay may cause adverse consequences."
  - "…the Agency should require all applicants and holders of approved applications for Fentanyl transdermal systems to conduct a study to support the safe and appropriate use of an overlay."



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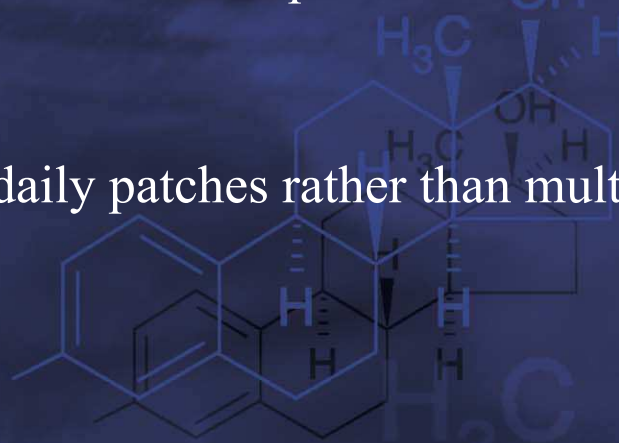
Adhesion, A Case in Point: Fentanyl (cont.)

- EMEA requiring similar wear studies including a demonstration of waterproofness (if relevant)
- Implications for the future
  - Products will have to demonstrate appropriate wear characteristics whether or not delivering controlled substances
  - Generic products will have to demonstrate comparable adhesion as innovator
  - Possibly shorter wear times (i.e., daily patches rather than multiple day)



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Residual Drug

- Had not been an issue historically
  - Vivelle® estradiol transdermal system 96% residual drug
- Became an issue with transdermal systems containing controlled substances
  - Duragesic® Fentanyl transdermal system
  - Daytrana™ Methylphenidate transdermal system
- Generics

"FDA's regulations recognize that extended-release products that deliver the identical amounts of active ingredient over the same dosing period can be pharmaceutical equivalents even if the residual (i.e., undelivered) volumes differ."

- FDA response to transdermal Fentanyl Citizen Petitions, 28 Jan 2005

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Residual Drug (Cont.)

- Safety issues
  - **Generic transdermal Fentanyl ANDAs denied due to safety concerns relative to residual drug**
- Abuse Potential
  - **Duragesic® Fentanyl transdermal system**
  - **Daytrana™ Methylphenidate transdermal system**

} Disposal: Fold and Flush

- Risk Management Programs
  - **May be required for transdermal products containing controlled substances**

"We conclude that both matrix and reservoir formulations may be subject to abuse…. We intend to monitor reports of abuse; RMPs may be considered in the future to address any concerns. We would support and assist any efforts by a manufacturer to develop an RMP."

- FDA response to transdermal Fentanyl Citizen Petitions, 28 Jan 2005

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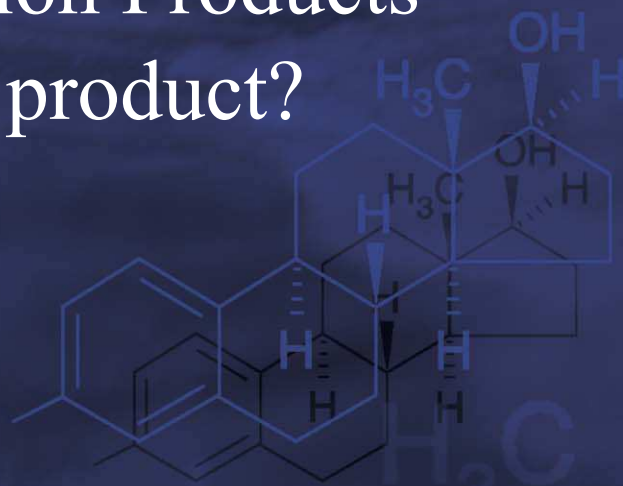
Active Transport Transdermal Systems

- Requirements for approval may be higher due to breaching the barrier function of the skin
- Submit a Request for Designation to FDA
  - Is it a drug, device, biological product, or combination product?
  - Office of Combination Products
- What is a combination product?
  - 21 CFR 3.2(e)



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Active Transport Transdermal Systems

- 21 CFR 3.2 (e) states…

(e) *Combination product* includes:

(1) A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity;

(2) Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products;

(3) A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or

(4) Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.

Conclusions

- Transdermal product approval requirements have increased in sophistication as transdermal products have increased in sophistication
  - Excipient performance AND nontoxicity
    - Justify residual solvents, monomers, penetration enhancers, etc.
  - Product performance much more critical for safety and efficacy
  - For innovators as well as generics, residual drug in the patch may be an issue
  - Risk Management Programs may soon be required
- Active transport transdermal products may be subject to higher level of review due to breach of barrier properties of the skin
  - The approval process may be more rigorous due to the possible designation as a Combination Product --- Device + Drug

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NOVEN – Bringing transdermal product innovations to market

Pavan Handa

Vice President – Business Development

NOVEN PHARMACEUTICALS, INC.

Novel drug delivery technologies can solve some of the major problems facing the pharmaceutical industry

- How to replace lost sales as R&D productivity continues to decline?
- How to extend product life cycle in the face of generic competition?
- How to manage the escalating costs of developing new products?
- What pharmaceutical industry biases need to be changed to improve product opportunities?

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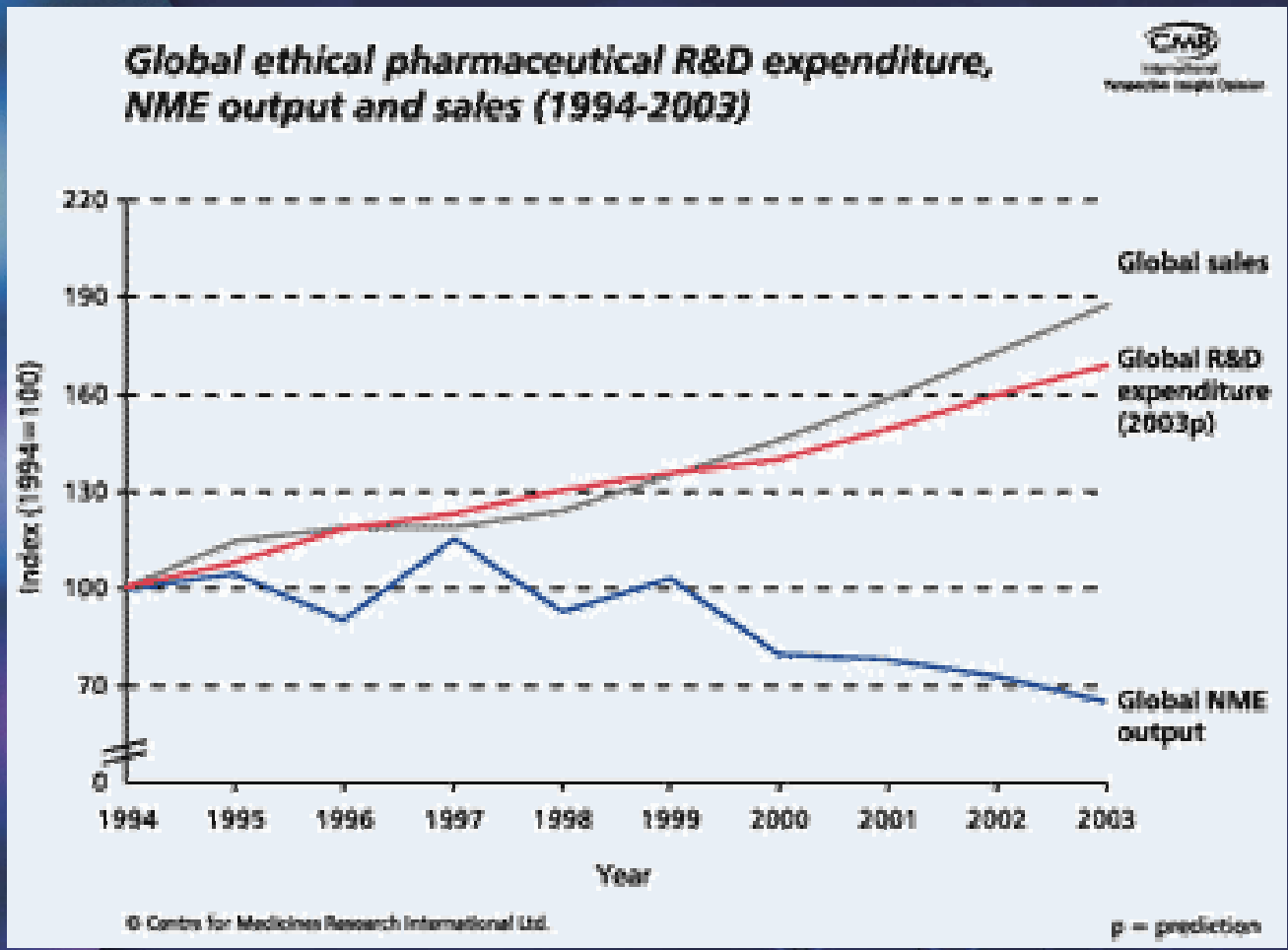
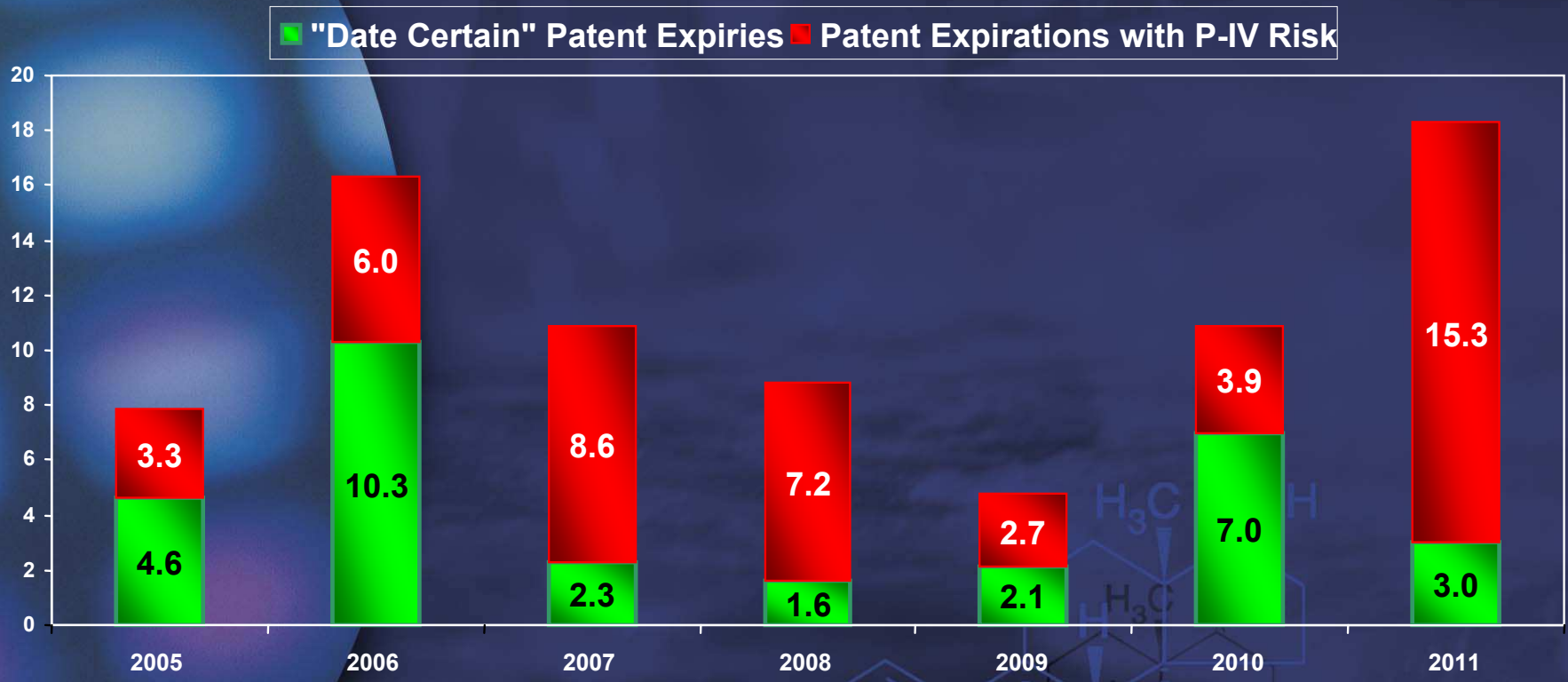
Over the last 10 years, both growth in R&D investment and sales of pharmaceuticals have almost doubled, while new product introductions continue to decline



Source: CMR International Limited, 2005: Innovation on the Wane? (www.cmr.org)

Pharmaceutical companies have $40 billion in U.S. sales exposed to generic competition and another $47 billion at risk to Paragraph IV patent challenges between 2005-2011



Major "Date Certain" Patent Expires

2005	2006	2007	2008	2009
Rocephin	Zocor	Zyrtec	Zometa	Flomax
Biaxin XL	Pravachol	Zoxyn	Serevent	Abilify
Prevacid	Zithromax			

Patent Expiries of Products with Current P-IV Risk

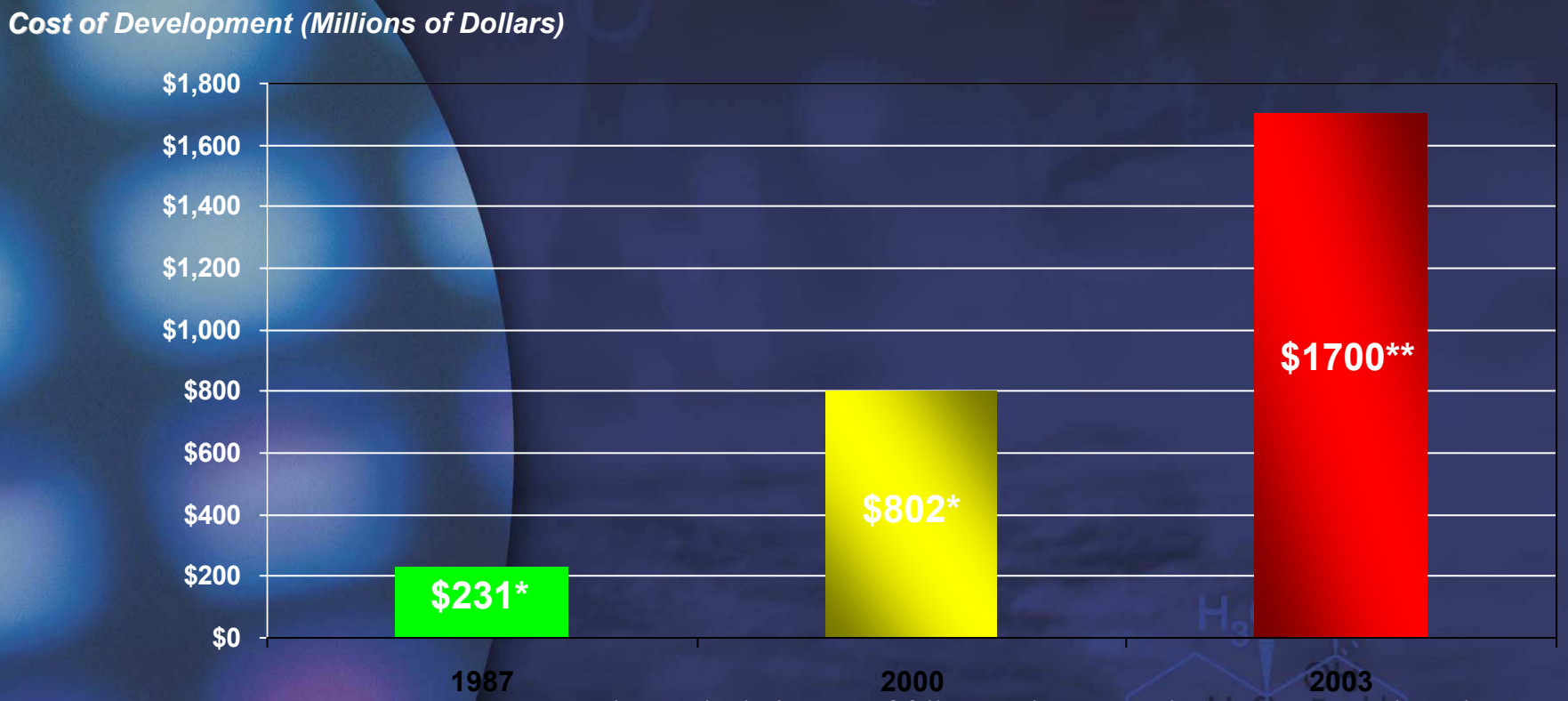
2006	2007	2008	2009	2011
Zoloft	Risperdal	Effexor	Valtrex	Zyprexa
Zofran	Norvasc	Fosamax	Lamictal	Lipitor
	Imitrex			

Lamictal

Zyprexa
Lipitor

Source: CIBC World Markets – Pricing Trends, August 11, 2005

Average risk-adjusted cost of bringing a new drug to market has grown more than six-fold between 1987 and 2003



Note: Estimates include cost of failure and opportunity costs: 2003 Bain estimates also include $250 million in drug launch costs

* The price of innovation: new estimates of drug development costs. Joseph A. DiMasi, Roland W. Hansen, Henry G. Grabowski, Journal of Health Economics 22 (2003) 151-185

** Bain drug economics model 2003; excerpt from "Rebuilding Big Pharma's Business Model", In-Vivo The Business & Medicine Report, November 2003

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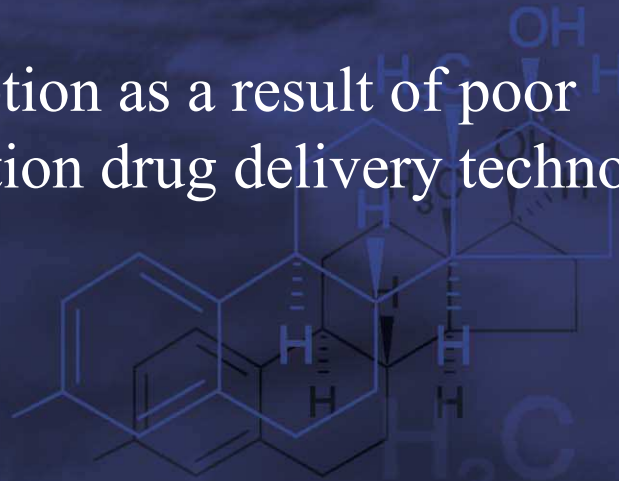
We need to overcome traditional pharma industry biases to prevent missed product opportunities

- Bias for only developing blockbuster brands
- Bias for oral route of delivery
- Bias for developing drugs targeting large primary care physician office markets
- Bias for shunning "not invented here" technologies
- Bias from negative perception as a result of poor performance of 1st generation drug delivery technologies



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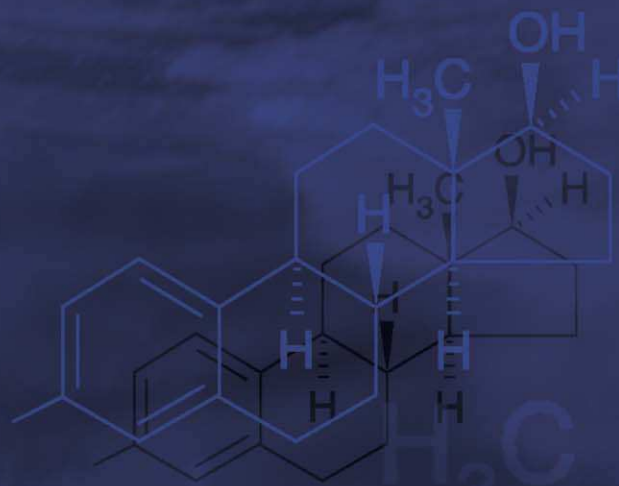
Examples of Transdermal Patch Innovations



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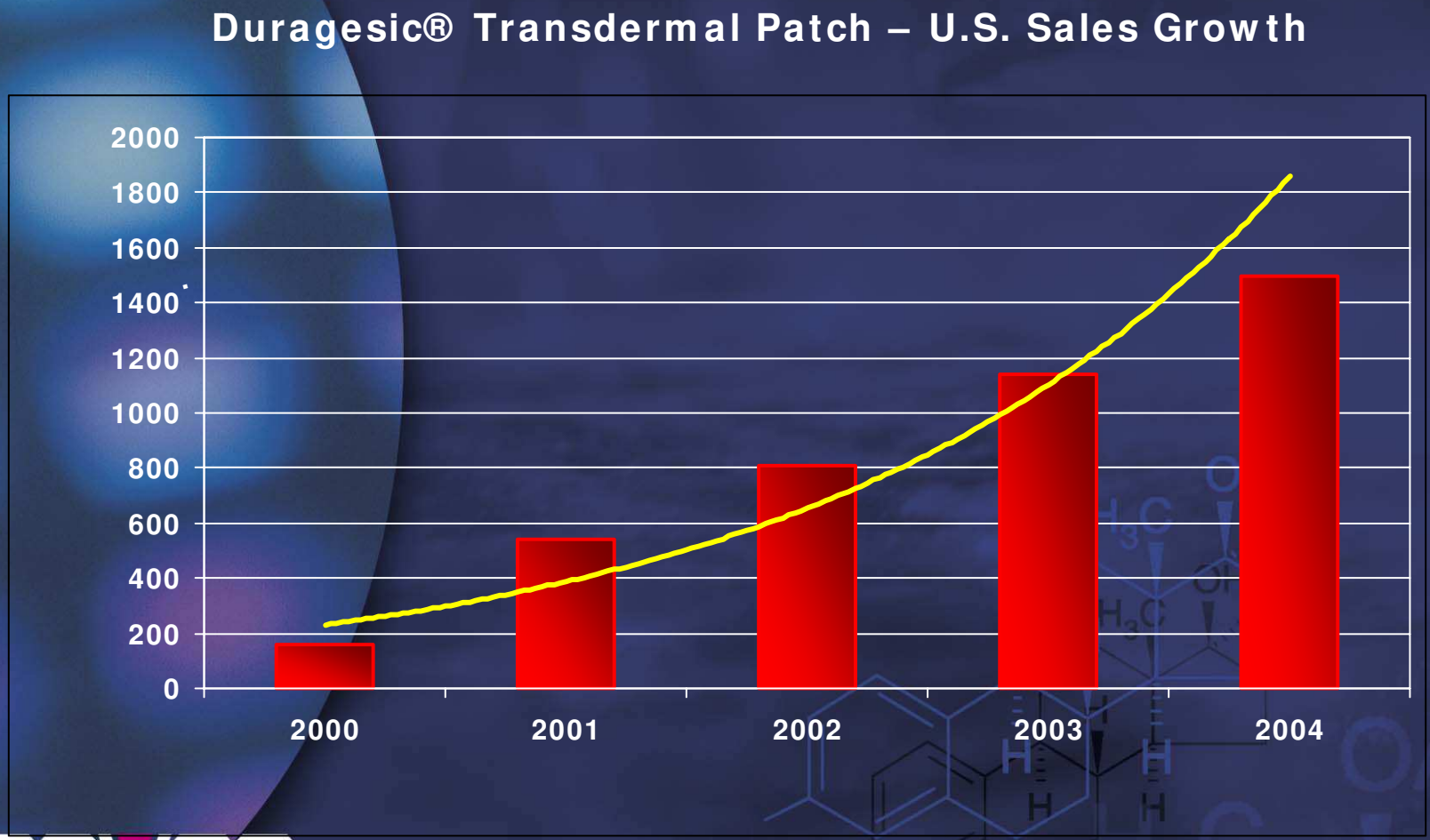
The 72-hour Duragesic transdermal patch revolutionized the use of fentanyl in chronic pain management and reached over $2 billion in sales before patent expiry in January, 2005



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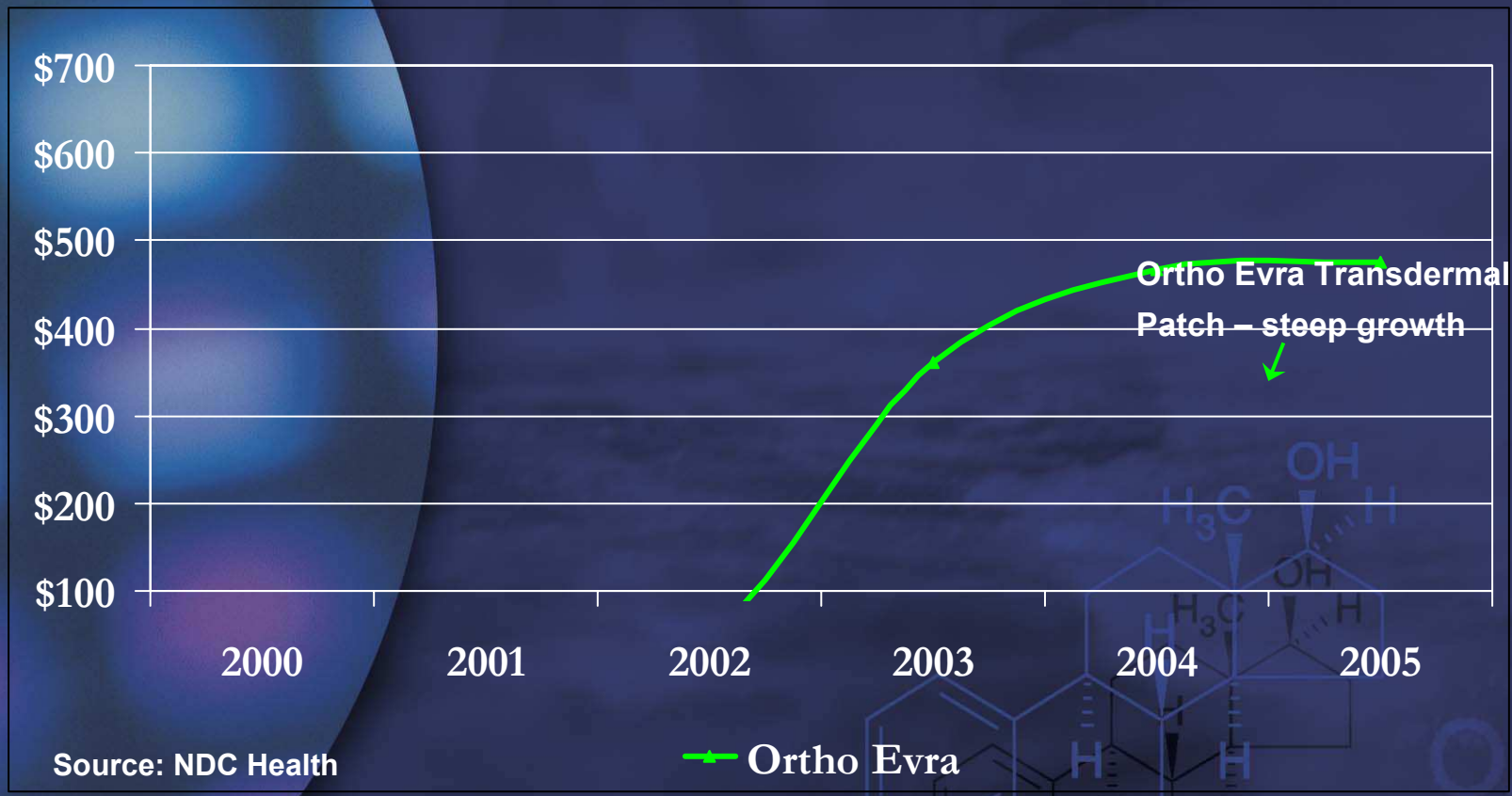
Source: IMS Health; NDC Health

J&J's Ortho Evra Transdermal Patch was named one of Time magazine's best inventions of 2002. After a successful launch product sales have fallen due to the possibility of delivering higher estrogen levels compared to oral product.



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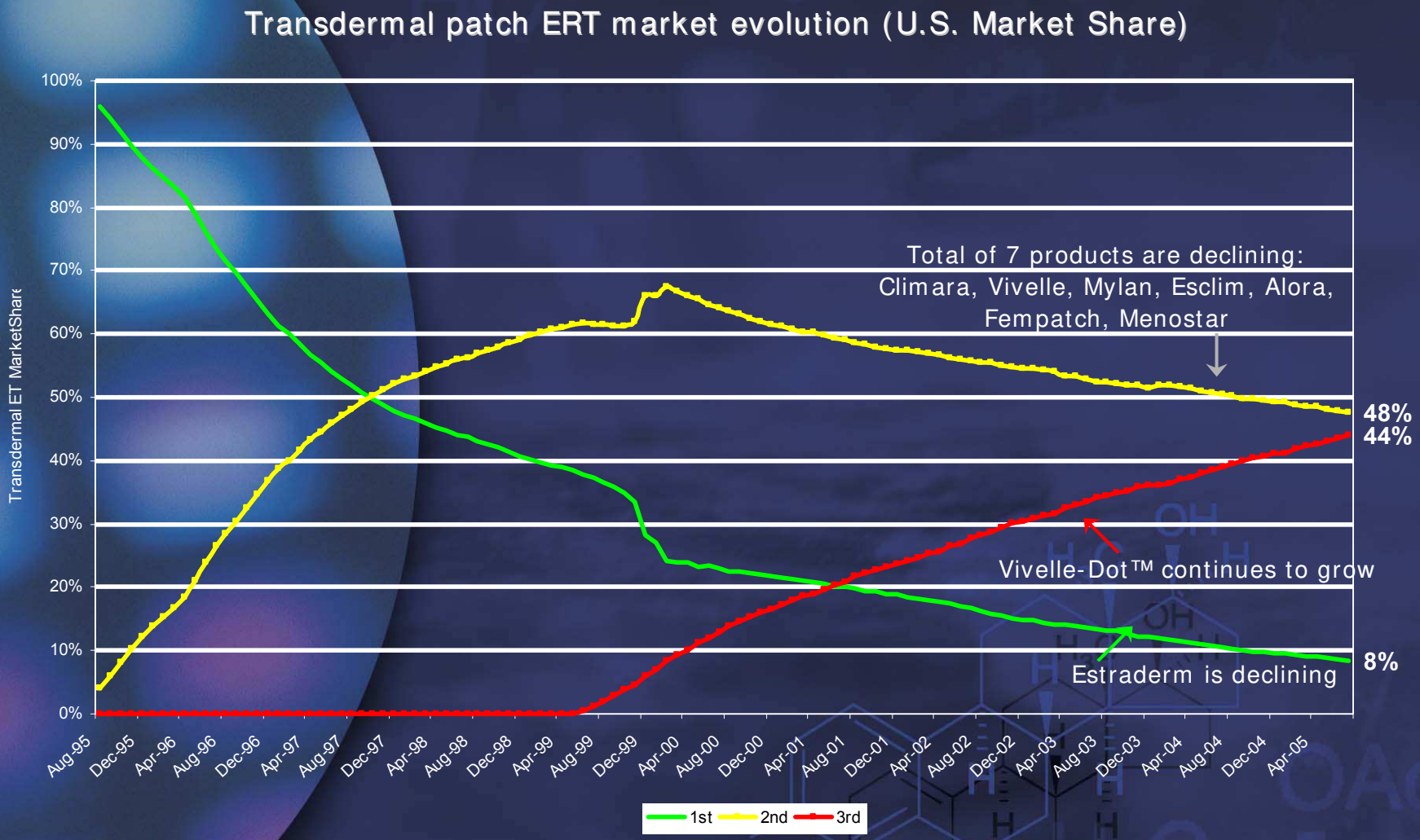
Innovative patch technologies such as Vivelle-Dot™ have displaced older technologies



1st generation reservoir patch = Estraderm
2nd generation matrix patch = Climara, Vivelle, Mylan, Esclim, Alora, Fempatch, Menorest
3rd generation Dot Matrix™ patch= Vivelle Dot™

Source: IMS Health; NDC Health

...Noven's Strategy

Leverage DOT Matrix Technology

- **We have patented, best-in-class transdermal drug delivery technology**
- **Our strategy is to create value by leveraging this technology across diverse markets with strong partners**
- **Our strategy is succeeding**

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Patch Partner of Choice

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Why Noven?

Leading Edge Technology : Commercialized Products

- **Vivelle®**
  - **First U.S. approved matrix estradiol patch**
- **DentiPatch®**
  - **The first FDA approved transmucosal patch**
- **CombiPatch®**
  - **The first 2-drug patch available in U.S.**
- **Vivelle-Dot™**
  - **World's smallest HT patch – by far!**
- **Daytrana™**
  - **The first and only patch approved for ADHD**

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Why Noven?

Leading Edge Technology : Developmental Products

- **FSD patch**
  - Targeting hypoactive sexual desire disorder
  - Partnership with P&G Pharmaceuticals
- **Partnered Development Pipeline**
  - Amphetamine patch with Shire
  - Undisclosed compounds with Endo and several other partners in multiple therapeutic areas
- **Noven's Development Pipeline**
  - Several compounds under development for internal commercialization or future out-licensing

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World's First Patch for ADHD

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Latest transdermal innovation from Noven – Daytrana™ Methylphenidate Patch for ADHD

- **True once daily therapy**
  - **Labeled 9-hour wear time, with therapeutic effect lasting several more hours**
- **Control over duration of dosing**
  - **Can be removed early if shorter duration is desired or late day side effects appear**
- **May be appropriate for patients who cannot swallow or tolerate pills**
- **Marketed by Shire plc, the market share leader in ADHD therapy**
- **Approved patch doses of 10, 15, 20 and 30 mg/day**
- **Dosage of 60mg/day in clinical trials demonstrating delivery of large doses through a small patch**

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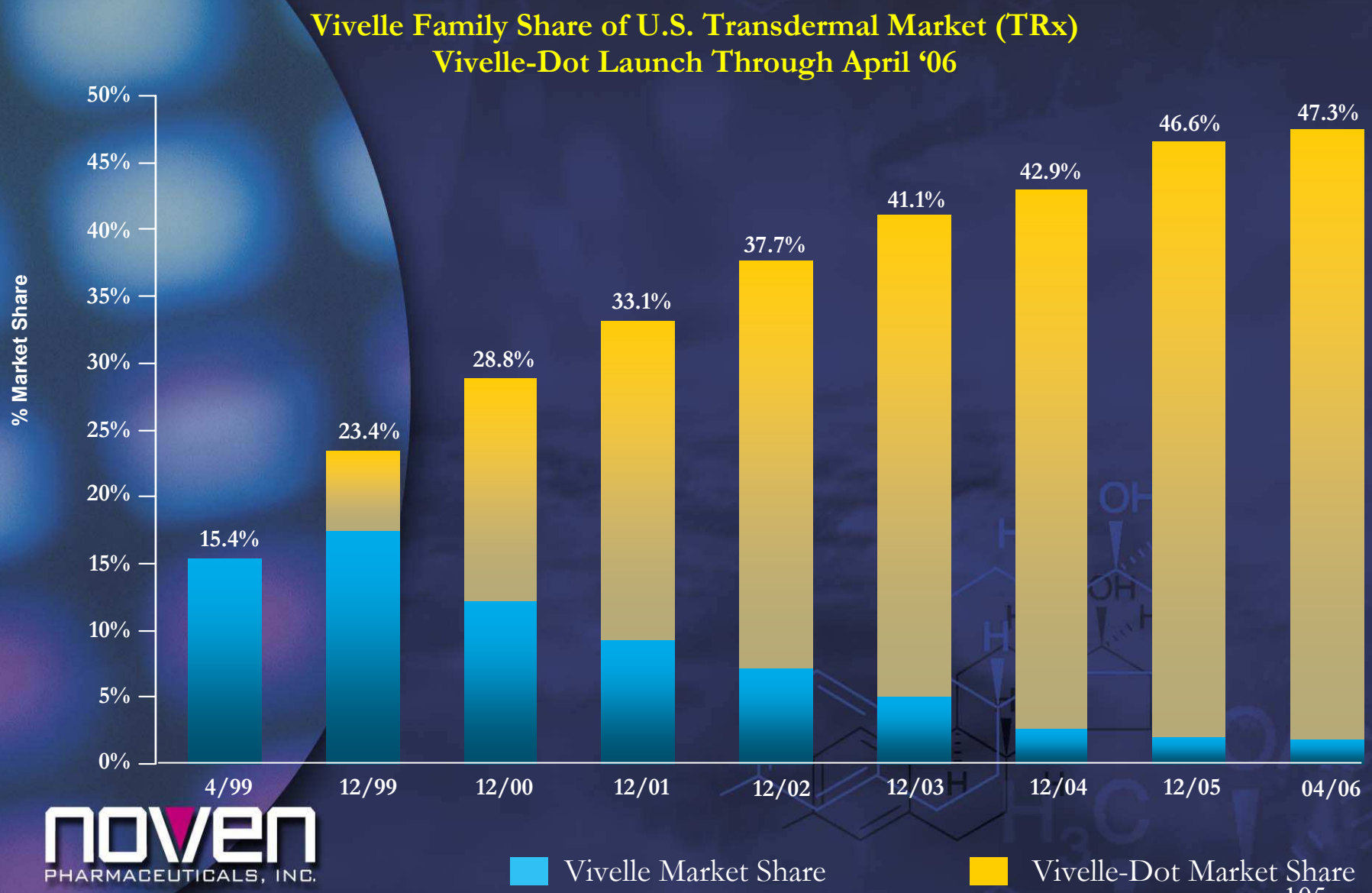
Sizing Up the Competition

Vivelle-Dot – the #1 ET patch in the U.S.

Vivelle Family Market Share: 47.3%



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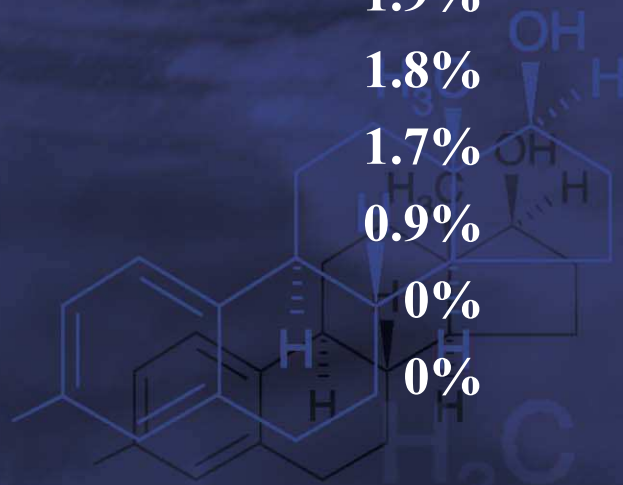
U.S. Transdermal Estrogen Market

Product	TRx Market Share as April '06
Vivelle Family	47.3%
- Vivelle-Dot	45.4%
Climara	25.5%
Mylan	14.4%
Estraderm	7.4%
EstroGel	1.9%
Menostar	1.8%
Alora	1.7%
Estrasorb	0.9%
Fempatch	0%
Esclim	0%



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DOT Matrix Opportunities

ADHD
Amphetamine

Allergies
Azelastine
Cetirizine

Alzheimer's
Tacrine

Angina
Nitroglycerin
Isosorbide Dinitrate

Anxiety
Alprazolam

Birth Control
Estrogen/
Progestin
Combinations

Depression
Buspirone
Bupropion

Epilepsy
Clonazepam

Hypertension
Enalapril
Ramipril
Clonidine
Timolol
Guanfacine

Hypogonadism/FSD
Testosterone

Incontinence
Tolterodine
Oxybutynin

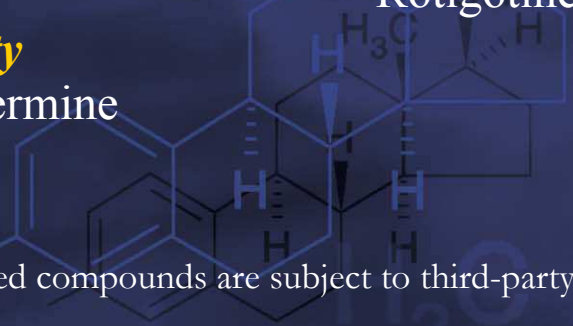
Motion Sickness
Scopolomine

Nausea
Granisetron

Obesity
Phentermine

Pain
Buprenorphine
Fentanyl
Sufentanil
Levorphanol
Lidocaine
Various NSAIDs
Various Triptans

Parkinson's
Pergolide
Pramipexole
Ropinirole
Rotigotine



Certain listed compounds are subject to third-party patents.

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Noven's Manufacturing Capacity

General & Controlled Substance Manufacturing

- Proven scale-up with four marketed products
  - Vivelle-Dot, Vivelle, CombiPatch & DentiPatch
- FDA and MHRA inspected and GMP compliant
- Recently established CS production capabilities
  - CS II vault/security/procedures
  - FDA and DEA inspected and cGMP compliant
  - Daytrana currently in production
- Expandable to meet additional demand/products

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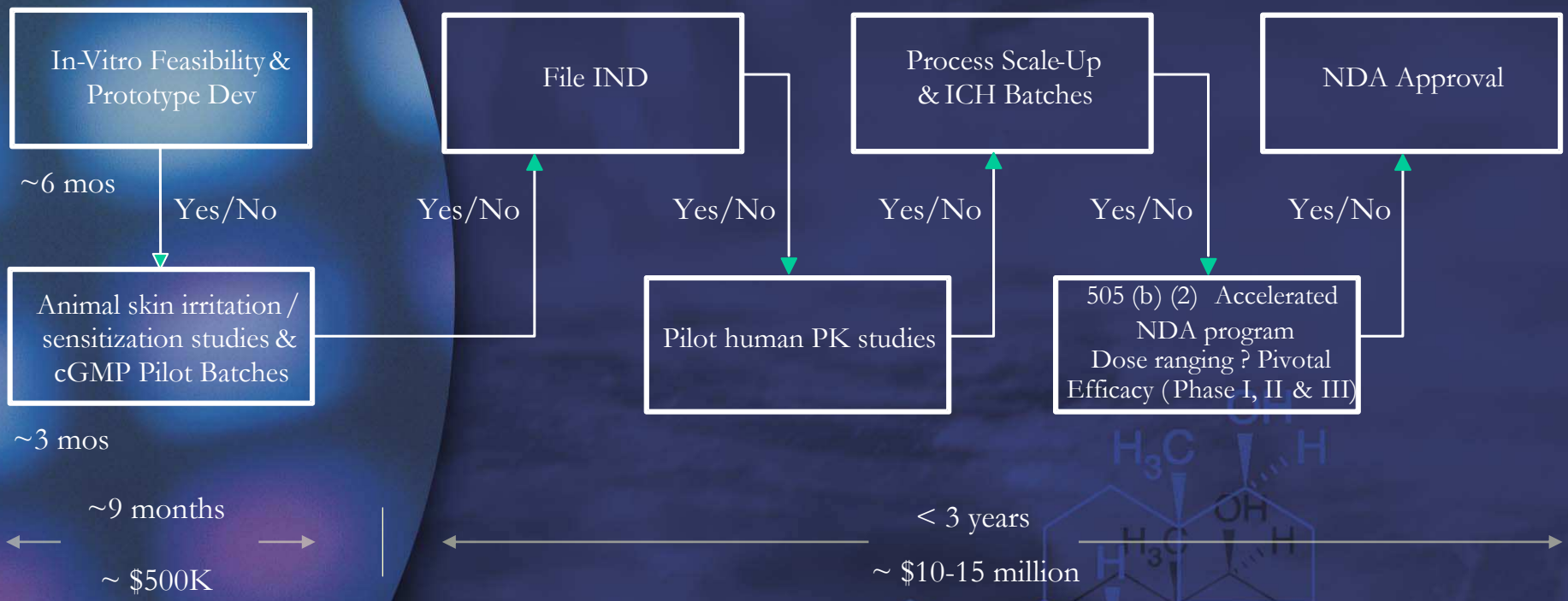
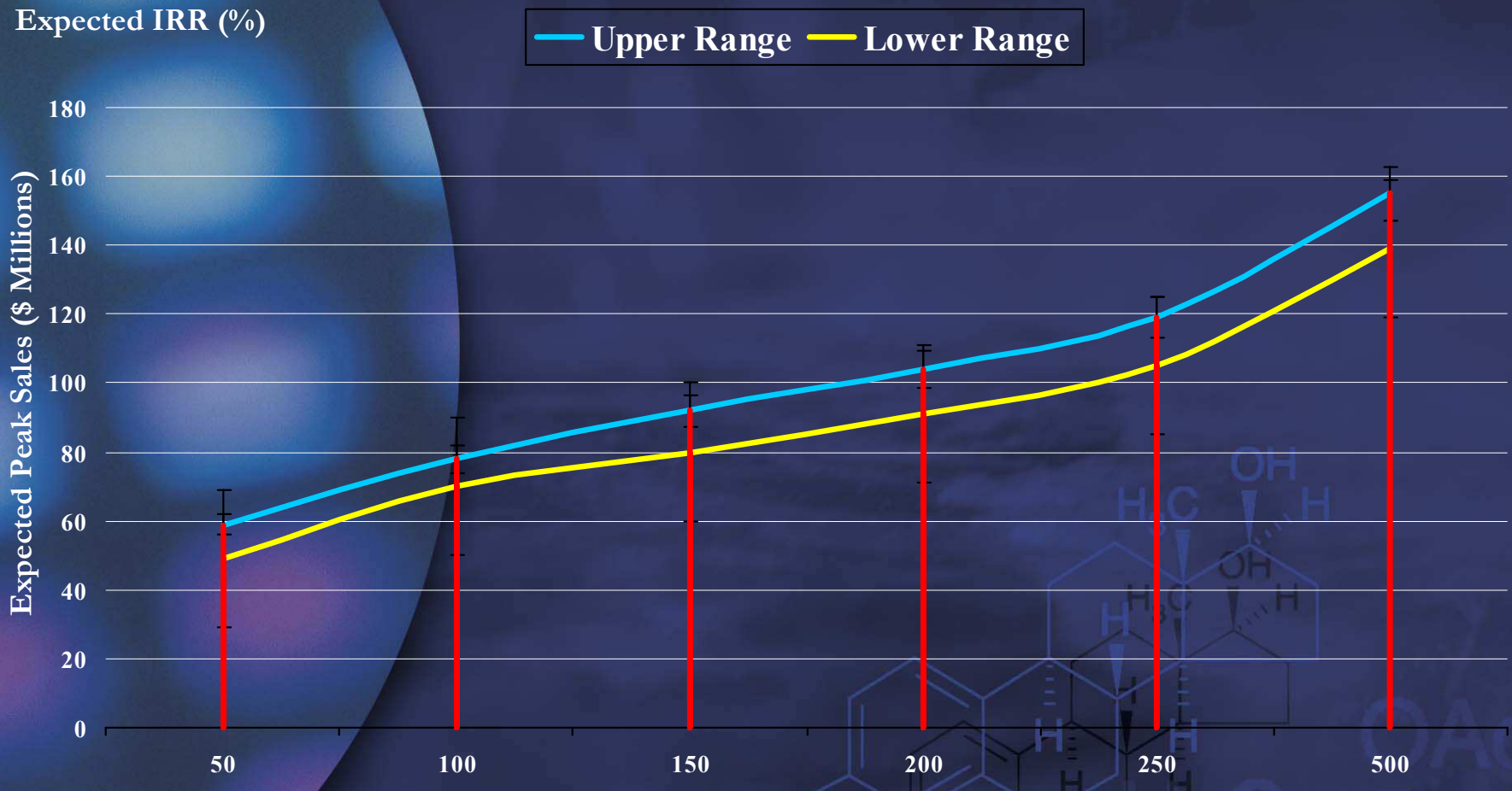
Transdermal drug development of known drugs can be short and inexpensive

Accelerated Transdermal Drug Development Program



Transdermal drug delivery for product-life and line-extension strategy has a compelling risk/reward profile

Illustration of expected return on investment for a hypothetical transdermal product (risk adjusted for success probability)



Key Assumptions

- ✓ $10 to 15 million cost of development
- ✓ Peak annual sales in the 4th year after launch
- ✓ 50% pre-tax profit margin, and 10 years of sales
- ✓ 4 years to market
- ✓ 70 to 80% probability of success
- ✓ Prior to value sharing with partner

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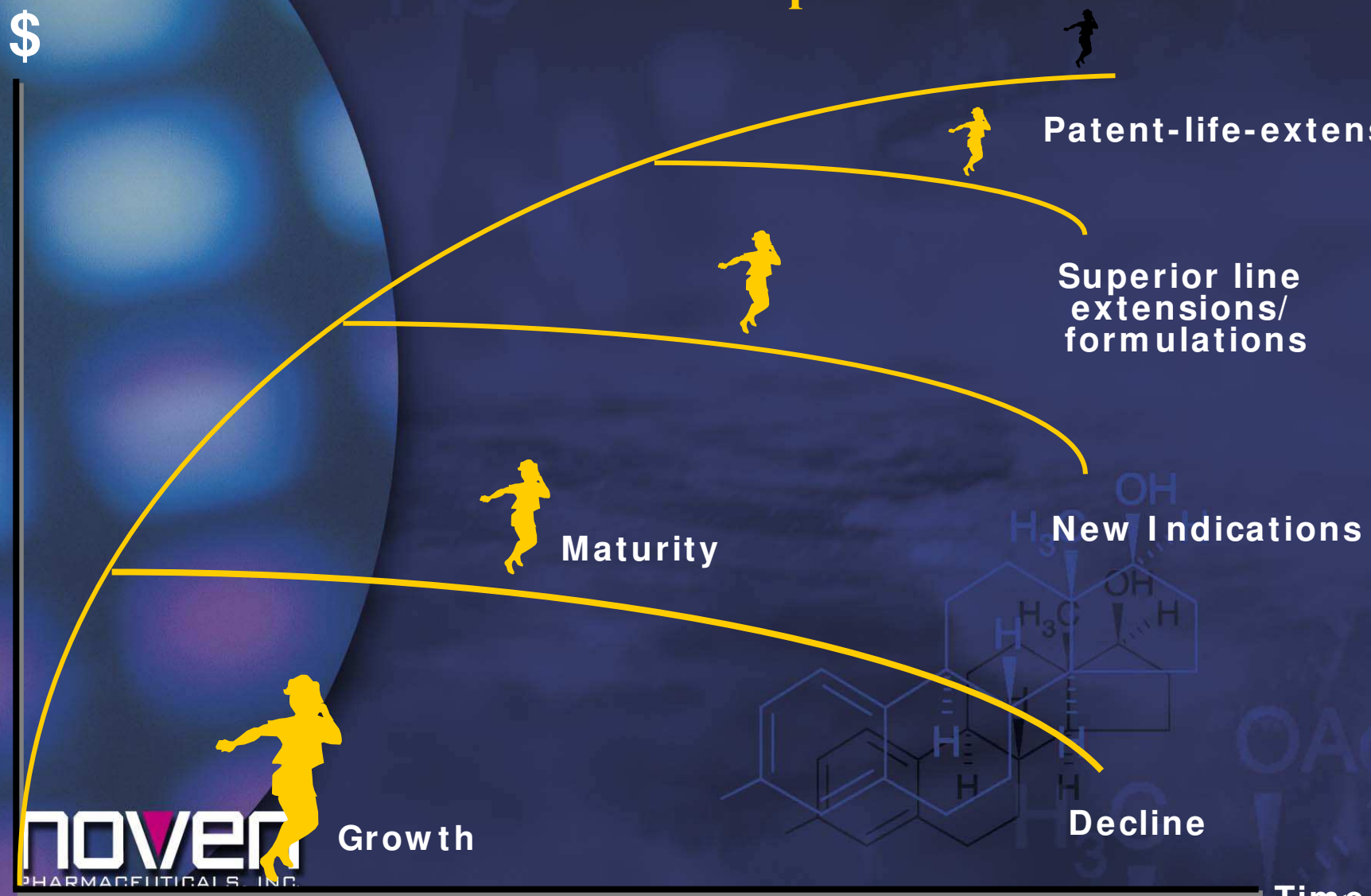
Novel drug delivery approaches have resulted in breathing new life into maturing brands or creating new blockbuster products from old compounds.



Patch Partner of Choice

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For Additional Information

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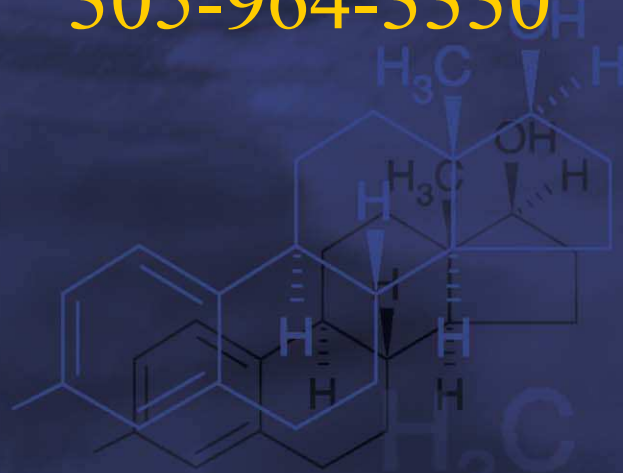
David Kanios	305-964-3171
Chris McDaniel	305-964-3212
Pavan Handa	305-964-3330



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