INTEGRATED DRUG DEVELOPMENT PROCESS
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Erika Zannou, Ph.D. & Tony Tong, Ph.D., Novartis Pharmaceuticals Corp.

• Developability Assessment Supporting Drug Candidate Selection
  • Profiling of key Physicochemical Properties
  • Biopharmaceutical Assessment

• Preformulation
  • Solubility, Stability, Dissolution Rate and Solid State Properties
  • Salt and Form Screening and Selection
  • Excipient Compatibility

• Dosage Form Design
  • Conventional
  • Non- Conventional

• Formulation Development, Evaluation and Scale-up

• Equipment and Processing

• Regulatory Considerations
INTEGRATED DRUG DEVELOPMENT PROCESS

** Colors used for Drug Substance, Drug Product and Clinical studies are matching
INTEGRATED DRUG DEVELOPMENT PROCESS

Figure 2.5
ALLOCATION OF DOMESTIC U.S. R&D BY FUNCTION, 1998

Synthesis and Extraction: 12.0%
Biological Screening and Pharmacological Testing: 15.1%
Toxicology and Safety Testing: 5.2%
Pharmaceutical Dosage Formulation and Stability: 9.0%
Clinical Evaluation: Phases I, II, and III: 28.3%
Clinical Evaluation: Phase IV: 5.8%
Process Development for Manufacturing and Quality Control: 9.9%
Regulatory: IND and NDA: 4.4%
Bioavailability: 2.4%
Other: 7.9%

Note: Totals may not add exactly due to rounding. R&D functions are not exactly sequential in practice.

INTEGRATED DRUG DEVELOPMENT PROCESS

- Phase I: Pharmacokinetics and Safety
  Small number of Healthy Volunteers

- Phase II: Safety and Efficacy
  Larger patient population

- Phase III – Pivotal Studies: Long-term Safety and Efficacy
  Several thousands of patients in multiple clinical centers

- Future: Clinical Trials Simulations
  Seamless Clinical Trial Designs
  Bio-Markers
DOSAGE FORM DESIGN

- Balance of Dosage Form Requirements
  Biopharmaceutics, Physical/Chemical, Process, Marketing, Regulatory

- Evolution with Time of Dosage Form Requirements & Knowledge
  Phase I through Phase III, Commercial Form, Product Line Extensions

- Classification of Various Dosage Forms
  Route of Administration
  Time Course of Drug Delivery
  Target Organ, Tissue of Cell for Drug Delivery
DOSAGE FORM DESIGN
Balanced Needs
INTEGRATED DRUG DEVELOPMENT PROCESS

** Colors used for Drug Substance, Drug Product and Clinical studies are matching
DOSAGE FORM DESIGN
Drug Product Attrition Curve

Attrition Curve

Managing Attrition Curve

Ref: R.L. Lipper, Modern Drug Discovery, Jan-Feb 1999, 55-60
DOSAGE FORM DESIGN
Evolution of Dosage Form Needs

• Preclinical (Toxicology) Dosage Forms
  – Biopharmaceutics - Emphasis is on Exposure, High Drug Concentration
    » Suspensions (NaCMC), Drug/Feed Mixtures
    » Specialized Forms (Yogurt)

• Phase I Clinical Dosage Forms
  – Biopharmaceutics - Simple, Flexible Dosing
    » Single/Multiple Dose Tolerability Studies, Healthy Volunteers
    » Efficacy Marker - Proof of Concept, Attrition Curve
    » Solutions, Powder-in-a-Bottle, Hard Gelatin Capsules

• Phase II Clinical Dosage Forms
  – Biopharmaceutics, Physico-Chemical, Processing - Larger, Longer Studies
    » Patients, Dose Finding and Proof of Concept
    » Blinded Capsules or Tablets
DOSAGE FORM DESIGN
Evolution of Dosage Form Needs

• Phase III Clinical Dosage Forms
  – Biopharmaceutics, Phy/Chemical, Processing - Even Larger, Longer Studies
    » Patients, Pivotal Efficacy and Safety
    » Capsules or Tablets, Blinded or Branded (Double Dummy)

• Marketed Forms
  – Biopharmaceutics, Phy/Chemical, Processing, Market, Regulatory
    » Consumers
    » Size, Shape, Color, Branded Tablets or Capsules

• Product Line Extensions
  – Biopharmaceutics, Phy/Chemical, Processing, Market, Regulatory
    » Protection from Generic Erosion
    » Controlled Release, Fixed Combination, Alternate Delivery Forms
DOSAGE FORM DESIGN

- Biopharmaceutical
  - Mechanism of Action
  - Target Organ
  - Dose (Potency)
  - Permeability (Passive, Active, Efflux)
  - Pharmacokinetics
    » Absorption
    » Distribution
    » Metabolism
    » Distribution
## Biopharmaceutics Classification System

<table>
<thead>
<tr>
<th>High Solubility</th>
<th>Low Solubility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Class II</td>
</tr>
<tr>
<td>High Permeability</td>
<td>Dissolution rate limits absorption</td>
</tr>
<tr>
<td>Low Permeability</td>
<td>Class III</td>
</tr>
<tr>
<td></td>
<td>Permeability limits absorption</td>
</tr>
<tr>
<td></td>
<td>Class IV</td>
</tr>
<tr>
<td></td>
<td>Significant problems for oral delivery expected</td>
</tr>
</tbody>
</table>

G. L. Amidon et al., *Pharm. Res.* (1995), 12, 413-420
DOSAGE FORM DESIGN
Biopharmaceutical Particle Size Needs

- Particles larger than 6 µm deposit in mouth and trachea.
- Particles between 6-2 µm deposit in bronchi & bronchioles.
- Particles less than 2 µm deposit in terminal bronchioles and alveoli.
DOSAGE FORM DESIGN
Physiological pH

Gastric pH in the fasted state and after food intake (pH 6, 458 calories and 400 ml total volume) in 10 healthy volunteers.

Duodenal pH in the fasted state and after food intake (pH 6, 458 calories and 400 ml total volume) in 10 healthy volunteers.

DOSAGE FORM DESIGN

• Physical/Chemical
  – Solubility (Dissolution)
  – log P, PSA, H-donors, H-acceptors
  – mw
  – Stability (Heat, Humidity, Light)
  – pH (Drug Substance and Excipients)
  – Excipient Compatibility
  – Morphology
  – Density (Bulk and Tap)
  – Particle Size
  – Wetting (Surface Energy)
  – Static Properties
  – Flow Properties
  – Compressibility and Compactability
  – Hygroscopicity
  – Polymorphism
DOSAGE FORM DESIGN

• Processing
  – Cost of Goods
    » Capital Investments
    » Dosage Form (Tablet vs. Hard Gelatin Capsules)
    » Size (6mm Tablet vs. 11mm Tablet)
    » Shape (Round Tablet vs. Unique Shaped - Keyed Tools)
    » Excipients (Alternate Suppliers)
    » Processing Efficiency (Number of Process Steps, Speed of Processing, Volume of Process)
    » Failure Rate (Rejected Batches)
DOSAGE FORM DESIGN

• Marketing
  – Time for Development
  – Patent Protection
  – Competitive Advantage
    » Aesthetics (Size, Shape, Color, Taste, Painless)
    » Patient Compliance (Once-A-Day vs bid)
    » Price (Cost of Goods)
DOSAGE FORM DESIGN

• Regulatory
  – Documented Formula, Process and Packaging
    » Active Ingredients
    » Excipients
    » Testing Methods
    » Specifications
    » Equipment
    » Unit Operations
    » In-Process Controls
  – Validation of the Process
  – Validation of the Release and Stability Testing Methods
  – Stability Report on Package Drug Product (Bulk, Primary)
  – Documents
    » IND, NDAs, Validation Reports
DOSAGE FORM DESIGN
Types of Formulations

• Route of Administration
  – Oral
  – Injectable
  – Topical
  – Inhalation

• Time Course of Drug Release
  – Immediate Release
  – Sustained Release
  – Controlled Release
  – Pulsed Release

• Targeted Release
  – Organ Specific
  – Tissue Specific (Tumor)
  – Cell Specific
Decision Tree Logic for First into Man Formulation

**SCHEME 3.1**
Considerations for CSF Development

- **CSF = Capsule formulation**
  - 10 mg, 50 mg, 100 mg
  - Fast dissolution rate
  - Chemically stable
  - No change of dissolution upon stability

- **Challenges:**
  - Very limited drug substance supply (280 g for development and clinical) - Flexibility with formulation required

- **Physico-chemical Properties**
  - Log P = 3.4
  - Log D (pH 6.0) = 3.4
  - \( pK_{a1} \approx 1.5 \) (base)
  - \( pK_{a2} = 5.33 \) (base)
  - \( pK_{a3} = 8.57 \) (acid)
  - MW free base = 400
  - Salt selection
Global Technical Research & Development

pH-Solubility Profile

Besylate counter ion
- $S_o = 0.0008 \text{ mg/mL at } 25^\circ \text{C}$
- $pK_a = 5.33$
- $MW = 400$

- $pH_{max} \sim 2.2$
- $pH$ of saturated solution
  $\sim 2.3 (0.57 \text{ mg/mL})$

Solid Phase:

![Graph showing pH-Solubility Profile]

- Besylate Monohydrate Salt
- pH max
- Free Base

Theoretical
- Free Base
- Maleate Salt
No change in besylate salt upon milling
Global Technical Research & Development

Solid State Characterization

Besylate Salt
- Dehydration $\sim 130^\circ$C
- m.p. $\sim 194^\circ$C

QAD171 Free Base
- m.p. = 296.30$^\circ$C

Stoichiometric monohydrate confirmed by:
- TGA ($\sim 3\%$)
- DSC
Chemical Stability

• Excellent solid state stability after 1 week at:
  – 80°C in tight container
  – 80°C/75% RH

• Non-hygroscopic

• No detectable degradation after 2 weeks at 50°C with 20% water (closed glass container) (1 month data point this week)

• pH-rate profile
  – No major instability over pH 1-13 after:
    » 2 weeks (4°C to 50°C)
    » 1 day at RT under light
  – Some instability over pH 1-13 under high intensity light
Excipient Compatibility

- No major incompatibility with diluents and lubricants noted by microcalorimetry
- Conventional HPLC studies
  - 1% drug loading, 50°C wet and dry conditions
  - No major incompatibility after 2 weeks
  - 1 month data this week

| Ingredients       | Formulation Range (%) | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
|-------------------|-----------------------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|
| Drug              | 5-50                  | ND| ND| ND| ND| ND| ND| ND| ND| ND| 0.1| ND| ND| ND| ND| ND| ND| ND| ND| ND| ND| ND|
| Lactose           | 30-80                 | ND| ND| ND| ND| ND| ND| ND| ND| ND| 0.1| ND| ND| ND| ND| ND| ND| ND| ND| ND| ND| ND|
| Mannitol          | 30-80                 | ND| ND| ND| ND| ND| ND| ND| ND| ND| 0.1| ND| ND| ND| ND| ND| ND| ND| ND| ND| ND| ND|
| Avicel            | 10-80                 | ND| ND| ND| ND| ND| ND| ND| ND| ND| 0.1| ND| ND| ND| ND| ND| ND| ND| ND| ND| ND| ND|
| Starch 1500       | 10-50                 | ND| ND| ND| ND| ND| ND| ND| ND| ND| 0.1| ND| ND| ND| ND| ND| ND| ND| ND| ND| ND| ND|
| Mg St             | 0.5-2                 | ND| ND| ND| ND| ND| ND| ND| ND| ND| 0.1| ND| ND| ND| ND| ND| ND| ND| ND| ND| ND| ND|
| Stearic ac.       | 2-5                   | ND| ND| ND| ND| ND| ND| ND| ND| ND| 0.1| ND| ND| ND| ND| ND| ND| ND| ND| ND| ND| ND|
| Cutina            | 2-4                   | ND| ND| ND| ND| ND| ND| ND| ND| ND| 0.1| ND| ND| ND| ND| ND| ND| ND| ND| ND| ND| ND|
| Crospovidone      | 2-5                   | ND| ND| ND| ND| ND| ND| ND| ND| ND| 0.1| ND| ND| ND| ND| ND| ND| ND| ND| ND| ND| ND|
| Croscarmellose Na | 2-5                   | ND| ND| ND| ND| ND| ND| ND| ND| ND| 0.1| ND| ND| ND| ND| ND| ND| ND| ND| ND| ND| ND|
| Na starch glycolate| 2-8                   | ND| ND| ND| ND| ND| ND| ND| ND| ND| 0.1| ND| ND| ND| ND| ND| ND| ND| ND| ND| ND| ND|
| CSD               | 0.1-0.5               | ND| ND| ND| ND| ND| ND| ND| ND| ND| 0.1| ND| ND| ND| ND| ND| ND| ND| ND| ND| ND| ND|
| Talc              | 1-10                  | ND| ND| ND| ND| ND| ND| ND| ND| ND| 0.1| ND| ND| ND| ND| ND| ND| ND| ND| ND| ND| ND|
| Povidone          | 0.5-5                 | ND| ND| ND| ND| ND| ND| ND| ND| ND| 0.1| ND| ND| ND| ND| ND| ND| ND| ND| ND| ND| ND|
| HPMC              | 2-5                   | ND| ND| ND| ND| ND| ND| ND| ND| ND| 0.1| ND| ND| ND| ND| ND| ND| ND| ND| ND| ND| ND|
| HPC               | 2-5                   | ND| ND| ND| ND| ND| ND| ND| ND| ND| 0.1| ND| ND| ND| ND| ND| ND| ND| ND| ND| ND| ND|
| Gelatin Capsule   |                       | ND| ND| ND| ND| ND| ND| ND| ND| ND| 0.1| ND| ND| ND| ND| ND| ND| ND| ND| ND| ND| ND|