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

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Drug Discovery / Development

R&D takes 6.5 - 13.5 years
$60 - 300 million

Source: PRTM
Historic NCE Pipeline Success

NCE Probability of Success by Phase: 1990s

100 Preclinical Candidates

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

![Bar chart showing reasons for product candidates failing.](chart.png)
Form & Formulation

Active compound → Optimized form → Effective formulation

Small molecule drugs:
- Solubility
- Dissolution Rate
- Bioavailability
- Release profile
- Stability

Biologics/Vaccines:
- Stability
- Solubility
- Activity, yield
- Efficacy
- Delivery profile

Maximize Product Value
Form & Formulation: Traditional

- Mostly manual experimentation
- Low throughput
New R&D Challenges

Resource constraints

Discovery revolution

Pharmaceutical Development

Time constraints

Drug Discovery
Preclinical development
Clinical development
Bringing High Throughput to the Process

- Drug Discovery
  - Solubility
  - Lead selection

- Preclinical development
  - Bioavailability
  - Stability
  - "Bricks"

- Clinical development
  - Dosage form
  - Regimen

- Regulatory
  - Rational process design

- Manufacture
  - COGS
  - Risk reduction

- Marketing/Sales
  - Product enhancements
  - IP

- Automated, high throughput experimentation
- Microscale
- Informatics driven

Optimal
Integrated Technology Platforms

Active pharmaceutical ingredient

CrystalMax™
Solid forms

INFORM
Informatics

FAST™/SFinX™
Formulations
Exploration of Solid Forms and Methods

Traditional

process impurity or degradate

solvent

TransForm (CrystalMax™)

salt former API

process impurity

process (t,T)

solvent

process (t,T)

temperature

Hydrates

solvent

Polymorphs
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?

100 µL evaporation study

- **MeOH/well**
- **Pentane/well**
- **MeOH/tube**
- **Pentane/tube**

**Volume remaining (%)**

**Time (min)**
Innovative Approach to Primary Analysis
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 compatibility

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”

Lead (active molecule)

Potency

Selectivity

Metabolism

Physical properties

Best leads

Potency

Selectivity

Metabolism

Physical / chemical properties

Biopharmaceutics

LO (optimized molecule)
Animal Studies: Bioavailability

- Improved oral bioavailability demonstrated with TPI formulations
- IV dosing enabled by TPI formulations
Applications in Pre-Clinical and Clinical Development
Development Risk: Norvir

PR Newswire July 27, 1998

ABBOTT ANNOUNCES DIFFICULTY MANUFACTURING NORVIR® (RITONAVIR) CAPSULES

— COMPANY PLANS TO SUBSTITUTE WITH LIQUID FORMULATION —


"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.
TransForm Solution: Norvir

Within 4 weeks:

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

TPI’s analysis required < 2 g of material
TPI 211: Identification of improved formulations

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

30 mpk P.O.

Salt form with “solubility modifier”

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Transdermal delivery
• Standard Diffusion Cell

Low throughput
Slow

• HT Diffusion Cell Array

High throughput
Fast

Transdermal patch
Receptor compartment

Skin
Skin permeation from HT system

Comparison of Fluxes
Comparison of 4 formulations

Cumulative Amount Transported (ug/cm²)

Time (hr)
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