Application of High Throughput technologies to Drug Substance and Drug Product Development

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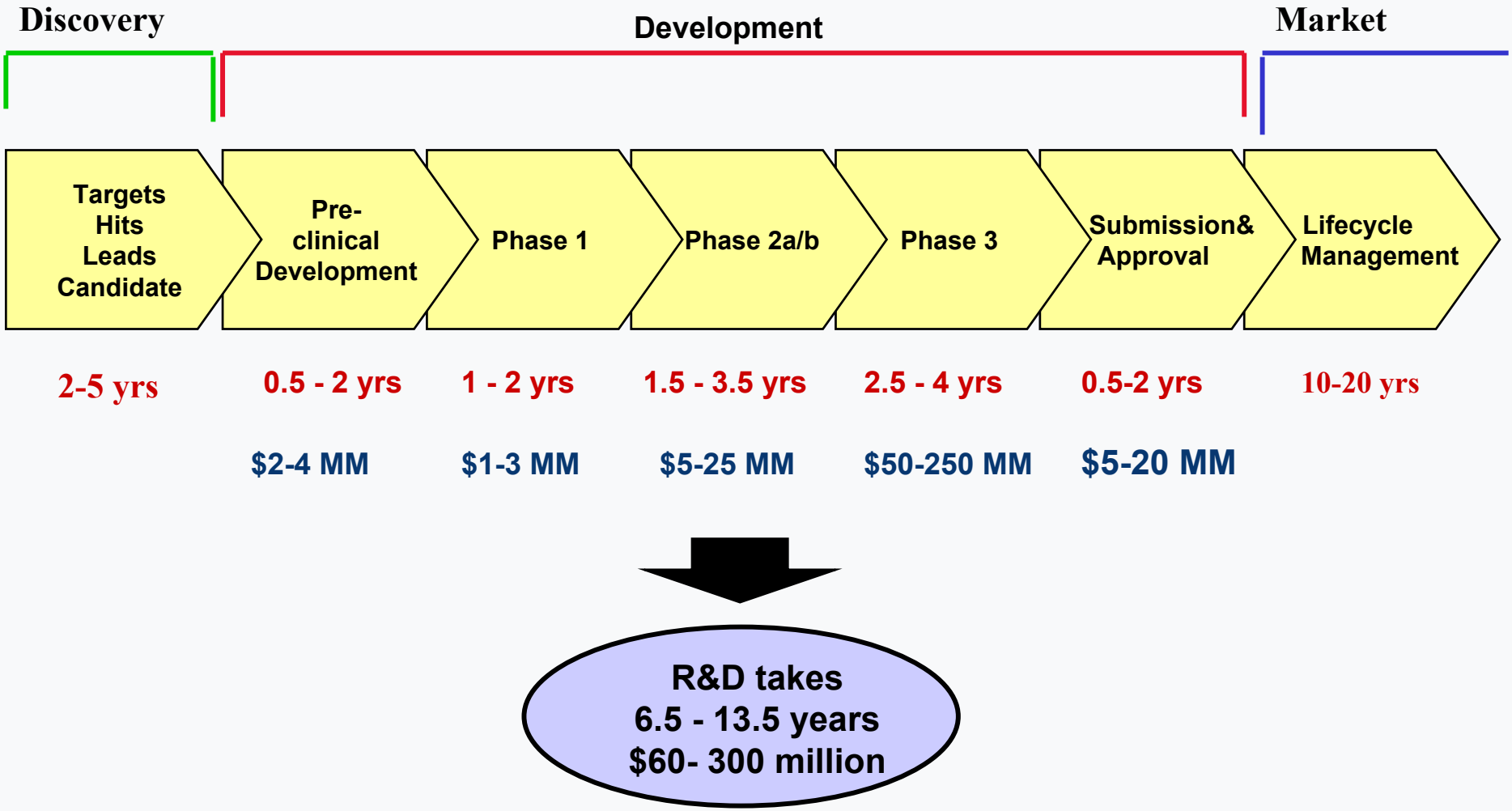
Drug Discovery / Development

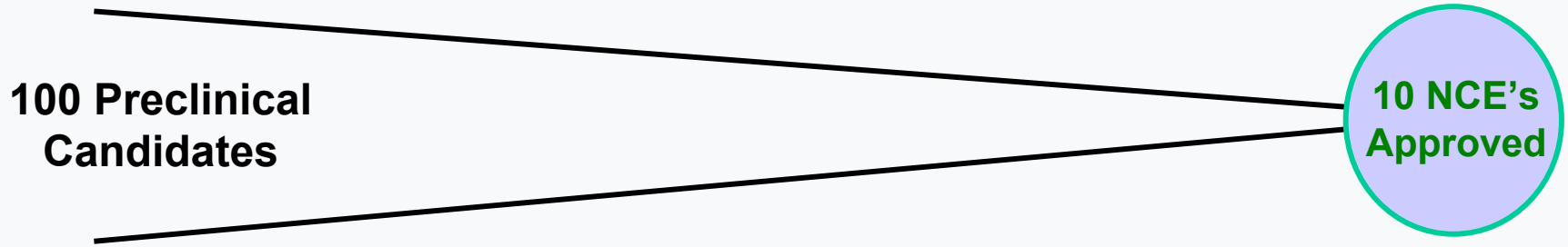


Source: PRTM

Historic NCE Pipeline Success

NCE Probability of Success by Phase: 1990s

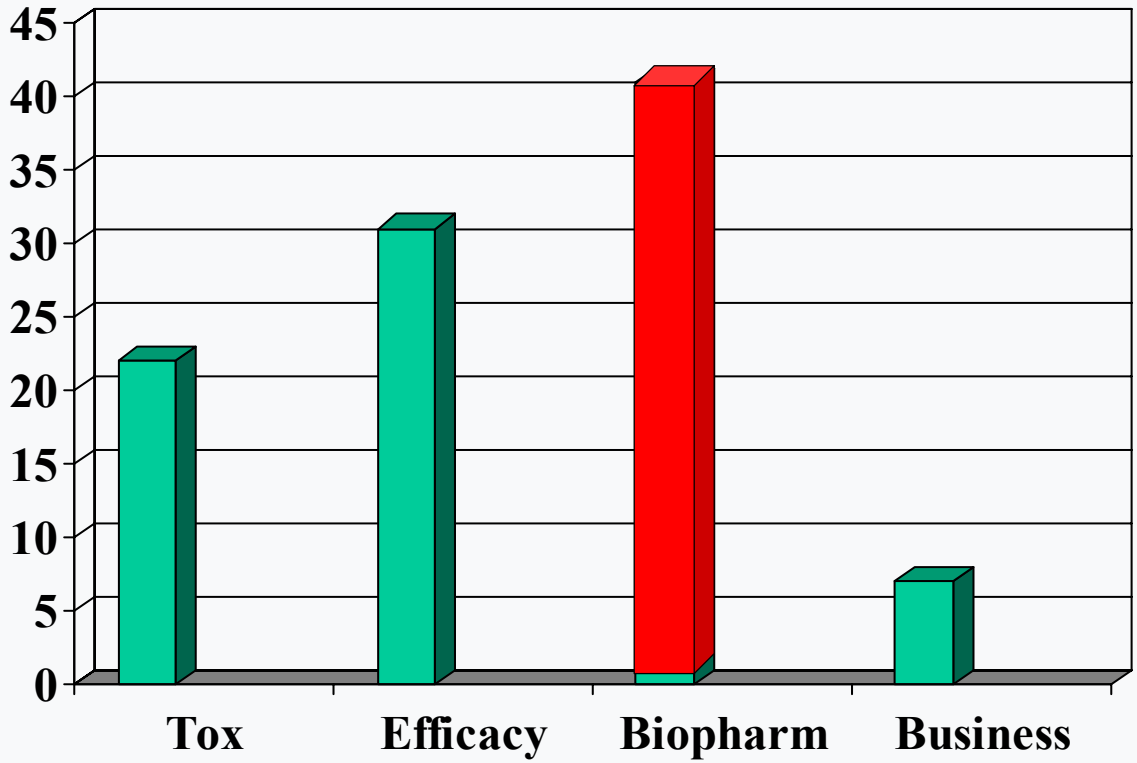
Estimates



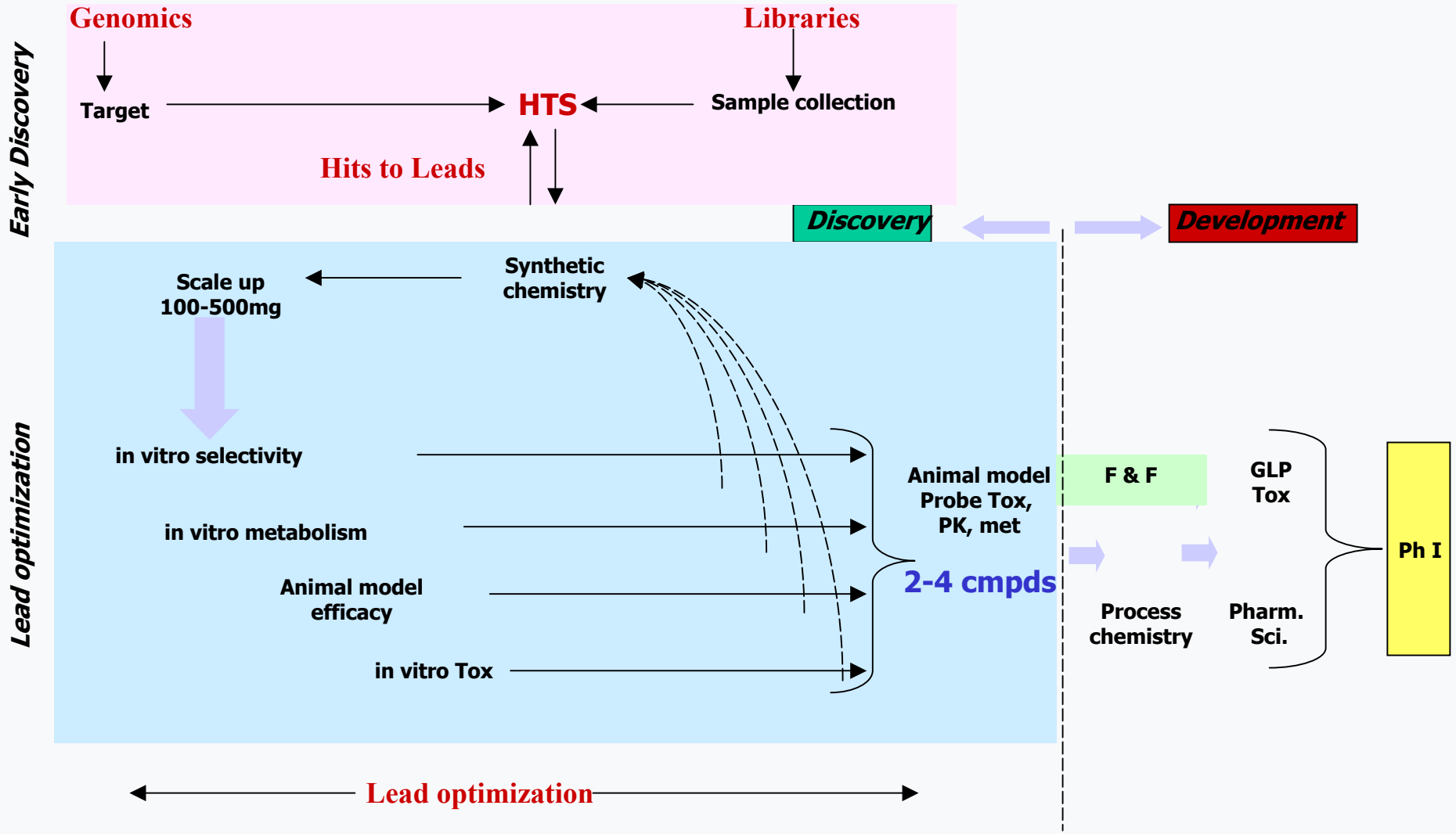
	Preclinical	Phase 1	Phase 2	Phase 3	Registration to Approval
Cumulative Success	25 – 50%	15 – 35%	7 – 20%	6 – 18%	5 – 16%
Probability of Success by Phase	25 – 50%	60 – 70%	50 – 60%	80 – 90%	90 – 95%

Source: SDG, London; GW Journal of Innovation, Vol 1, Issue 3, 1995; PRTM estimates

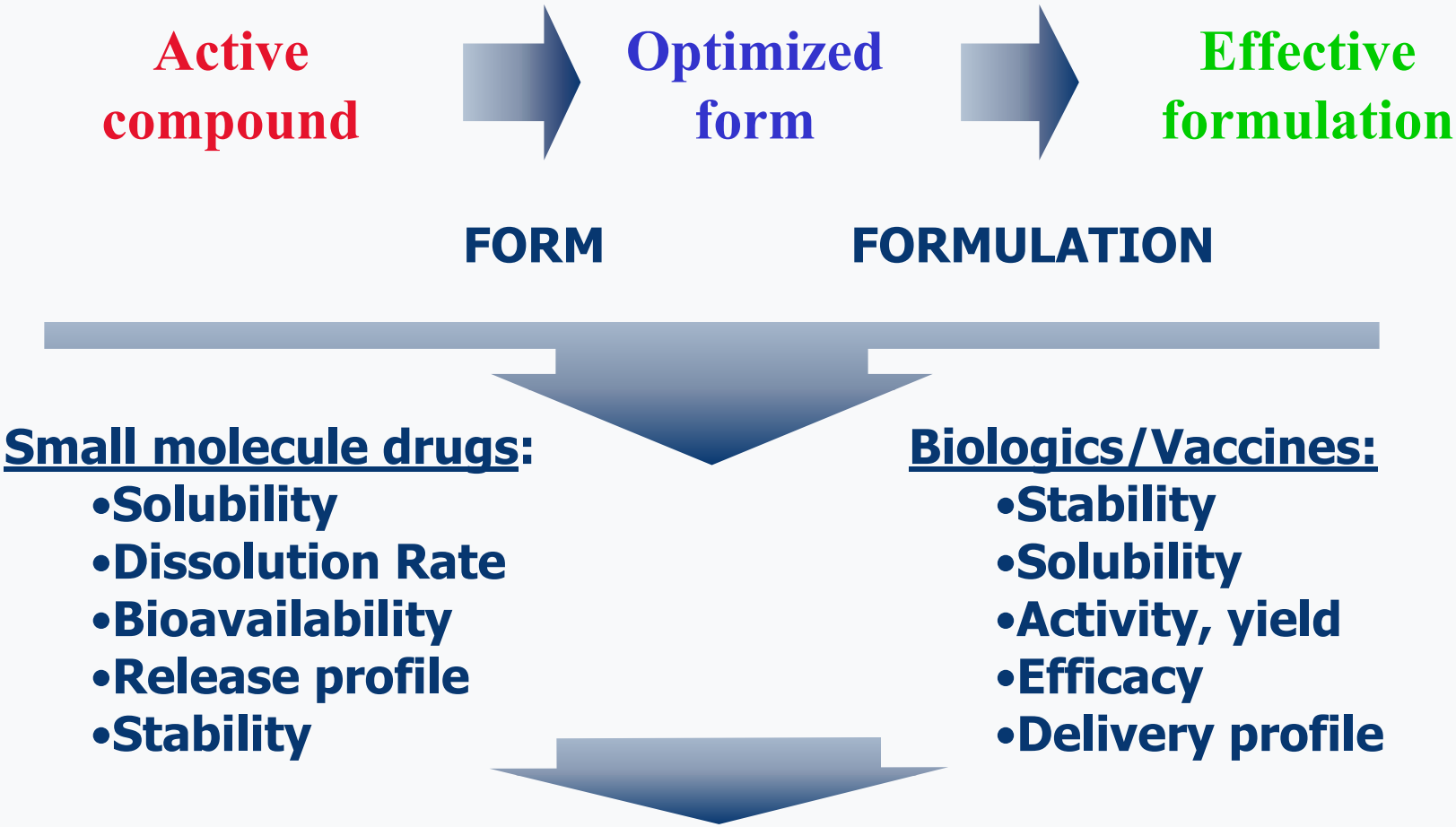
Why Product Candidates Fail



Global view: Pre-clinical R & D Process

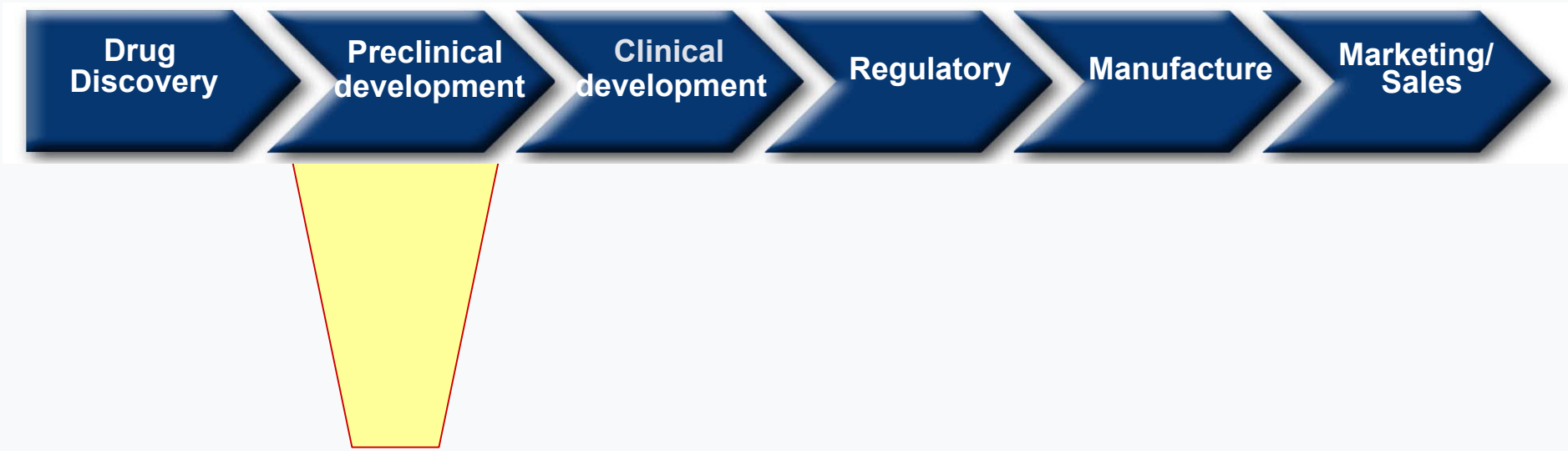


Form & Formulation



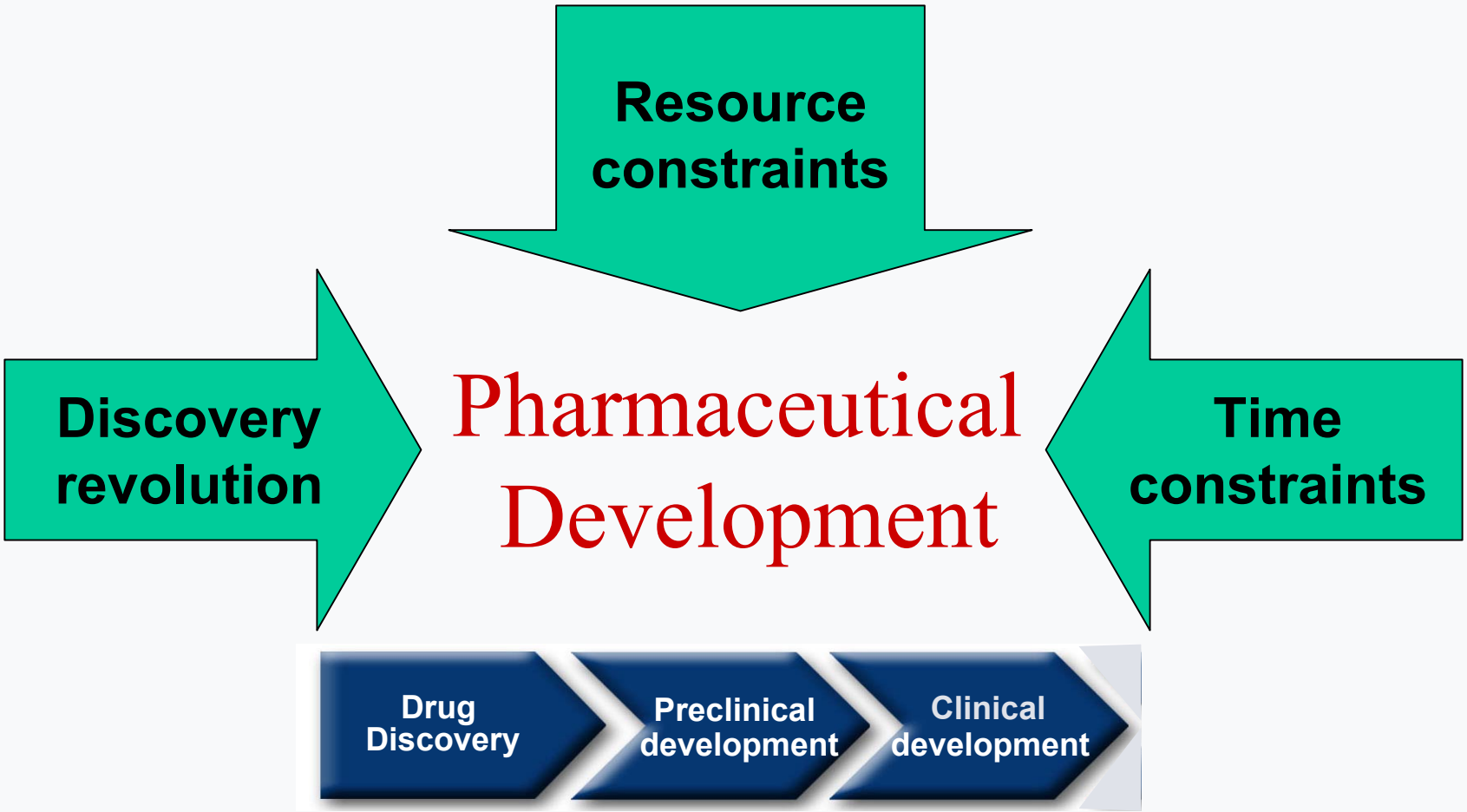
Maximize Product Value

Form & Formulation: Traditional



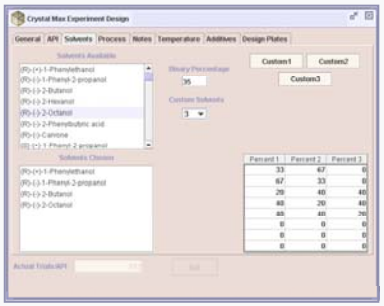
- Mostly manual experimentation
- Low throughput

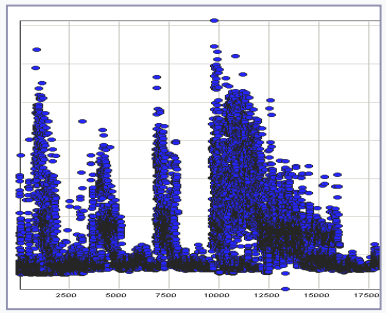
New R&D Challenges



Bringing High Throughput to the Process

Drug Discovery	Preclinical development	Clinical development	Regulatory	Manufacture	Marketing/ Sales
• Solubility • Lead selection	• Bioavailability • Stability • "Bricks"	• Dosage form • Regimen	• Rational process design	• COGS • Risk reduction	• Product enhancements • IP

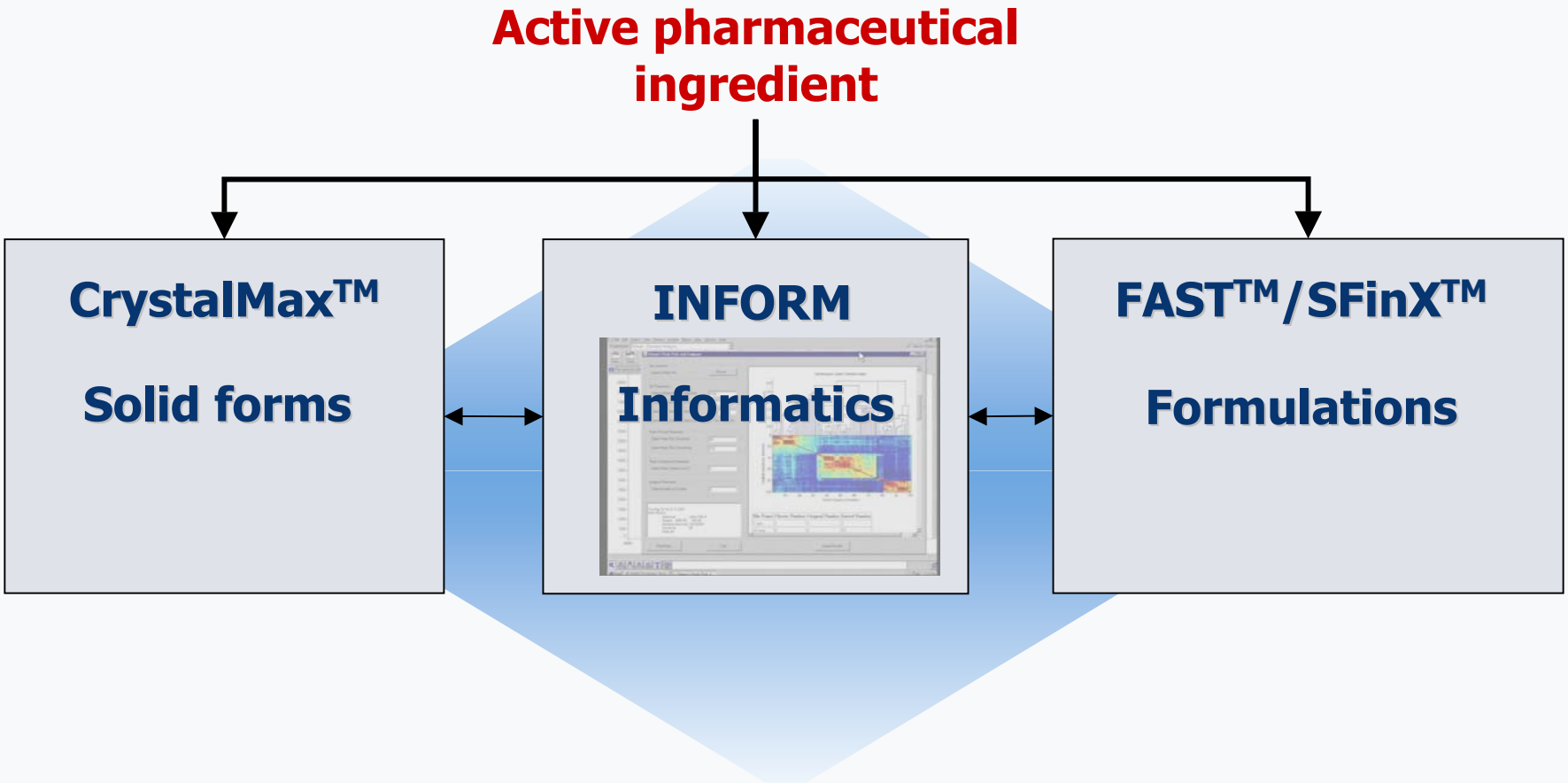




- Automated, high throughput experimentation
- Microscale
- Informatics driven

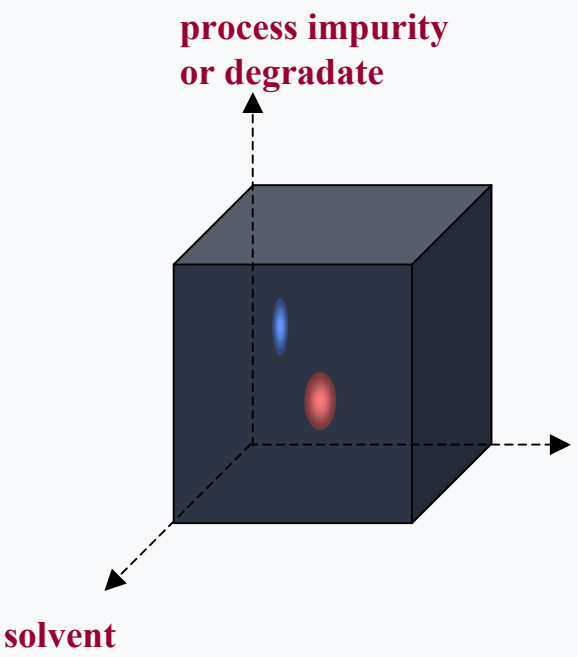
} Optimal

Integrated Technology Platforms

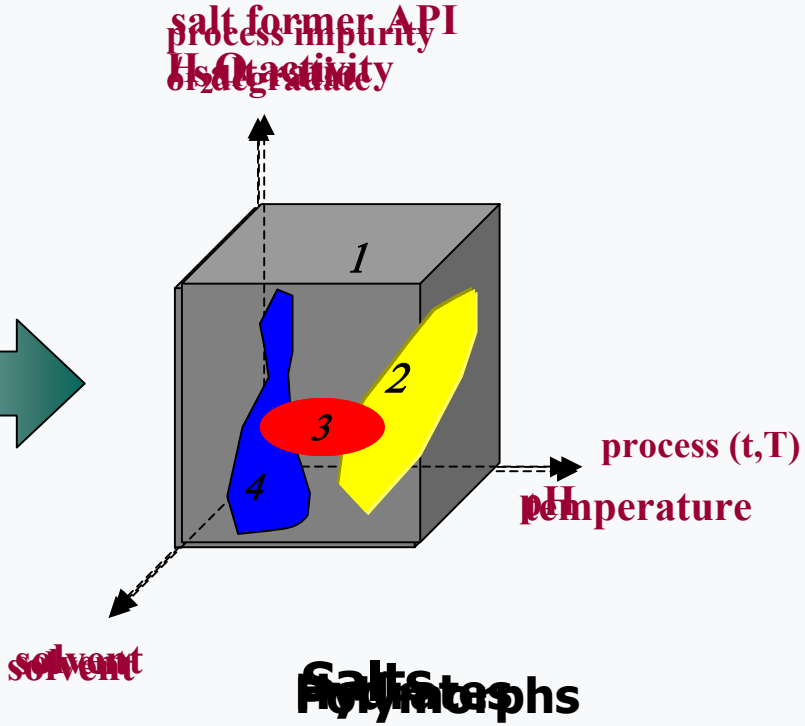


Exploration of Solid Forms and Methods

Traditional



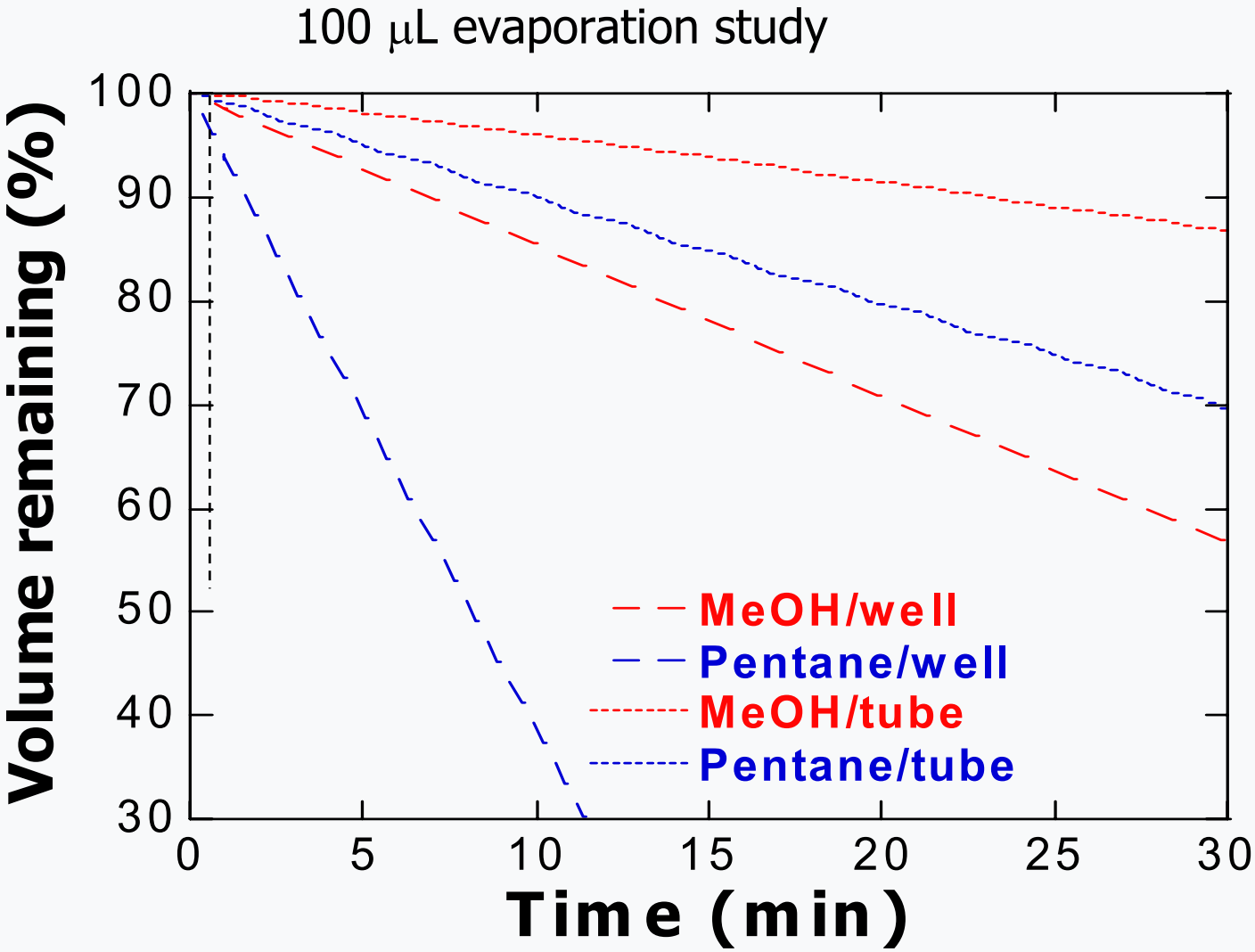
TransForm (CrystalMax™)

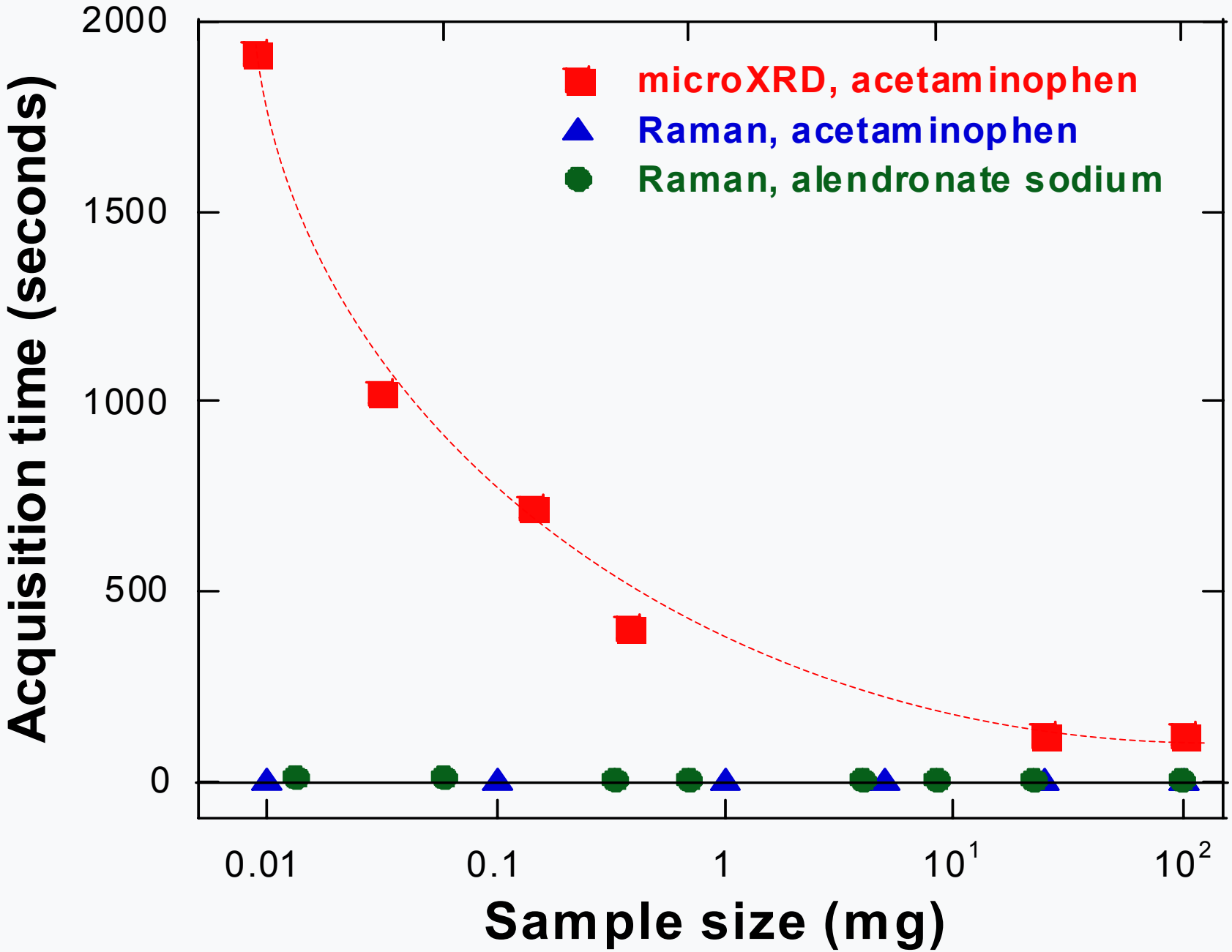


CrystalMax™

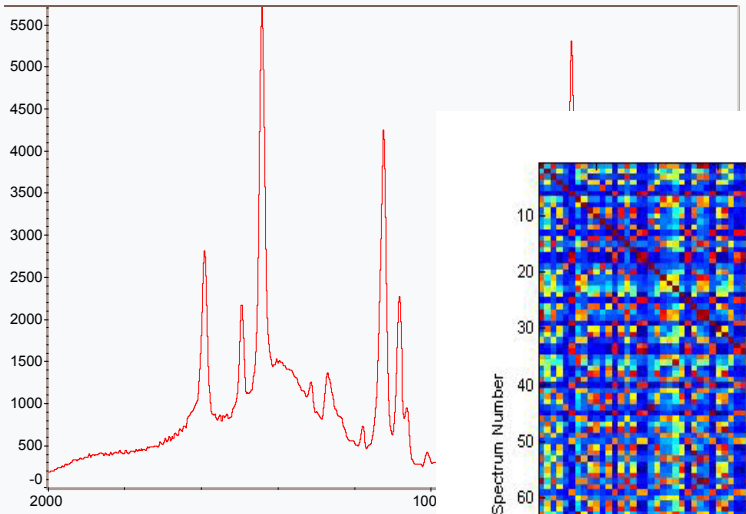
- Best solid form
- Efficient
  - micro-scale (sub-mg)
  - massively parallel (20,000)
- Comprehensive exploration of ‘space’
- Automatic data capture

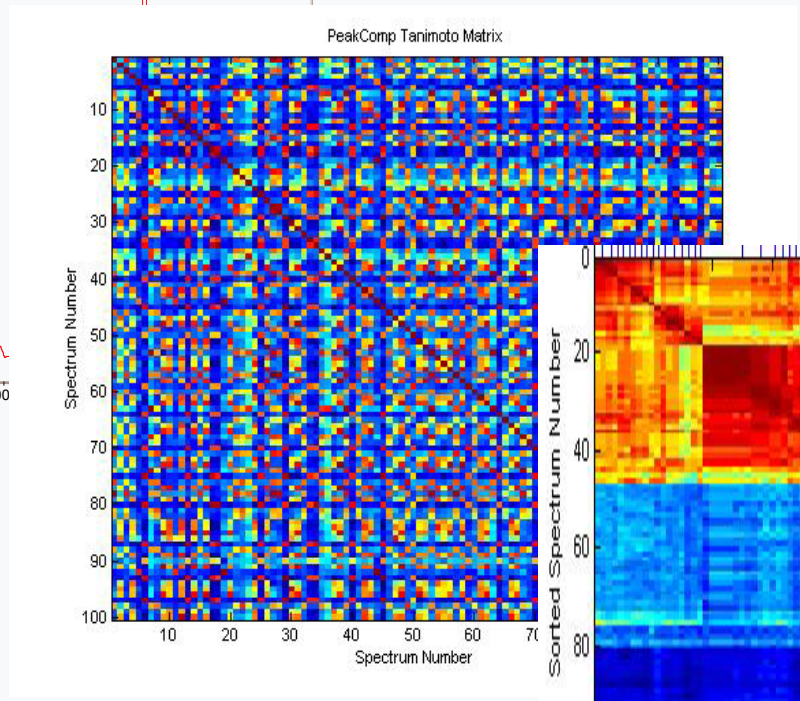
Why Use Tubes Rather Than Plates?

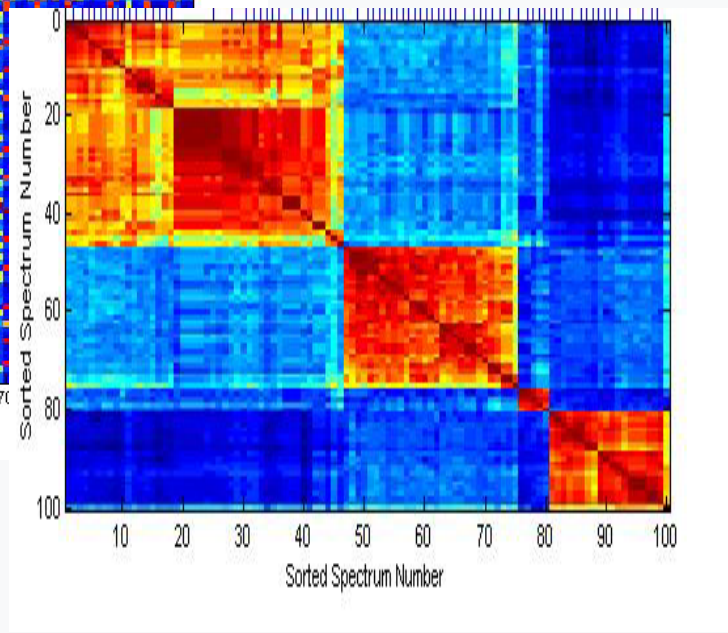



microXRD, acetaminophen
Raman, acetaminophen
Raman, alendronate sodium
Acquisition time (seconds)
2000
1500
1000
500
0
0.01
0.1
1
10^1
10^2
Sample size (mg)

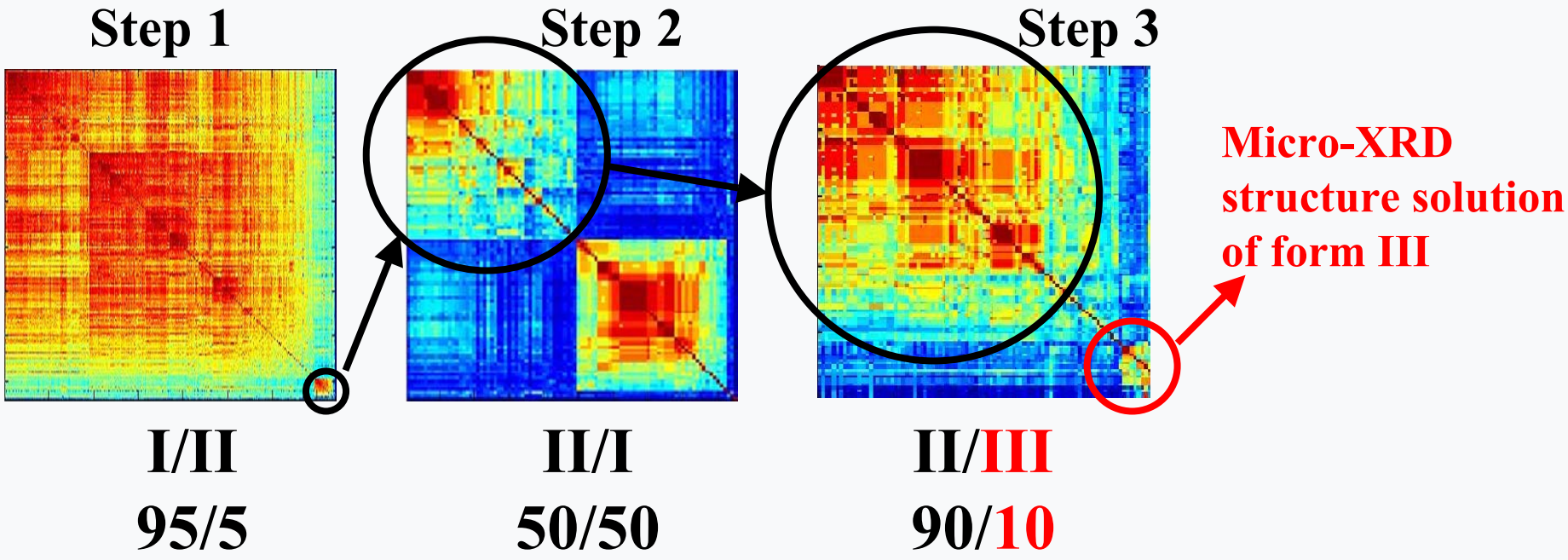
Innovative Approach to Primary Analysis







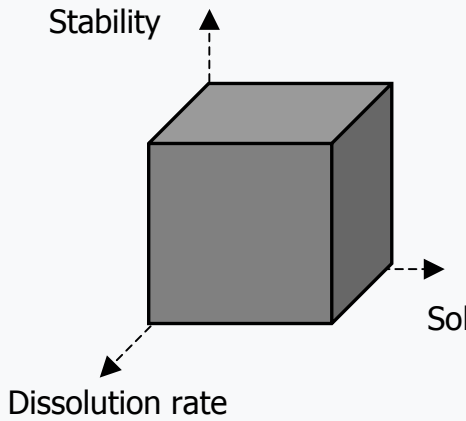
Acetaminophen: Iteration to Find Form III



- Three polymorphs of acetaminophen identified and characterized using informatics-driven, iterative experimentation
- Different process modes: thermal, evaporative and melt
- Over 10K experiments to explore HT polymorph diversity in < 6 weeks

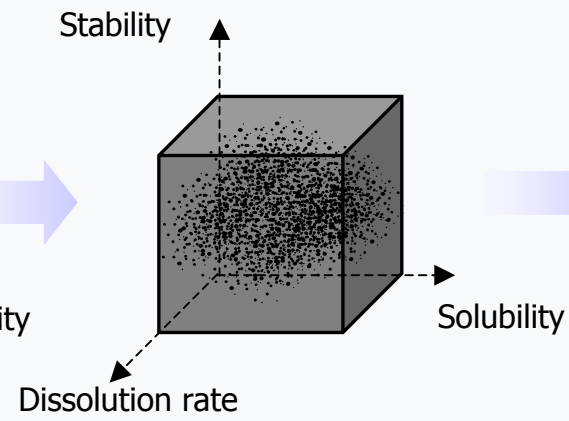
High Throughput Formulation Discovery

Traditional



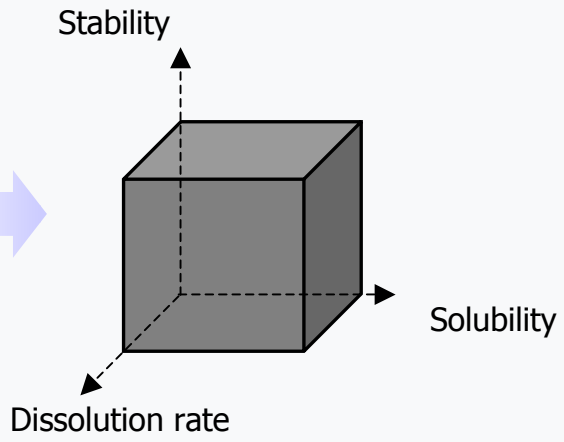
- Limited experiments
- No informatics
- "Good enough" formulation

TransForm HT Platforms (FAST™ & SFinX™)



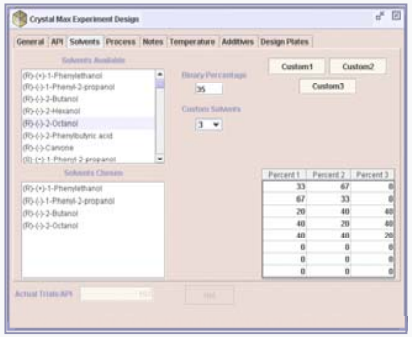
- Many experiments
- Comprehensive data capture
- New knowledge

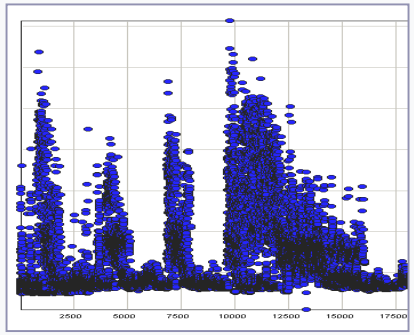
Informatics-Enhanced Experimental Design



- "Smarter" experiments
- Data capture & mining
- New knowledge
- Optimized formulations

FAST™





Best formulation for specific application
- **solubility, stability, device compatibity**

Efficient
- **micro-scale (ug range)**
- **massively parallel (>5,000)**

Comprehensive exploration of 'space'

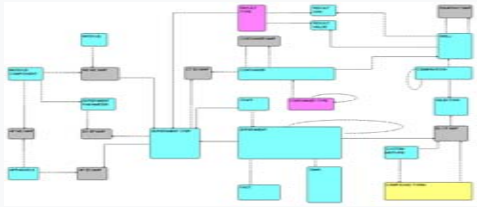
Automated data capture

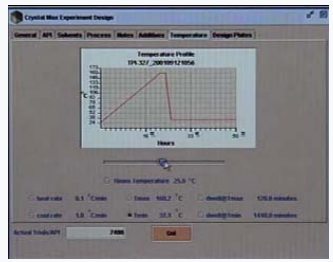
End-to-end automation

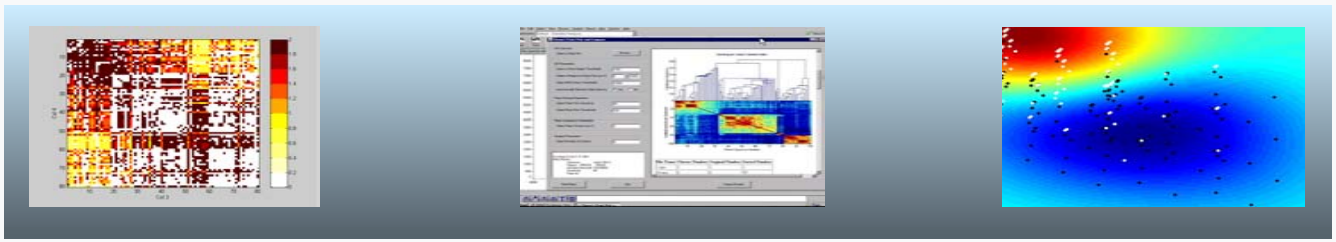
- ***Small molecules***
- *Biologicals*
- *Vaccines*

Inform™: Informatics

Desktop design **Relational database** **Process control**





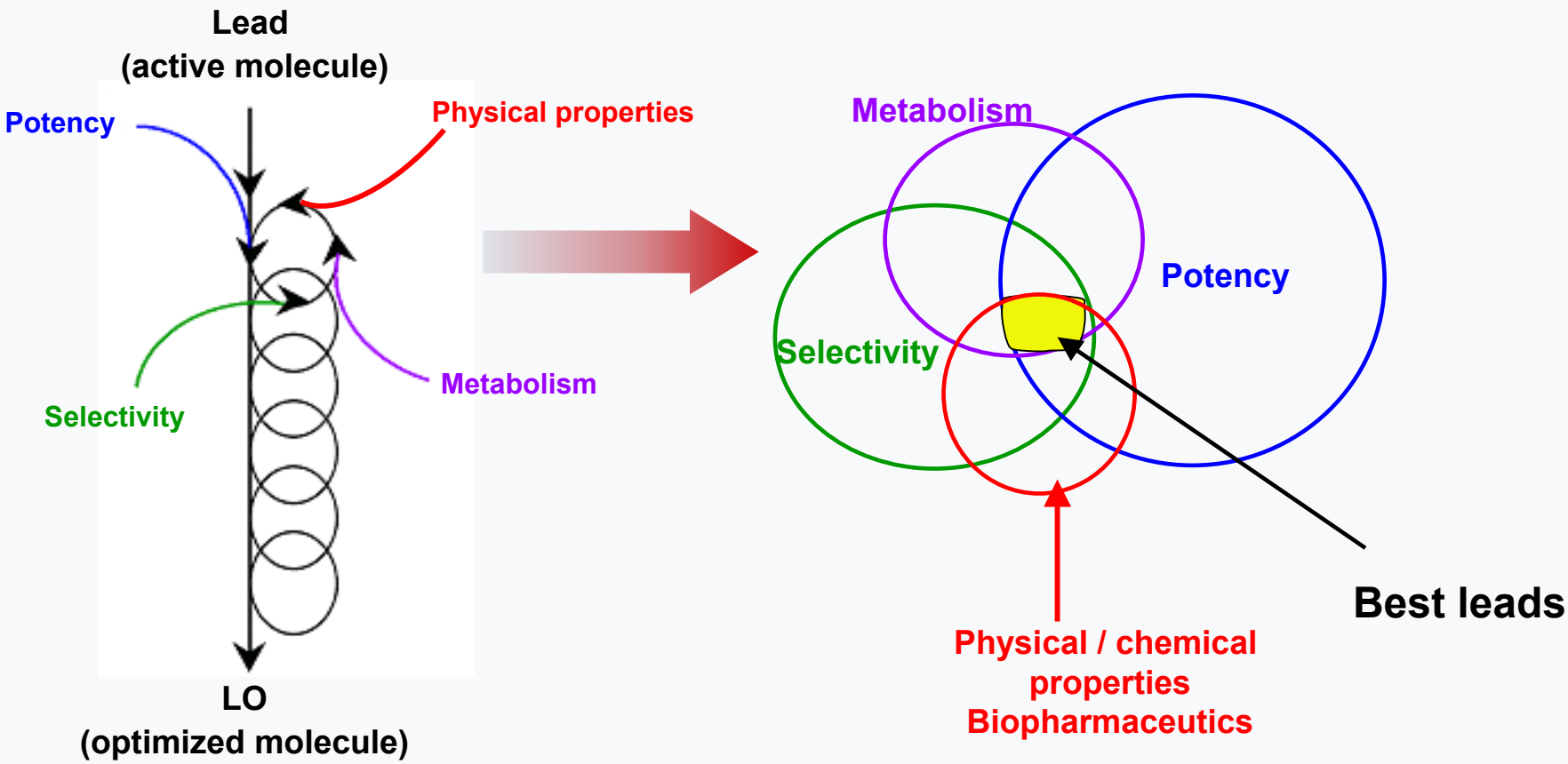


Analysis and Predictive Modeling Software

- Integrated data capture, storage and analysis
- Knowledge-driven discovery
- Designed for U.S. regulatory compliance (CFR 21.part 11)
- Proprietary design

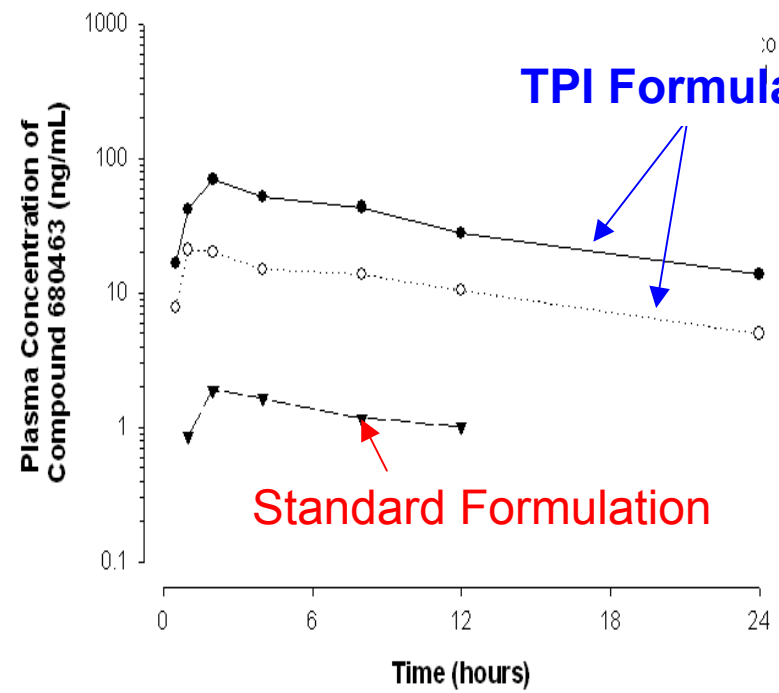
Discovery Applications

Building in "Developability"

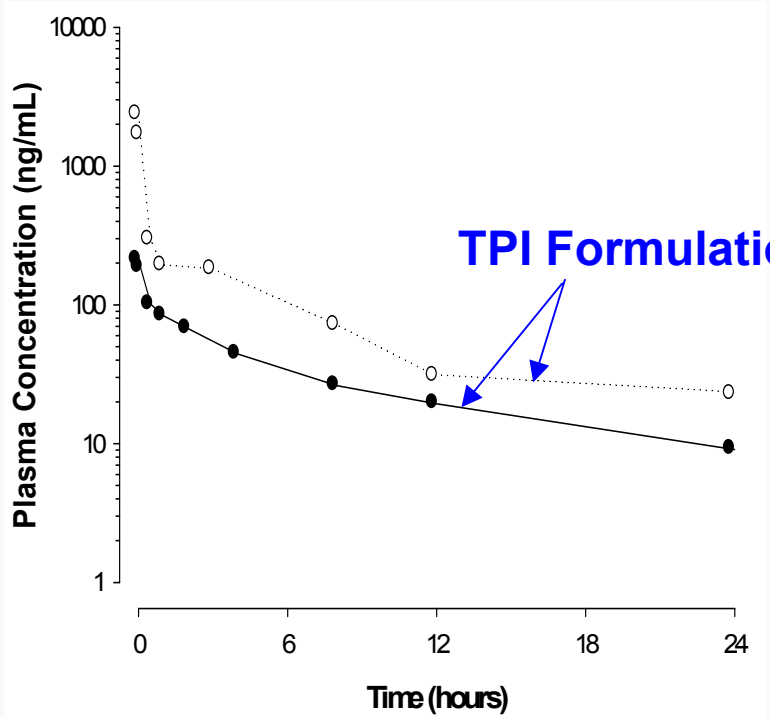


Animal Studies: Bioavailability

Oral Formulations



Intravenous Formulations



- Improved oral bioavailability demonstrated with TPI formulations
- IV dosing enabled by TPI formulations

Applications in Pre-Clinical and Clinical Development

Development Risk: Norvir

news & media

Press Release

ABBOTT ANNOUNCES DIFFICULTY MANUFACTURING NORVIR® (RITONAVIR) CAPSULES

— COMPANY PLANS TO SUBSTITUTE WITH LIQUID FORMULATION —

Abbott Park, Illinois, July 27, 1998 — Abbott Laboratories announced that it is experiencing manufacturing difficulties with the capsule formulation of its HIV protease inhibitor, Norvir® (ritonavir).

"We have encountered an undesired formation of a Norvir crystalline structure that affects how the capsule form of Norvir dissolves," said Arthur Higgins, senior vice president, pharmaceutical operations, Abbott Laboratories. "Although maximum efforts are underway, to date we do not have a solution to the capsule problem."

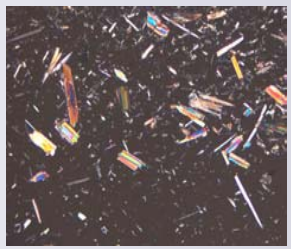
The manufacturing difficulties with Norvir capsules will result in shortages and interruption in supply of capsules. Abbott is planning to supply Norvir oral solution (liquid formulation) to provide continued Norvir therapy for patients.

PR Newswire July 27, 1998

TransForm Solution: Norvir

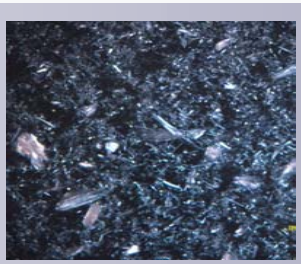
Within 4 weeks:

- Both known forms identified/characterized
- Three new forms discovered
- Novel, robust methods identified to make each form



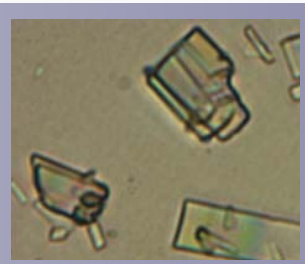
Form I

Form II



Form III

Form IV



Form V

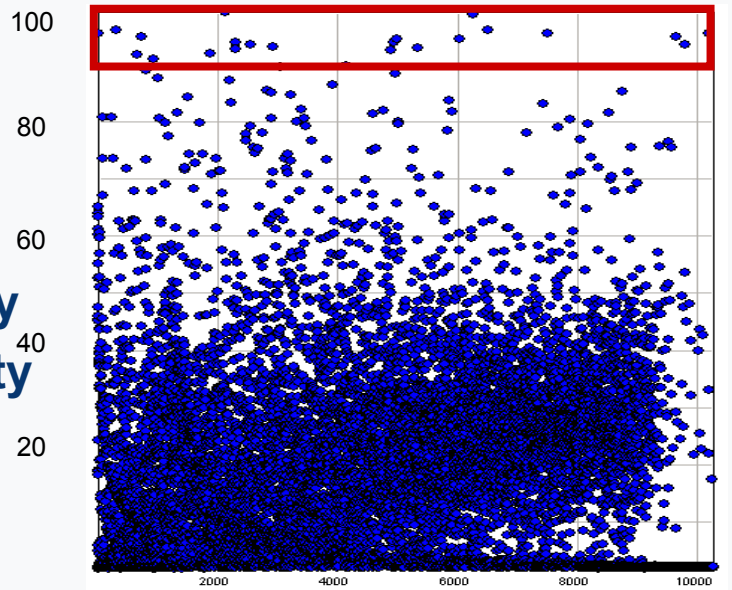
TPI's analysis required < 2 g of material

TPI 211: Identification of improved formulations

TPI 211: Marketed intravenous anti-cancer drug
Excipient-related adverse effects

Challenge

- Eliminate toxicity
- Maintain
  - solubility
  - physical stability
  - chemical stability



TransForm Solution

- 4 lead formulations identified from 96,000 experiments
- Scale-up
- >24 weeks stability
- Better animal tolerance

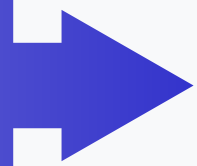
Applications in Life Cycle Management / Line Extensions

Oral delivery

High-throughput salt screening

Experimental variables:

- Salt-forming reagents
  - pharma acceptable
  - > 40 acids (basic compounds)
  - > 20 bases (acidic compounds)
- API/salt former ratio
- pH
- ionic strength
- solvent composition

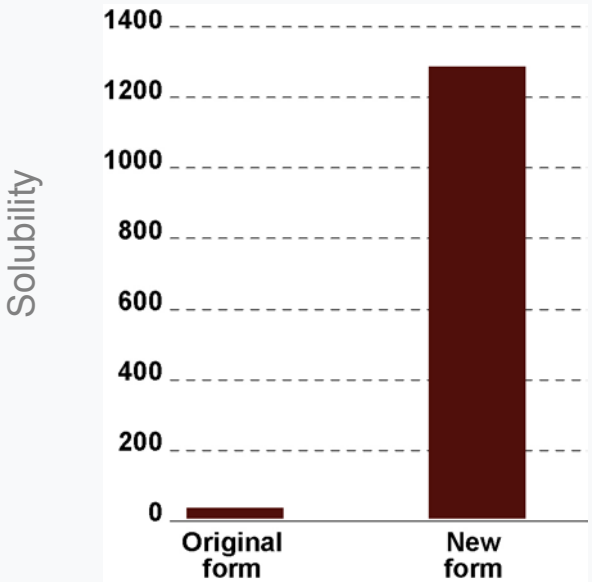


Complex system

TPI 745: New Form for Faster Onset and New Delivery Systems

Problem: Potential new indications complicated by slow onset and side effects at high dosage levels

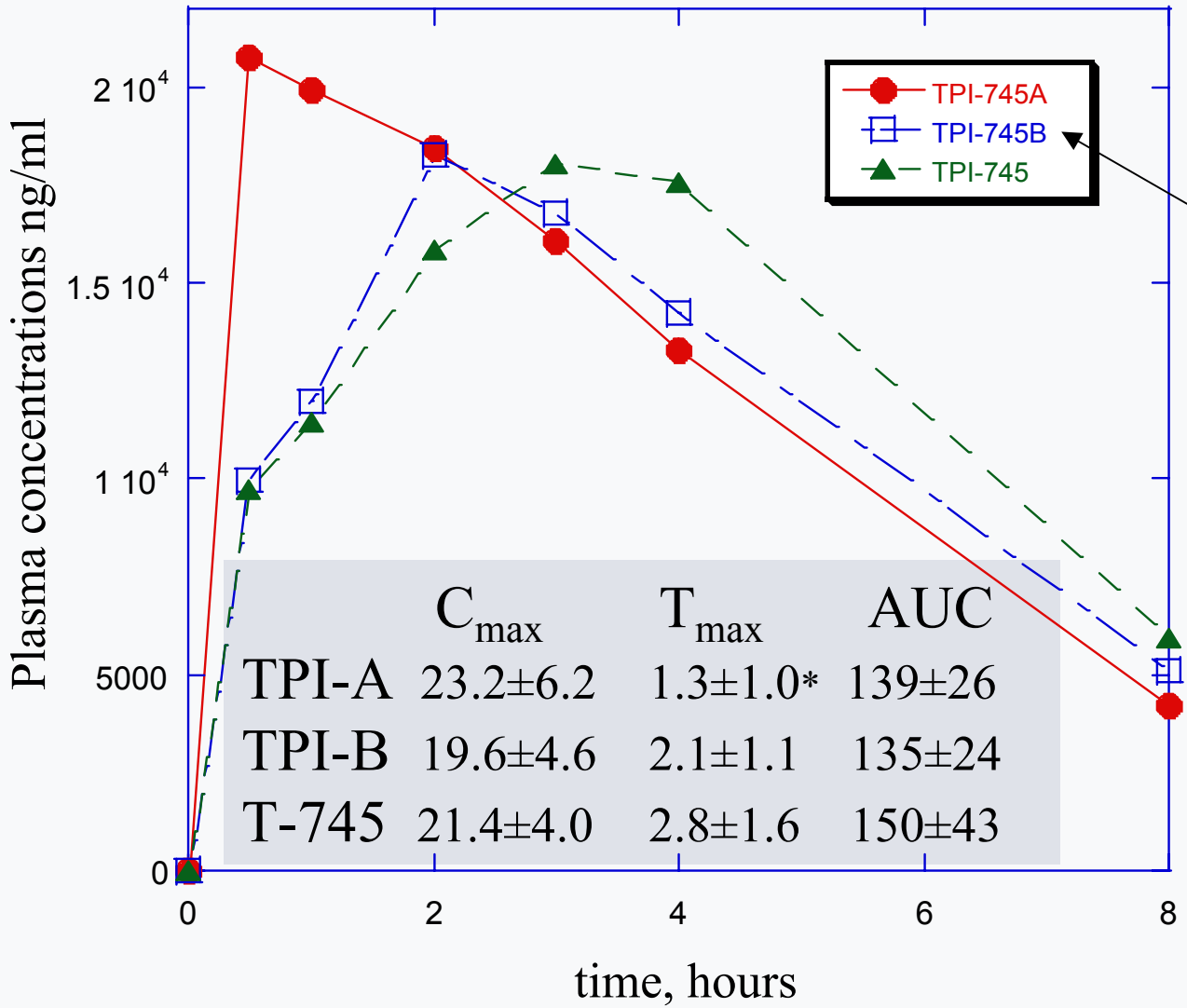
May require new controlled release delivery system



TransForm Solution

- New form with superior solubility
  - Within 2 weeks
  - 100X more soluble than parent drug
  - New IP
- Potential to reformulate with controlled release

New TPI-745 Form Has Faster Onset & Better Bioavailability



	C_{max}	T_{max}	AUC
TPI-A	23.2±6.2	1.3±1.0*	139±26
TPI-B	19.6±4.6	2.1±1.1	135±24
T-745	21.4±4.0	2.8±1.6	150±43

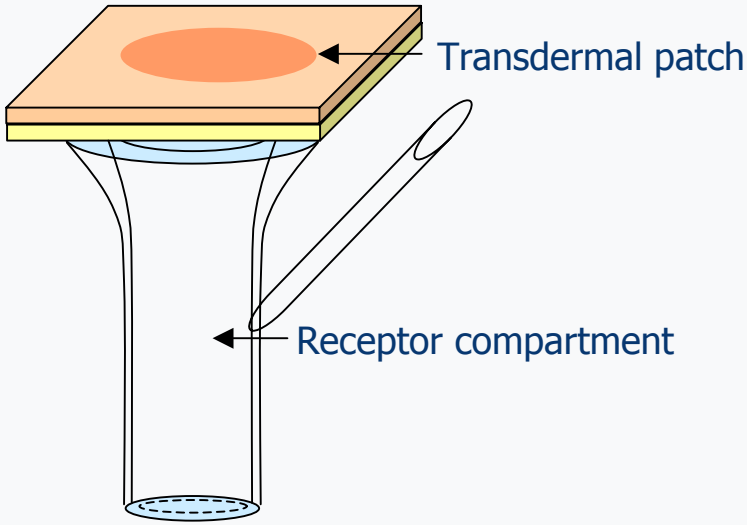
30 mpk P.O.

Salt form with "solubility modifier"

Transdermal delivery

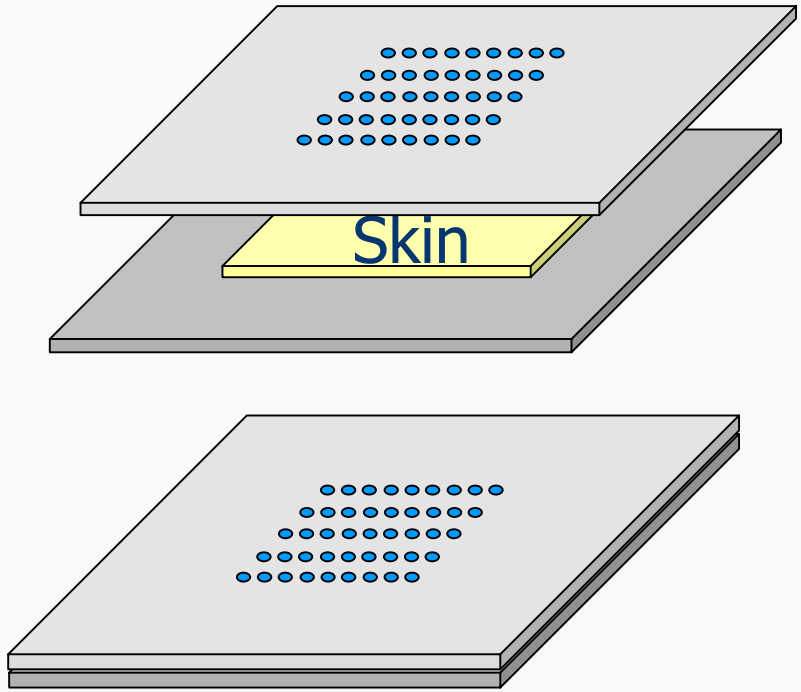
- **Standard Diffusion Cell**

Low throughput
Slow

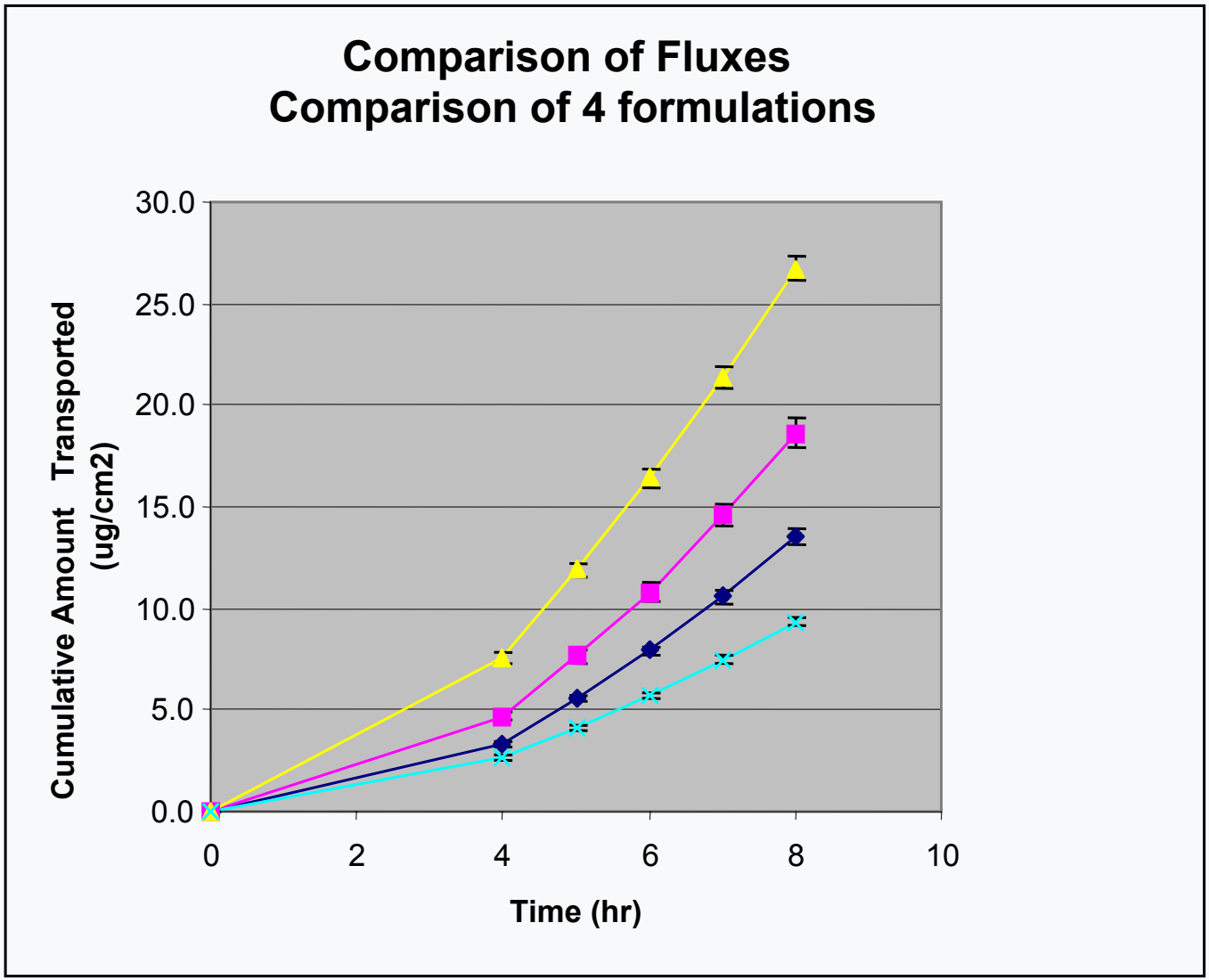


- **HT Diffusion Cell Array**

High throughput
Fast



Skin permeation from HT system



Conclusions

- "Developability" is a key factor in finding new drugs
  - Potent active compounds are not necessarily drugs – other properties are critical
- HT form and formulation techniques are important
  - Discovery: helps medicinal chemists with SAR
  - Pre-clinical: optimizes products
  - Marketed products: improves product performance and provides new IP
- High throughput technologies do not replace good science and engineering – they provide more data and enable better decisions