Industry Challenges in Oral Drug Development

“Faster and more cost-effective development of treatments with optimized therapeutic performance.”

Efficient Development
Faster Development Pathway
Better Therapeutic Performance

Target Product Profile

- Understand molecule Physicochemical Properties
- Preclinical and clinical proof of concept
- Solution for PK/PD challenges
- Stability and robustness of formulation
- Optimal delivery technology and dose forms

DESIRED OUTCOME

- Optimal Molecule form
- Optimized formulation for best bioavailability
- Optimized Final Dose Form & Dosing Profile
## Getting to Clinic Faster with a Suitable Formulation is Key to Early Stage Development

<table>
<thead>
<tr>
<th><strong>CHALLENGES</strong></th>
<th><strong>DESIRED SOLUTIONS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited amount of material available</td>
<td>Ability to handle pre-formulation with <strong>minimal amount of material</strong></td>
</tr>
<tr>
<td>New molecules present complex bioavailability and formulation challenges not</td>
<td><strong>Expert advice</strong> on formulation options and technology expertise to solve complex bioavailability challenges</td>
</tr>
<tr>
<td>easily overcome by simple methods</td>
<td></td>
</tr>
<tr>
<td>Quick and timely entry into toxicity and phase I studies</td>
<td><strong>Speedy</strong> execution of product development</td>
</tr>
<tr>
<td>Limited funding prior to phase I</td>
<td><strong>Efficient</strong> and <strong>cost effective</strong> way to assess development pathway minimizing cash burn</td>
</tr>
<tr>
<td>Resource constraints on project management</td>
<td>Getting the right partner for <strong>easier and simpler project management</strong></td>
</tr>
</tbody>
</table>
Bioavailability Challenges Substantially Complicate Achieving Targeted Efficacy

Only 1 in 10 new molecules in active clinical development are readily bioavailable

Solubility of Pipeline Products (2013)

... and even those molecules may not be sufficiently absorbed when dosed at escalated levels

Traditional “Powder in Bottle” is Unlikely to Achieve Targeted Efficacy for Most New Oral Molecules

R. Lipp; The Innovator Pipeline: Bioavailability Challenges and Advanced Oral Drug Delivery Opportunities, Am. Pharm. Rev., 2013

Pointeaux T et al., Drug Development and Delivery, 2011, 11(8):60-66
Several successful bioavailability enhancement formulation technologies have brought **100+ drug products to market.**

- Lipid-based formulation
- Solid Dispersion
- Particle Size Reduction
- Salt Form

### Table: NMEs Approved and Using Solubilization Technologies

<table>
<thead>
<tr>
<th>Decade*</th>
<th>NMEs approved</th>
<th>NMEs using solubilization technologies</th>
</tr>
</thead>
<tbody>
<tr>
<td>1940 - 1969</td>
<td>543</td>
<td>NA</td>
</tr>
<tr>
<td>1970 - 1979</td>
<td>170</td>
<td>0.6%</td>
</tr>
<tr>
<td>1980 - 1989</td>
<td>217</td>
<td>4.1%</td>
</tr>
<tr>
<td>1990 - 1999</td>
<td>311</td>
<td>5.1%</td>
</tr>
<tr>
<td>2000 - 2009</td>
<td>235</td>
<td><strong>10.2%</strong></td>
</tr>
<tr>
<td>2010 - 2013</td>
<td>109</td>
<td>6.4%</td>
</tr>
</tbody>
</table>

*Source: CPhI Pre-connect, 10/2014*
Bridging Drug Compound Properties to Formulation Approaches... Developability Classification System

Courtesy of R. Savla
We All Know The BCS But...

Gordon’s Real BCS

Solubility

High

Low

Permeability

High

Low

Formulation

Purgatory

Bioavailability

Limbo

... How does it help us select a suitable Formulation?
Developing a Modified Classification System

**BCS – a regulatory tool**
- Conservative, efficacy and patient safety in mind
  - When is there no bio-inequivalence risk?
- Useful in late development and post-launch

**DCS – a developability tool**
- Aim: realistic, product development issues in mind
  - What factors are likely to control the extent of oral absorption?
    - Permeability, solubility/dose, dissolution rate
- Particularly useful in evaluating potential new drug candidates

*Butler & Dressman  2010  J. Pharm. Sci. 99 (12) 4940–4954*
Use of Correlation to Further Improve Intestinal Solubility Estimates

P Augustinjs et al.; A review of drug solubility in human intestinal fluids: Implications for the prediction of oral absorption, Eur. J. Pharm Sci – This work was contributed to the OrBiTo project (http://www.imi.europa.eu/content/)
DCS vs. BCS Classification of Compounds

DCS (Developability) vs. BCS Classification

Source: Dr. S. Page, Roche, CRS Meeting July 12-16, 2008, NY

Source: Butler, J. The optimal use of biorelevant media & simple modeling for the prediction of in-vivo oral behaviour (http://www.apsgb.co.uk/Events/PastEvents/20110609/James%20Butler.pdf)
Some Key Features of the DCS

**Solubility limited absorbable dose (SLAD)**
- Assumes a 500ml volume available for drug dissolution.
- Peff >1x10^{-4} cm/sec assumed to proportionally increase the effective volume available for dissolution of highly permeable drugs.
- Represents the dose above which absorption is solubility limited. i.e. beyond this:
  - Linear exposure/dose response may be lost
  - Solubility related food effects are likely
  - Reducing particle size alone cannot achieve complete absorption

**Recommended particle size**
- Derived from “dissolution number” equation
- Approach: set target dissolution number to 1, solve the equation for particle diameter, use this as the target x90.

\[ Dn = \left( \frac{3D}{r_0^2} \right) \left( \frac{C_s}{\rho} \right) \langle t \rangle \]

Dn concept from Oh et al, Pharm Res 1993 10 (2) 264-270

J. Butler, 2013  Phys Chem Forum
Setting the Right Formulation Strategy for the Right Compound

Formulation strategies for DCS IIb compounds

**DCS: developability classification system**

*Source: Butler, J. The optimal use of biorelevant media & simple modeling for the prediction of in-vivo oral behaviour (http://www.apsgb.co.uk/Events/PastEvents/20110609/James%20Butler.pdf)*
The Role of Lipid-based Drug Delivery Systems: Achieving pre and post Administration Solubility

Dispersion

Digestion

Precipitation ?

TG $\rightarrow$ DG $\rightarrow$ MG + FA

Formation of colloidal structures with endogenous biliary lipids

Avoid drug substance precipitation upon dispersion and digestion

Fig from Porter CJH et al., Nature Reviews | Drug Discovery, 2007, 6:231-248
Solid Amorphous Dispersions for DCS IIb drugs...

- Amorphous forms of drugs are high energy forms.
- Since there is no crystal lattice structure (no long range order), the energy barrier to dissolution is much reduced.
- Inherently unstable, and will tend to revert to the stable and usually least soluble form. Need to be stabilized (solid solutions, dispersions) with polymers.
  - Hot Melt Extrusion and Spray Drying as processing technologies
Solubility: Many compounds in Quadrant II!
NEW OptiForm® Solution Suite: Enhanced Bioavailability in 12 Weeks

OptiForm® Solution Suite is an integrated offering designed to efficiently and rapidly help solve complex bioavailability and formulation challenges for early stage compounds.

OptiForm® Solution Suite matches the best formulation technologies to your molecule, and utilizes an accelerated parallel screening and development approach, based on rigorous science and best-in-class scientific expertise, all in 12 weeks!
Catalent’s Structured Approach Designed to Help Ensure Bioavailability Enhancement

<table>
<thead>
<tr>
<th>OptiForm® Solution Suite Process Roadmap</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1 ASSESS</strong></td>
</tr>
<tr>
<td>High throughput molecule characterization</td>
</tr>
<tr>
<td>Physicochemical Properties</td>
</tr>
<tr>
<td>BCS / DCS Classification</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>2 ENHANCE</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DCS IIa Dissolution Issues</strong></td>
</tr>
<tr>
<td>• Particle size reduction</td>
</tr>
<tr>
<td>• Salt form</td>
</tr>
<tr>
<td><strong>DCS IIb Solubility Issues</strong></td>
</tr>
<tr>
<td>• Lipid formulation</td>
</tr>
<tr>
<td>• Solid dispersion or solution</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>3 DELIVER</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ENHANCED Bioavailability</strong></td>
</tr>
<tr>
<td>• Expert Technical Report</td>
</tr>
<tr>
<td>• Candidate Formulation Materials</td>
</tr>
</tbody>
</table>
We Can Help Improve Your Molecule at Every Stage of Development

<table>
<thead>
<tr>
<th>PRE-CLINICAL</th>
<th>PHASE I &amp; BEYOND</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OPTIFORM® SOLUTION SUITE</strong></td>
<td><strong>DRUG DELIVERY SOLUTIONS</strong></td>
</tr>
<tr>
<td><em>Enhanced Bioavailability in 12 Weeks</em></td>
<td></td>
</tr>
<tr>
<td><strong>1</strong></td>
<td><strong>2</strong></td>
</tr>
<tr>
<td><strong>ASSESS</strong></td>
<td><strong>ENHANCE</strong></td>
</tr>
<tr>
<td>• Molecule Characterization</td>
<td>• Expert Consultation</td>
</tr>
<tr>
<td>• Assess Salt Form Benefits</td>
<td>• Extensive analytical data report</td>
</tr>
<tr>
<td>• Preliminary Consultation to select formulation technologies for ENHANCE</td>
<td>• 1-4 animal PK study material</td>
</tr>
<tr>
<td></td>
<td>1. Lipid system</td>
</tr>
<tr>
<td></td>
<td>2. Solid dispersion</td>
</tr>
<tr>
<td></td>
<td>3. Micronized Material</td>
</tr>
<tr>
<td></td>
<td>4. Salt Form (optional)</td>
</tr>
</tbody>
</table>
Playing Russian Roulette With Tyrosine Kinase Inhibitors

RZ Szmulewitz$^1$ and MJ Ratain$^1$

Clin Pharmacol Ther, 2013
Russian Roulette (from wikipedia.org)

Russian roulette is a potentially lethal game of chance...

Dr. M. Ratain, 2016, Catalent Fierce Pharma Webinar
WARNING: QT PROLONGATION AND SUDDEN DEATHS

See full prescribing information for complete boxed warning.

- Tasigna prolongs the QT interval. Prior to Tasigna administration and periodically, monitor for hypokalemia or hypomagnesemia and correct deficiencies (5.2). Obtain ECGs to monitor the QTc at baseline, seven days after initiation, and periodically thereafter, and following any dose adjustments (5.2, 5.3, 5.7, 5.15).

- Sudden deaths have been reported in patients receiving nilotinib (5.3). Do not administer Tasigna to patients with hypokalemia, hypomagnesemia, or long QT syndrome (4, 5.2).

- Avoid use of concomitant drugs known to prolong the QT interval and strong CYP3A4 inhibitors (5.8).

- Avoid food 2 hours before and 1 hour after taking the dose (5.9).
Figure 4. AMN107 serum concentration (ng/mL) vs. placebo- and baseline adjusted QTcF (ΔΔQTcF) (ms) – Study 2119 – Sponsor’s Analysis.

(Sponsor’s figure 11-5 page 72 of study 2119 study report)

Dr. M. Ratain, 2016, Catalent Fierce Pharma Webinar

WARNING: QT PROLONGATION AND SUDDEN DEATHS

See full prescribing information for complete boxed warning.

• Tasigna prolongs the QT interval. Prior to Tasigna administration and periodically, monitor for hypokalemia or hypomagnesemia and correct deficiencies (5.2). Obtain ECGs to monitor the QTc at baseline, seven days after initiation, and periodically thereafter, and following any dose adjustments (5.2, 5.3, 5.7, 5.15).

• Sudden deaths have been reported in patients receiving nilotinib (5.3). Do not administer Tasigna to patients with hypokalemia, hypomagnesemia, or long QT syndrome (4, 5.2).

• Avoid use of concomitant drugs known to prolong the QT interval and strong CYP3A4 inhibitors (5.8).

• Avoid food 2 hours before and 1 hour after taking the dose (5.9).
Clinical Pharmacokinetics of the BCR–ABL Tyrosine Kinase Inhibitor Nilotinib

C Tanaka¹, OQP Yin¹, V Sethuraman¹, T Smith², X Wang¹, K Grouss¹, H Kantarjian³, F Giles⁴, OG Ottmann⁵, L Galitz⁶ and H Schran¹
In other words, if you take nilotinib with breakfast, you might die!!!

WARNING: QT PROLONGATION AND SUDDEN DEATHS

See full prescribing information for complete boxed warning.

- Tasigna prolongs the QT interval. Prior to Tasigna administration and periodically, monitor for hypokalemia or hypomagnesemia and correct deficiencies (5.2). Obtain ECGs to monitor the QTc at baseline, seven days after initiation, and periodically thereafter, and following any dose adjustments (5.2, 5.3, 5.7, 5.15).
- Sudden deaths have been reported in patients receiving nilotinib (5.3). Do not administer Tasigna to patients with hypokalemia, hypomagnesemia, or long QT syndrome (4, 5.2).
- Avoid use of concomitant drugs known to prolong the QT interval and strong CYP3A4 inhibitors (5.8).
- Avoid food 2 hours before and 1 hour after taking the dose (5.9).

Dr. M. Ratain, 2016, Catalent Fierce Pharma Webinar
Why are We Still Playing Russian Roulette with Tyrosine Kinase Inhibitors… Nilotinib

**Weak base, highly insoluble**
- max. dose 150-200 mg
- FaSSIF solubility 0.2 µg/mL
- FeSSIF solubility 0.9 µg/mL
- Estimated permeability $6.9 \times 10^{-4}$ cm/sec

**BCS II, DCS IIb**
- Highly solubility limited
- Recommended max particle size: 5 µm ($d_{90}$)
- Solubility Limited Absorbable Dose 1 mg (FeSSIF 3 mg)

**34 - 72% inter variability**
- **31% intra variability**
- **82 % positive food effect**

Marketed formulation is granulated API in capsule with poloxamer (DCS IIa option)
- DCSIIb system cancel food effect (solid dispersions)
Why are We Still Playing Russian Roulette with Protein Kinase Inhibitors...

All listed molecules are solubility limited at target dose. FeSSIF solubility drives a significant change in SLAD.
## Why are We Still Playing Russian Roulette with Protein Kinase Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Marketed Dose Form</th>
<th>Dose (mg)</th>
<th>DCS</th>
<th>Dose/Solubility Ratio</th>
<th>SLAD (mg)</th>
<th>Particle Size (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nilotinib</td>
<td>Capsule</td>
<td>400</td>
<td>IIb</td>
<td>2,000,000</td>
<td>1</td>
<td>3.5</td>
</tr>
<tr>
<td>Ceritinib</td>
<td>Capsule</td>
<td>750</td>
<td>IIb</td>
<td>11,177</td>
<td>219</td>
<td>63.3</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>Tablet</td>
<td>1250</td>
<td>IIb</td>
<td>192, 308</td>
<td>22</td>
<td>19.7</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>Tablet</td>
<td>150</td>
<td>IIb</td>
<td>32,609</td>
<td>17</td>
<td>16.6</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>Tablet</td>
<td>800</td>
<td>IIb</td>
<td>53,333</td>
<td>53</td>
<td>29.9</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>Tablet</td>
<td>250</td>
<td>IIa</td>
<td>1,688</td>
<td>535</td>
<td>94.1</td>
</tr>
</tbody>
</table>
Marketed Protein Kinase Inhibitors Overview
Formulation to Differentiate PKIs under Development

- 82% low solubility
- 40% narrow therapeutic index
- 78% non-optimized DDS
- 22% milled API and surfactants
- 31% HAVE A NON ADEQUATE DOSING REGIMEN

7 Black Labels

Catalent Pharma Solutions data analysis from 29 marketed PKIs, August 2015
Take Abiraterone vs Enzalutamide as an example...is good enough good enough???

Both Compounds are Highly Similar
Neutral, highly insoluble
Solubility 2 µg/mL
Estimated permeability 7.4 x 10^{-4} cm/sec

BCS II, DCS IIb
Highly solubility limited
Recommended max particle size: 11 µm (d_{90})
Solubility Limited Absorbable Dose: 7 mg

Enzalutamide suspension and solid form in early clinical evaluation always below lipid solutions
Lipid solution removes food effect and enables linear escalation up to 600 mg
Phase I-II: Liquid filled hard gelatin capsule
Market ready: Soft gelatin capsule
Zytiga® vs Xtandi® as an example...is good enough good enough???

**Abiraterone acetate** DCSIIa formulation

**API in Tablet Formulation**
- Indication: Treatment of patients with metastatic castration-resistant prostate cancer (CRPC) in combination with prednisone
- Dosage: 1,000 mg (4 X 250 mg) once daily
- Product Administration Directions: Must be taken on an empty stomach (no food at least 2 hours before and 1 hour after consumption)
- Food Effects: Approximately 17-fold and 10-fold higher, Cmax and AUC respectively, when a single dose of abiraterone acetate was administered with a high-fat (57% fat, 825 calories) meal compared to overnight fasting

**Enzalutamide** DCSIIb formulation

**Lipid in Softgel & Spray Dried Dispersions**
- Indication: Treatment of patients with metastatic castration-resistant prostate cancer (CRPC)
- Dosage: 160 mg (4 X 40 mg) once daily
- Product Administration Directions: Can be taken with or without food
- Food Effects: A high-fat meal did not alter AUC to enzalutamide or N-desmethyl enzalutamide

Zytiga is a registered trademark of Johnson & Johnson. Xtandi is a registered trademark of Astellas Pharma.
## Comparability in DCSIIB Formulations Performance
**Rp Scherer Softgel vs Spray Dried Dispersions**

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters (Units)(^a)</th>
<th>Tablet Formulation, Fasted Conditions (Test)</th>
<th>Liquid-Filled Soft Gelatin Capsule Formulation, Fasted Conditions (Reference)</th>
<th>Ratio(^b) (%)</th>
<th>90% Confidence Interval (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>28</td>
<td>29</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>AUC(_{\text{Day1-7}}) (μg•h/mL)</td>
<td>177 (24)</td>
<td>185 (25)</td>
<td>95</td>
<td>92</td>
</tr>
<tr>
<td>AUC(_{0-4}) (μg•h/mL)</td>
<td>255 (29)</td>
<td>269 (30)</td>
<td>95</td>
<td>92</td>
</tr>
<tr>
<td>AUC(_{0-\text{inf}}) (μg•h/mL)</td>
<td>263 (28)</td>
<td>278 (29)</td>
<td>94</td>
<td>92</td>
</tr>
<tr>
<td>C(_{\text{max}}) (μg/mL)</td>
<td>2.98 (24)</td>
<td>5.16 (20)</td>
<td>57</td>
<td>54</td>
</tr>
<tr>
<td>t(_{\text{max}}) (h)</td>
<td>4.00 (2.00 - 6.00)</td>
<td>1.00 (0.75 - 3.00)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>t(_{1/2}) (days)</td>
<td>3.45 (36)</td>
<td>3.67 (32)</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

Reference: PCT/US2013/059223
Important Points to Take Home Today

1) An increasing number of oral drug candidates fall into the poorly soluble space which is split between two categories: dissolution rate limited compounds (IIa) and solubility limited compounds (IIb).

2) Selecting the right delivery technology is not a game of chance and DCS is a valuable tool for guiding the selection of suitable formulation strategies in the early development phases.

3) DCS IIa and IIb compounds do not require similar delivery solutions. A non-proper technology selection can result in detrimental outcomes: non-ability to dose escalate, sub-optimal efficacy/safety profiles.

4) Optiform® Solution Suite is a screening platform offered by Catalent enabling rapid delivery technology selection which can be executed in the early development stage in 12 weeks or less.
OptiForm® Solution Suite Aims to Boost Early Access to Pre-clinical and Phase I Studies

**Easier**
Integrated solution at one price with minimal material needed.

**Simpler**
Optimal recommendations based on real data from a dedicated scientific advisor.

**Faster**
Accelerated parallel process with superior technologies allowing for optimized animal PK prototypes in 12 weeks!