Designing Quality into ER Products:
Technology Selection

2nd FDA/PQRI Conference on Advancing Product Quality
Dissolution Testing and Specification for Extended Release Products
N. Bethesda, Maryland

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Outline

- **ER Technology Selection** (thoughts -> models -> feasibility)
  - Selection Process
  - Formulation Platform Toolbox

- **ER Formulation Digital Design**
  - Osmotic Bilayer Tablet (example of predictive design tool)
  - Prototype in-vitro testing (dissolution & stability)

- **Early Clinical Concept Testing (PK)**
  - Rapid design & small scale manufacture
  - Extemporaneous Preparation
    - Pharmacy Compounding

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Today’s talk will focus on ER design for PK performance.
Defining Pharmaceutical Quality

- **Pharmaceutical Quality:**
  The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength, and purity.

  ICH Q6A Guidelines step 4 version 6-OCT-1999, p.19

- Dr. Janet Woodcock, defined high quality drug products as those that,
  - 1) consistently and reliably deliver the clinical performance and other characteristics stated on the label,
  - 2) are free from contamination, and
  - 3) are available.

  Reference: CMC Strategy Forum Europe 2014, Sarah Kennett, Ph.D.
Defining and Selecting the MR (e.g., ER, DR, CR) Dosage Form

1. Define CR Dosage Form Objectives and Medical Need
2. Define PK and PD Relationship to Medical Need
3. Draft the Idealized PK Profile
4. Define any PK Profile Limitations
5. Refine the Achievable PK Profile
6. Define the In-Vivo Release Profile
7. Define Dosage Form(s)
8. Model Dosage Form Release and Select Dosage Form

**Note:** Process generally takes ~2 weeks, but can be longer if dose changes (e.g., as clinical study design progresses the formulation dose may change to cover a different range)
MR (e.g., ER, DR, CR) Feasibility Assessment Flowchart

Initial "criteria"
- dose; half-life stability; pH-solubility profile
- dose/solubility ratio
- therapeutic index
- regional permeability
- metabolism

Define CR objectives
Confirm initial criteria are met

Define CR objectives
Confirm initial criteria are met

Excipient compatibility
Regional permeability
rat/dog/human
Caco-2 absorption
Predicted or actual human ADME

pH-solubility profile
pH-stability profile
Evaluate potential for precipitation in GI tract
Evaluate potential for degradation in GI tract

Define target dose and release profile

Desired PK profile
Dose solubility maps
Understand technology attributes
Potential drug release profiles
PGS attributes Equipment, expertise, cost, precedence
IP matters & competitive analysis

Simulations

Select technology via decision trees

Recommendations
- Degree of difficulty & probability of success
- Resources/timeline
- Solubilization strategies
- Recommend excipients
- Scale-up plan and path to commercialization

Reference:
Assessment of the feasibility of oral CR in an exploratory development setting
DDT • Volume 10, Number 17 • September 2005, A. Thombre
Some Key Considerations for Technology Selection

- **Dose-Solubility Map**

![Dose-Solubility Map Diagram]

- **Special Considerations (Patient Demographics)**
  - Children / Pediatrics (i.e., small dosage forms, chewable, multiparticulates, taste masking)
  - Elderly (e.g., small tablets...easy to swallow, QD dosing, combinations)
Solid Oral ER Formulation Toolbox

• **Osmotic Tablets**
  - **Benefits**: good IVIVC expected, administration w/food does not affect release rate
  - **Limitations**: higher dose (>500 mgA) design can be challenging for single unit

• **Matrix Tablets**
  - **Benefits**: higher doses more feasible, simple manufacturing, highly used in industry, good performance for diffusion based or broad therapeutic index
  - **Limitations**: Erosion based release mechanism challenging due to food effects, longer initial development time needed (multiple steps to refine PK performance), more clinical experience (PK/scintigraphy) helps to better understand performance

• **Multiparticulates / Beads**
  - **Benefits**: Dose flexibility, more consistent transit
  - **Limitations**: More complicated processing, no EP currently in Pfizer, but can dose manufactured beads/multiparticulates in early studies

Example Dissolution for Osmotic Tablet

Some Pfizer Example Products Below:
- Procardia XL (Osmotic)
- Detrol LA (Beads in Capsule)
- Pristiq ER (Matrix)
Digital Design
(Osmotic Design Model Example)

• What does the model do?
  – Allows for computer design of tablet weight, dimensions, coating components (e.g., different pore
    formers/permeability enhancers), coating composition, and coating amount to achieve a desired
    target release rate.

• Why use the model?
  – Quickly test different scenarios to get the formulation properties ~1 day
  – Reduces the need to iterate for different tablet sizes and release rates (get the coating composition
    right first time, saves experimental time, saves weeks)

• What happens next?
  – Make small scale lab prototype (generally <100 tablets, <25g API) ~ 1 week
  – Confirm dissolution profile and collect stability data, documentation ~6 weeks
  – Rapid small scale clinical manufacture and release ~4 weeks

• Goal (support efficient project progression to evaluate new treatments)
  – Enable project teams to go from concept (i.e., let’s evaluate ER) to having clinical supplies ready/
    released in less time than it takes to write the clinical protocol and file regulatory docs (~ 3 months)
Bilayer Osmotic Design (Example Inputs)

- **Model Inputs**
  - Drug loading
  - Tablet core properties
    - Influenced by dose
  - Osmotic pressure
  - Target release T80
  - Expected time lag
  - Coating properties
    - To achieve a target coating thickness & weight
    - Influenced by release rate (i.e., target duration) & core surface area
Bilayer Osmotic Design
(Example Outputs)

- **Model Outputs**
  - Simulation meets Pfizer Best Practice condition!
  - Tablet core properties
  - Release Rate & expected Time for 50% released
  - Coating properties
**Digital Design (Osmotic Tablet) (Understanding Design Space w/ a Model)**

- Model (select inputs and outputs) for enhanced design
  - Example of optimizing for coating thickness.

<table>
<thead>
<tr>
<th>Target T80 (hrs)</th>
<th>Active Layer/Core weight (mg)</th>
<th>Core Diam. (mm)</th>
<th>Core Thick. (mm)</th>
<th>Coating CA:PEG</th>
<th>Coating Thickness (um)</th>
<th>Coating Weight (%)</th>
<th>Pfizer Best Practice Condition?</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>100/150</td>
<td>7.1</td>
<td>4.4</td>
<td>9:1</td>
<td>120</td>
<td>13.4</td>
<td>Yes</td>
<td>Baseline</td>
</tr>
<tr>
<td>6</td>
<td>100/150</td>
<td>7.1</td>
<td>4.4</td>
<td>9:1</td>
<td>67</td>
<td>7.5</td>
<td>No</td>
<td>Permeability too low</td>
</tr>
<tr>
<td>6</td>
<td>100/150</td>
<td>7.1</td>
<td>4.4</td>
<td>8:2</td>
<td>117</td>
<td>13.0</td>
<td>Yes</td>
<td>Higher permeability</td>
</tr>
<tr>
<td>16</td>
<td>100/150</td>
<td>7.1</td>
<td>4.4</td>
<td>9.5:0.5</td>
<td>144</td>
<td>16.1</td>
<td>Yes</td>
<td>Lower permeability</td>
</tr>
<tr>
<td>16</td>
<td>280/420</td>
<td>9.5</td>
<td>6.6</td>
<td>9.5:0.5</td>
<td>103</td>
<td>8.2</td>
<td>Yes</td>
<td>Larger tablet increased mass &amp; surface area</td>
</tr>
</tbody>
</table>

**Software recommendation**

Best Practice Recommendations:
- These are not considered best practice conditions.
- Coating may be too thin (<70 microns). Consider using a lower CA:PEG ratio and more coating.
Extemporaneous Preparation
Pharmacy Compounding

• When
  – Early in Development (Pre-POC)
  – Later in Development (Post POC)
  – Product Enhancement (Post Commercial Launch)

• Why
  – Formulation flexibility or optimization
    (multiple concepts/formulations/doses)
  – Reduced material waste/cost
    (API, drug product, no release testing, no long term stability)
  – Reduced iteration time and speed to clinic
    (~3 months, very helpful for matrix tablets!)
  – When there is low probability of success
  – Demonstration of new product ideas (for buy up)

  – Ensure clinical supply quality via R&D design, Pharmacy
    regulations, practices, good clinical practice.

Project Team:
Can Extended Release Drug Delivery Help?
- Provide QD dosing
- Reduce Cmax
- Change shape of PK profile
- Achieve Cmin target
- Reduce adverse Events...

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- Finding innovative ways to scale a batch down to 1 unit (~1g)
  - Active ingredient weighted for each subject (Current Pfizer practice for EP-CR Solids)

<table>
<thead>
<tr>
<th>Weighing (Excipient Premix + Active Ingredient)</th>
<th>Blending Containers</th>
<th>Blenders</th>
<th>Tablet Compression</th>
<th>Dosage Form Assembly (if needed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xcelodose or Hand Weigh</td>
<td>Gelatin Capsules or Glass Vials</td>
<td>Silamat S6 (high shear) or Turbula T2 (low shear)</td>
<td>Natoli NP-RD10</td>
<td>Osmotic Capsule Parts</td>
</tr>
</tbody>
</table>

**Pharmacy Quality:** Active and Excipient weight within range

**R&D Quality:**
- Verify residuals in mixing containers are acceptable
- Verify good mixing of single units (i.e., based on dissolution profile for ER formulations)

**Pharmacy Quality:** Visual Inspection
- Confirm tablet weight
- Confirm tablet thickness

**Pharmacy Quality:** Visual Inspection
- Confirm Capsule closure

**R&D Quality:**
- Verify residuals in mixing containers are acceptable

**Pharmacy Quality:** Visual Inspection
- Confirm tablet weight
- Confirm tablet thickness
Osmotic Capsules for EP Controlled Release

- **Benefit:** Osmotic drug delivery provides highly reliable IVIVC
  - Similar PK performance for compounded and manufactured dosage forms

- **Pre-manufactured components (2 durations off the shelf)**
  - Capsule Body/Cap, Push/Sweller tablet released by Pfizer QA (GMP)
  - Available in Pfizer Inventory Management for supply to PCRU on demand

- **EP components:**
  - Drug layer (i.e., the active tablet) is compounded in the Pfizer Pharmacy by established EP compounding practices
  - Capsule is assembled by Pharmacist
Phase I Osmotic Case Study (Test Duration & Food Effect)

- Osmotic capsule (ER delivery) provided very good PK results
  - Tested Short Duration (~7 hr) & Long Duration (~14 hr)

- EP-osmotic capsules gave two distinct controlled-release PK profiles
  - Colonic absorption (good!)
  - Food effect (Cmax and AUC48 higher in fed state than fasted state for both durations)

- Recovery of EP-Capsules from subjects
  - Indicates that ≥95% of the drug was released in-vivo for expected transit times
Summary

• Covered ER selection process, key parameters & ER formulations
  – We have been using this process for many years

• Example of digital design for ER osmotic tablets
  – A model where we have high confidence in formulation design and performance
  – Rapid manufacture of osmotic platforms allows for similar development time as EP.

• Example of extemporaneous preparation for rapid evaluation of ER formulation PK
  – Showed osmotic tablet/capsule example
  – EP is very helpful for matrix tablet development...

• Thanks for your time! Questions?
References:

1. Assessment of the feasibility of oral controlled release in an exploratory development setting, A. Thombre
   Drug Discov Today, 2005 Sep;1:10(17):1159-66

2. Extemporaneously Prepared Controlled Release Formulations for Accelerating the early phase development of drug candidates, A. Thombre, A. Berchielli, and J. Rogers

Controls to Ensure Subject Safety and Dosage Form Quality

• Extemporaneous Dispensing Record (EDR) verified analytically
  – Additionally, for ER we assess dissolution after a practice run conducted at CRU prior to preparation and of subject doses.

• Double signatures during execution of compounding steps

• Pfizer Advisory Board
  – Multidisciplinary group to guide and decide upon proposals for non-standard Pfizer EP requests
Regulatory Aspects (A Formulators Perspective)

• **File appropriate regulatory documents**
  – Example: IND for US study

• **Formulation sections:**
  – P1 Description & Composition of Drug Product
  – P2 Pharmaceutical Development
  – P3 Manufacture
    • **EP is not manufacturing**, but some information may be needed for pre-manufactured components
    • Generally include the preparation steps and process flow diagram for EP (very limited information/development for EP)

• **EP practices rely on the standards of quality in a clinical pharmacy (governed by state laws, good clinical practices)**
  – Formulators need to be ready to answer regulatory queries from FDA or for studies outside the US the Pharmacist may handle this (e.g., Singapore).