Combining Drug Delivery and Device Technologies: Challenges and Opportunities

Jayne E. Hastedt, PhD
ALZA Corporation

Outline

- Regulatory Considerations
  - Definitions
  - Review Process
  - Regulatory Review teams
- Combination Product Development
  - Technical Challenges
  - Product Development Teams
  - A History Lesson
- Industry Challenges and Opportunities
  - Current Pharma Challenges
  - From “smart delivery” to “smart medicine”
- Case Study: Insulin Drug Delivery
  - Challenges and Successes
- Observations and Opportunities

Combination Product

- FDA Definitions:
  - A Combination Product is a product comprised of any combination of a drug and a device; a device and a biological product; a biological product and a drug; or a drug, a device, and a biological product.
    - Single-entity
    - Kits
    - Cross-labeled products
  - Primary Mode of Action: The single mode of action of a combination product that provides the most important therapeutic action of the combination product.

21 CFR 3.2(e)

Drug Delivery and Convergence

- **Drug Delivery Devices** are specialized tools for the delivery of a drug or therapeutic agent via a specific route of administration. Such devices are used as part of one or more medical treatments.
- **Technological Convergence** refers to a trend where some technologies having distinct functionalities evolve to technologies that overlap, i.e. multiple products come together to form one product, with the advantages of each initial component.

Wikipedia: http://en.wikipedia.org/wiki/Main_Page accessed 13Sept2008

Examples of Combination Product Components

- Technologies
  - Drug eluting stents and catheters
  - Pre-filled syringes
  - Dry powder inhalers
  - Auto-injectors
  - Active and Passive Transdermal patches
  - Metered dose inhalers
  - Infusion pumps
  - Jet/Needle-free injectors
- Molecular Entities
  - Macromolecules
  - Small molecules
  - Antivirals
  - PEGylated or Glycosylated molecules

FDA Division Designation and Drug/Device Approval

- FDA Review will be performed by a combination of Divisions; however, one will be designated as the primary jurisdiction. Decision based on primary mode of action (PMOA) and Request for Designation (RFD)
  - CDRH: regulated as a Device
  - CDER: regulated as a Drug
  - CBER: regulated as a Biologic

	Approved Device	Investigational Device
Approved Drug	+	++
Investigational Drug	+++	++++

+ → +++ indicates increasing difficulty of approval process

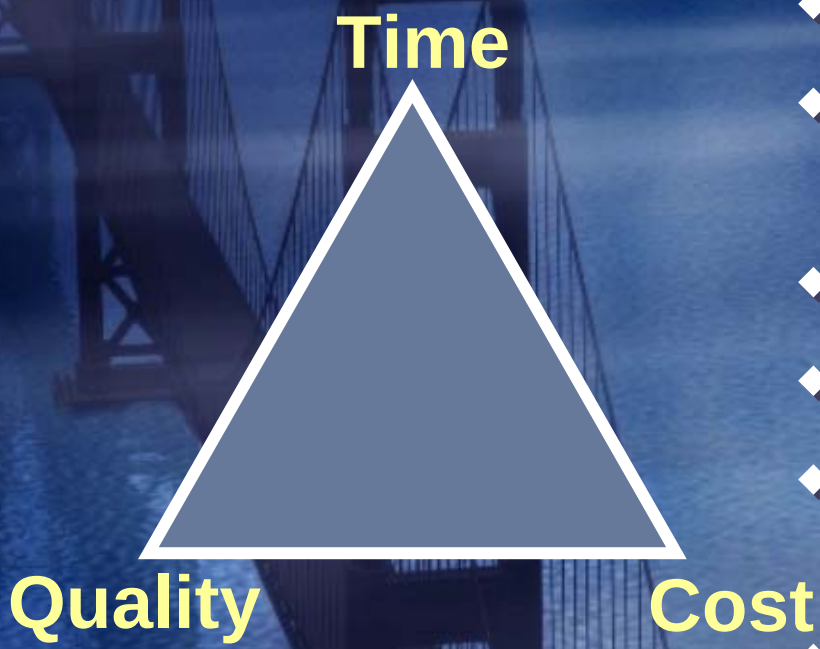
Example of FDA Combination Product Review Team Structure

- CDRH Review Team
  - Lead Reviewer
  - Clinical Reviewer
  - Engineering Review Team
    - Mechanical
    - Electrical/Software
    - Biocompatibility / Sterility / Shelf Life
  - Branch Chief
  - Deputy Division Director
  - Other Division Senior Management
- CDER Review Team
  - CDER Project Manager
  - Clinical Reviewer
  - Drug Review Team
    - Chemistry
    - Pharmacology
    - Toxicology
  - Supervisory Chemist
  - Supervisory Pharmacologist
  - Other Division Senior Management

S. Portnoy, S.Koepke, PharmNet Consulting Group, 2005.
http://www.pharmanet.com/pdf/whitepapers/Combo_Products.pdf

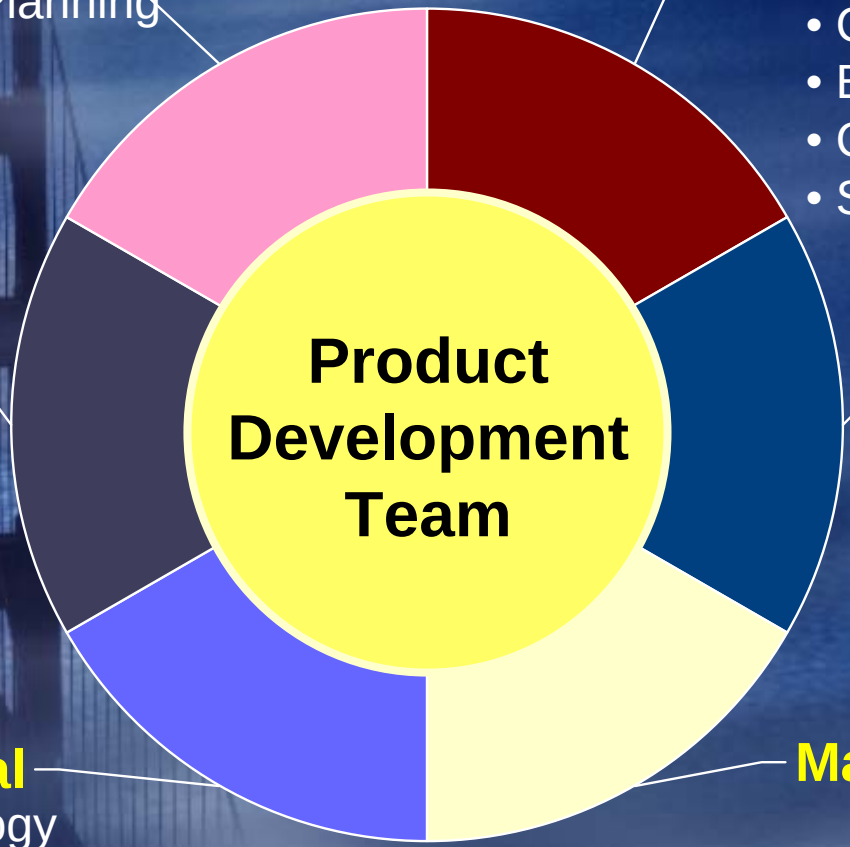

Combination Product Development

Common Technical Challenges



- Materials/Components
- Compatibility
- Device Design and Development
- Formulation Development
- Manufacturing Capability
- Specifications/Content Uniformity/Drug Release
- Stability/Shelf Life/Sterility
- Patient interface - Biology
- Risk Assessment and Management

Multi-Functional Product Development Team



Project Management
- Project Planning
- Finance

Clinical
- Clinical Research
- Biostats
- Clinical Pharmacology
- Safety

CM&C
- Analytical
- Engineering
- Formulation
- Manufacturing
- Supply Chain
- Process Chemistry
- Preformulation
- Quality

Regulatory
- Operations
- Device
- Drug

Nonclinical
- Toxicology
- Biology
- Pharmacology

Marketing
- Market Research
- NPP
- Reimbursement

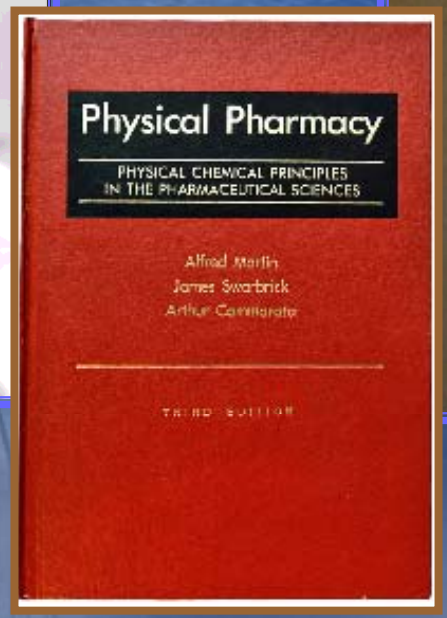
Product Development CM&C Teams for Combination Products

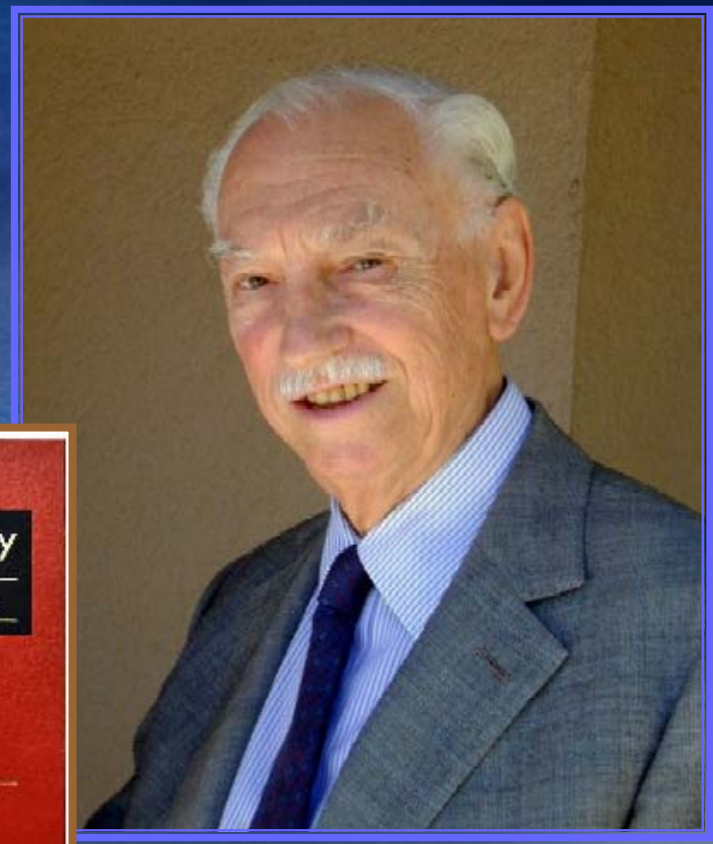
- Chemistry
  - Drug Discovery Chemists
  - Process Chemists
- Formulation
  - Pharmaceutical Scientists
  - Analytical Chemists
  - Material Scientists
  - Preformulation Scientists
- Device Engineers
  - Device Design Engineers
  - Device Development Engineers
- Product Process Engineers
  - Process Scale-up Engineers
  - Packaging Engineers
  - Validation Engineers

Requires <u>Cross-Functional</u> and Diverse Development AND Regulatory Review Teams – Collaboration is Critical!

Physical Pharmacy Meets Drug Delivery

Father of Physical Pharmacy
Tak Higuchi





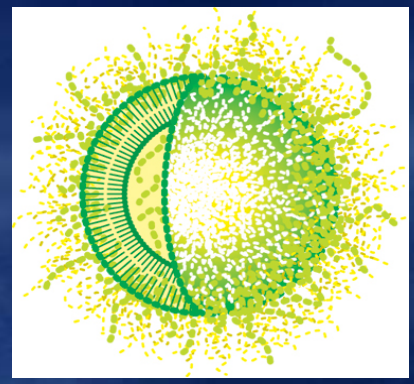
Father of Drug Delivery
Alejandro Zaffaroni

ALZA Drug Delivery Technologies

D-TRANS®
Transdermal

E-TRANS®
Electrotransport

Macroflux®
Transdermal



STEALTH®
Liposomal

OROS®
Oral

DUROS®
Implant

ALZAMER®
Depot

Drug Delivery Successes

Delivery Mechanisms	1970s	1980s	1990s	2000s	2010s
Diffusion (ALZA)	★ Ocusert® (1974) ★ Progestasert® (1976) ★ D-TRANS™(1981)				
Osmosis (ALZA)	★ Alzet® (1977)	★ OROS® (1983)	★ RUTS® (1989)	★ DUROS™(2000)	
Electrokinetics (ALZA)				★E-TRANS™ (2006)	

Drug Delivery Successes

Delivery Mechanisms	1980s	1990s	2000s	2010s
Erosion (Astra Zeneca) (Tap Pharmaceuticals)		★ ZOLADEX® (1989) ★ Lupron® (1995)		
PEGylation (ENZON)		★ ADAGEN (1990)		
Liposomes (Sequus)		★ Doxil (1995)		
Drug Eluting Stents (Cordis) (Boston Scientific) (Medtronic) (Abbott)			★ OCP Established ★ Cypher® (2003) ★ Taxus® (2004) Endeavor® (2008) ★ Xience® (2008) ★	
Pulmonary Inhalation – systemic delivery (Nektar)				★ Exubera (2006)

New Drug Delivery Technology Advances Are Not Short Term Efforts

- OROS® Systems ~ 15 Years
- Transdermal Systems ~ 9 Years
- Electrotransport Patches ~ 21 Years
- Pulmonary Systemic Delivery ~ 15 Years

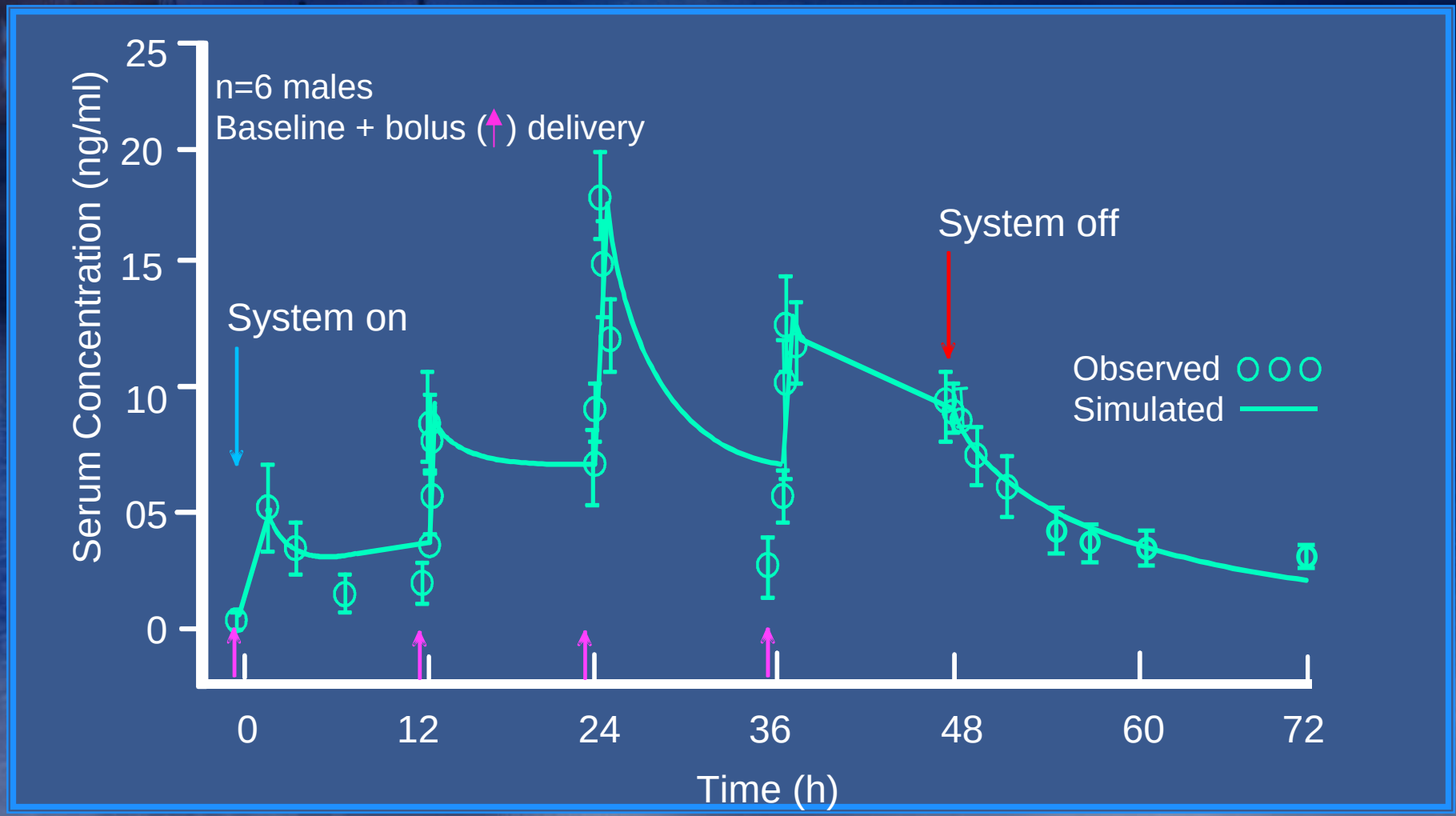
Average cost for development of a new biotechnology product is now $1.2B

Tufts CSDD, 2006

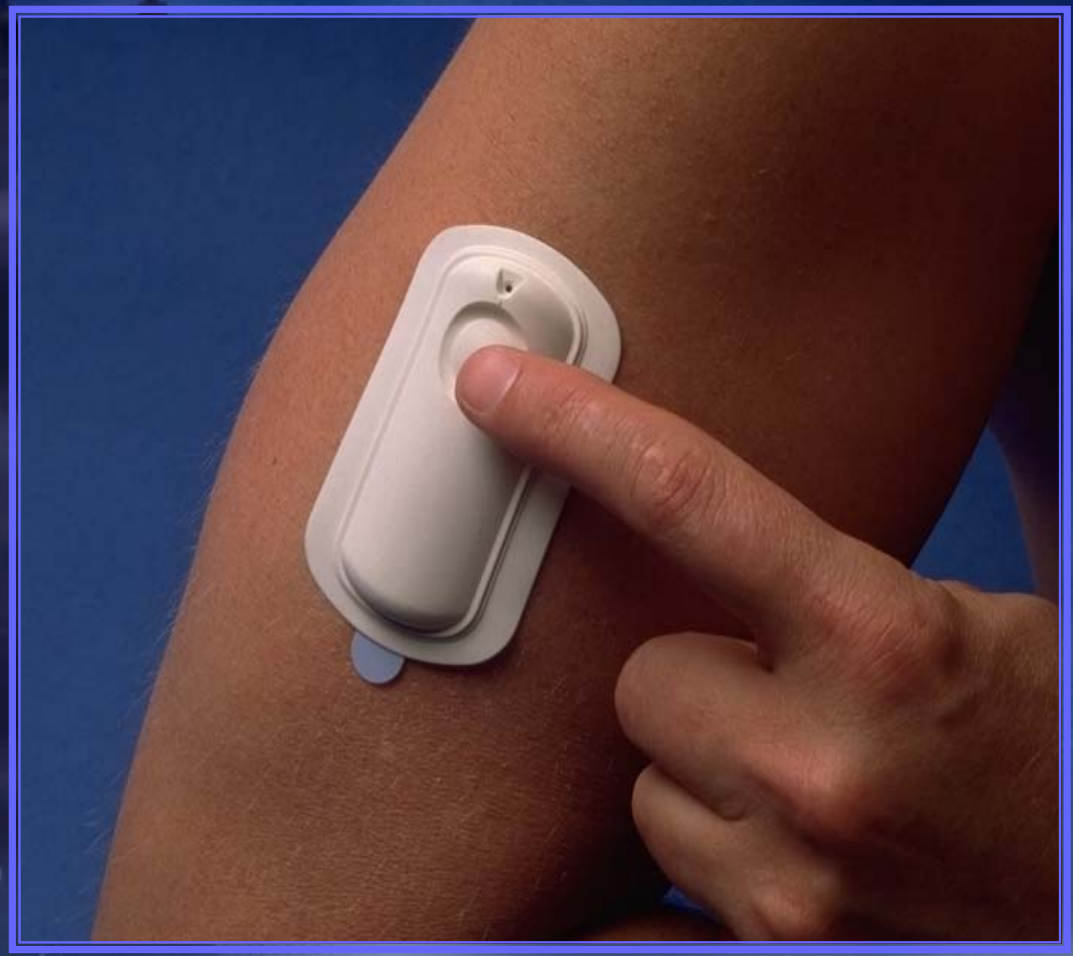
Key Learning: To Develop the Technology - Understand the Science of Drug Delivery

- **Dosage Form Design (Basic Pharmaceutics and Engineering)**
  - Mechanism of Delivery
  - Route of Administration
  - Dosage Form and Device Construction
    - API selection, prototype testing, scale up, manufacturing
    - Product performance, quality, stability, specifications
    - DOE, PAR, Validation, FMEA, Risk Assessment
- **Dosage Form – Body Interface**
  - Biopharmaceutics preclinical/clinical
  - Risk/Benefit, RMP, REMs, etc.
- **Delivery Rate Selection and Clinical Pharmacology**
  - Zero Order Pharmacology
  - Rate of Rise Dependent Pharmacology
  - Circadian Pharmacology
  - Site Specific Pharmacology

E-TRANS™ Technology for the Pulsatile Delivery of Fentanyl



E-TRANS™ Electrotransport Device Technology



Revenue from Drug Delivery Products

Peak Sales:

$1.0BN[2]

Peak Sales:

$300MM[1]

Peak Sales:

$300MM[2]

Peak Sales:

$2.1BN[2]

Peak Sales:

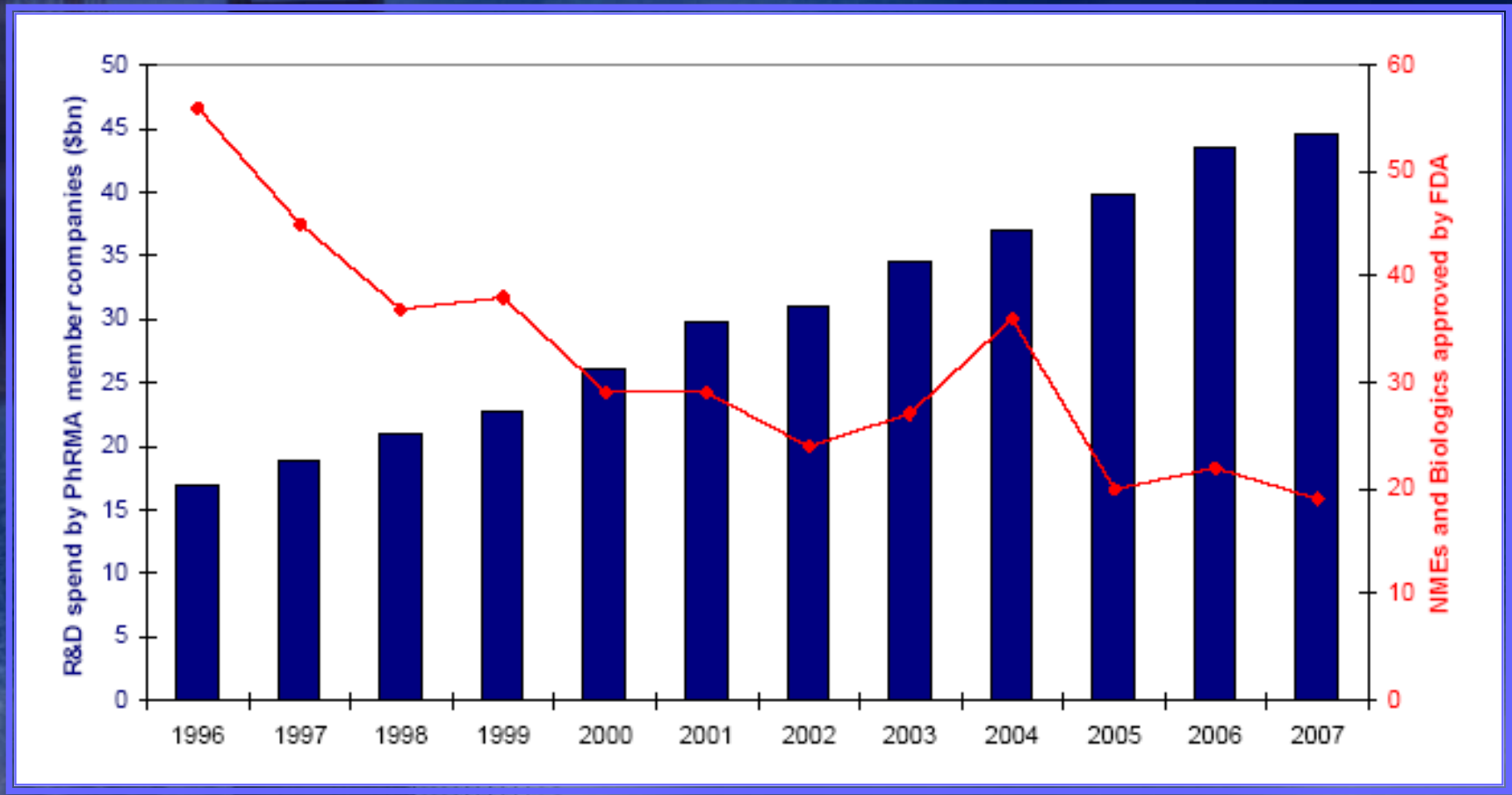
$1.4BN[2]

1) Peak sales estimate based on research reports.

2) Estimate of peak sales based on publicly available information and company reports.

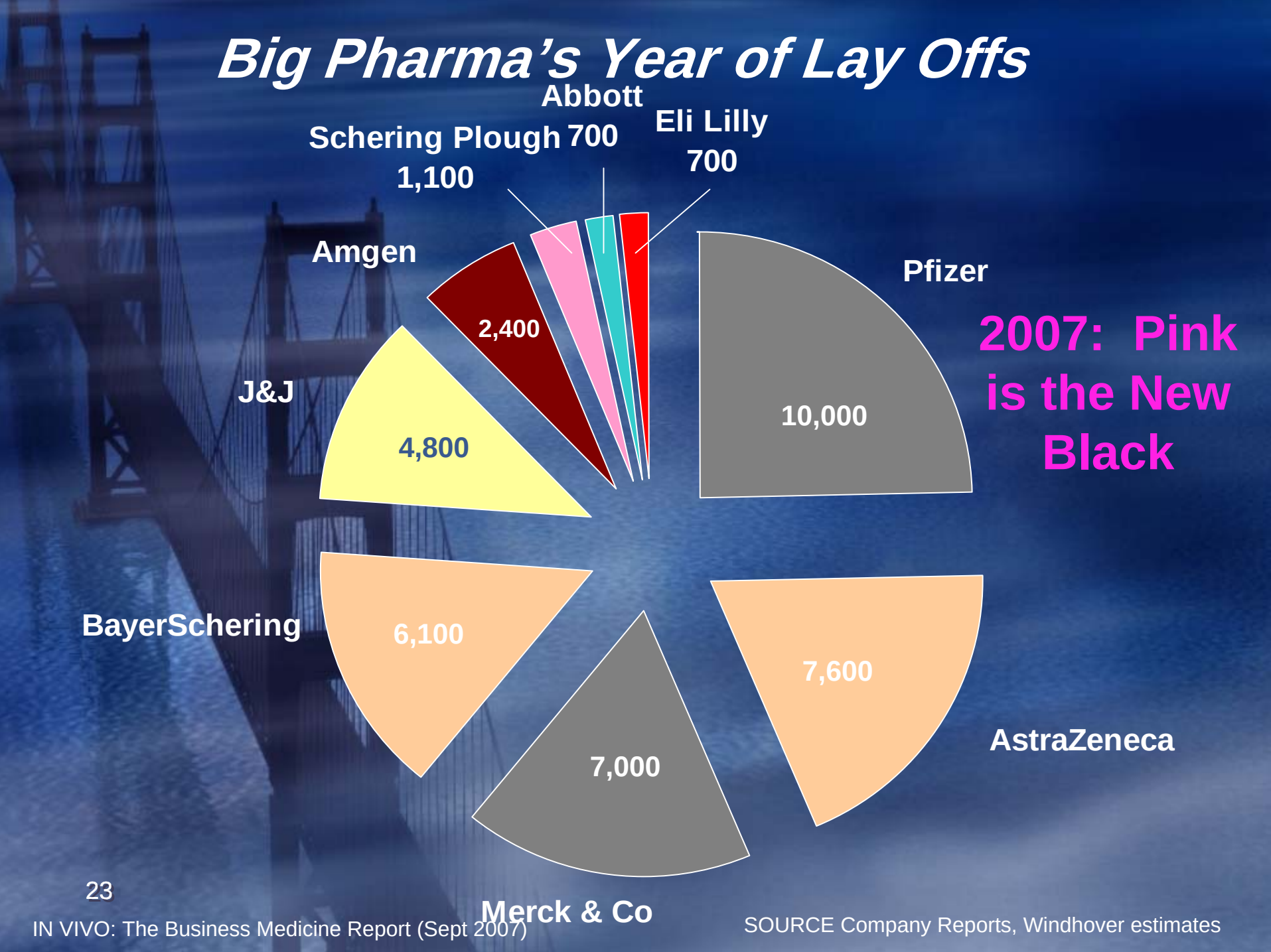

Big Pharma Challenges:
Productivity & Innovation

Declining Productivity: R&D Spend Increases as FDA Approvals Decrease



Source: PhRMA Pharmaceutical Industry Profile 2007, FDA

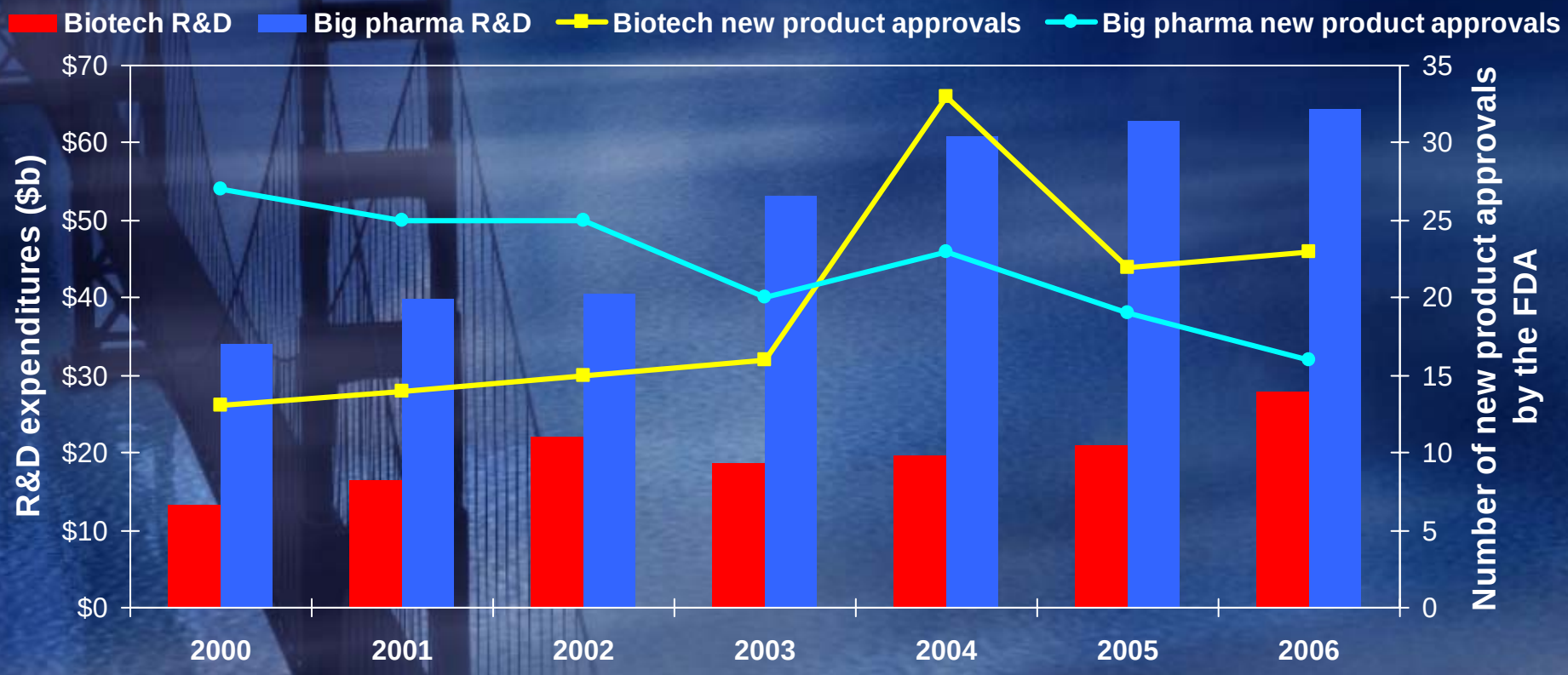
Big Pharma's Year of Lay Offs



IN VIVO: The Business Medicine Report (Sept 2007)

SOURCE Company Reports, Windhover estimates

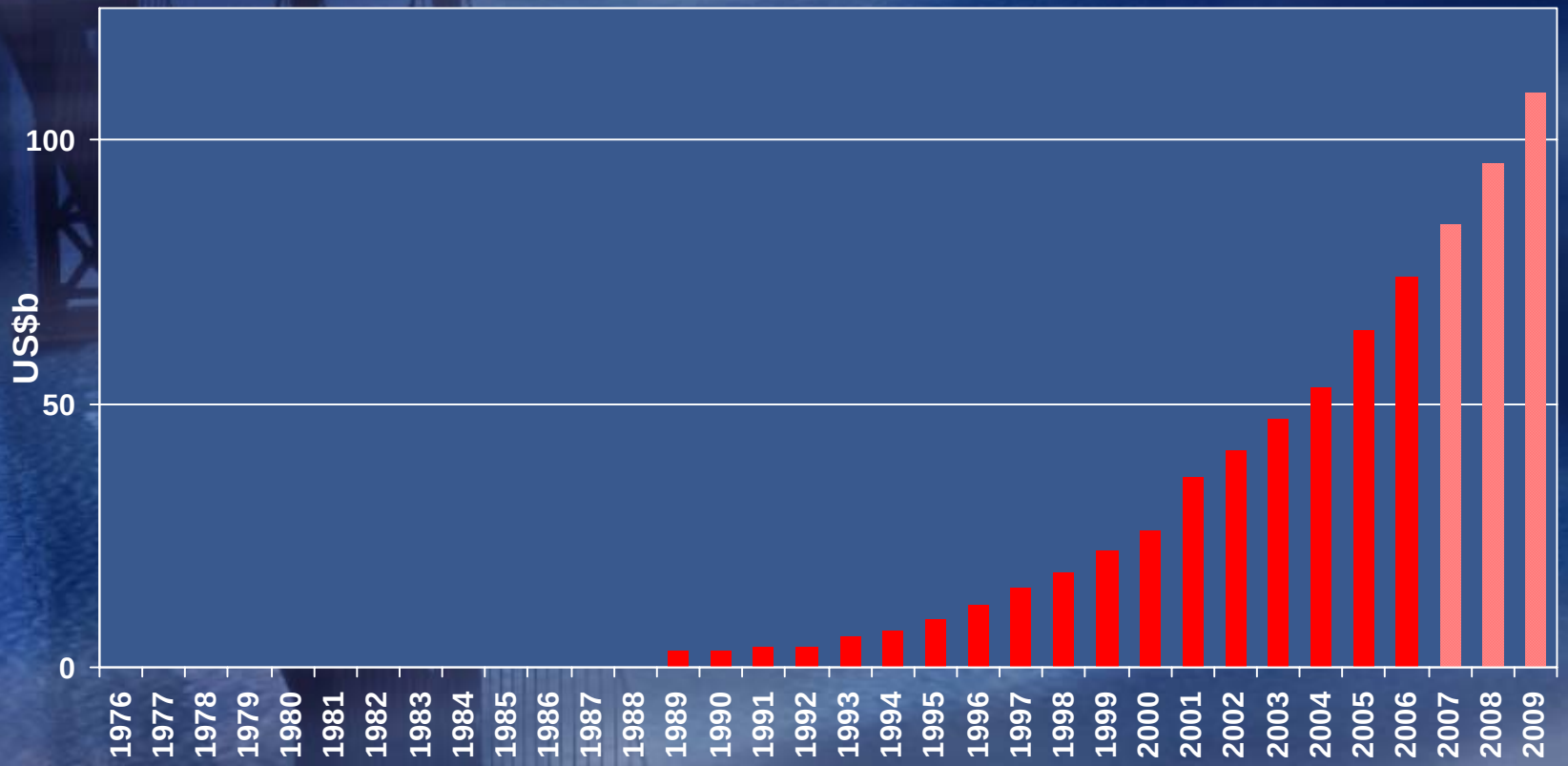
Biotech Business Trends



Source: Ernst & Young **Global Biotechnology Report 2007.**

Biotech is Viewed as a Large and Growing Market

Biotech is on track to become a US$100 billion industry by the end of the decade

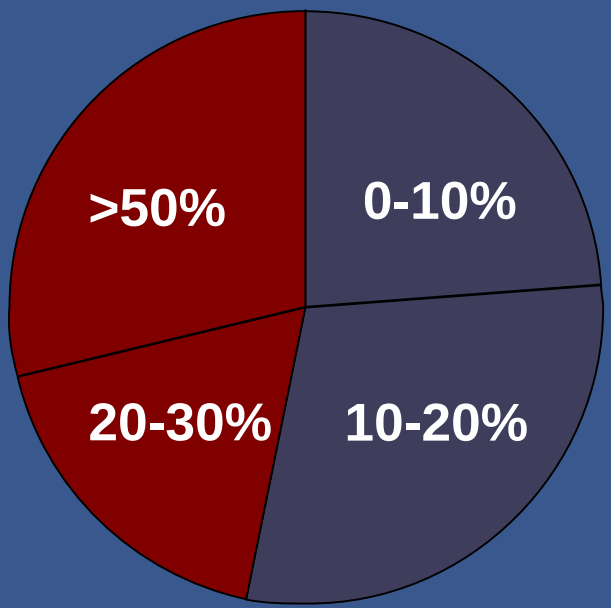


Source: Ernst & Young **Global Biotechnology Report 2007.** Forecast assumes 14 percent annual growth rate and no major acquisitions of biotech companies.

Pharma Increasingly Dependent on Delivery, Biotech, and Specialty Players for Product Innovation

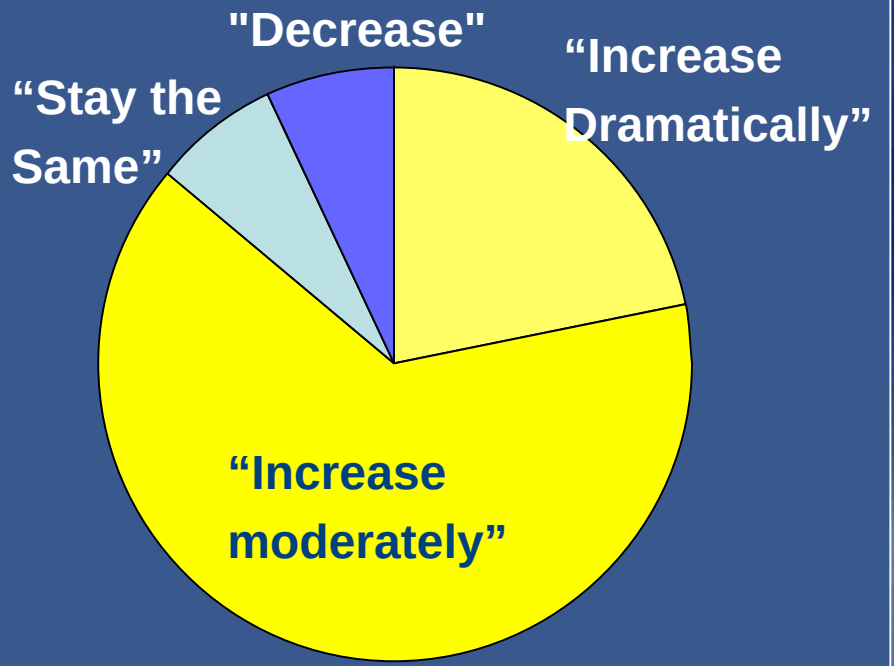
Nearly 50% of respondents attributed at least 20% of revenue to alliances…

Estimated percent of revenue from Alliances percent of respondents



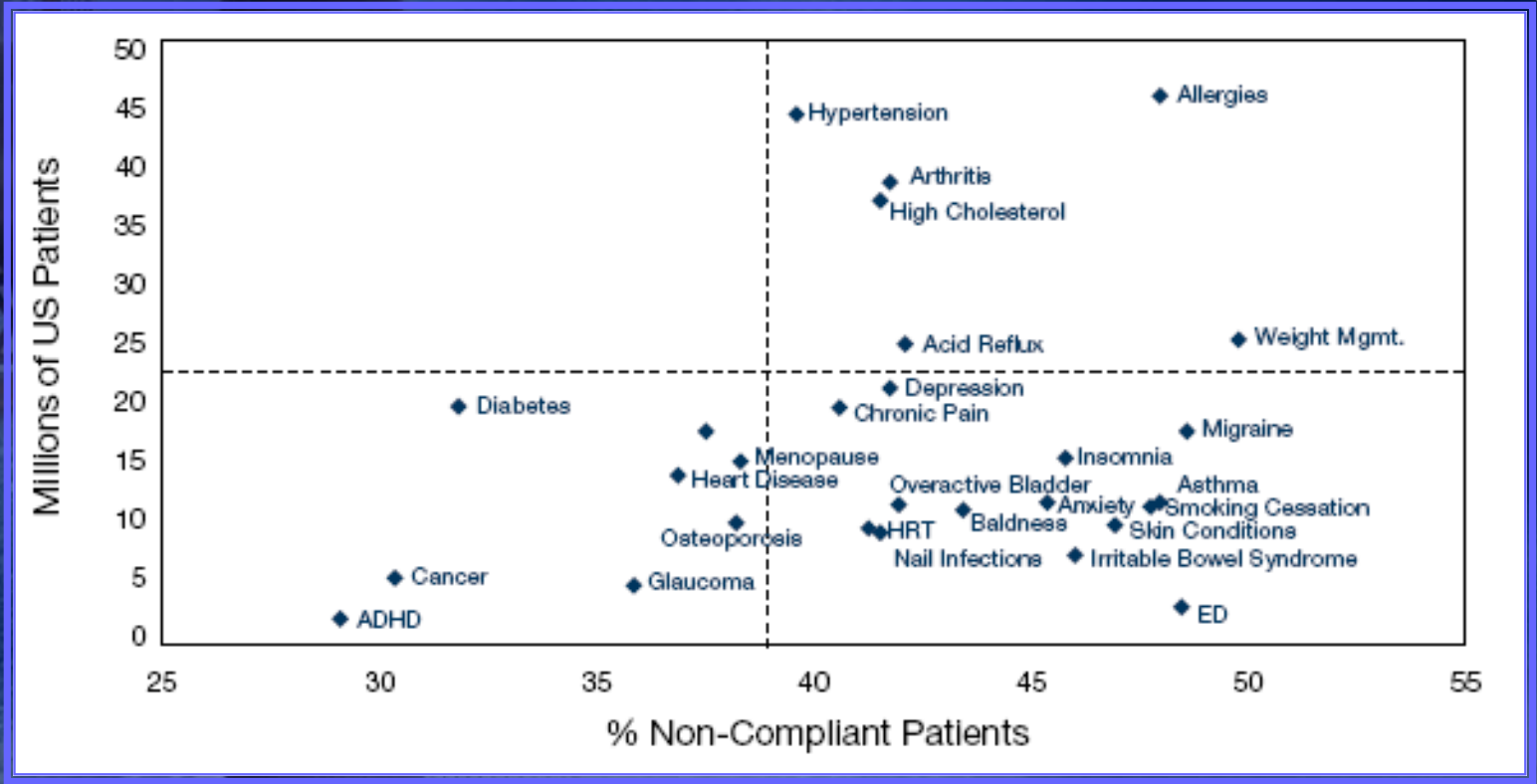
…and an overwhelming majority expect the frequency of alliances to increase

Expected frequency of alliances over next 5 years percent of respondents



Source: McKinsey Pharmaceutical and Biotechnology Alliances Survey

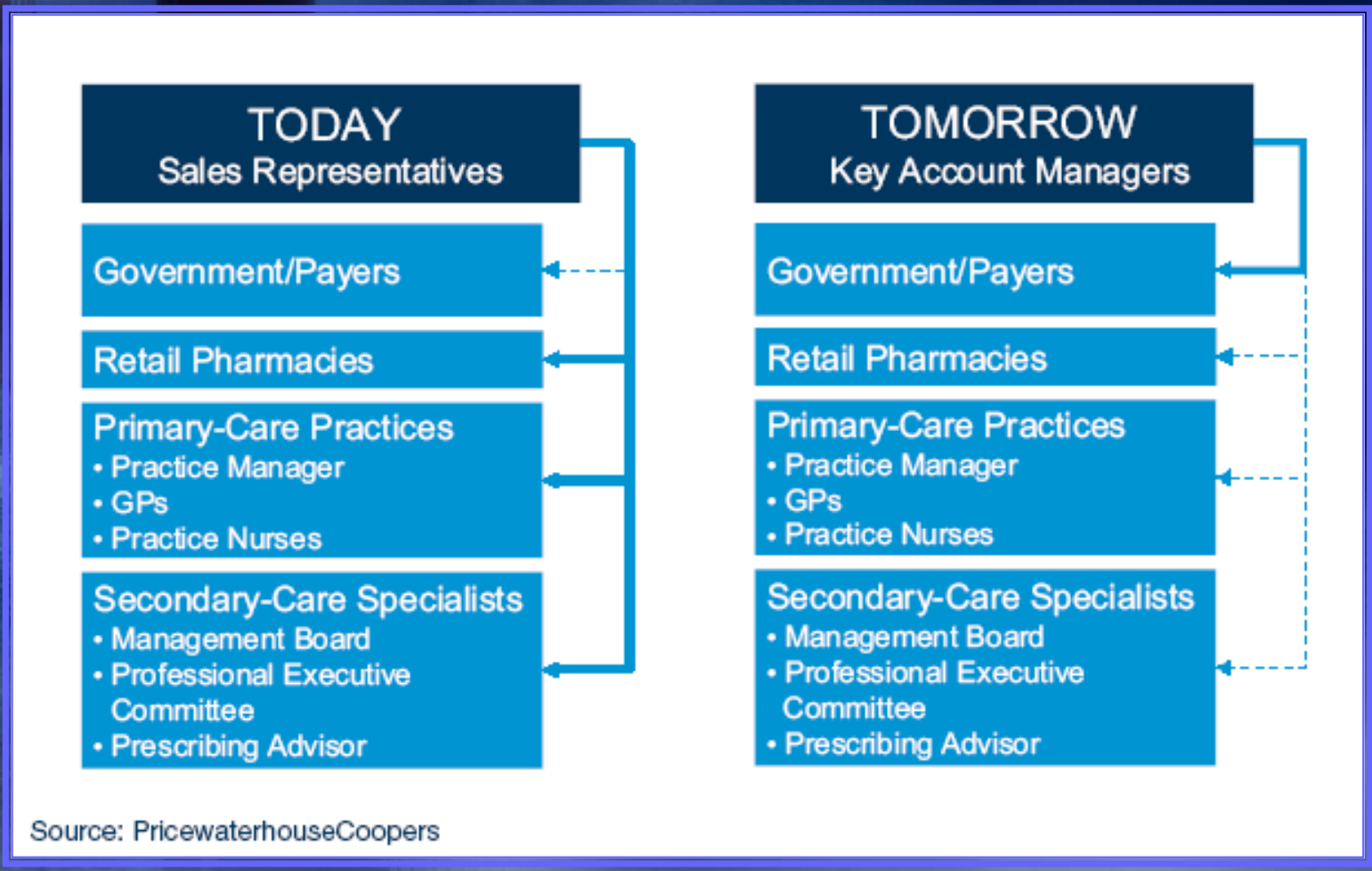
Reducing Non-Compliance Rates Could Dramatically Increase Sales for Some Drugs



Non-compliance is a major problem in people with minor and serious illnesses alike.

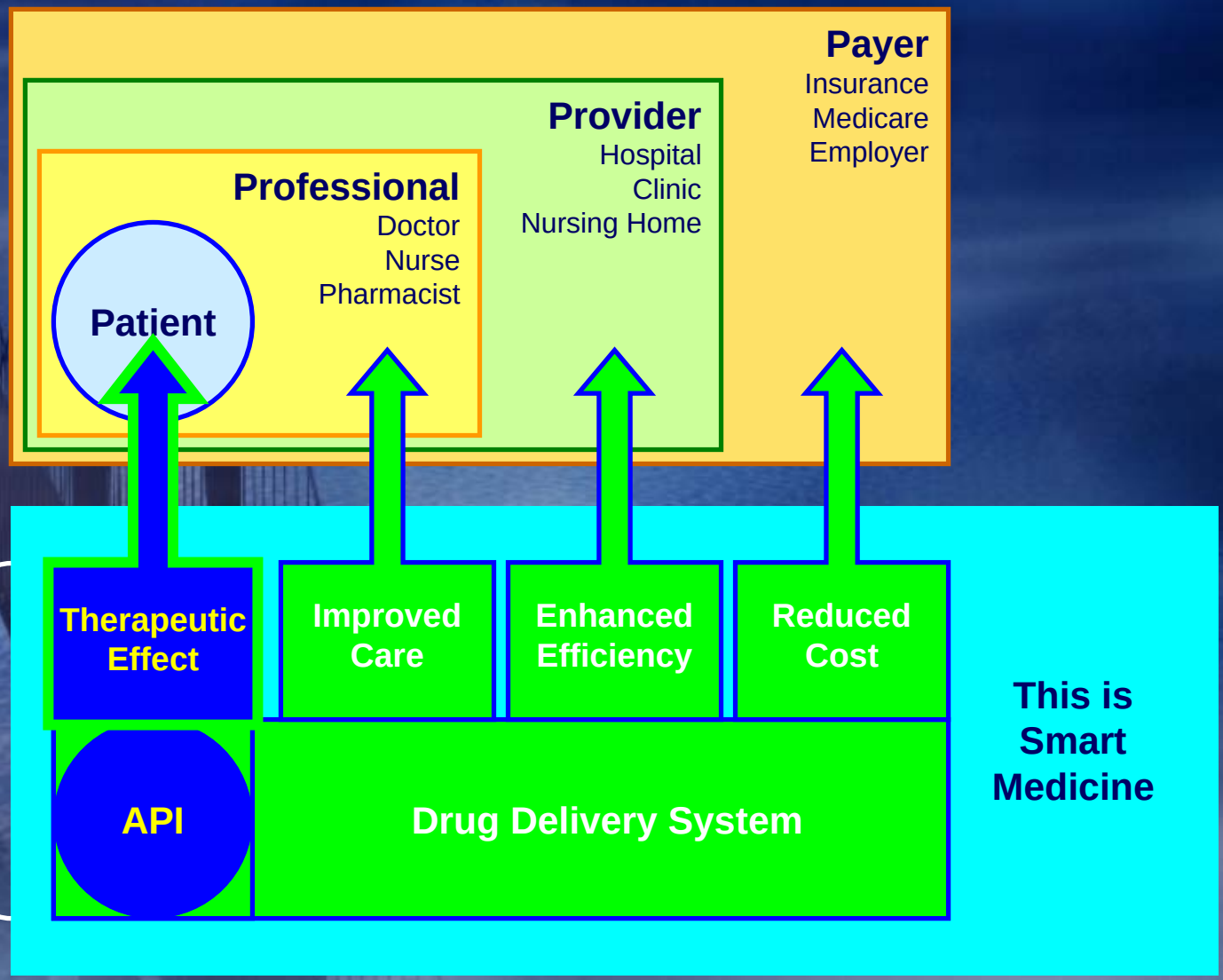
Source: Manhattan Research, 2004; as shown in Pharma 2020: The Vision, 2007.

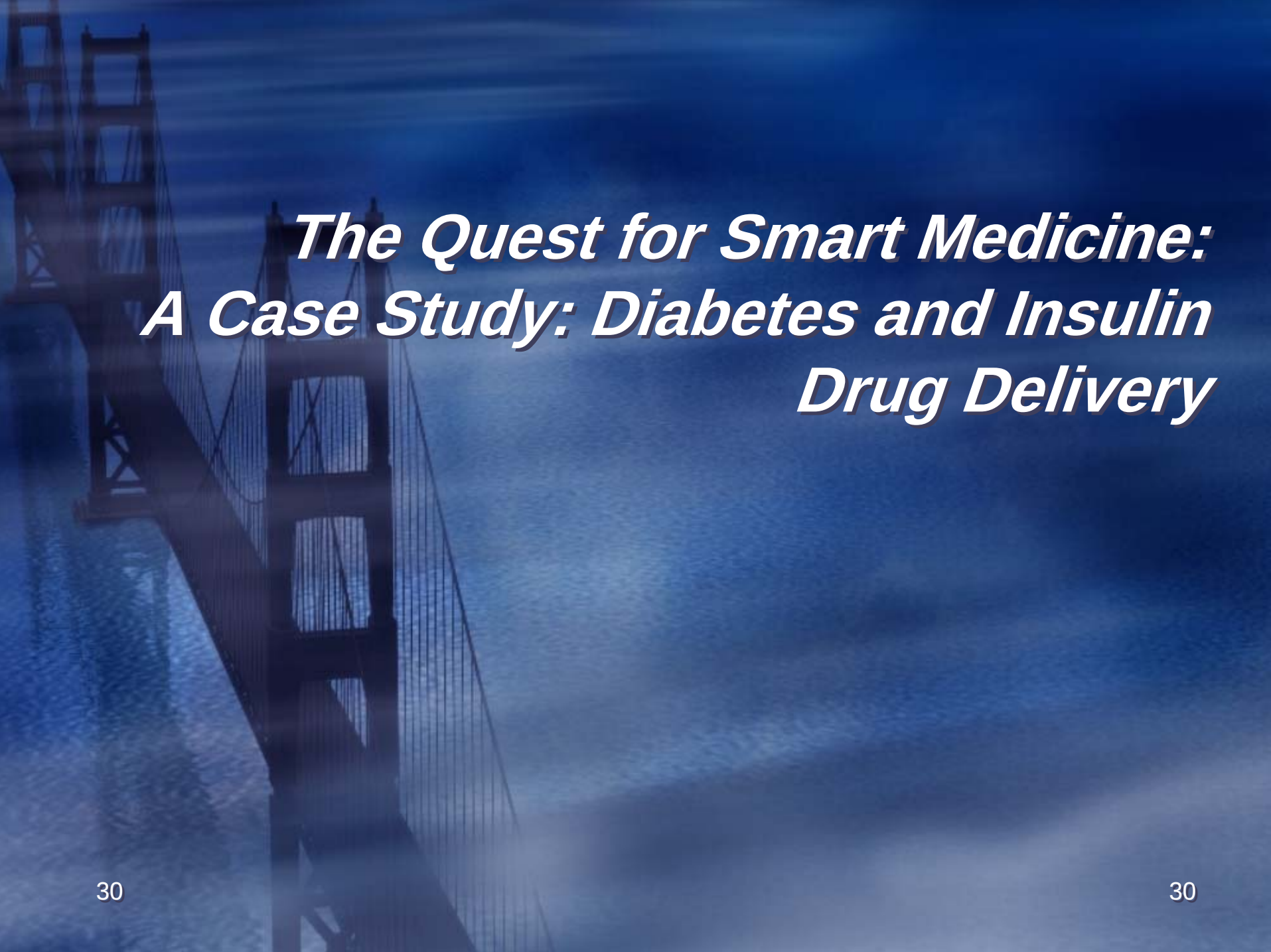
The Future: Marketing Focus Is Changing – Enter "The Payer"



Source: PricewaterhouseCoopers

Evolution: From Drug Delivery to "Smart Medicine"




The Quest for Smart Medicine:
A Case Study: Diabetes and Insulin
Drug Delivery

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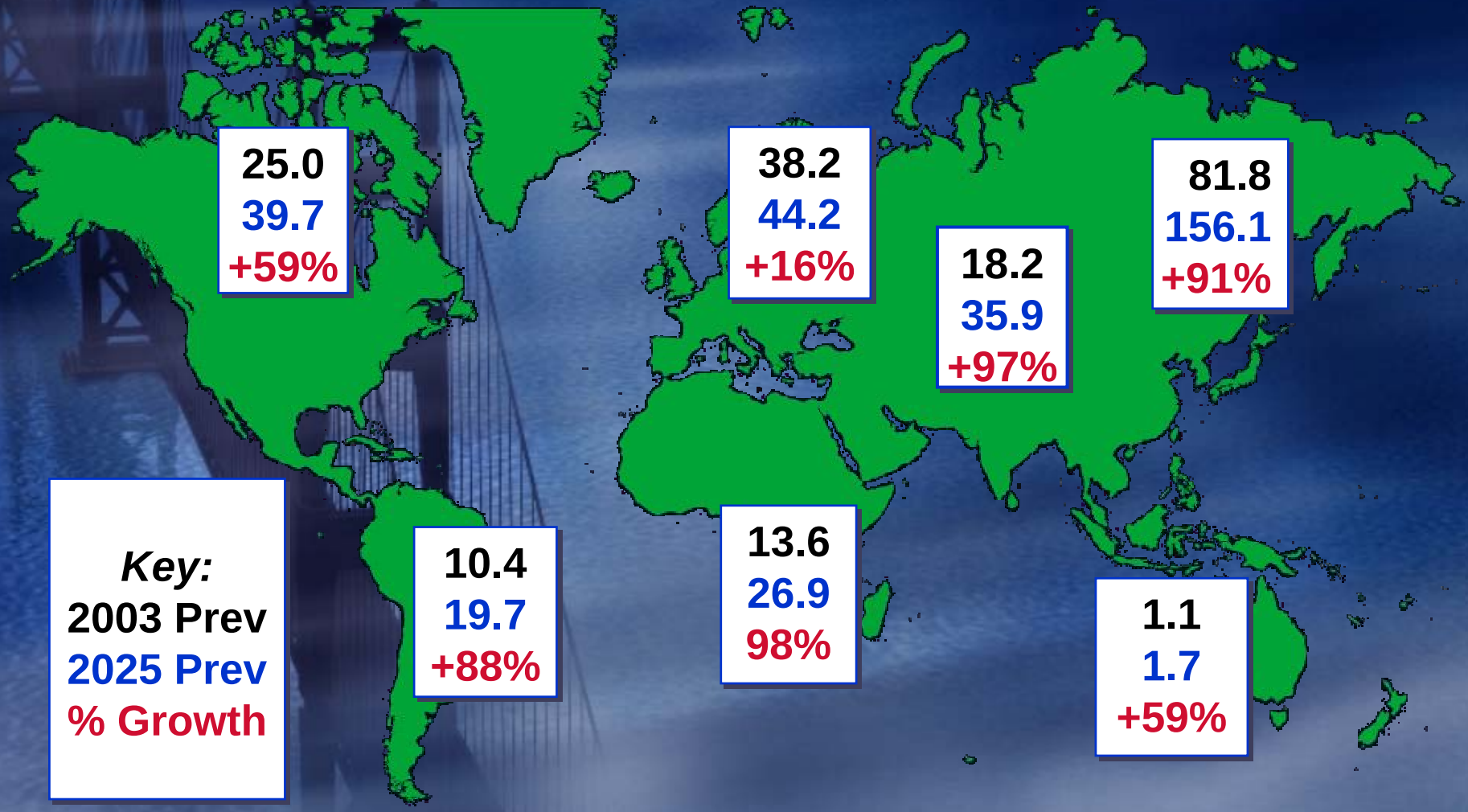
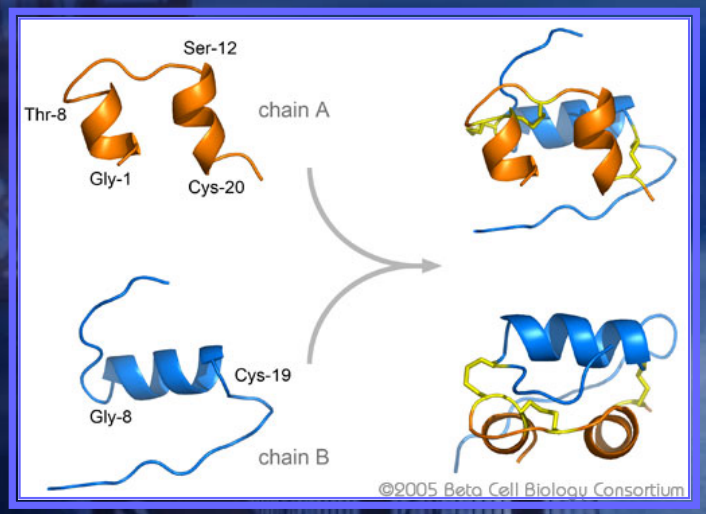
A Worldwide Type 2 Diabetes Epidemic

72% Growth Anticipated (189MM to 324MM)



Source: WHO 2003

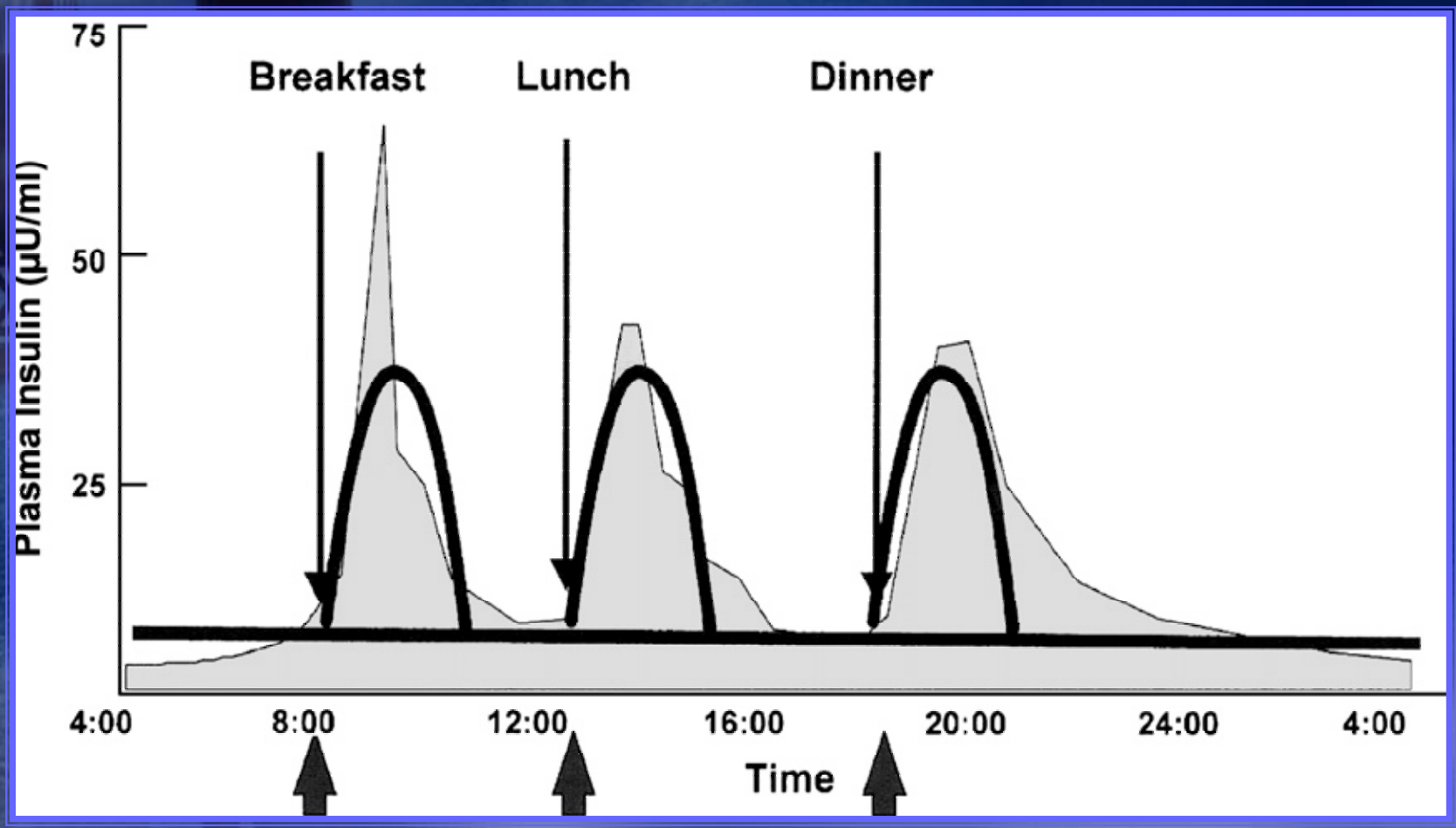
Diabetes Treatment: Insulin



- Pancreas origin of diabetes: 1889
- Successful extraction: 1921
- Mass production of naturally sourced insulin by Eli Lilly: 1923
  - Sourced from Pigs/Cows/Sheep
- Genentech/Eli Lilly introduced recombinant source of Insulin: 1982

Charles Best and Dr. Frederick Banting

Insulin Drug Delivery: Basal/Bolus Delivery Pattern



Insulin Drug Delivery Platforms

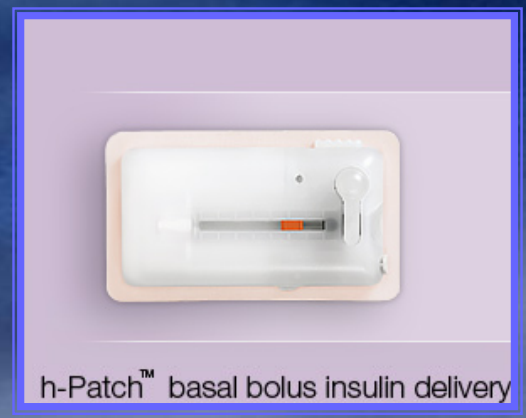
Pens

Needle Free Injectors

Pumps

Syringes

Pulmonary DPI



Transdermal

Key Learnings: Insulin Drug Delivery

- 86 years - large advances made in insulin engineering and delivery
- In 2000, 4 million years of life still lost to Type I diabetes
- Much learned about pulmonary delivery of biomolecules
- Market always driving toward more patient friendly compliant dosage forms
- Closed loop delivery system is almost a reality

Observations and Opportunities

What have we learned from combining drug delivery and device technologies?

Drug Delivery and Devices: Some Observations

- Technology differentiated products provide new solutions and create high value
  - Taxus and Cypher drug eluting stents
    - Significantly improved clinical outcomes
    - Revolutionized interventional cardiology market
  - Duragesic
    - Injectable transformed into a transdermal product
    - New indication for old drug
  - Exubera
    - Revolutionary needle-free pulmonary delivery for insulin
    - Approved by FDA, but no longer marketed

Opportunities

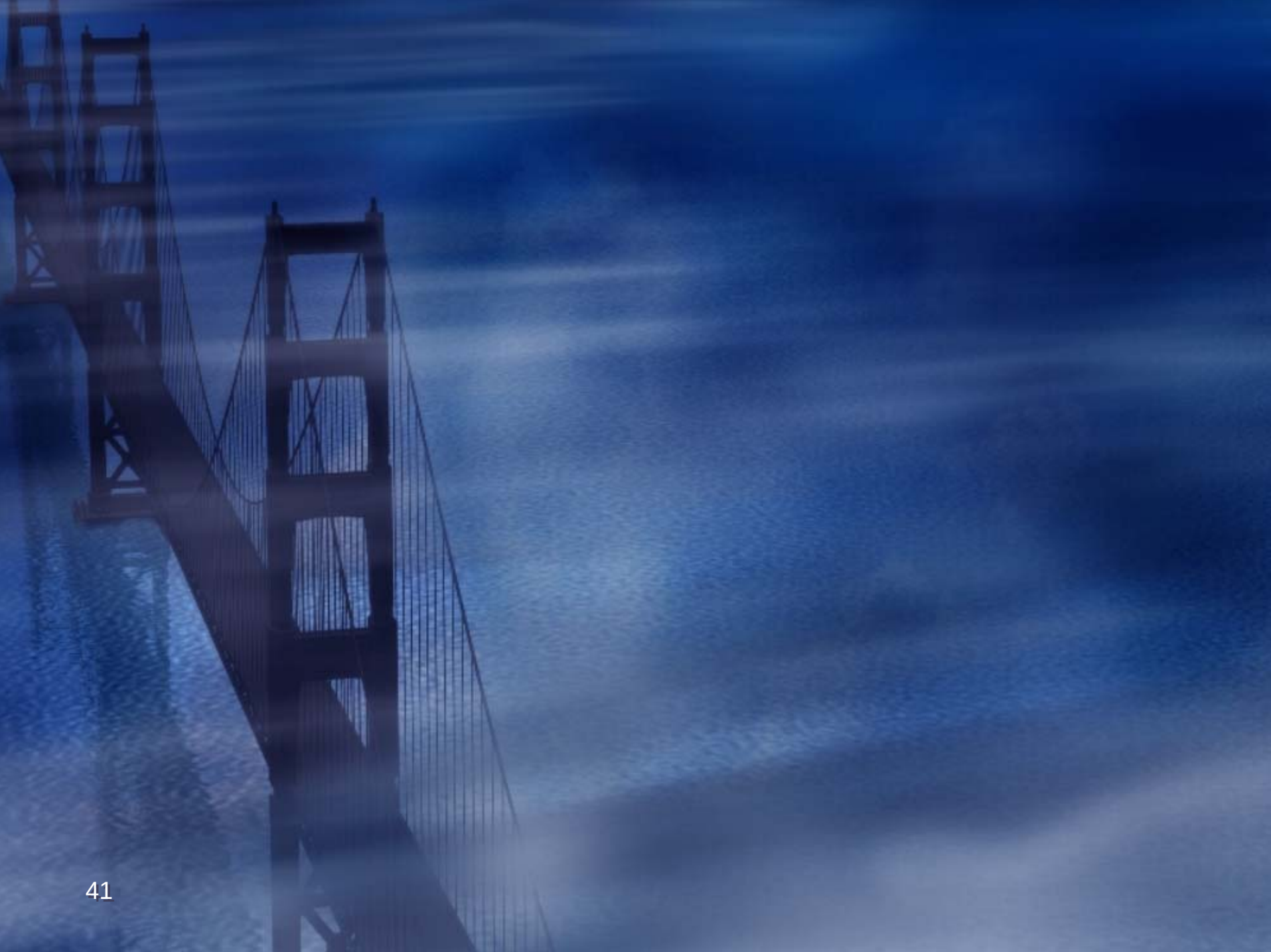
- Drug delivery is always evolving
- Cross-functional collaborations are critical
  - Don’t underestimate biological complexity
  - Utilize combined pharma and device skills to continue to bring products to the market and advancing patient care – don’t work in silos!
- Be aware of stakeholders beyond the regulator and the patient
  - The health care professional
  - The health care provider
  - The health care payer
- Combination drug delivery and device products, though currently complex, provide new treatment opportunities
  - Continued collaboration and expansion of scientific understanding will reduce complexity

Acknowledgements

- John Patton, Nektar
- Brad Phipps, ALZA Corporation
- Felix Theuwees, Durect
- Gene McNally, Pharma Dev Concepts
- The Organizing Committee for BioInterface 2008

"Building truly convergent technologies represents multifactorial complexity in no small part because it requires the coordination of a multidisciplinary team of experts, each of whom has a very different notion about how to build things and why things work. Finding and managing this disparate pool of talent is one of the most overlooked and misunderstood challenges of developing convergent technologies. It is rare to find the compatibility required."

- John Patton, on Managing Technology Development Teams; from *Nature Publishing Group*, 2006



Combination Products Include:

1. A product comprised of two or more regulated components physically, chemically, or otherwise combined or mixed and produced as a single entity
   - ie., drug/device, biologic/device, drug/biologic, or drug/device/biologic
2. Two or more separate products packaged together in a single package or unit
   - i.e., drug and device, device and biological, or biological and drug
3. Combination of approved individual drug, device, or biological products resulting in a label change of the approved combination product
   - change in intended use, dosage form, strength, route of administration, or significant change in dose
4. Combination of a separately packaged investigational drug, device, or biological product for use only with another individually specified investigational drug, device, or biological product
   - both are required to achieve the intended use, indication, or effect

21 CFR §3.2(e)

Diabetes: The Worldwide Epidemic

- $177 million worldwide (5% of population)
- Numbers expected to double by 2030
- $19 billion – WW estimate of drug and device for treatment
  - $12.5 billion – US only
- $132 billion (US only) spent on diabetes treatment and complications
- 5-10% of cases are Type 1, rest are Type 2

Insulin Drug Delivery Systems

- Approved
  - Syringes
  - Insulin Pens
  - Jet/Needle Free Injectors
  - Subcutaneous Infusion Sets
  - Insulin Pumps (external)
  - Insulin Inhalers
- On The Horizon
  - Transdermal
  - Nasal
  - Buccal
  - Oral
  - Insulin Pumps (implanted)
  - Beta cell replacement (transplantation)
  - Bariatric surgery/gastric bypass

Insulin Drug Delivery System Requirements

- Highly complex natural control of blood glucose levels
- Fast onset/long-acting
- Flexible/adjustable
  - Daily variability due to exercise/meal time/food combinations
- Easy to use, discrete format

Insulin Pens

- Subcutaneous dosing
- Prefilled /Disposable
- Alternative to vial and syringe
- Discreet (pocket/purse)
- Dial in dosing (1-60 units)
- Resets to zero during injection
- Accurate/affordable/easy to use
- Once in use - stable @ controlled RT for 42 days
- Junior versions
- Memory (date/time/amount dosed)

Insulin Needle Free Injection Technologies

- Delivery through skin without use of needle
- High velocity delivery of liquid/powder though orifice
- Jet opens and forms hole in skin (fraction of a second)
- Attributes:
  - Enhanced compliance
  - Improved Safety
  - Not necessarily decreased pain, rather decreased fear
  - Significant ease of self use (some devices)
  - Fixed volume (< 1.5mL)

Insulin Pumps

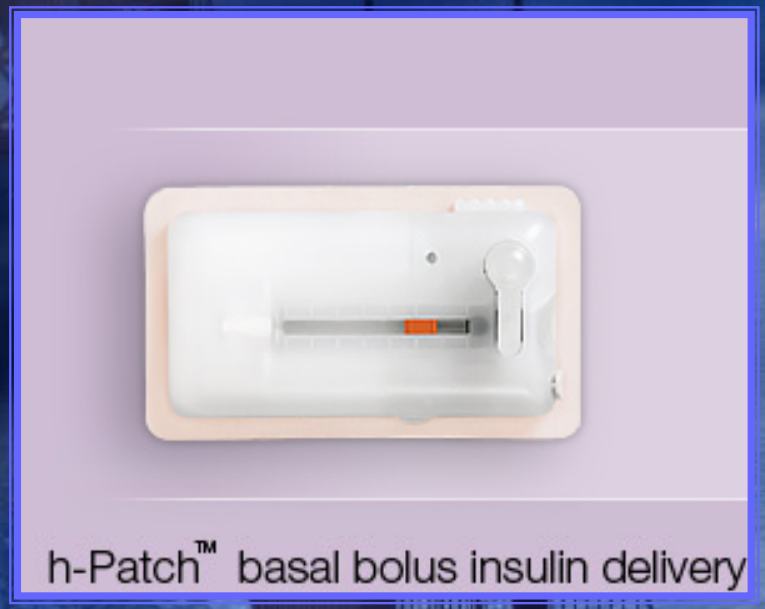
OneTouch Ping

- Combination meter and pump
- Wireless communication
- Pump calculates infusion rates and boluses based on meter readings
- Hands-free insulin delivery; patient must confirm dose
- Downloads to data management software
- Not closed loop - requires calibration to blood glucose q 12 hr.

Insulin Pulmonary Delivery

- Highly effective
- Non-invasive
- Exubera approved in January 2006 -withdrawn October 2007
  - Long term pulmonary safety concerns
  - Cost effectiveness concerns
  - Dose adjustment (3 units vs 1/20th unit from pump)
  - Not a discrete device
  - Daily injection of long acting insulin still required
  - Physician/patient conversion

Transdermal Insulin Delivery



Valeritas' V-Go™

- Micro-needle based technology
- Small disposable waterproof device
- Changed daily - rotate site
- Delivers continuous basal dose
- On demand bolus dosing
- FDA approved device (510(k))
- Type II diabetic market