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

Jack Cook
Clinical Pharmacology
Pfizer

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:
  - Momper JD, Mulugeta Y, Burckart GJ. Failed Pediatric Drug Development Trials. Clin Pharmacol Ther. 2015 Sep;98(3):245-51. doi: 10.1002/cpt.142 (Difference in E-R not a significant factor in failure)
  - Mehrotra N, Bhattaram A, Earp JC, Florian J, Krudys K, Lee JE, Lee JY, Liu J, Mulugeta Y, Yu J, Zhao P, Sinha V. Role of Quantitative Clinical Pharmacology in Pediatric Approval and Labeling. Drug Metab Dispos. 2016 Jul;44(7):924-33. doi: 10.1124/dmd.116.069559.
- Lack of evidence of failures and wide practice/acceptance of approach for different populations

Review of Current Practices

Acknowledgements – Things are better than they were …

Specific Populations - What's Required

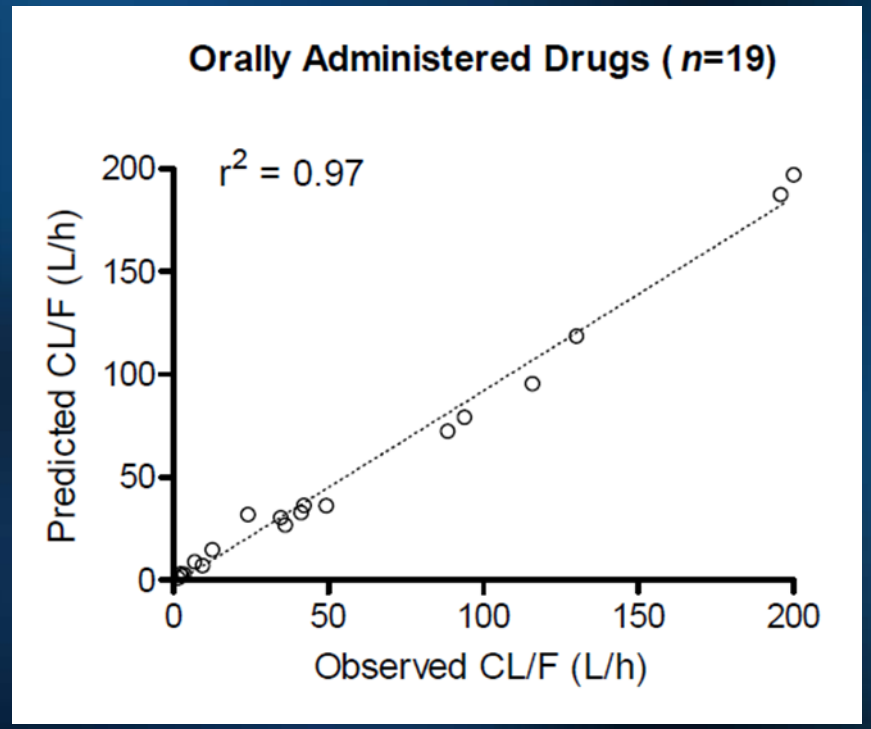
- 21 CFR 201.56(d) mandates labeling information for:
  - Pregnancy
  - Lactation
  - Females and Males of Reproductive Potential
  - Pediatric use
  - Geriatric use
- FDA Guidance for Industry: Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products — Content and 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



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

Incentives to Study Pediatrics

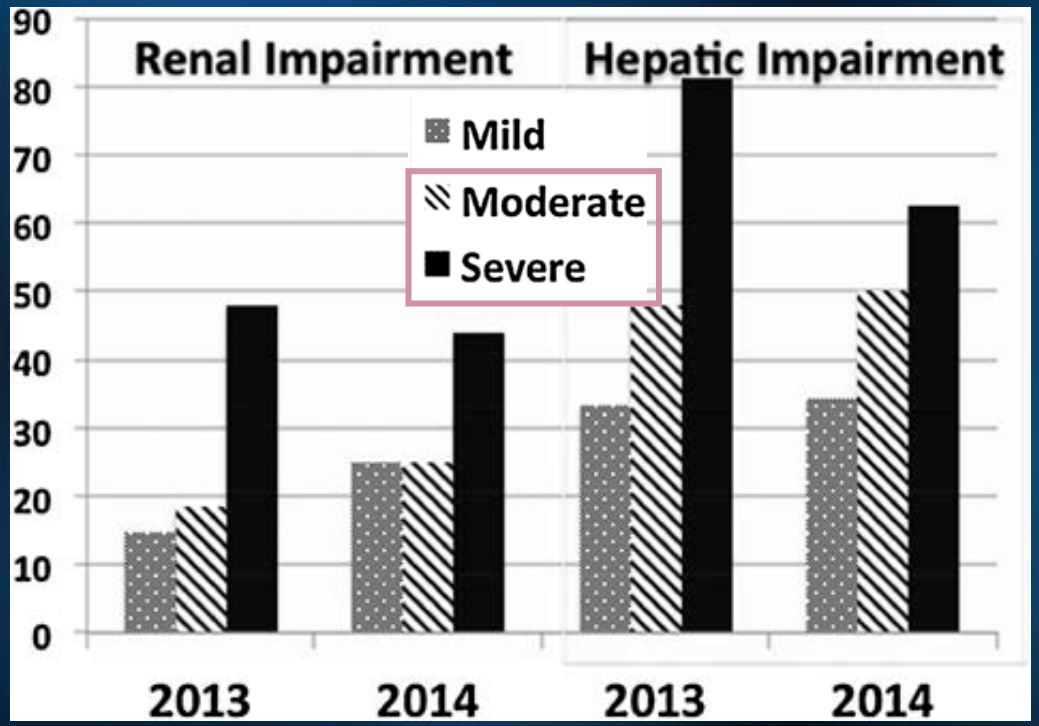
- Best Pharmaceuticals for Children Act/Pediatric Research Equity Act
- EMA's Pediatric Regulation

- Carrot (exclusivity extension)
- Stick (must study … withhold market authorization)

- Effectively assures drugs are studied in this population

We don’t do much for some specific populations

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



Population	Proportion[a]	
	2013 (n = 27)	2014 (n = 32)
Pregnancy	70%	100%
Labor and delivery	100%	100%
Nursing mothers	92.5%	100%
Pediatrics	88.8%	97%
Geriatrics	22.2%	25%
Female and male reproductive potential	63%	84%

Timing

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).

The Journal of Clinical Pharmacology, Volume: 55, Issue: 10, Pages: 1073-1078, First published: 24 June 2015, DOI: (10.1002/jcph.579)

Labels don't recognize comorbidities

Label Patients

	Dose
Adult patients	X mg BID
Patients receiving: • **Strong CYP3A4 inhibitors or** • **Moderate CYP3A4 with strong CYP2C19 inhibitor(s)**	X mg QD
Patients with: • **moderate or severe renal impairment or** • **moderate hepatic impairment**	X mg QD

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

*Morgan ET. Impact of infectious and inflammatory disease on cytochrome P450-mediated drug metabolism and pharmacokinetics. Clin Pharmacol Ther. 2009;85(4):434–438.

**Hanley MJ, Abernethy DR, Greenblatt DJ. Effect of obesity on the pharmacokinetics of drugs in humans. Clin Pharmacokinet. 2010;49(2):71-87.

***Gwilt PR, Nahhas RR, Tracewell WG. The effects of diabetes mellitus on pharmacokinetics and pharmacodynamics in humans. Clin Pharmacokinet. 1991 Jun;20(6):477-90.

Pivotal Trials exclude some populations

Phase 3 Patients

Example Phase 3 Exclusion Criteria:
Renal and hepatic impairment: • **GFR ≤50 mL/min** • **Total bilirubin, AST or ALT ≥ 2xULN** • **… severe … renal, hepatic, … disease.**
CYP3A4, 5,7 Inhibitors

Real Patients

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Reminder
Specific Populations – labeling guidance

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Interpretation?

If labels are silent ….
No adjustment in dose is needed

- 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:
  - Major burns: drug distribution, metabolism, and elimination are grossly distorted. (Udy AA, Roberts JA, Lipman J, Blot S. The effects of major burn related pathophysiological changes on the pharmacokinetics and pharmacodynamics of drug use: An appraisal utilizing antibiotics. Adv Drug Deliv Rev. 2018 Jan 1;123:65-74)
  - Morbid obesity: clearance typically proportional to lean body weight (rather than actual) (Barras M, Legg A. Drug dosing in obese adults. (Barras M, Legg A. Aust Prescr. 2017 Oct;40(5):189-193)
  - Pregnancy: Increased cardiac output, glomerular filtration rate, decreased albumin and altered metabolic activity. (Pariente G, Leibson T, Carls A, Adams-Webber T, Ito S, Koren G. Pregnancy-Associated Changes in Pharmacokinetics: A Systematic Review. PLoS Med. 2016 Nov 1;13(11):e1002160)

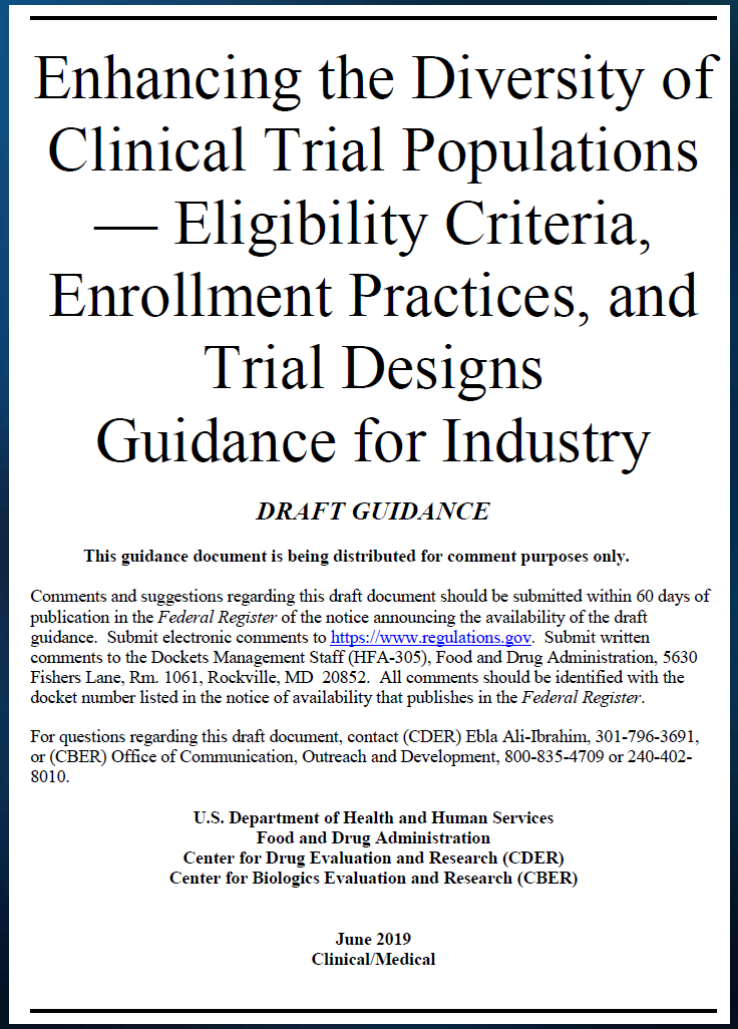
Interpretation?

- “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



Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs
Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Ebla Ali-Ibrahim, 301-796-3691, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

June 2019
Clinical/Medical

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

Presented at Pharmaceutical Science and Clinical Pharmacology Meeting - May 7, 2019 by Richard Graham on behalf of the IQ consortium

Leverage what we do well – use of data already generated across compounds

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

Editor's Choice: Commentary

ACCP

A Proposal for Scientific Framework Enabling Specific Population Drug Dosing Recommendations

The Journal of Clinical Pharmacology
2015, 55(10) 1073–1078

DOI: 10.1002/jcph.579

Pravin R. Jadhav, PhD, MPH[1], Jack Cook, PhD[2], Vikram Sinha, PhD[3], Ping Zhao, PhD[3], Amin Rostami-Hodjegan, PharmD, PhD[4], Vaishali Sahasrabudhe, PhD[2], Norman Stockbridge, MD, PhD[5], and J. Robert Powell, PharmD[6]

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

PROPERTIES - Lessens the frequency and increases the force of the heart's action. An indirect diuretic.
POISONOUS - Antidotes -- emetics, and afterwards alcoholic stimulants.
DOSE - ½ to 1 teaspoonful (2 to 4 Cc.) of an ounce to the pint infusion.

~1910

Today

Electronic Patient Characteristics

Dose algorithm

Technology currently exists

Another opportunity for Industry/FDA/practitioners /…

Suggested Dose for XXXX Is XXXX mg

Factors considered:
- ✓ Body size
- ✓ Renal f(x)
- ✓ BMI
- …

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?