The Importance and Role of Formulation in Antiviral Drug Development Programs

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What is formulation?
The science of transforming an Active Pharmaceutical Ingredient (API) into a Drug Product (DP) in a specific dosage form.
Three major needs that the formulation into a specific dosage form directly address
Industry needs: Optimizing the quantitative drug characteristics.
   ◦ Drug product viability

Patient needs: Optimizing the qualitative drug characteristics.
   ◦ Patient compliance

Reformulation needs: Improving upon API challenges and issues.
Rational Formulation Development

Drug Discovery
- Dose
- Solubility
- Melting Point
- Log P
- Permeability
- Bioavailability
- Metabolism
- Surface Area

Pre-formulation
- Excipient selection
- API/excipient solubility & stability
- Drug absorption

Formulation
- Dosage form selection
- Formulation stability
- In vitro testing
- In vivo testing

Scale up and production
- Feasibility
- Clinical
- Shelf Life
- Scale-up
- Industrial

GO / NO GO

Pre-formulation

Drug Discovery
Routes of Administration

- Inhalation
- Oral
- Topical
- Injection
62% of the field

- Dissolves in GI fluids
  - Controlled release via ‘pill’ coating
- Tablet
  - 5 – 10% API
  - Easily manufactured

- Capsule
  - Formulation for poorly soluble API
  - High potent API
Oral Drug Delivery

Liver Metabolism (First Pass)
GI Wall Metabolism
Transporters
Gut Lumen

Drug in Systemic Circulation

Disintegration
Dissolution
Degradation

STOMACH / INTESTINE
Route of Administration: Topical

~18% of the field
- Applied to the skin or mucous membranes
- Cream, Ointment, Gel, Foam, Patch, Film
- Wide range of drug delivery targets:
  - Systemic delivery
  - Localized delivery
- API characteristics dictate formulation
  - Molecular Weight
  - Permeability
  - Lipophilicity
  - Potency
Topical Drug Delivery

Dissolution

Stratum Corneum
Epidermis
Dermis

Diffusion

Drug in Systemic Circulation
Route of Administration: Injection

~16% of the field

- Liquid
  - Stable and soluble compounds
    - Dissolved solutions
    - Emulsion suspension
- Lyophilized
  - Administration includes premixing
  - Less stable API
  - Long term storage stability
- Often require specific storage and handling
- Primary dosage for protein API
Parenteral Drug Delivery

Intravenous (IV)  Subcutaneous (SC)  Intramuscular (IM)

Source: Merck 2012
~4% of the field

- Systemic and local drug delivery
- Rapid drug delivery to capillaries
  - Lungs
  - Nose to brain
- Surface Area of Drug
  - Small particle sizes required: ≤5µm
  - Small volumes delivered: 50 – 200 µL
## Antiviral Administration

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trade Name</th>
<th>Class</th>
<th>Route of Administration</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>Zovirax</td>
<td>Nucleoside Analog</td>
<td>Intravenous / Topical</td>
<td>Herpes Simplex</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>Heptovir</td>
<td>NRTI</td>
<td>Oral</td>
<td>HIV / HepB</td>
</tr>
<tr>
<td>Zanamivir</td>
<td>Relenza</td>
<td>Neuraminidase Inhib.</td>
<td>Inhalation</td>
<td>Influenza</td>
</tr>
<tr>
<td>Lopinavir</td>
<td>Kaletra</td>
<td>Protease Inhib.</td>
<td>Oral</td>
<td>HIV</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Kaletra</td>
<td>Protease Inhib.</td>
<td>Oral</td>
<td>HIV</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>Retrovir</td>
<td>NRTI</td>
<td>Intravenous</td>
<td>HIV</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>Viramune</td>
<td>NNRTI</td>
<td>Oral</td>
<td>HIV</td>
</tr>
<tr>
<td>Ganciclovir</td>
<td>Cytovene</td>
<td>Nucleoside Analog</td>
<td>Intravenous</td>
<td>Cytomegalovirus</td>
</tr>
</tbody>
</table>
Effect of formulation on drug delivery

- Comparison between Liquid and Solid dosage
  - Lamivudine in solution and tablet formulation

Kasirye et al. Clinical Pharmacology and Therapeutics; 2012
Effect of formulation on drug delivery

- Comparison between Capsules and Tablets
  - Lopinavir/ritonavir tablets and capsules

Hull et al. Journal of Clinical Pharmacology; 2009
Why is Rational Formulation Important?

- The driving goal for an NCE is to make it to toxicity studies and FIH trials

<table>
<thead>
<tr>
<th></th>
<th>NCE</th>
<th>Formulation Enabled Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to Approval</td>
<td>12 – 15 years</td>
<td>6 – 7 years</td>
</tr>
<tr>
<td>Clinical Development and Approval Success Rate</td>
<td>16%</td>
<td>25%</td>
</tr>
<tr>
<td>Development Cost</td>
<td>$1.2 billion</td>
<td>$98 million</td>
</tr>
</tbody>
</table>

Source: BCC Research 2012
Rational Formulation

CLASS I
High solubility
High permeability
35% 5%

CLASS II
Low solubility
High permeability
30% 70%

CLASS III
High solubility
Low permeability
25% 5%

CLASS IV
Low solubility
Low permeability
10% 20%

Source: L. Benet – Bulletin Technique Gattefossé - 2012
Importance of Formulation

Science!

- Solubility enhancing excipients
- Solubilizers
- Enhancing drug delivery
  - Encapsulation
  - Polymer/peptide conjugation

Entire industry specifically to address the solubility of NCEs
Importance of Formulation

- However...

- Patent Extension
  - Reformulation of existing products
  - Optimizing R&D ROI
- Competitive Edge
- Swift development and entry into market

Commercial value of formulation
Other Business Considerations

- Scale-up and Manufacturing
- Target population
- Formulation optimization based upon economy
  - Reducing cost with alternative materials
  - Streamlining synthetic pathways
  - Enhancing bioavailability to reduce dosage
  - Increasing shelf life
Role of Formulation within the Drug Development Process

Development Stage

Drug Discovery / Preclinical
- Pre-formulation
- Formulation Development
- Support for Preclinical studies

Clinical
- Supply of clinical trial materials

Life Cycle Management
- Reformulation
- 2nd generation products
- Rx to OTC transition
The success of bringing any new medicine to the market is can be facilitated by rational formulation design early in the development.

Formulation development is influenced by considerations both upstream and downstream the drug pipeline that will ultimately determine success.
ImQuestSUCCESS

At the intersection of science and business