Does Drug Development Provide the Information Necessary to Allow Precision Dosing?

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Acknowledgements – Big Assumption

Exposure Matching

- For special populations, matching exposure results in the same/adequate safety and efficacy
Supporting Evidence

• Pediatric population appears to generally have same E-R for drugs where at least partial extrapolability is possible:

• Lack of evidence of failures and wide practice/acceptance of approach for different populations
Acknowledgements – Things are better than they were ...
Specific Populations - What’s Required

- 21 CFR 201.56(d) mandates labeling information for:
  - Pregnancy
  - Lactation
  - Females and Males of Reproductive Potential

- FDA Guidance for Industry: Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products — Content and Format ...
  recommended subheadings:
  - Above and
  - Male and Female Patients
  - Racial or Ethnic Groups,
  - Patients with Renal Impairment
  - Patients with Hepatic Impairment.
  - other specific populations if informative for clinical use of the drug.
What We Do Well – ID Routes of Elimination and Drug Interactions

• Can extrapolate results from one DDI study to other drugs (e.g.)
  • If no effect on an investigational drug when co-administered with a strong CYP3A4 index inhibitor → no effect with any strong, moderate, or weak CYP3A4 inhibitors.
  • If one strong CYP2D6 index inhibitor results in a significant interaction → significant effect for other strong CYP2D6 inhibitors

• Preclinical data can rule out some clinical DDIs

• PBPK simulations have been used to support dose and administration instructions for scenarios that were not studied (e.g. co-administration with moderate CYP3A4 AND CYP2D6 inhibitors).
What we do well – Pediatric Populations

Predict adolescent doses well, other groups typically adequately

Incentives to Study Pediatrics

• Best Pharmaceuticals for Children Act/Pediatric Research Equity Act
• EMA’s Pediatric Regulation
• Carrot (exclusivity extension)
• Stick (must study ... withhold market authorization)
• Effectively assures drugs are studied in this population

Lily Mulugeta, Pharm.D, Adolescent PK Studies Under PREA and BPCA.
FDA Advisory Committee for Pharmaceutical Science and Clinical Pharmacology Meeting March 14, 2012, National Harbor, MD
We don’t do much for some specific populations

Proportion of 2013 and 2014 Approvals Without Explicit Dosing Recommendations at the Initial Approval

<table>
<thead>
<tr>
<th>Population</th>
<th>2013 (n = 27)</th>
<th>2014 (n = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td>70%</td>
<td>100%</td>
</tr>
<tr>
<td>Labor and delivery</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Nursing mothers</td>
<td>92.5%</td>
<td>100%</td>
</tr>
<tr>
<td>Pediatrics</td>
<td>88.8%</td>
<td>97%</td>
</tr>
<tr>
<td>Geriatrics</td>
<td>22.2%</td>
<td>25%</td>
</tr>
<tr>
<td>Female and male reproductive potential</td>
<td>63%</td>
<td>84%</td>
</tr>
</tbody>
</table>

a The numbers indicate the proportion of approvals for which dosing recommendations were not explicitly available (this may include labeling language such as “drug has not been studied” or representation of data without dosing recommendations).
## Labels don’t recognize comorbidities

### Label Patients

<table>
<thead>
<tr>
<th>Patients receiving:</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult patients</td>
<td>X mg BID</td>
</tr>
<tr>
<td>• Strong CYP3A4 inhibitors or</td>
<td>X mg QD</td>
</tr>
<tr>
<td>• Moderate CYP3A4 with strong CYP2C19 inhibitor(s)</td>
<td>X mg QD</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients with:</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>• moderate or severe renal impairment or</td>
<td>X mg QD</td>
</tr>
<tr>
<td>• moderate hepatic impairment</td>
<td>X mg QD</td>
</tr>
</tbody>
</table>

### Real Patients

- **Comorbidity Example†**
  - US: 22.7% of adults have arthritis*
  - 27.7% are also obese**
  - 33.7% also have diabetes***
  - 36.4% also have heart disease

* ↓ CYP activity
** ↑ CYP 2E1 and phase II conjugation activity
*** Altered renal clearance

*Content source: Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Division of Population Health - [https://www.cdc.gov/arthritis/data_statistics/national-statistics-text-version.html#cormobidities-text](https://www.cdc.gov/arthritis/data_statistics/national-statistics-text-version.html#cormobidities-text)*


Pivotal Trials exclude some populations

Phase 3 Patients

- Renal and hepatic impairment:
  - GFR ≤50 mL/min
  - Total bilirubin, AST or ALT ≥ 2xULN
  - ... severe ... renal, hepatic, ... disease.
  - CYP3A4, 5,7 Inhibitors

Example Phase 3 Exclusion Criteria:

Real Patients

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Reminder
Specific Populations – labeling guidance

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  • Geriatric use

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Interpretation?

• Likely assumptions
  • **Everything** important to dosing a drug is in the label.
  • If it is not in the label, its not important

• Known – Special Populations not usually studied:
Interpretation?

- “Hepatic Impairment: Use with caution”
- “… is primarily metabolized in the liver”
- Does “use with caution” mean that the physician should:

  Slowly write the prescription?
Opportunities -
We’ve come a long way AND can go further
The Obvious – Study a Wider Variety of Patients

Pharmaceutical Science and Clinical Pharmacology Meeting - May 7, 2019

• DISCUSSION: Please discuss what alternative drug development paradigm(s) would encourage the inclusion of patients with all (or most) degrees of renal impairment in late stage clinical trials, without the need for a stand-alone renal impairment study …
Industry Perspectives on Approaches to Evaluate the Effect of Renal Impairment on Drug Exposure

Approaches to Evaluate the Effect of RI on Drug Exposure:
Potential Approaches to Enroll RI Subjects into Late-Stage Trials

• Sequential approach
• Adaptive design
• Renal impairment group in a sub-study
• Open label extension study

Points to Consider for Potential Approaches to Enroll RI Subjects into Late-Stage Trials

• Examples provided may be an over-simplification
• Sample size of POC studies may not allow for enrollment of enough RI subjects for decision making
• Organizational complexity with analyzing safety and/or PK from blinded, ongoing, late-stage trial
• Operational complexity especially for the adaptive approach
• Concerns with the potential for “contamination” of the safety/efficacy analysis population
• IRB and/or PIs may not be comfortable with a modeling approach to un-gate enrollment
• Potential for renal function to change over time can lead to under or over-dosing

Several obstacles to these approaches, none of which are insurmountable
Leverage what we do well – use of data already generated across compounds

- Create predictive models
  - Like for DDIs (PBPK) and Pediatrics (semi-empirical)

Components:
- **Knowledge management**: Standardized database populated with data
- **Modelling**: Develop predicted models
- **Qualification**: Agreement on what constitutes an adequately predictive model.
- **Regulatory**: A pathway for gaining world-wide regulatory acceptance

Requires sharing of data across companies and a willingness for industry, academia, regulatory and other interested parties to work together
Drug Label Evolution

~1910

PROPERTIES - Lessens the frequency and increases the force of the heart's action. An indirect diuretic.
POISONOUS - Antidotes -- emetics, and afterwards alcoholic stimulants.
DOSE - $\frac{1}{2}$ to 1 teaspoonful (2 to 4 Cc.) of an ounce to the pint infusion.

Today

Electronic Patient Characteristics

Suggested Dose for XXXX
Is XXXX mg

Factors considered:
✔ Body size
✔ Renal f(x)
✔ BMI
...

Technology currently exists

Another opportunity for Industry/FDA/practitioners /...

Tomorrow
Conclusions

• Understanding of PK and disease has greatly improved “dosing” over the last 50+ years

• Opportunities exist to better serve patients through
  • Enhancing diversity of patients enrolled in clinical trials
  • Considering patient populations not routinely studied
  • Fully integrating totality of knowledge when providing dosing recommendations
Questions?