Why and how does a pharmaceutical company take the risk to use novel excipients?

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Global Excipient Acceptability Evaluation for Regulatory acceptability including Japan

- Ideally – listed in major compendia (USP/NF, PhEur, JP/JPE)
- Not Listed – additional tox data may be needed
- Clinical use vs. Registered use
- Maximum Daily Allowed:
  - JPE allowed limits
  - Listed in FDA Inactive Ingredients Guide
  - *Handbook of Pharmaceutical Excipients*
  - Vendor information
  - Approved in marketed Rx products
    - Approved in non-Rx products
    - Approved in foods
  - WHO listing
Collaboration between Wyeth, BASF and IPEC

- In 2007, Jay Goldring from Wyeth Consumer Division and the Chair of IPEC Tox Committee started a job rotation program in Wyeth Early Pharmaceutical Development.

- Dr. Ku approached several excipient suppliers for possible collaboration in the IPEC new excipient review process.

- BASF took the challenge and agreed to collaborate and pay for the Tox consultant fee.

- The first case 18 months after IPEC proposed it.

- As the first excipient through the system, FDA agreed to review the package and reply with assessment.

- USP/NF Monograph issued. Solutol becomes compendial and no more hassle.
The Right First Time FIH Formulation Approach: No Human PK Bridging

One Formulation from FIH to POC at 90%
POC to Commercial at 80%

- Enhance Bioavailability with Less Food Effect
- Reduce PK variability to allow dose separation
- Control impurity/degradant levels below the ICH qualification threshold
- Room temperature storage with 2 year shelf life
- Scalability to a manufacture scale at batch sizes of 5,000-20,000 dose units
An industrial-wide trend for new clinical leads to be less soluble and permeable

Marketed Compound
N=141 (130 from WHO)

Wyeth NME N>100
(larger BCS 2 slice)
Choice of Formulation Strategy in Wyeth

Reference: M Sherry Ku 2006

- **Prior to 1993 for FIH clinical products**
  - Dry Blend
  - Dry Granulation
  - Wet Granulation

- **1993 Solid Dispersion**: Comelt, Sheeting, Milling, Encapsulation

- **1995 Semi-Solid Capsule**: Modified H&K machine to allow hot fill and cool to semisolid.

- **2001 CFS 1000 Liquid Capsule**: spray seal Licap

- **2003 Melt Granulation**: Comelt, High Shear Granulate

- **2004 LEMS 30**: Large-scale Liquid Cap manufacture

- **2005 Softgel capsule machine**
**Formulation Decision Tree**

**BCS Class 2 Compound**

Reference: M Sherry Ku 2006

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**DV: dose volume**

human dose divided by solubility at pH 6 for base or at pH 5 for acid or water solubility for salt form and non-ionizable compound
Distribution across 55 FIH projects from 2003 to 2009

FIH Formulations by Process

% of Products

- 23.6% Dry blend
- 40% Wet granulation
- 18.2% Solution/semisolid cap
- 1.8% Roller compaction
- 7.3% Melt granulation
- 5.5% Solid dispersion
- 3.6% Modified Release
- 23.6% Solid dispersion
BCS Compound distribution by FIH Formulation Process

- % of FIH Process Category

Bar chart showing the distribution of BCS compounds by process category:

- **Dry Blend**
  - BCS1
  - BCS2
  - BCS3
  - BCS4

- **Wet Granulation**
  - BCS1
  - BCS2
  - BCS3
  - BCS4

- **Solution/Semisolid**
  - BCS1
  - BCS2
  - BCS3
  - BCS4
Excipient Selection

Goal: To have the best formulation in terms of delivering the drug, room temperature stability, global acceptability and reasonable cost

- Very dependent on API properties
- Toxicity
- Regulatory (global acceptability)
- Source (including BSE)
- Cost
- Other considerations:
  - Functionality
  - Batch-to-batch variability
  - Chemical reactivity/stability
  - Experience
Excipient Compatibility Decision Tree

M Sherry Ku 2008 accepted for publication
Case History: Cremophor vs Solutol

- BASF solubilizer excipients, Cremophor® EL (Polyoxyl 35 Castor Oil, NF) and Cremophor® RH40 (Polyoxyl 40 Hydrogenated Castor Oil, NF) were developed by BASF prior to the development of Solutol® HS 15. Polyoxyl 35 Castor Oil is in 8 FDA-approved drugs and Polyoxyl 40 Hydrogenated Castor Oil is in 7 FDA-approved drugs as seen FDA’s Inactive Ingredient Database. In contrast to Cremophor®, Solutol® HS 15 is known to have less significant histamine release in animal toxicity studies. Polyoxyl Stearates are used in about 35 FDA-approved drugs as seen from the FDA inactive ingredient database.

- BASF excipient Solutol® HS 15 is a non-ionic solubilizer and emulsifying agent composed of polyglycol mono- and di- esters of 12-hydroxystearic acid (lipophilic part) and about 30% of free polyethylene glycol (hydrophilic part). It has been used in an injectable human drug, Oxidize® (Diclofenac sodium) manufactured by Beta S.A., Buenos Aires, Argentina. Solutol HS 15 has been used in Canada since 1989 in multivitamin injections in two injectable formulations, a 2 mg/mL formulation containing 7% Solutol HS 15, and a 10 mg/mL formulation containing 10% Solutol HS 15.
Dilemma: Whether to use of Solutol HS-15 in Formulation for Clinical Study

- Solutol HS-15 is classified as “new” excipient since it hasn’t been used in the U.S. in any marketed product
- Classification as “new” defines regulatory status
  - “New” excipients not approvable in NDAs without safety data
  - 2005 FDA Guidance: “[New excipients] are not fully qualified by existing safety data with respect to the currently proposed level of exposure, duration of exposure, or route of administration.”
  - Circular definition: approval in an NDA signifies qualification; unqualified excipients are not qualified
- JECFA has established an ADI for similar excipients, PEG-8-Stearate and PEG-40-Stearate. Solutol HS-15 is a PEG-15-HydroxyStearate and should have a very similar safety profile as the other PEG-Stearates.
- While Solutol HS-15 does cause the release of histamine from mast cells, it is less allergenic than the closely related structure Cremophor approved by FDA.
Contributed Human Experience – Clinical Studies Formulation containing Solutol HS-15

- Two (2) phase 1 studies have been clinically completed in the United States
  - A ascending single dose (SAD) study conducted in healthy subjects and a ascending multiple dose (MAD) study conducted in healthy subjects.
- In a Phase 2 POC study (6 weeks dosing), and an endoscopic examination (7 days GI safety study) was performed at up to 5 capsules of the placebo were dosed.
  - No AE’s in 12 patients dosed.
- Overall the AE profile from this study shows that a single oral dose of up to 10 capsules of the Wyeth formulation (containing 150 mg Solutol/capsule) are generally safe and well tolerated
Opportunities

- Stay ahead of excipient trends
- Establish relationships with excipient suppliers
- Participate in excipient qualification program
- Advocate for new excipient evaluation procedure
- Use services of IPEC
- Improve clinical product quality via use of novel and safe excipients.