



# ***WORKSHOP: ROLE OF SOLID FORMS IN LIFE CYCLE MANAGEMENT***

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# SCHEDULE

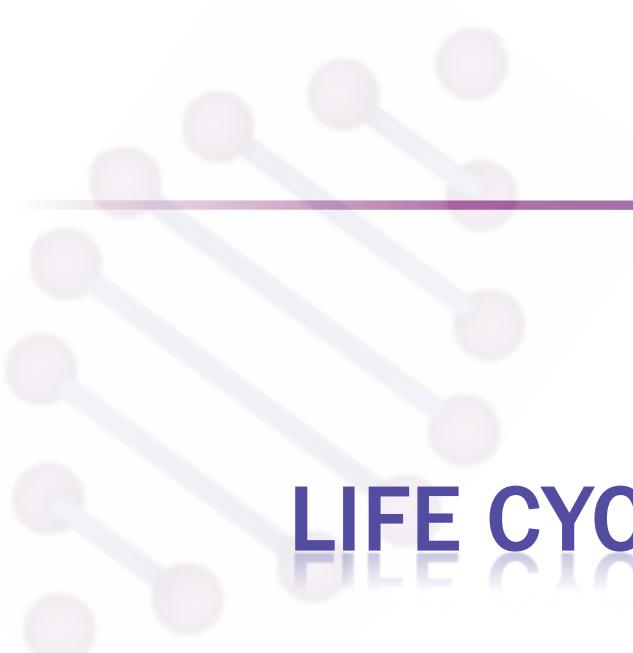
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8:45 – 9:45 Solid Forms

9:45 -10:00 Break

**10:00 -11:00 Life Cycle Management**

11:00-11:30 Questions and Discussion



# LIFE CYCLE MANAGEMENT

Part 2: Solid Form Selection and Drug Delivery Options

# OUTLINE

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- What is LCM
  - and what it is not....
- The Current State of Our Industry
  - And why integration of LCM in the development process is becoming increasingly important
- LCM Strategies
  - LCM opportunities and risks
  - Reformulation, form selection, and drug delivery
  - Timing for LCM activities
- LCM Case Studies
  - Solid forms and drug delivery

# LIFE CYCLE MANAGEMENT PROVIDES.....

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- A benefit to patients by:
  - Increasing compliance resulting in a reduction of return visits to clinics, doctor's offices, emergency rooms, and hospitals and therefore achieving improved outcomes
  - Providing easier access to the product by transitioning products to OTC status when sufficient safety data are available
  - Reducing side effects by reformulating the product/form for a different route of administration and delivery profile while maintaining efficacy and therefore achieving increased compliance and improved outcomes
    - Nanotechnology, pulmonary, transdermal, oral controlled release, PEGylation, etc.
    - Polymorphs, salts, cocrystals, amorphous dispersions
    - Changing BCS 2 compounds to BCS 1 and BCS 4 compounds to BCS 3 through increase in dissolution rate due to form selection

## LIFE CYCLE MANAGEMENT IS NOT.....

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- A means to continue to monopolize on a product without providing patient benefit
- A means to deliver an existing drug that does not provide a value to the patient when compared to other formulations of the drug
- .....

# TERMS USED TO DESCRIBE LIFE CYCLE MANAGEMENT

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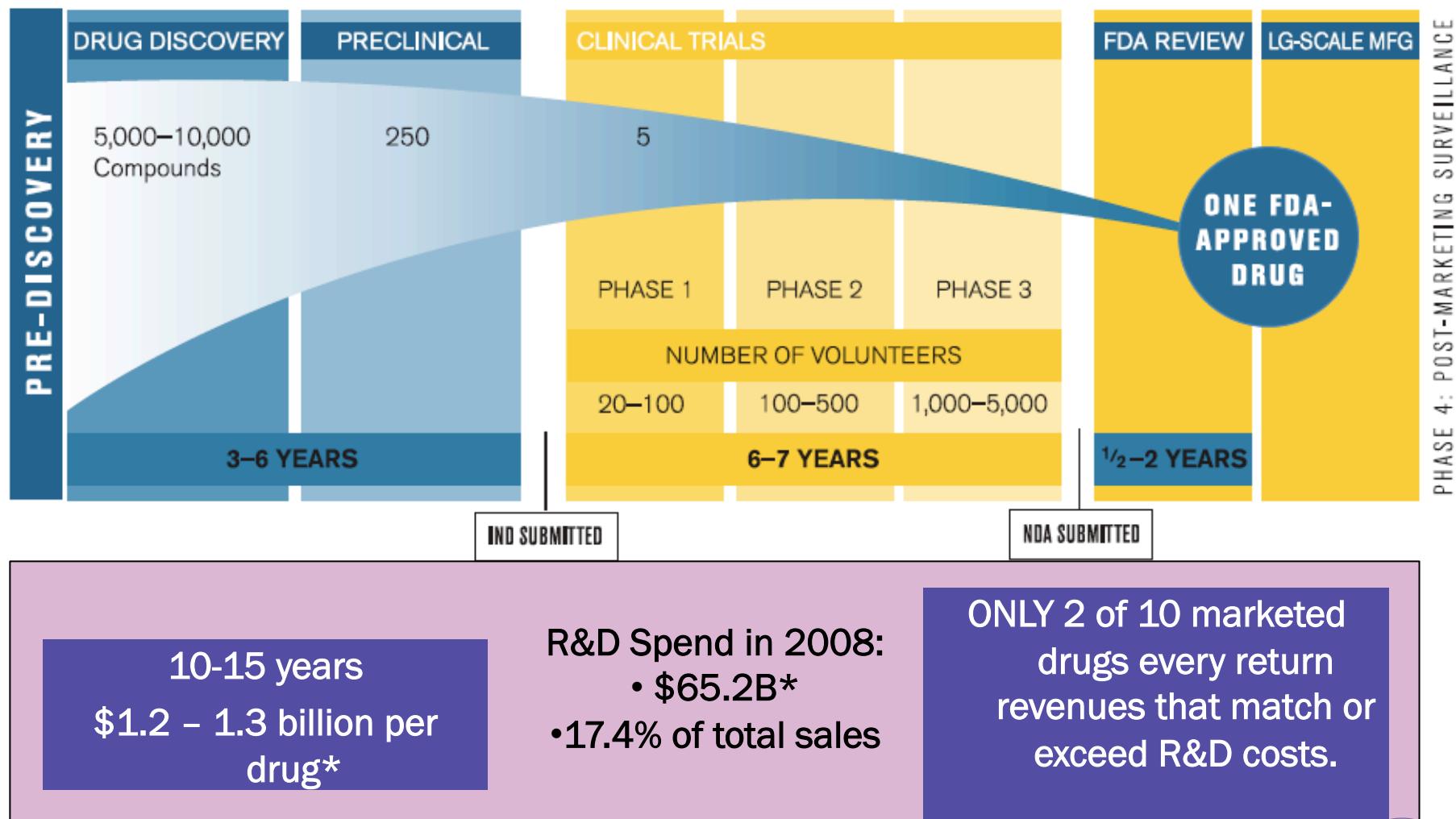
- Line Extensions
- Product Portfolio Management
- Patent Extensions
- Directed Molecular Evolution
- Incremental Innovation
- Live License Extensions



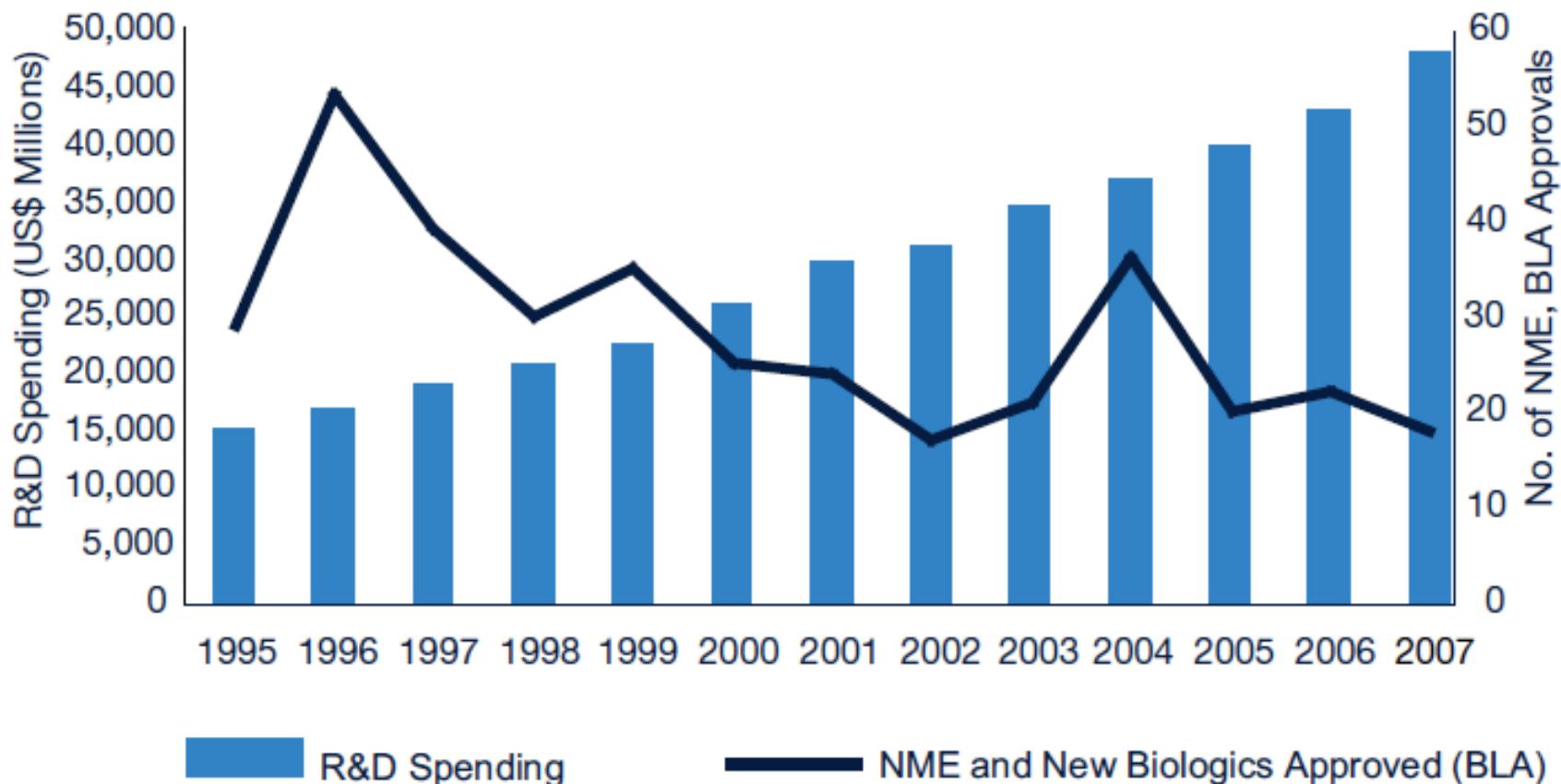
# THE CURRENT STATE OF THE PHARMACEUTICAL INDUSTRY

A place for LCM in the changing paradigm

# THE COSTLY, COMPLEX, AND LONG INNOVATOR PRODUCT DEVELOPMENT CYCLE



# INCREASING DEVELOPMENT COSTS HAVE NOT RESULTED IN INCREASED PRODUCTIVITY

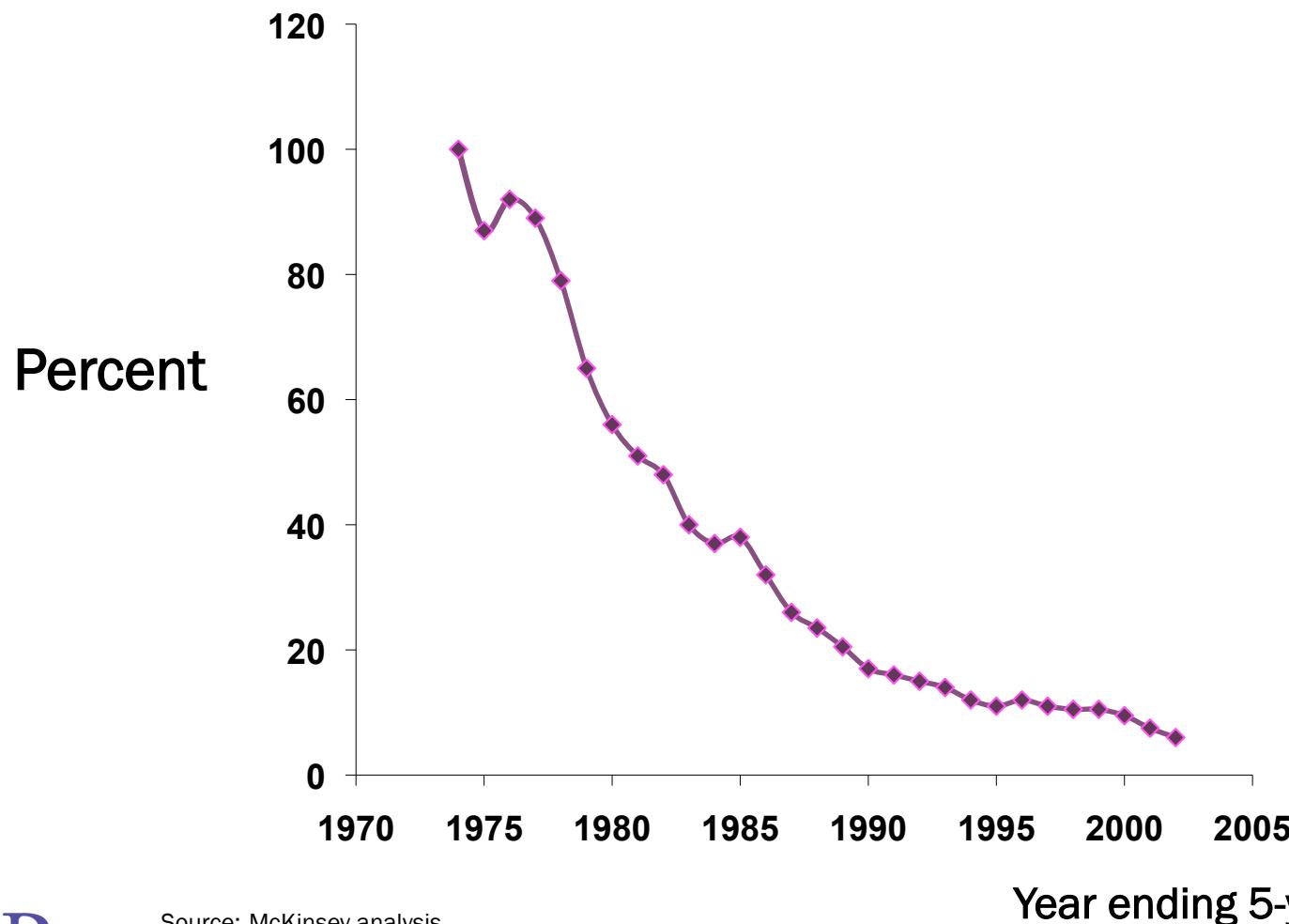


Source: FDA CDER, PhRMA and PricewaterhouseCoopers analysis

Note: Data on R&D spending for non-PhRMA companies are not included here.

# THE INNOVATION DEFICIT: CHALLENGING THERAPIES

NME output per R&D spend (normalized to 1970-1975)

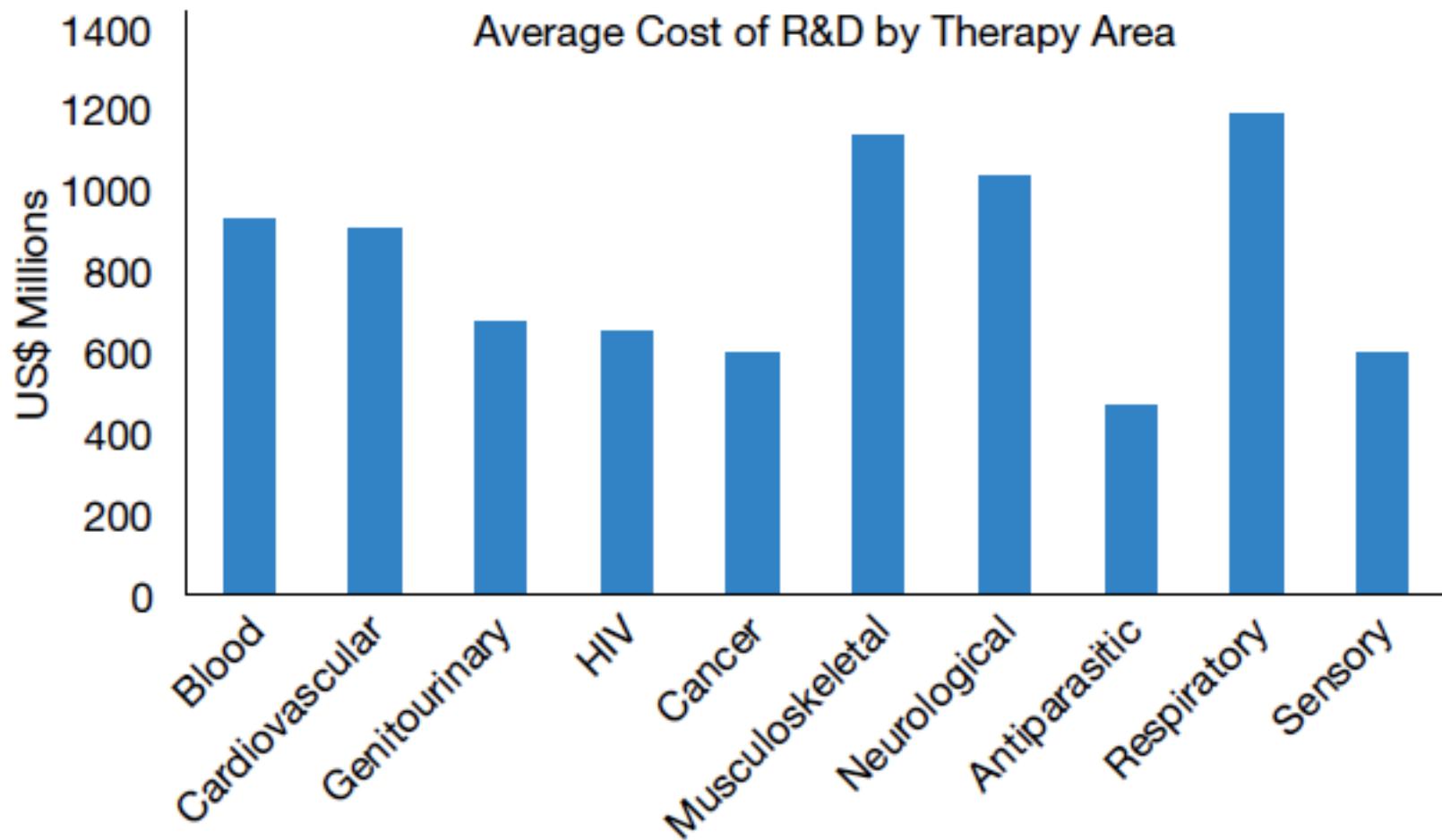


Source: McKinsey analysis

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Year ending 5-year frame

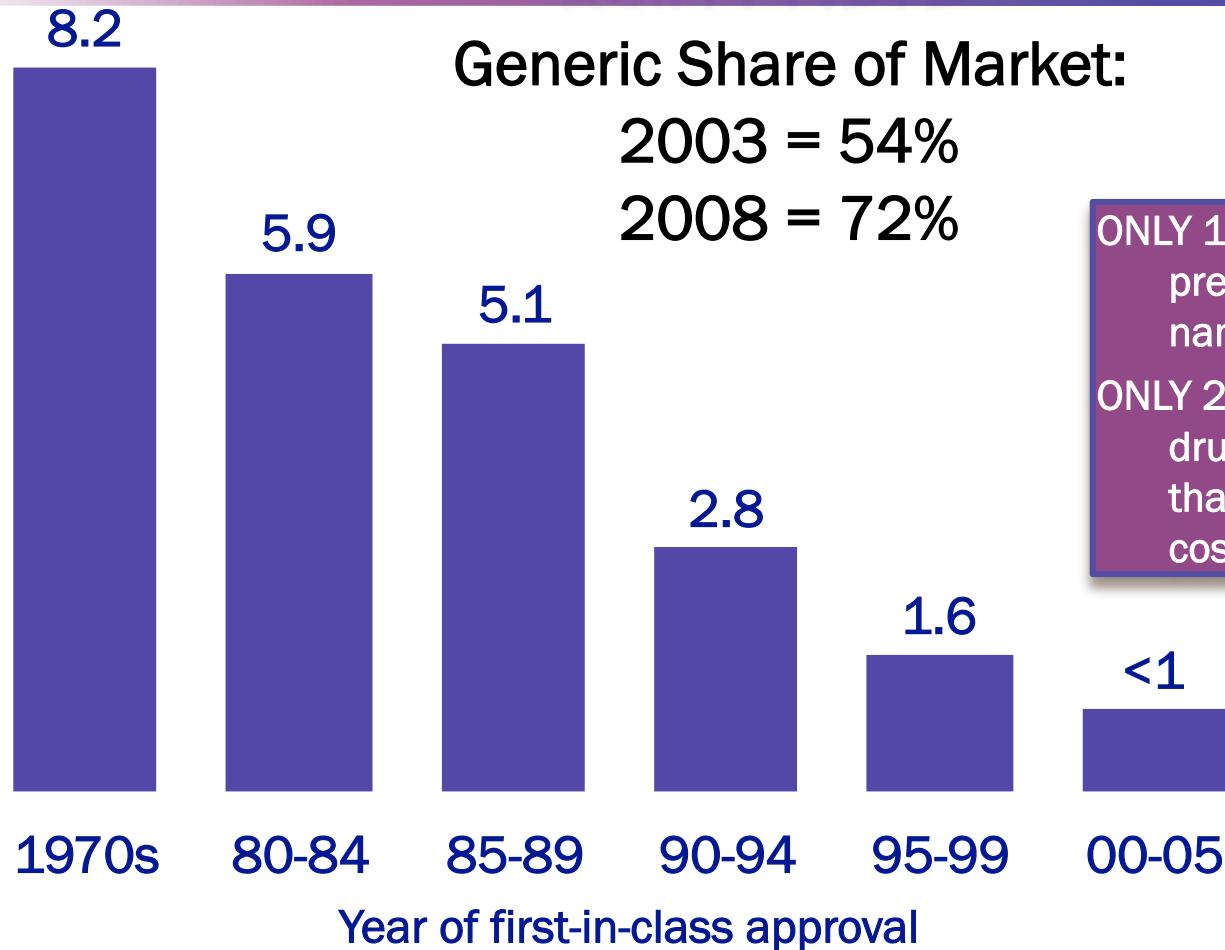
# R&D COSTS BY THERAPEUTIC AREA



Source: Christopher P. Adams & Van V. Brantner, "Spending on New Drug Development"

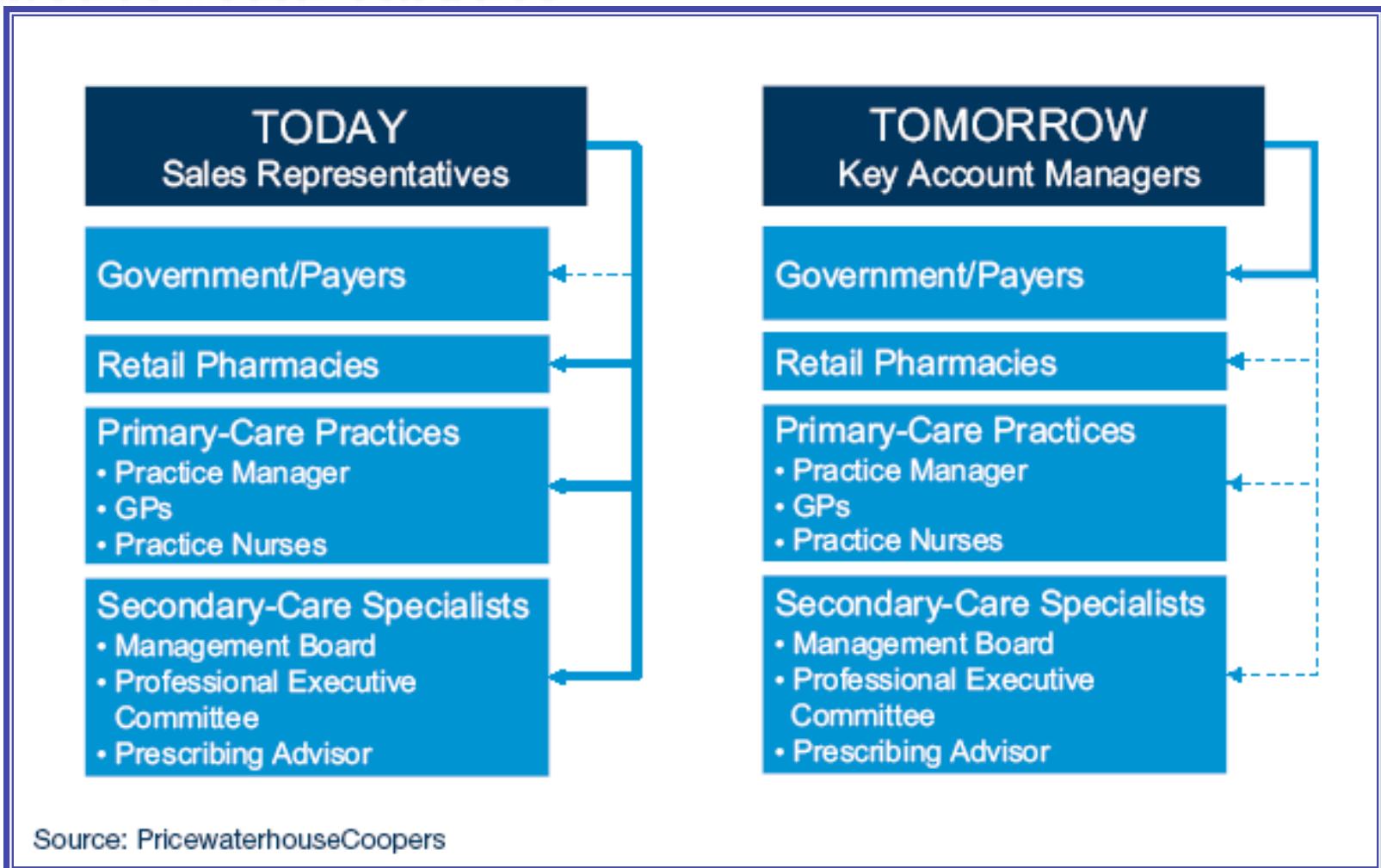
Pharma 2020: Virtual R&D

# INNOVATORS HAVE LESS TIME TO RECOUP THEIR R&D COSTS



ONLY 11 of the top 50 most prescribed drugs are brand name products.  
ONLY 2 out of 10 marketed drugs ever return revenues that match or exceed R&D costs.

# MARKETING APPROACHES ARE CHANGING – ENTER “THE PAYER”



# RESULTING IN JOB LOSSES.....

Company	Announced Job Cuts
Pfizer	10,000
AstraZeneca	7,600
Merck & Co.	7,200
Bayer	6,000
Schering-Plough	5,500
Johnson & Johnson	5,000
GlaxoSmithKline	5,000
Amgen	2,600
Novartis	2,500
Wyeth	1,200
sanofi-aventis	700
Total	53,300

Pharma 2020:  
Marketing the  
Future

Source: PricewaterhouseCoopers

# PHARMA INDUSTRY CHALLENGES ARE NUMEROUS AND ARE STIFLING CREATIVITY AND PRODUCTIVITY

- Increasing R&D costs and reduced productivity
- Challenging product portfolios and pipelines
- The need to form multiple business alliances
- Inability to recoup R&D costs for innovator products
- Aggressive generic competition
- Pricing and marketing pressures from insurance companies



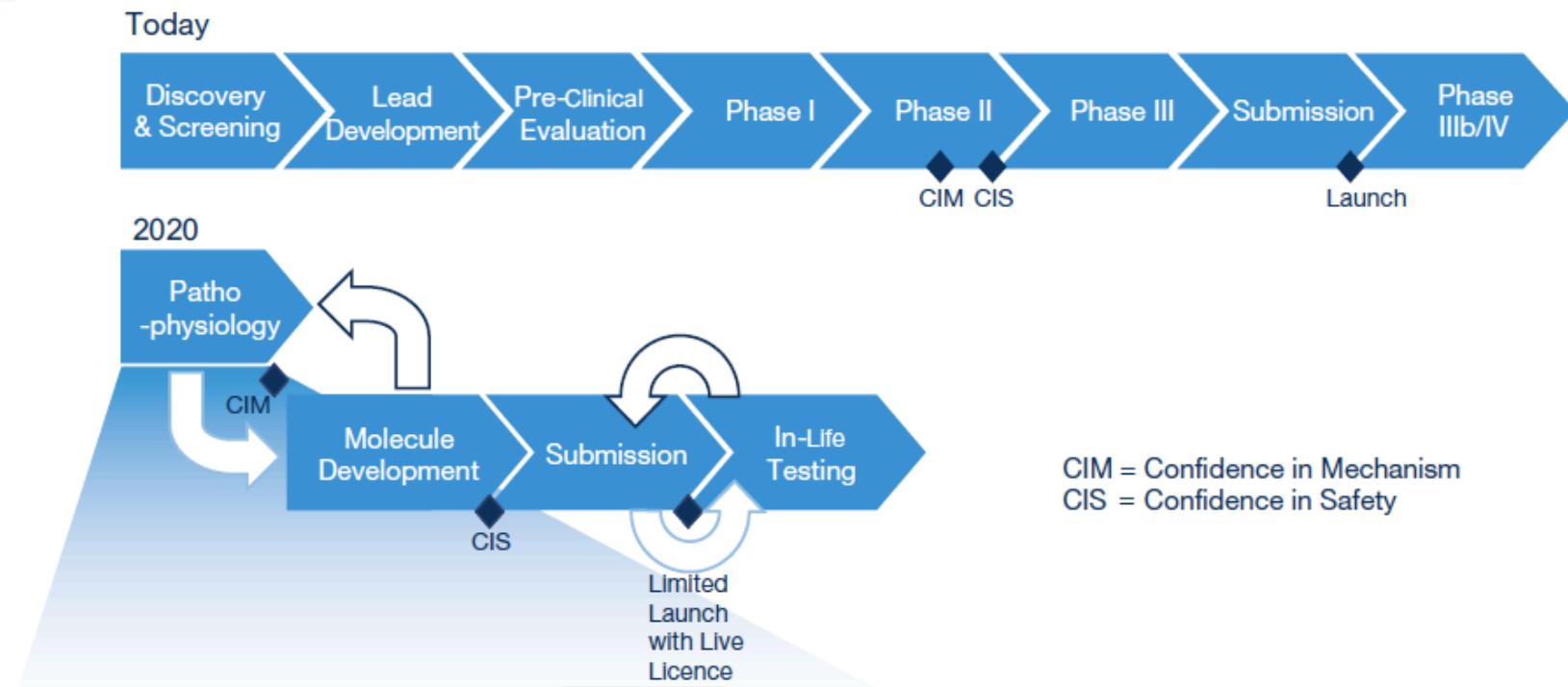


# INCREASING PRODUCTIVITY WITH LCM

## Strategies and Opportunities:

- Cost Containment
- Increased Efficiency
- Increased Innovation
- Live Licensing

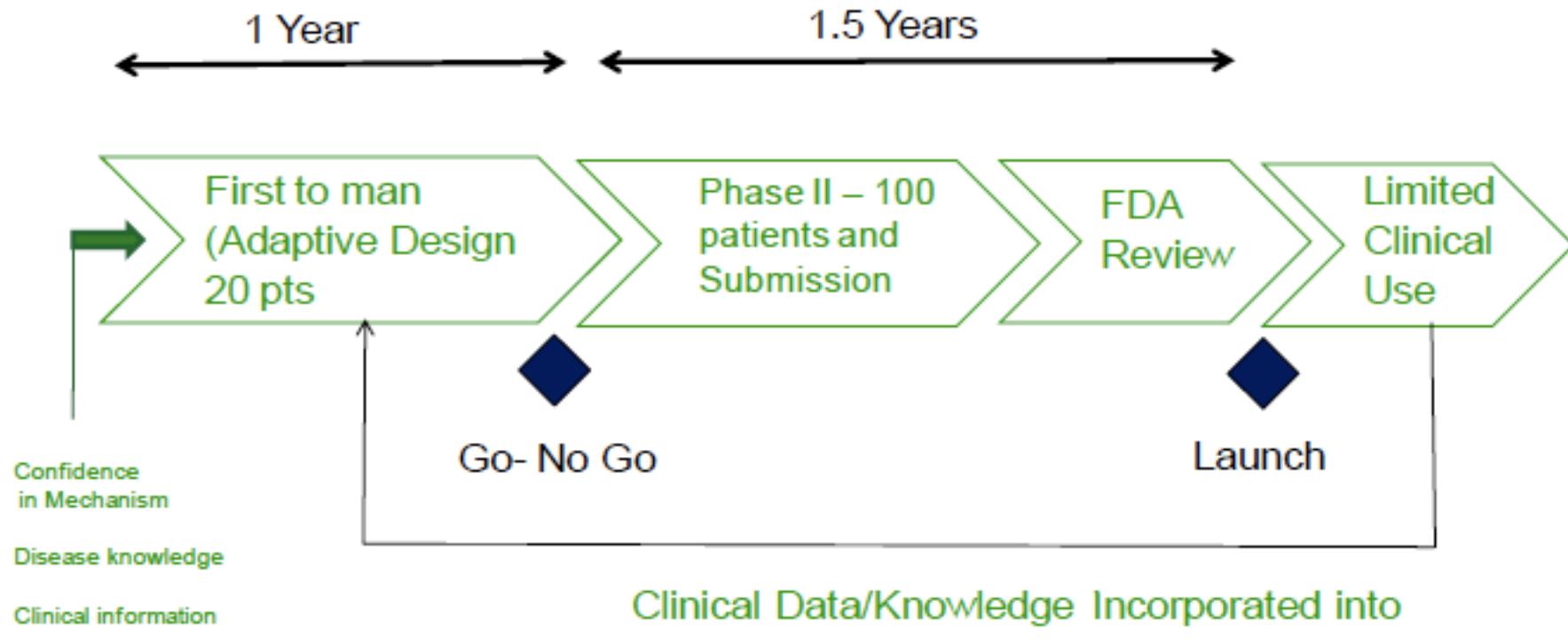
# PHARMA 2020 PRODUCT DEVELOPMENT STRATEGY



## Pharma 2020's Vision for Future Product Development:

1. Initiate molecule development only when Confident in Mechanism
2. Submit regulatory documentation once CIM and Confidence in Safety (CIS) is confirmed
3. Limited launch in small patient population
4. Pricing determined and launch population broadened only after efficacy is demonstrated in larger groups

# MODIFIED PROGRESSIVE STRATEGY



AND/OR USED FOR LCM PRODUCT DEVELOPMENT OPPORTUNITIES

# LCM STRATEGIES FOR EXISTING DRUGS

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- Incremental Improvements:
  - New Delivery Methods:
    - Offers patients different ways to take their existing medicines
  - New Indications for Old Drugs:
    - Offers patients new treatment options at lower overall development costs
  - Combination Products:
    - Offers patients simplicity and increases compliance

# LCM STRATEGIES FOR EXISTING DRUGS

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- Reformulation and drug delivery technologies:
  - Leverage existing safety profile for existing product
  - Relatively low cost to assess technical feasibility
  - High probability of success versus looking for new molecule/indication
  - Short development and approval time (particularly if bioequivalent)



# WHERE ARE THE OPPORTUNITIES?

Adding Value to the Patient

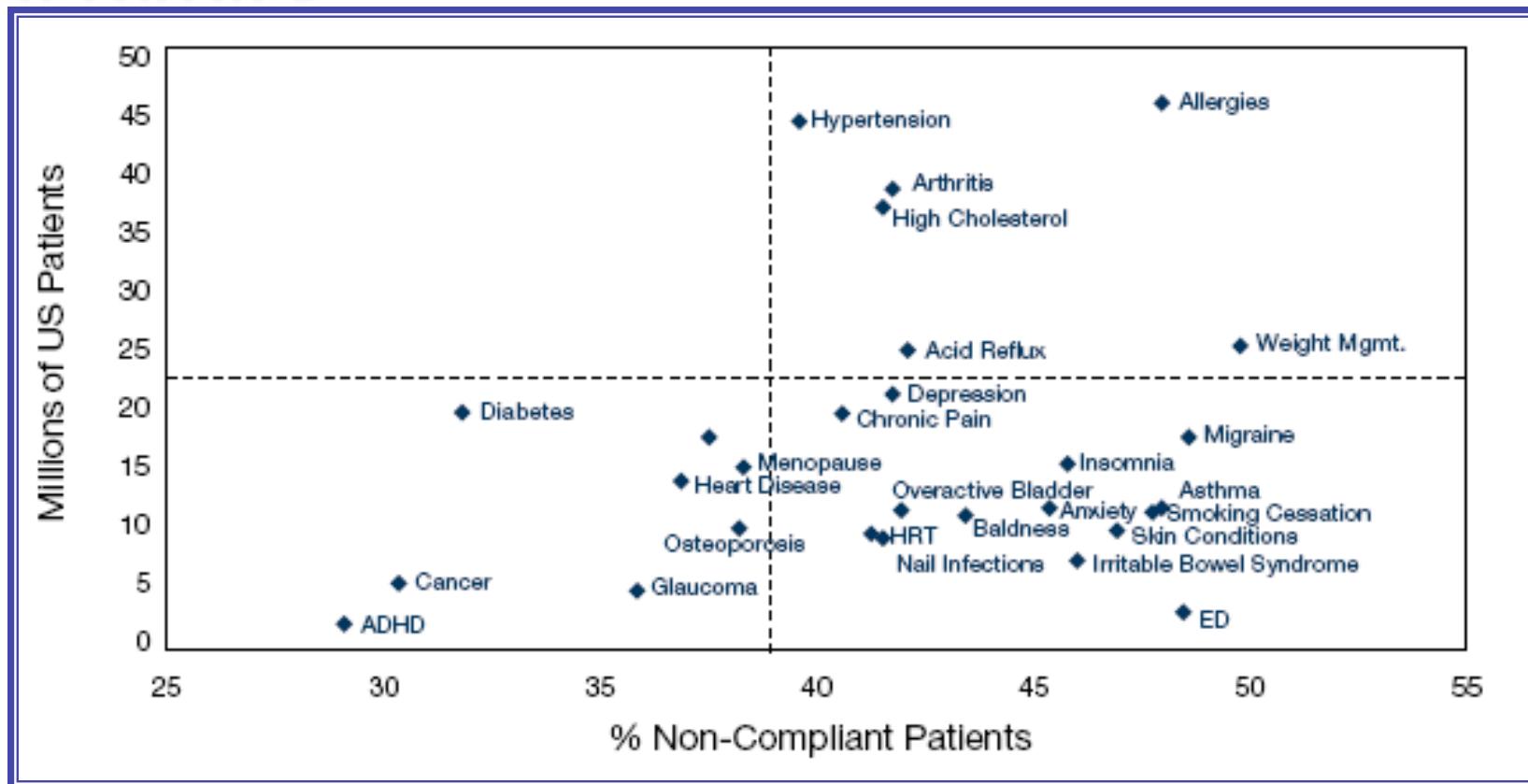
# OPPORTUNITY TO INCREASE EFFICACY OF EXISTING DRUGS

	Efficacy rate (%)
Alzheimer's:	30
Analgesics (Cox-2):	80
Asthma:	60
Cardiac Arrhythmias:	60
Depression (SSRI):	62
Diabetes:	57
Hepatitis C (HCV):	47
Incontinence:	40
Migraine (acute):	52
Migraine (prophylaxis)	50
Oncology:	25
Rheumatoid arthritis	50
Schizophrenia:	60

**“Vast majority of drugs (>90%) only work on 30-50% of patients.”\***

\*Dr. Allen Roses, VP Genetics, GSK, Dec 2003  
<http://www.independent.co.uk/news/science/glaxo-chief-our-drugs-do-not-work-on-most-patients-575942.html>

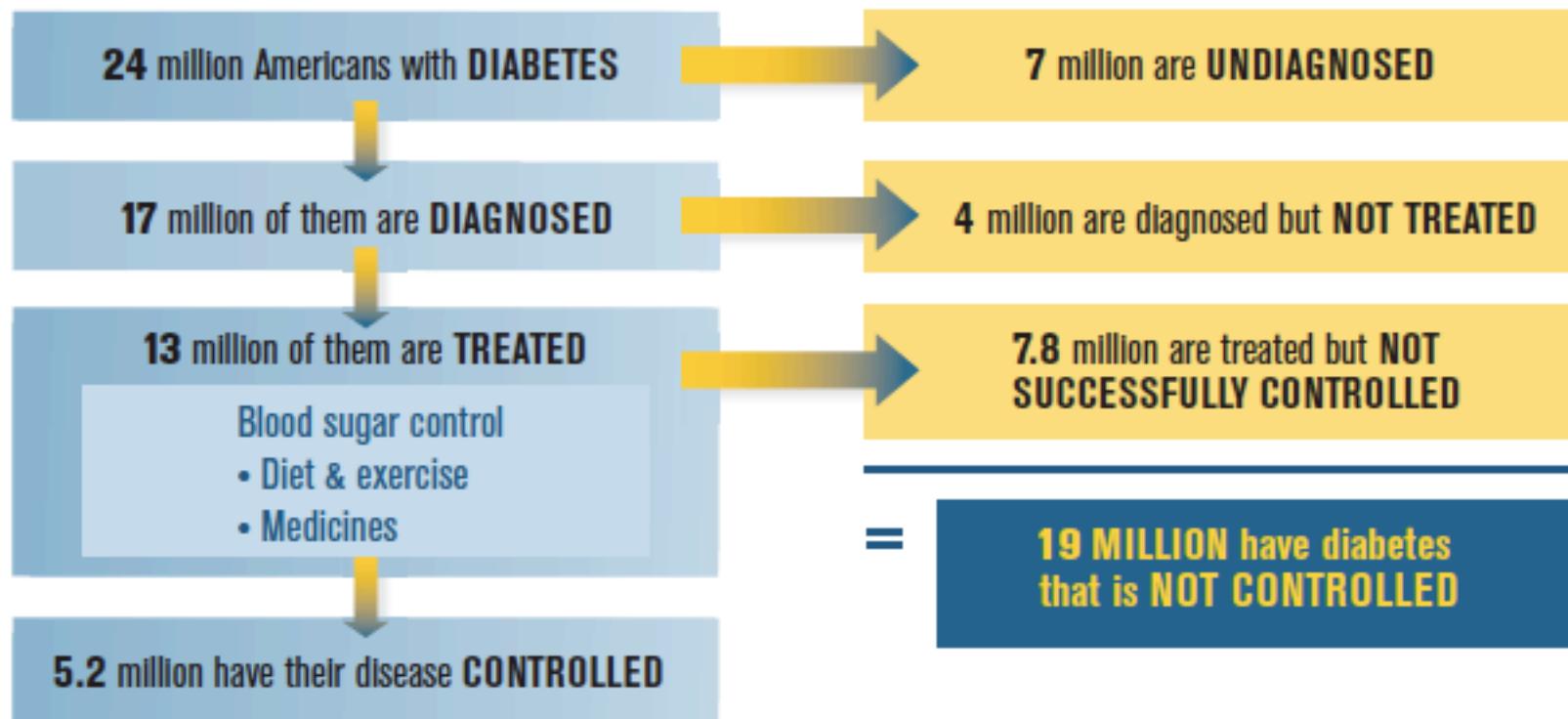
# NON-COMPLIANCE RATES ARE HIGH FOR MANY THERAPIES



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

# UNTREATED OR POORLY CONTROLLED CHRONIC DISEASES

## Diabetes: An Example of the Problems of Underdiagnosis and Undertreatment



Note: Figures may not sum due to rounding.

SOURCES: PhRMA analysis of data from National Health and Nutrition Examination Survey, 2003–2004; American Diabetes Association, "Diabetes Statistics," [www.diabetes.org/diabetes-statistics.jsp](http://www.diabetes.org/diabetes-statistics.jsp) (accessed 6 February 2009).

# MULTIPLE OPTIONS FOR DIABETICS: INSULIN DRUG DELIVERY PLATFORMS



Syringes



Pens



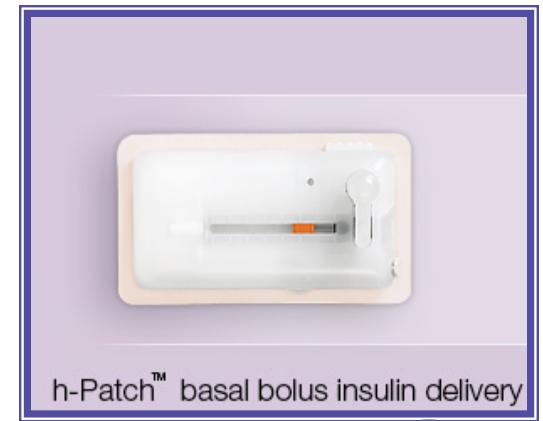
Pulmonary DPI



Needle Free  
Injectors



Pumps



h-Patch™ basal bolus insulin delivery

Transdermal





# DRUG

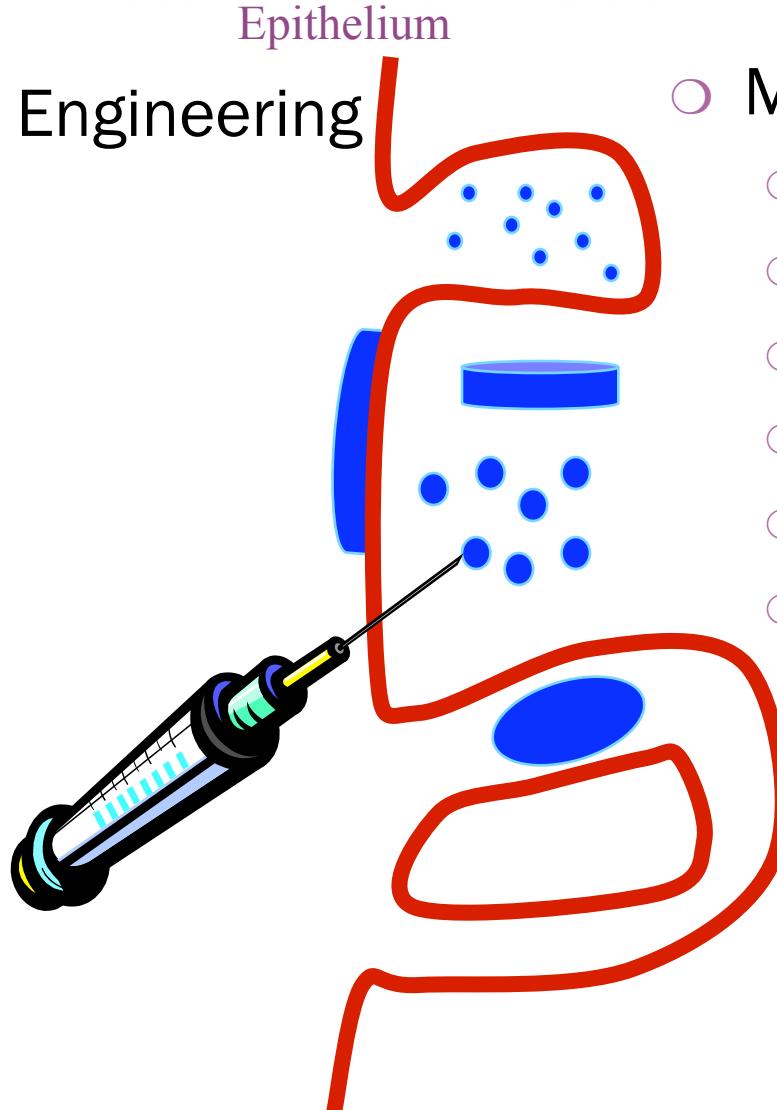


DELIVERY  
ΔΕΓΙΛΕΥΣ

What if you need technology for the LCM product?

# DRUG DELIVERY AND LCM

- Dosage Form Engineering
  - Solution
  - Particle
  - Device
- Molecule Engineering
  - Medicinal chemistry
  - Salt form
  - Polymorph
  - Amorphous
  - Amorphous dispersions
  - Cocrystal



# MATCHING FORM AND DRUG DELIVERY TECHNOLOGY: CONSIDERATIONS

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- Dissolution rate requirements (slow or fast) and appropriate crystalline and/or salt form selection
- Salt selection and form for specific route of administration
- Stability of form in product/device (e.g., glass stabilization for amorphous dispersions)
- Toxicology requirements associated with salt/ form and route of administration

# DRUG DELIVERY TECHNOLOGIES

<b>Delivery Mechanism</b>	1970s	1980s	1990s	2000s	2010s
Diffusion-based (depots and passive patches)		★ Ocusert® (1974) ★ Progestasert® (1976) ★ D-TRANS™ (1981)			
Osmotic-based (tablets and implants)		★ Alzet® (1977) ★ OROS® (1983) ★ RUTS® (1989)			★ DUROS™ (2000)
Drug Eluting Stents (coated implants)				★ Cypher® (2003)	
Iontophoresis (active patches)				★ E-TRANS™ (2006)	
Pulmonary Inhalation (systemic delivery)				★ Exubera (2006)	



# FINDING THE GAP: DEFINING THE IMPROVED PRODUCT

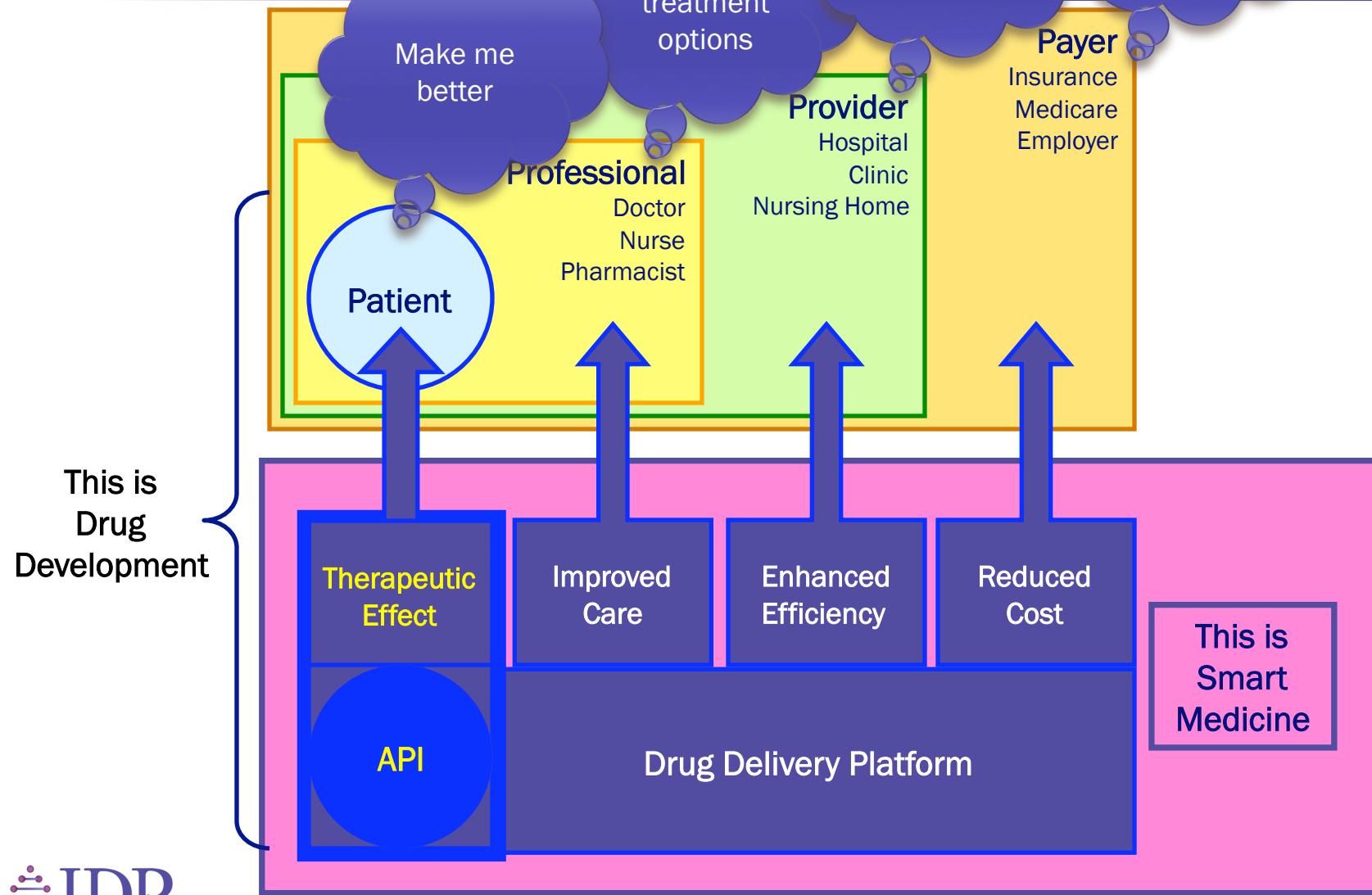
Understanding Your Key Stakeholders, Risks, and Building the  
Target Product Profile

# EVOLUTION: FROM DRUGS TO “SMART MEDICINE”

*...Connecting the Dots...*

TO

Have patients go home sooner  
Reduce frequency of office and ER visits



# BALANCING THE RISKS OF LCM

Additional Investment \$\$\$

Patents

People

Market Research

New Molecules vs. Incremental Dev.

ROI expectations – reimbursement

Reduced Side Effects

Expanding Indications

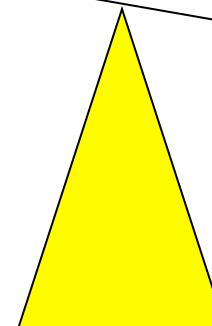
Expanding delivery options

Reimbursement

Commercial Value (NPV, ROI, etc)

RISK

BENEFIT

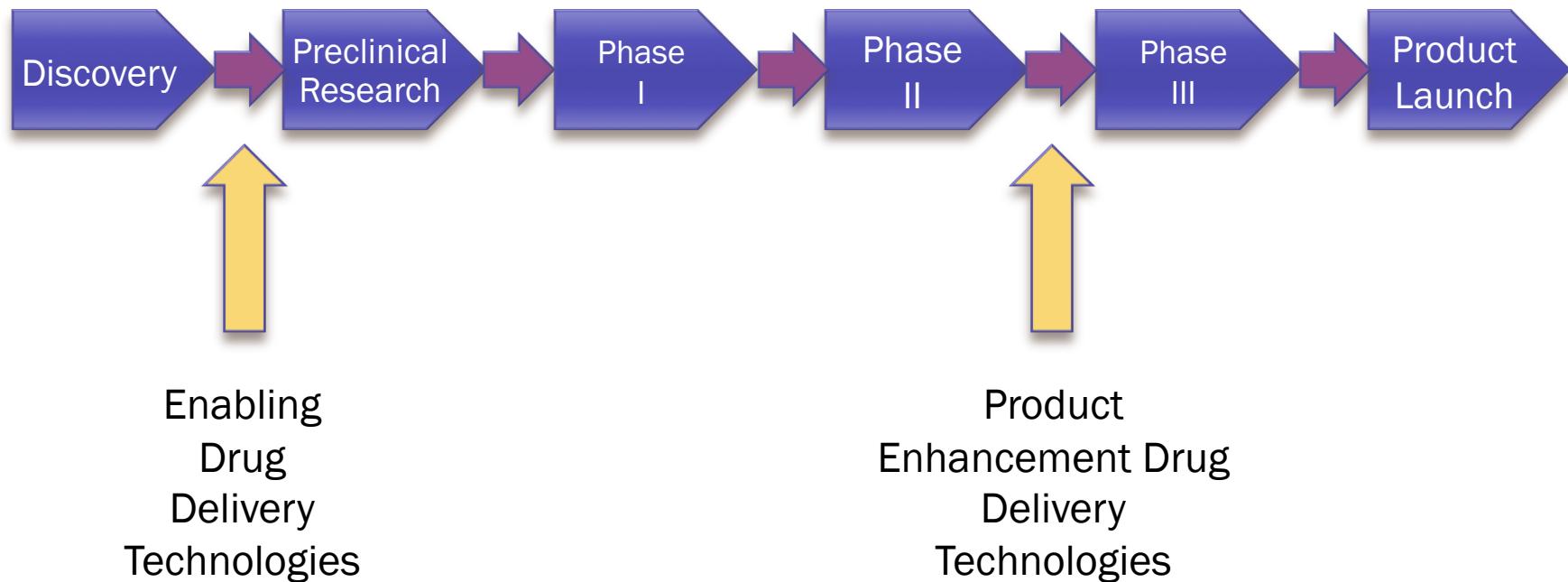




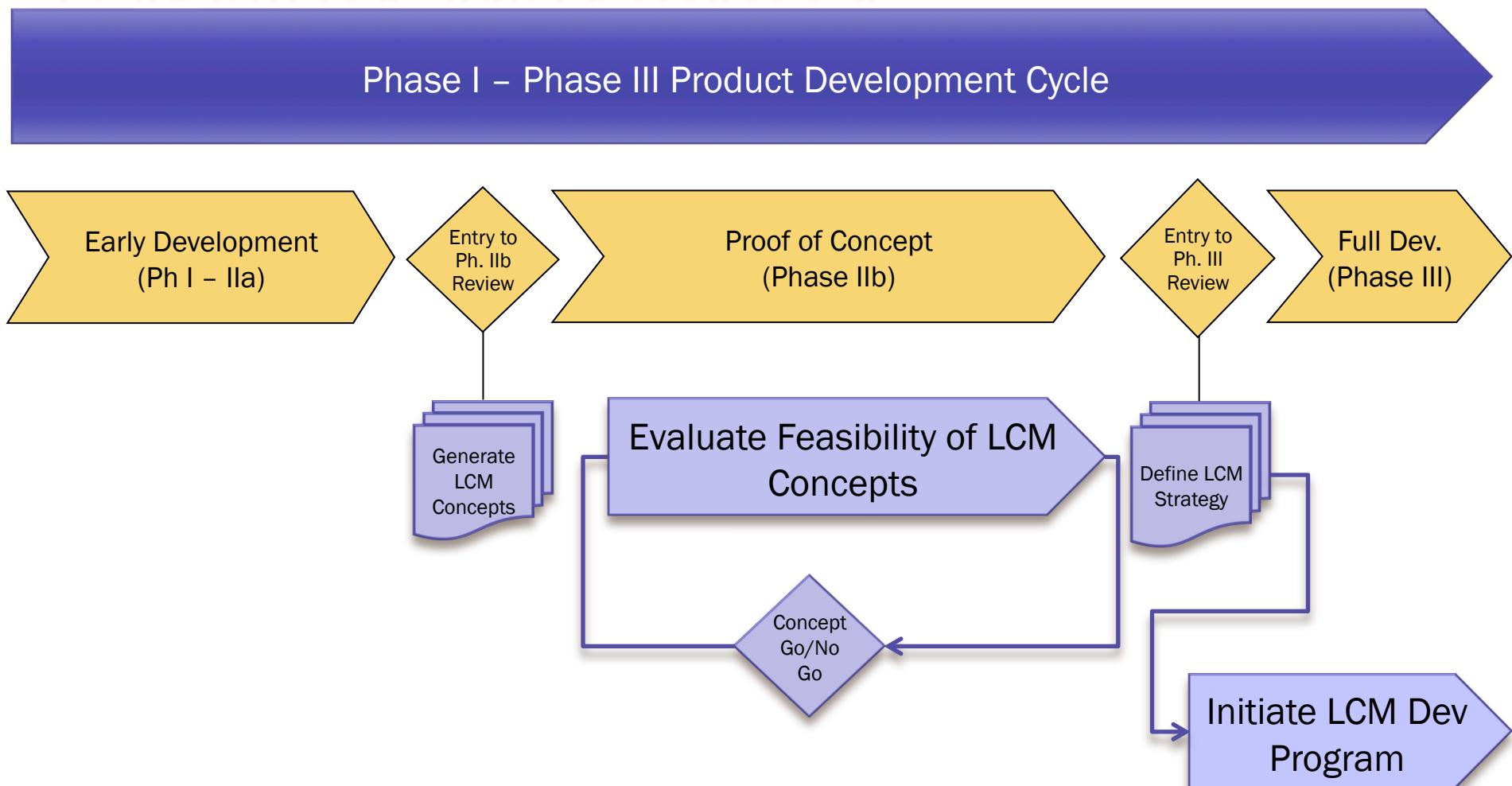
# INITIATION AND INTEGRATION OF LCM INTO PRODUCT DEVELOPMENT

LCM is an opportunity for incremental improvement throughout the product life cycle

# INSERTING DRUG DELIVERY LCM INTO THE PRODUCT DEVELOPMENT PROCESS

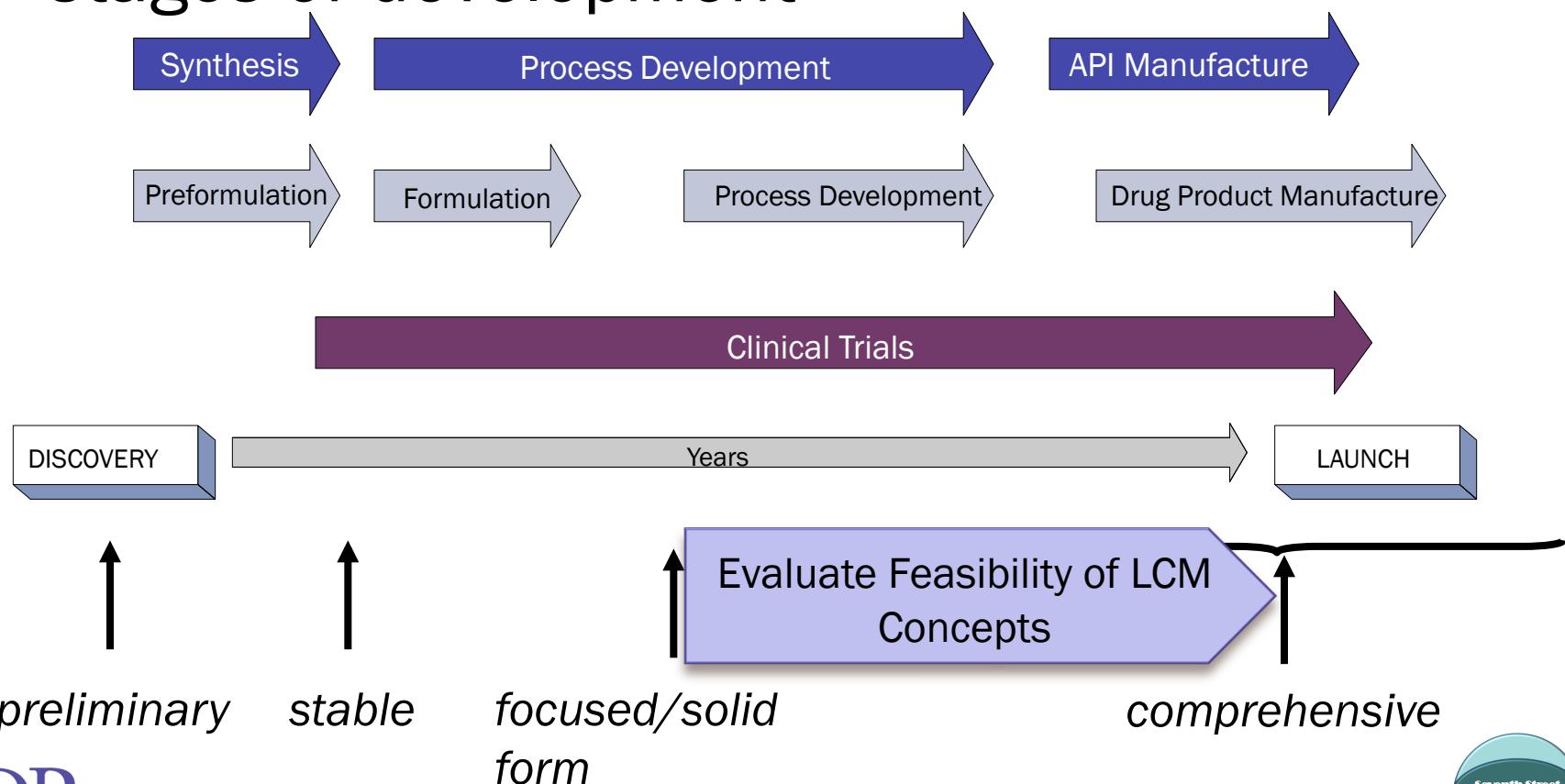


# INCORPORATING LCM INTO R&D – CONCEPTS, FEASIBILITY, AND STRATEGY



# POLYMORPH AND LCM SCREENING STUDIES

Different screens can be performed at various stages of development



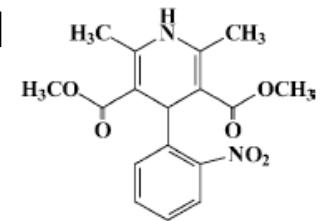
# LIFE CYCLE MANAGEMENT EXAMPLES

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- Class development for better outcomes:
  - Nifedipine: better safety profile due to Cmax reduction and controlled release
  - Oxybutynin: lower side effects due to drug delivery absorption region targeting
  - Ritonavir: improved product stability through form change
- New delivery methods for better compliance:
  - Oxybutynin: patient choices due to multiple delivery platforms
- New indications for approved drugs:
  - Metoprolol: additional indication due to delivery profile
- Combination products for simplicity and better compliance:
  - Kaletra: single tablet by combination of ritonavir and liponavir

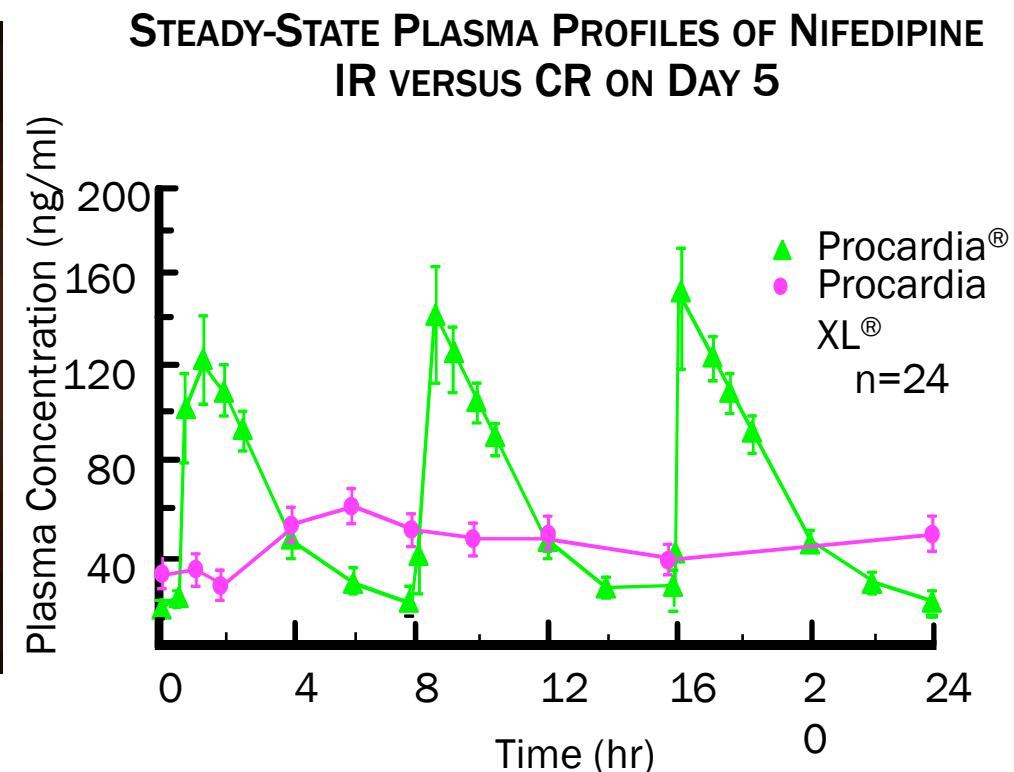
# NIFEDIPINE: LOOKING FOR BETTER PATIENT OUTCOMES

- Nifedipine, a calcium channel blocker, was originally marketed as an IR product by Pfizer in 1982 as Procardia for the treatment of angina
- The drug substance is a yellow crystalline BCS 2 compound with low aqueous solubility of 3 – 13 ug/mL and low and irregular BA
- The melting point of nifedipine is 172 – 174 °C and a Tg of approximately 42 °C
- The half life of the drug in plasma is approx. 2 hours
- Common side effects included: headache, flushing, dizziness, and palpitations
- Since the introduction of the drug, solid dispersions, micronization, cocrystal formation, and drug delivery approaches have been studied with the aim of enhancing drug dissolution, increasing absorption, and reducing side effects

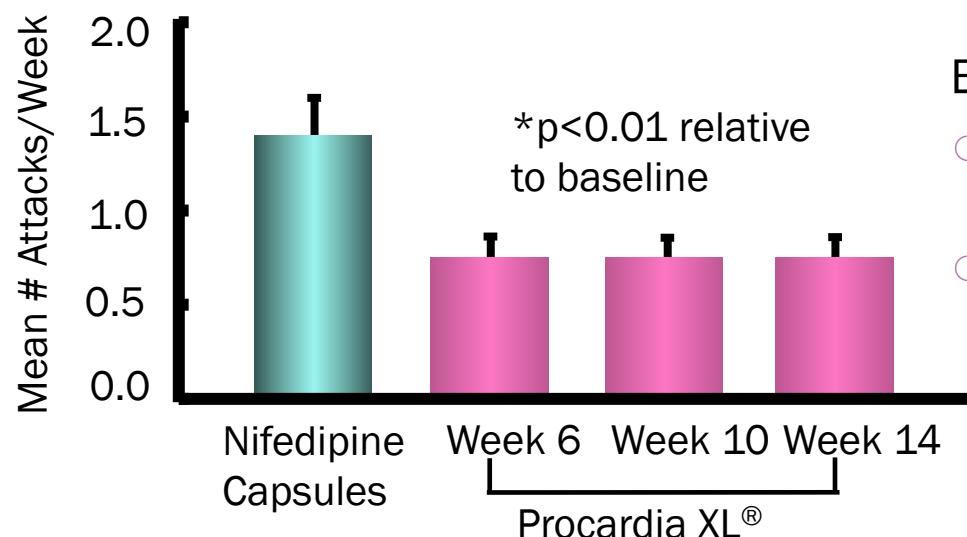


# PROCARDIA LCM USING CR DRUG DELIVERY

- Initial goal was to reduce frequency of dosing for patients
- OROS® osmotic-driven nifedipine oral CR formulation developed
- Drug layer formulation contained micronized nifedipine and Polyox and HPMC which formed a dispersion upon activation of the delivery system
- Three dosage strengths were developed - 30, 60, and 90 mg
- ALZA OROS® Push-Pull System
- Indication: angina while looking for reduced side effects compared to IR form

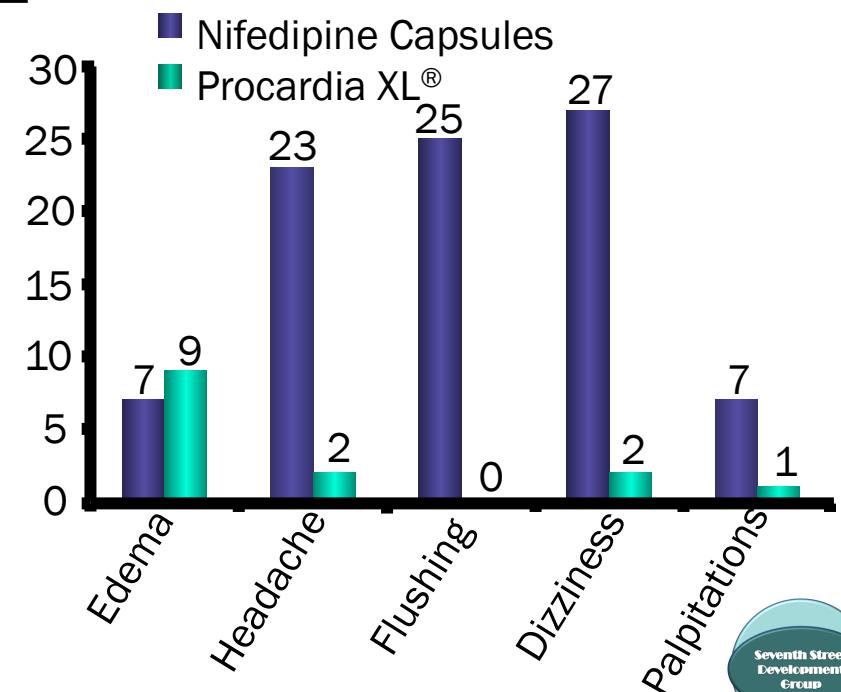


## BETTER OUTCOMES OBSERVED FOR PATIENTS TREATED WITH CR ONCE DAILY FORMULATION COMPARED TO IR PRODUCT



Better Outcome:

- Reduction of side effects observed using CR formulation of nifedipine
- Relative BA of 90% compared to IR

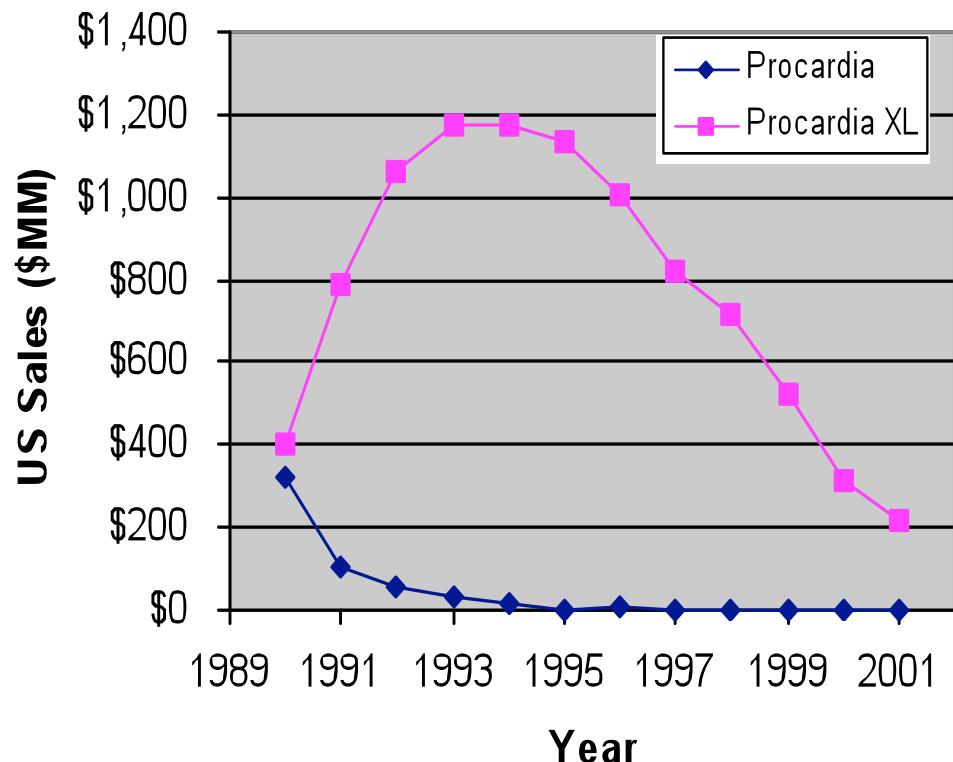


Better Outcome:

- Reduction of number of angina attacks using CR formulation of nifedipine

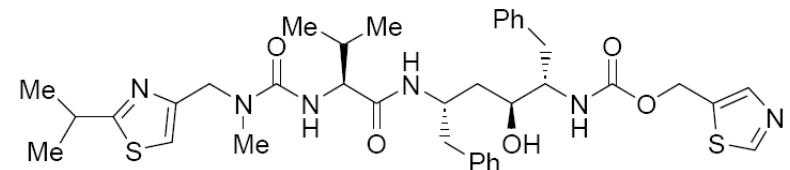
From: Vetrovec et al, Am. J. Med. (1987)

## SUCCESSFUL LCM FOR THE PROCARDIA FRANCHISE



- Procardia XL launched in 1989 by Pfizer, 7 years after Procardia.
- Cardiologists recommended a switch to long acting  $\text{Ca}^{2+}$  channel blockers for patients with ischemic heart disease due to better safety profiles
  - New indication for old drug!
- The product generated almost \$10B in additional revenue and cannibalized Procardia sales
- Revenues dropped in the mid-90s due to entry of generics and other long acting  $\text{Ca}^{2+}$  channel blockers

# RITONAVIR CASE STUDY: ENHANCED STABILITY



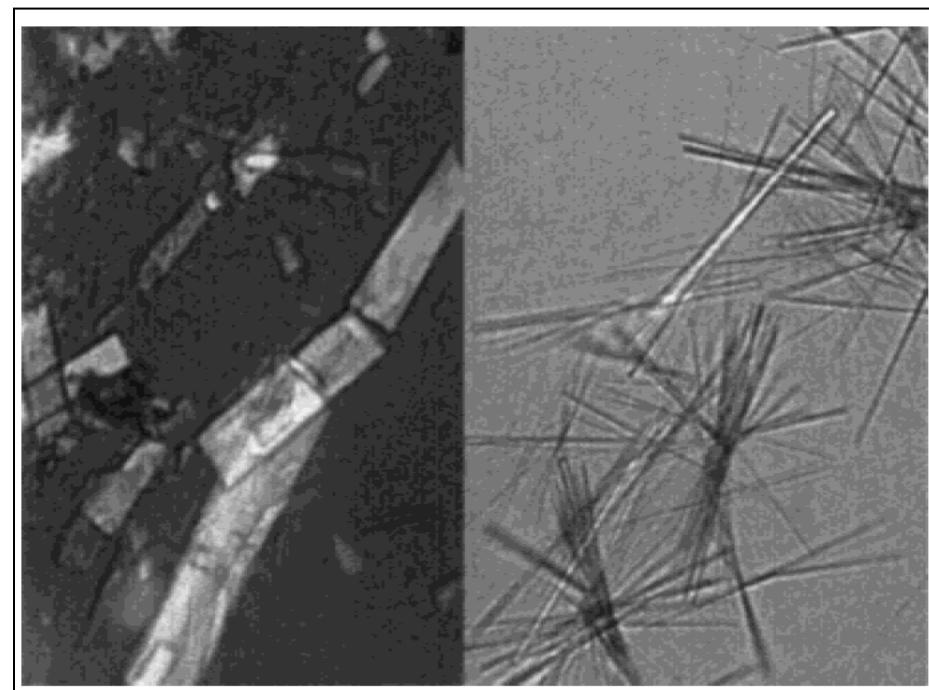
## ○ Ritonavir

- Novel protease inhibitor used to treat AIDS
- Discovered in 1992
- Marketed in 1996 as Norvir by Abbott
  - oral liquid and Norvir semi-solid capsules
- Ritanovir is a BCS 4 drug and not bioavailable from the solid state and not water soluble, so both formulations contained ritonavir in ethanol/water-based solutions
- Only one crystal form was identified during development
- 240 lots of Norvir capsules were produced without stability problems

Bauer et al. *Pharm. Res.* 2001, 18, 859-866; Goho. *Science News*, 2004, 166, 122  
 Chemburkar et al, *Organic Process Research and Development* 2000, 4, 413

# NEW POLYMORPH IDENTIFIED IN MARKETED PRODUCT

- Polymorph appearance
  - 1998 Norvir soft gelatin capsules failed dissolution
  - A new polymorph, Form II, was identified in the capsules

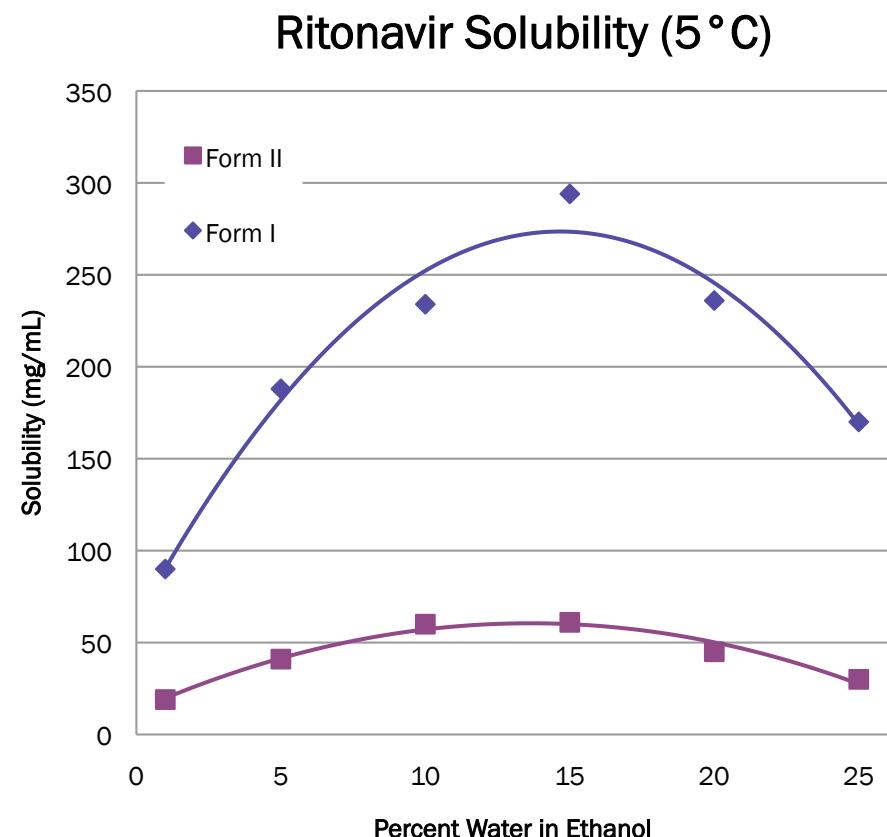


Form I

Form II

# SOLUBILITY DIFFERENCES NOTED

- Form II was found to be significantly less soluble than Form I
- Ethanol/water solutions for the capsules were not saturated with respect to Form I, but were 400% supersaturated with Form II
- Oral solutions could no longer be stored at 2-8°C without risk of crystallization



## COULD NO LONGER MAKE FORM I PRODUCT

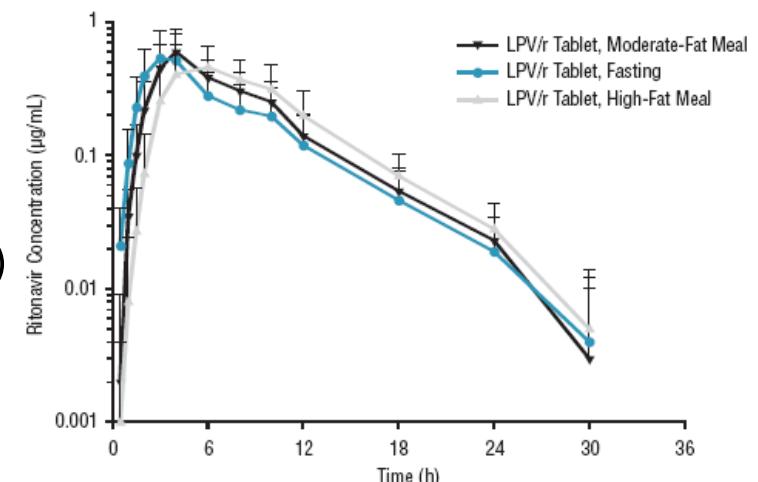
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- Presence of Form II made the original formulation unmanufacturable
- Crystallization of Form II resulted in limited inventory and seriously threatened the supply of the product
- Product had to be removed from the market
- New formulation developed using Form II
- Estimated losses:
  - Hundreds of millions spent trying to recover Form I
  - \$250 million in lost sales

# IMPROVED COMBINATION PRODUCT WITH NEW FORM LAUNCHED

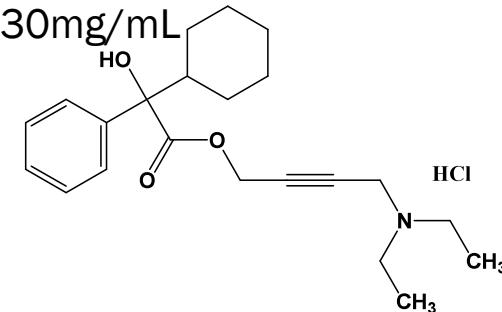
- Kaletra

- Ritonavir and lopinavir combination product
- Oral soft gelatin capsule and solution introduced in 2000
  - Both refrigerated storage
- Improved melt extrusion-based tablet formulation introduced in 2005
  - amorphous dispersion produced
  - based on melt extrusion technology
  - patients take fewer tablets (from 6 to 4)
  - needs no refrigeration
  - no food effect



# OXYBUTYNIN CHLORIDE: BETTER OUTCOMES 25+ YEARS OF LCM

- Oxybutynin IR (Ditropan), an anticholinergic agent and smooth muscle relaxant, was launched by Dow Marion Roussel in 1975 for the treatment of overactive bladder and symptoms of urge urinary incontinence, urgency, and frequency.
- Properties of oxybutynin:
  - Short half-life (2-5 hours after IV administration) resulting in BID or TID dosing for the IR product
  - Maximum dose of 20mg/day
  - Water soluble hydrochloride salt, estimated at greater than 30mg/mL
  - Chiral molecule
    - R isomer associated with anticholinergic activity
    - No stereoselectivity for antispasmodic or local anesthetic actions
  - Metabolized by CYP450-3A4
    - Bioavailability is ≤ 6% orally, relative to IV
    - Metabolite, desethyloxybutynin, is equipotent to oxybutynin in in vitro studies and is thought to be responsible for the main side effect of the molecule
  - Main side effect is dry mouth and is the major reason for patients to discontinue therapy



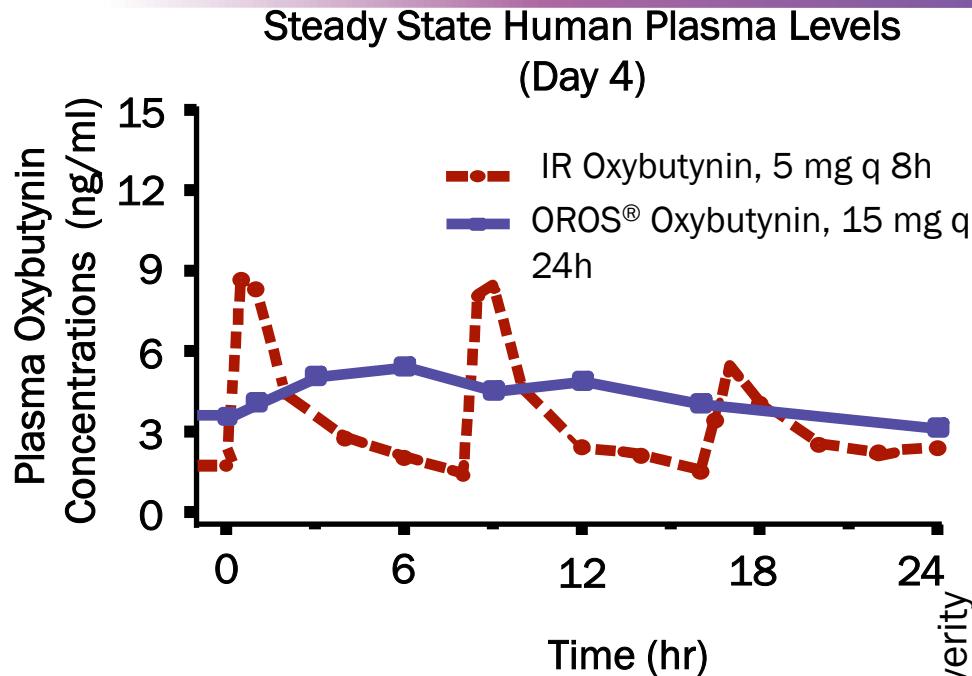
J. Douchamps; *Eur. J. Clin. Pharmacol.*; **35**, 515-520 (1988).  
L Noronha-Blob, et al.; *J. Pharmacol. Exp. Ther.*; **256**, 562-567 (1991).

# HOW TO IMPROVE ON IR OXYBUTYNIN?

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- Can reformulating oxybutynin as a controlled release dosage form:
  - Reduce side effects?
    - By maintaining a zero-order release, a slow rate of rise in blood levels, all resulting in a reduction in peak-to-trough variations
    - By-passing the pre-systemic CYP450 metabolism and conversion to active metabolite
  - Reduce the impact of drug-drug interactions?
    - By delivering to colon instead of the upper GI tract to reduce impact of drugs which interfere with CYP450 metabolism
  - Reduce the frequency of dosing?
    - By delivering with a dosage form that remains in the body and delivers drug sufficient for once-a-day dosing

# DITROPAN XL LAUNCHED BY ALZA IN 1999

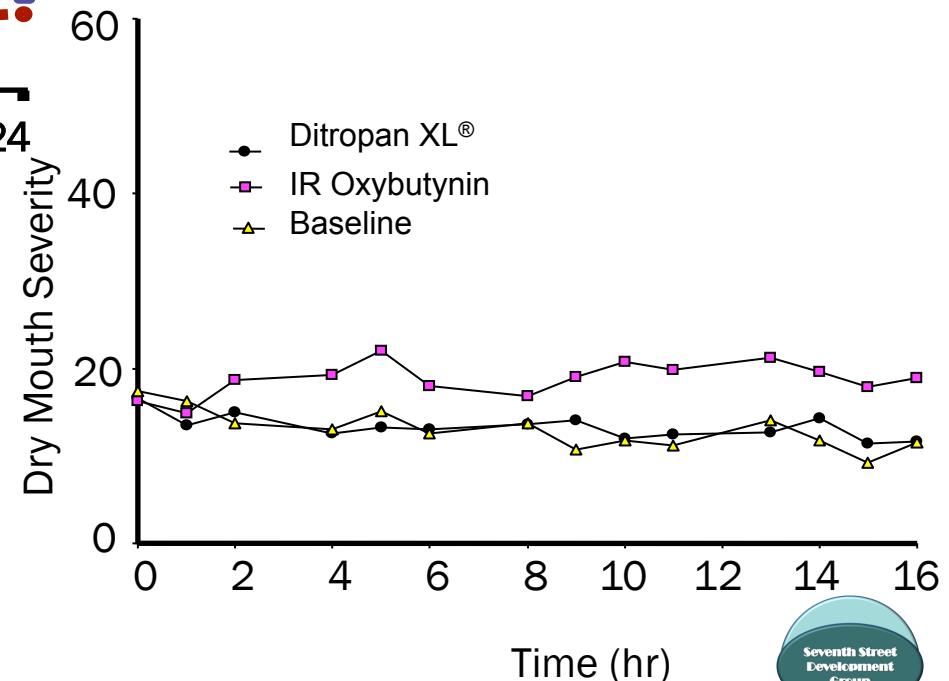


Better Outcome:

- Once-daily dosing with CR platform produced relatively constant plasma levels over a 24-hour period.

Better Outcome:

- Fewer subjects reported dry mouth with OROS® oxybutynin than with IR oxybutynin.
- Higher BA when administered via CR – possibly due to reduction of CYP-450 interaction



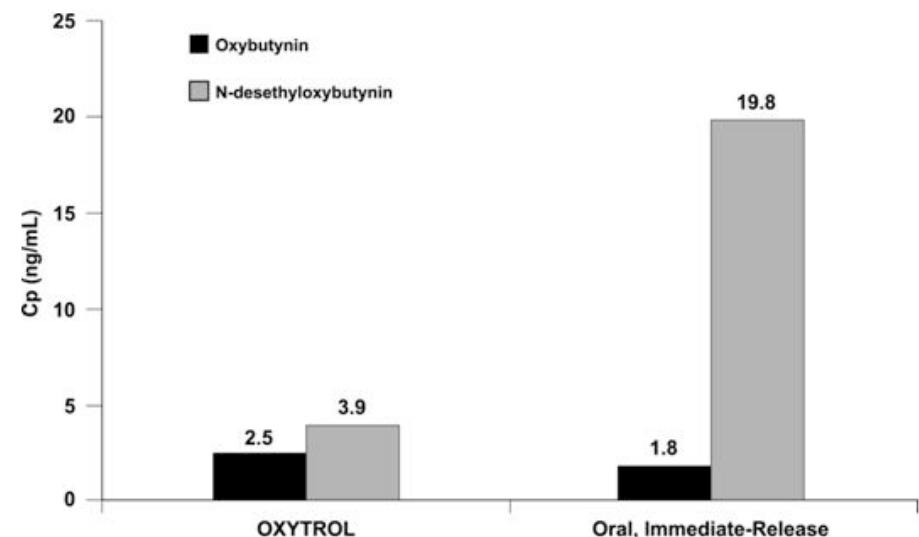
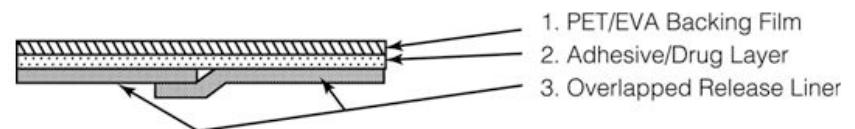
G. Sathyan, et al.; *Br. J Clin Pharmacol*, 52 409-417 (2001).

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**BUT THAT IS NOT THE END OF OXYBUTYNIN'S  
LCM STORY....**

# WATSON LAUNCHES OXYTROL TRANSDERMAL PATCH IN 2003

- Goal: Completely bypass the 1<sup>st</sup> pass metabolism and CYP3A4 metabolism to reduce side effects; same indication
- Reformulate using free base instead of salt to allow for better skin transport
- Design to deliver oxybutynin over a 3 to 4-day interval delivering 3.9mg/day
- Better outcome: reduction in side effects and better patient compliance



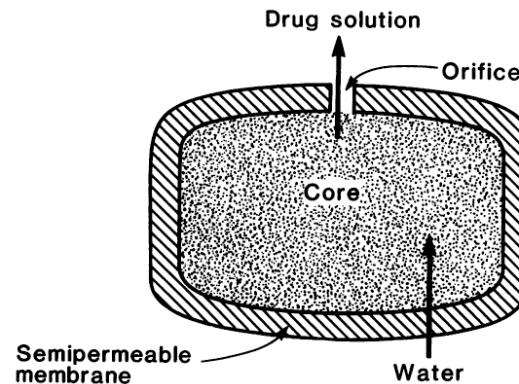
# METOPROLOL: NEW INDICATION FOR AN OLD DRUG

- Metoprolol salts are water soluble and highly permeable (BCS 1) with a short half life
  - Requires BID dosing
  - Solubility of tartrate salt: 750mg/mL in water at 25 °C
- The free base is a waxy white solid and has a T<sub>m</sub> of 45 °C
- Originally approved as Lopressor (metoprolol tartrate) for hypertension in 1978

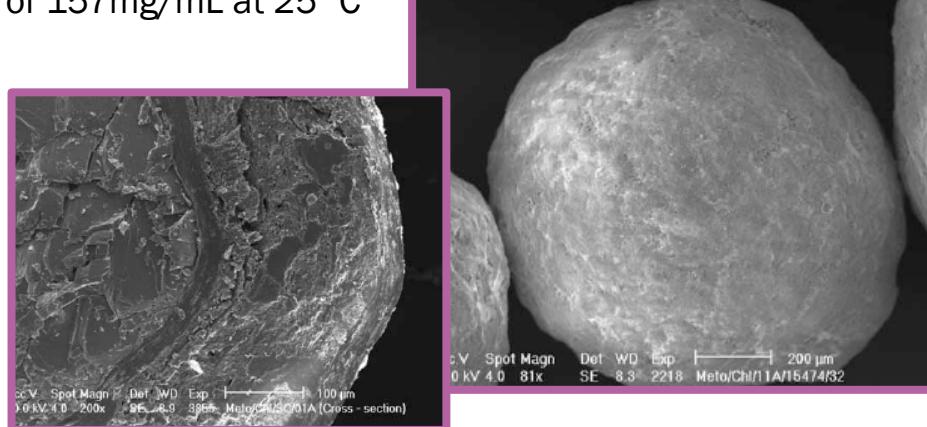


# DRUG DELIVERY AND USE OF OTHER SALTS OF METOPROLOL

- Metoprolol succinate and metoprolol fumarate used to develop CR dosage forms
  - Fumarate for osmotic delivery due to osmotic pressure properties
    - Aqueous solubility of 435mg/mL at 25 °C
    - Osmotic pressure of sat'd soln = 32.5 atm
  - Succinate for use in multiparticulate CR beads/systems
    - Aqueous solubility of 157mg/mL at 25 °C



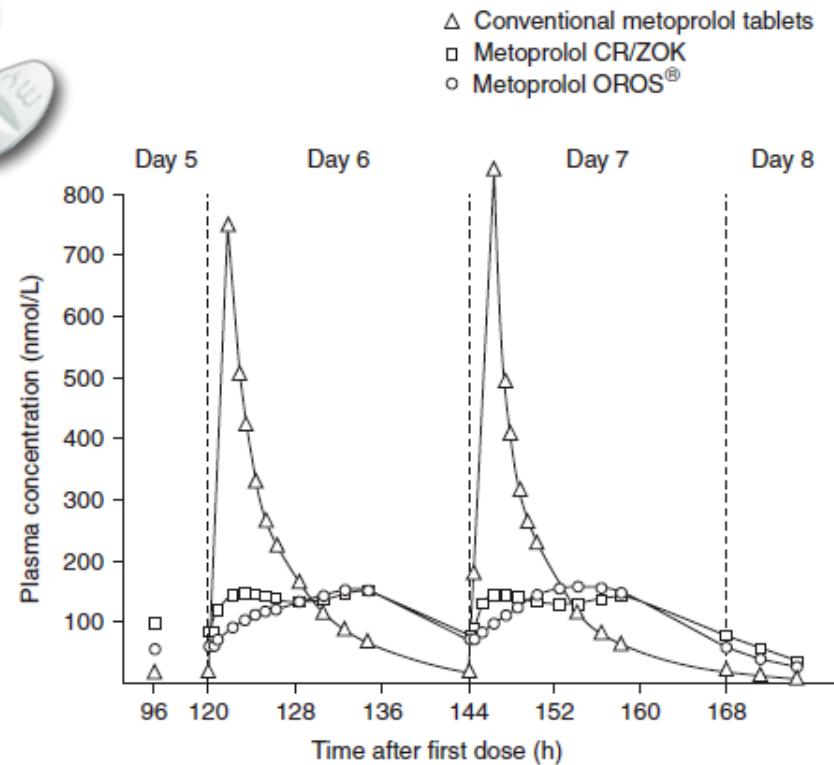
$$\left( \frac{dm}{dt} \right)_z = \frac{A}{h} \cdot k (\Pi_f - \Pi_e) S_d$$



Theeuwes, et. al., Br. J. Clin. Pharmac. (1985), 19, 69S-76S

# TOPROL-XL: METOPROLOL SUCCINATE

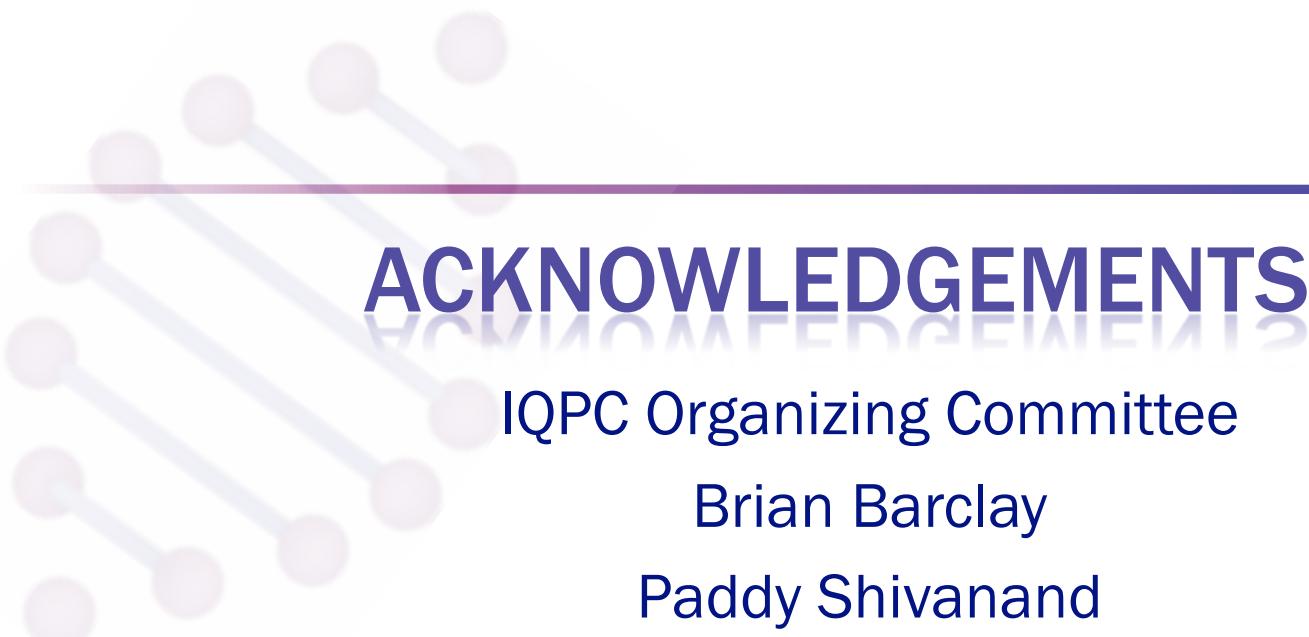
- Result: Improved Outcomes
  - From BID/TID to QD dosing
  - Reduced peak-to-trough ratio compared to IR
  - Expanded indication
- AstraZeneca received approval for Toprol XL in 1992 for treatment of hypertension and angina and in 2001 broadened the approved indications to include Congestive Heart Failure (CHF)



**Fig. 1.** Mean plasma concentrations of metoprolol on days 5 through 8 following once daily administration of metoprolol controlled-release/zero-order kinetics (CR/ZOK), metoprolol OROS®, and conventional (immediate release) metoprolol tablets (reproduced from Sandberg et al.,<sup>[13]</sup> with permission from Kluwer Academic/Plenum Publishers).

# THE USE OF LCM TO ENHANCE PRODUCT PERFORMANCE

- LCM is product improvement of existing therapies and drugs that results in an overall benefit the patient
- LCM approaches
  - Form changes (e.g., salts and polymorphs), drug delivery/route, reformulation
  - Start activities once efficacy is established in patients (after Phase 2) – conduct hand-in-hand with form focus/solid form and comprehensive screening
  - Pharma 2020 FDT and LCM
    - Faster time to market will require LCM for all products in the Live License paradigm
- Obtain input from the key stakeholders (patient, doctors, nurses, hospitals, payers)
  - Understand benefit/risk balance and develop the right product
- Benefits
  - Enhanced compliance = reduced hospitalizations, office visits
  - Enhanced product stability/shelf life = better product supply chain
- Enhanced BA and efficacy = better outcomes for patients



# ACKNOWLEDGEMENTS

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# QUESTIONS??

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# EXTRAS

# LEGAL BASIS FOR GENERIC DRUG APPROVAL

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- Waxman-Hatch Amendments (Drug Price Competition and Patent Term Restoration Act of 1984)
  - Statutory authority for FDA approval of pre and post 1962 generic drugs
  - Make available high quality, low cost generics - reducing health care costs
  - Eliminate costly and unnecessary duplicative safety and efficacy studies
  - Assure continued development of new drugs through patent extension and exclusivity granted to certain NDA's

# LEGAL BASIS FOR GENERIC DRUG APPROVAL

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- Once an NDA is approved, the patent(s) identified in the filing are listed in the Orange Book
  - Expiration date and exclusivity data are listed for each patent.
- NDA holders need to inform FDA of the existence of qualified patents to be listed in the Orange Book
  - <http://www.fda.gov/cder/ob/>
  - If there are patents in the Orange book for this drug, the FDA cannot approve the ANDA until the listed patents have expired.
- Patent Certification – confirm the following:
  - No patent information concerning the listed drug has been filed with FDA
  - Any listed patent claiming the listed drug has expired
  - The listed patent will expire on a particular date
  - The relevant listed patent is invalid or will not be infringed by the product for which approval is sought
    - the application must also include a statement that the applicant will inform the NDA and patent holders of its challenge to the patent

# GENERIC DRUGS

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- There are four certifications that the generic company must choose and are called Paragraphs I, II, III, and IV after the paragraph numbers in Hatch-Waxman Act:
  - *Paragraph I. There are no patents listed in the Orange Book*
    - Patents may exist, but the company that filed the NDA did not list them in the Orange Book
    - The FDA may approve the application immediately if all requirements have been met
  - *Paragraph II. The patent listed in the Orange Book has expired*
    - An ANDA application is eligible for immediate effective approval if all requirements have been met
  - *Paragraph III. There is a listed patent in the Orange Book that has not expired and the generic company does not intend to market the product until after the patent has expired*
    - The FDA cannot approve the ANDA until after the patent expiration date

# GENERIC DRUGS

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- Paragraph IV. The generic company plans to challenge the listed patents and claim that they are invalid, unenforceable, or will not be infringed by the generic product
  - A generic company will make a Paragraph IV certification when its intent is to market the drug product prior to the expiration of the patent
  - Once the ANDA filing is submitted and it is determined that it will be reviewed, the FDA sends an acknowledgement letter to the company
  - The generic company must then send a notice to the company that listed the patent in the Orange book. The notice must contain the ANDA number, the proposed drug product, the patent number and expiration date of the patent being challenged, and an explanation why the generic company believes that the patent will not be infringed, is invalid, or unenforceable.
  - The company that filed the NDA can initiate a lawsuit in the federal district court within 45 days of receipt of the ANDA notice. **If a lawsuit is initiated, the FDA cannot approve the ANDA for 30 months.** This allows the parties time to litigate.

# EXCLUSIVITY PERIODS

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## ○ Exclusivity (under Title I)

- NCE submitted between 1/82 - 9/24/84: 10 years; New NDA or Supplement, no clinical trial: 2 years
- NCE submitted after 9/24/84, Exclusivity: 5 years
- sNDA with essential clinical trial, Exclusivity: 3 years
- Orphan Drug NDA Exclusivity: 7 years
- Rx-to-OTC Switch Exclusivity: 3 years
- NDA Exclusivity Extension: 5 years + 30 month stays
- ANDA Exclusivity: 180 days
- Pediatric Exclusivity: 6 months x 2

## EXCLUSIVITY PERIODS

### ○ Patent Term Extension/Restoration (Title II)

- Up to 5 years patent extension may be obtained
  - Delay due to FDA - half of the IND testing time as a basis
  - Must have been “due diligenced” on the part of manufacturer
  - Only one patent may be extended per regulatory review period
  - The applicant must request extension within 60 days of NDA approval
- No patent could be extended beyond 14 years
- GATT of 1995 change over (delta period)
- Pipeline drug patent restoration
- Pediatric patent extension: 6 months x 2