FDA Lactation Workshop

"What do we currently know?"

An Example from Industry

Marie Teil, MD
UCB

27 April 2016
Rockville, MD

Disclosures

- Current employee of UCB Biopharma

Presentation Overview

Background

Understanding the therapeutic environment and the scientific rationale

- **One of UCB's main focus is the immunology therapeutic area in particular chronic rheumatic diseases and Crohn's Disease**
- **UCB's Immunology women of childbearing age (WoCBA) program is focused on studies with certolizumab pegol and is driven by patients and physicians needs:**
  - Disease onset tends to overlap with a woman's peak reproductive years
  - Balancing disease control and family planning wishes
  - High disease activity in the post-partum period
    - Need for treatment → Many women are prescribed anti-TNFs post-partum to control for rebound/flare after delivery while breast feeding
  - Limited published data on transfer of biologics into breast milk → Uncertainty around whether to take treatment for flare management and whether to choose to breastfeed
- **Immunology WoCBA Program Goal:** Provide robust data to better inform treatment decisions for women with autoimmune conditions planning for pregnancy and/or breastfeeding

Identifying Data Gaps and Potential Hurdles

What data are available to inform decision making regarding lactation and use of biologics?

- ✓ **Limited information in Package Inserts**
- ✓ **Systematic literature review:**
  - Limited data, mostly from case reports
  - Variability in breast milk sampling protocols
  - Lack of information on validation of assays
  - Inconsistency of available breast milk transfer data

Conflicting Messages

- ✓ **Potential hurdles faced by industry:**
  - Lack of experience in clinical studies on lactating women
  - Ethical and study design challenges

Evidence Based Approach

What methodology could be used to fill the data gap?

- **Review of pre-clinical data**
  - Assess potential concerns linked to drug molecular structure
  - Limited data available in lactation
- **Assay requirements and challenges**
  - Aim for a high sensitivity in lower ranges to ensure an informative lower limit of quantification (LLOQ)
  - Validation in milk matrix, including drug stability in milk
- **FDA draft guidance – February 2005**:
  - Guidance for Industry: “Clinical Lactation Studies – Study Design, Data Analysis, and Recommendations for Labeling”

Data Collection and Evaluation (1/3)

Study design considerations

- **Colostrum vs. mature milk study**
  - Breast feeding should be well-established (mature breast milk)
  - Sampling should not take place before 6 weeks post-partum when maternal physiology has largely returned to pre-pregnant state
- **Mother-infant pair vs. lactating mother only (milk only vs. milk and plasma)**
  - Milk only study can provide information regarding: (1) Timing of maternal dose relative to breast feeding, (2) Duration recommended to discard milk and (3) When to resume breast feeding relative to dose/exposure
    - If concentration of drug in breast milk is exceedingly low, this could preclude the need for further studies
- **Exclusive breastfeeding vs. supplemental**
  - Inclusion criteria allowed for exclusive and supplemental breastfeeding in order to provide closer to *real life* data

Data Collection and Evaluation (2/3)

Study design and Data collection consideration

- **Providing investigational drug vs. enrolling patients already on treatment**
- **Milk Sampling period**
  - Sampling should occur when drug is at steady-state
  - Sampling should cover the complete dosing interval
- **Study sample size**
  - Phase I – Clinical Pharmacology Study
  - FDA feedback
- **Balance between burden of data collection on mother vs. the need for enough information for data evaluation**
  - In order to account for high sampling frequency required, limit clinical data collection from mothers
  - The study should support continued breast milk feeding and to avoid disruption of breast feeding routine

Data Collection and Evaluation (3/3)

Data evaluation

- **Mothers and baby demographics**
- **Pregnancy outcome information**
- **Concomitant medications**
- **Breastfeeding information**
- **AEs of interest**
- **Drug concentration in milk**
- **Calculation of Average Daily Infant Dose (ADID)**
  - Dose ingested ≠ dose absorbed

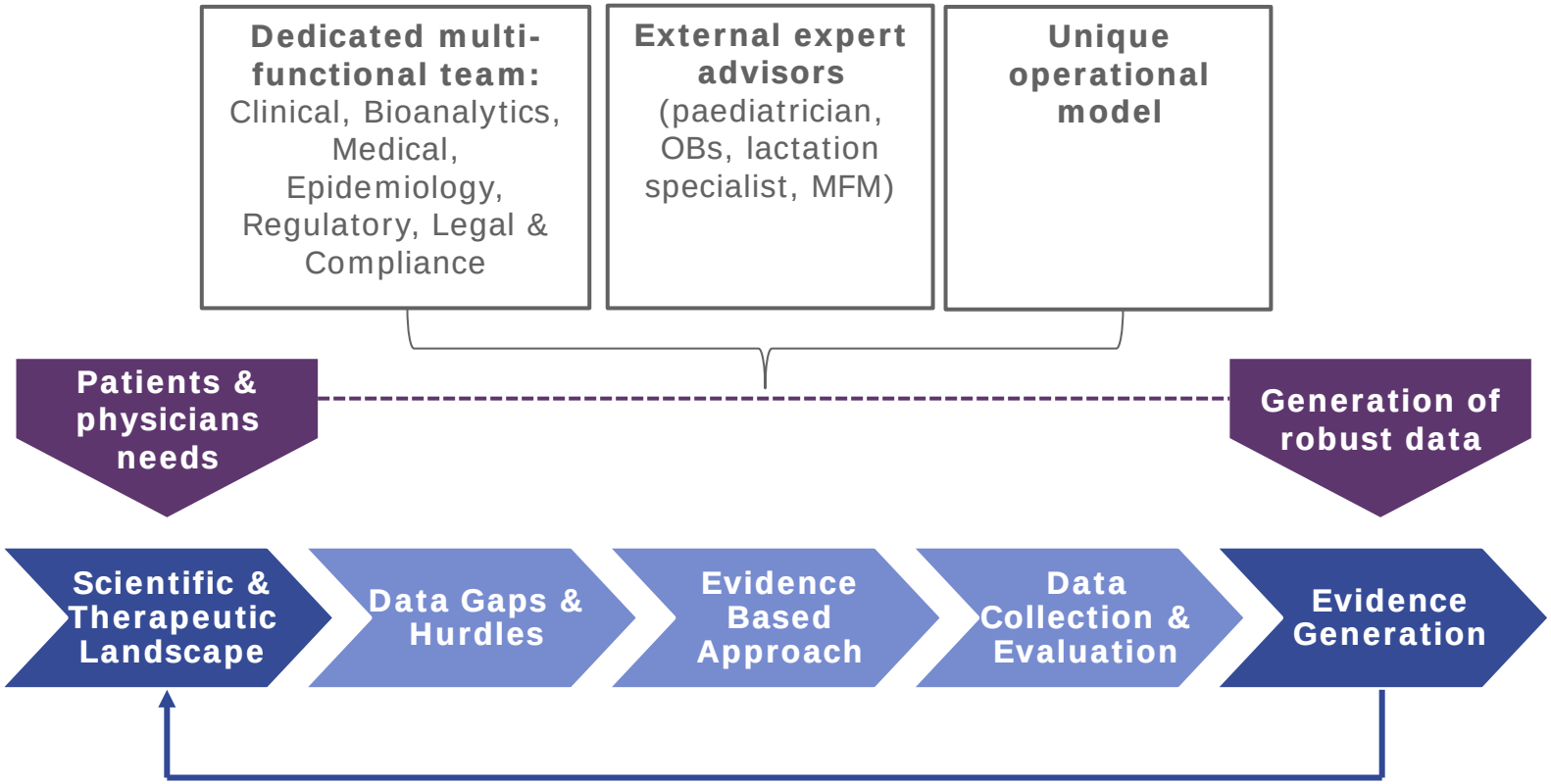
Study Overview

Clinical Study Objectives	
Primary	Determine the concentrations of CZP in human breast milk and to calculate the daily infant dose of maternal CZP

Clinical Study Design	
Population	Lactating women who were already prescribed commercial CZP for an approved indication in accordance with the current approved prescribing information
Methods	8–9 milk samples from lactating mothers across a single dosing period via use of in-home nursing visits
Sample size	17 lactating mothers taking CZP
Assay	UCB developed assay - validated in milk - LLOQ=0.032µg/mL Transferred to CRO

Summary

Factors contributing to success and the need for continued evidence generation



The more **relevant, high quality data** available, the more we **empower physicians and their patients**