



Roadblocks to Clinically Relevant Information Regarding Drug Use and Lactation

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Disclosure

Mary Short is an employee and stockholder of Eli Lilly and Company.

Agenda

- ◆ What are roadblocks to obtaining clinically relevant information related to lactation?
- ◆ What are the roadblocks to incorporating lactation information that is already known into labeling?

Sponsor responsibility: Characterize benefit /risk profile of the product for the indicated population to inform the provider and patient

Scope

- ◆ Primary focus is on lactation studies as described in the FDA Guidance
- ◆ Secondary focus is in other approaches to obtaining data for Lactation section of labeling

Circumstances for which the FDA (2005) recommends clinical studies in lactating women

- ◆ A drug under review for approval is expected to be used by women of reproductive age
- ◆ After approval, use of a drug in lactating women becomes evident (e.g., via reports in the medical literature or lay press)
- ◆ A new indication is being sought for an approved drug and there is evidence of use or anticipated use of the drug by lactating women
- ◆ Marketed medications that are commonly used by women of reproductive age (e.g., antidepressants, antihypertensives, anti-infectives, diabetic and pain medications)

When is lactation data most relevant to patient care?

- ◆ Case by case determination of benefit /risk question
 - Mother
 - Infant
 - When do benefit/risk balances suggest need for data to advise clinicians?
 - When is use expected in nursing mothers?



How do we obtain lactation data for the label? Observational

◆ Observational

- Accidental exposure during clinical trials
- Post- marketing
 - Case reports and case series
 - Registries
 - Real world evidence

How do we obtain lactation data for the label? Interventional

◆ Interventional

- The influence of lactation on maternal PK and when appropriate PD
- The extent of drug transfer into breast milk
- The effects of drugs on milk production and composition
- The extent and consequent effects on breast-fed infants of exposure to drugs in breast milk

2005 FDA Draft Guidance for Industry Clinical Lactation Studies

What are roadblocks to obtaining clinically relevant information?

- ◆ Scientific validity concerns
- ◆ Ethical considerations
- ◆ Feasibility
- ◆ Quality of data



Issues with scientific validity

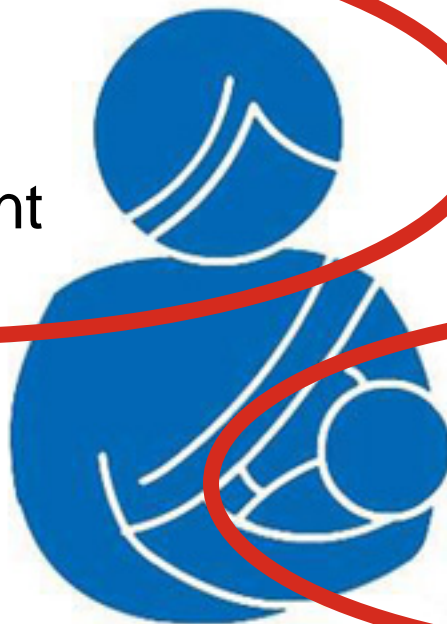


- ◆ Effect of drug on quality and quantity of milk requires a study before, during and after exposure
- ◆ Inter- and intra-individual variation in milk production
- ◆ Power to detect a safety signal for adverse outcome in infants
- ◆ Drug only vs drug and active metabolite
- ◆ Timing of lactation study in relation to:
 - birth – “mature milk”
 - infant physiologic development
- ◆ In utero exposure vs lactation exposure
- ◆ Infant PK obtained in lactation study vs pediatric program

Ethical considerations



Mother:
Patient
Research Participant



Infant:
Vulnerable Person
Research Participant

Feasibility: Lactation studies in ClinTrials.gov accessed January 2016



| Condition | Status | Design | Phase | Total N | Study start Date | Est. Study Completion |
|--|---|--|-------|---------|------------------|-----------------------|
| Fabry Disease | Recruiting | NR, PK study, single group assignment, OL | IV | 10 | Aug-2006 | Jan-2020 |
| Constipation - Irritable Bowel Syndrome | Recruiting | Interventional, PK study, single group, OL | I | 8 | Jul-2014 | Jul-2016 |
| Thrombocytopenia | Withdrawn (no patients after 5 yrs recruitment) | Interventional, PK study, single group, OL | IV | | | |
| Glycogen Storage Disease - Pompe Disease | Recruiting | Observational, Prospective | IV | 5 | Mar-2012 | Dec-2021 |
| Multiple indications | Completed | Interventional, PK study, single group, OL | I | 17 | Sep-2014 | Jan-2016 |
| HIV | Completed | Interventional, PK study, single group, OL | IV | 9 | Apr-2010 | Dec-2012 |
| Multiple indications | Recruiting | Observational, Prospective | IV | 484 | Jul-2009 | Dec-2019 |
| Type 2 Diabetes - Pregnancy | Recruiting | Observational, Prospective | IV | 200 | Jan-2009 | Jan-2020 |

Limited Experience



- ◆ Sponsors
 - limited experience in clinical pharmacology lactation studies
 - very limited in lactation studies with intent to follow infant outcomes
- ◆ OB/GYN subspecialty academics/clinicians
 - historically clinical trials have not included their patients
- ◆ What does our experience in conducting pregnancy registries inform us on studying a similar population?

Pregnancy registries: Enrollment challenges



- ◆ Stigma of taking medications during pregnancy
- ◆ Limited patient population
- ◆ Limited incentives
 - HCPs to participate
 - Patient recruitment
- ◆ Perception of legal risk
 - Limits HCP participation
 - Challenge to recruiting patients
- ◆ Limited avenues for recruiting patients & increasing awareness of the registry's existence

Pregnancy registries: Study design challenges



- ◆ Registries introduce patient selection bias
- ◆ Data less generalizable
- ◆ Timing of enrollment impacts ability to incorporate meaningful outcomes related to early pregnancy
- ◆ Due to design & enrollment challenges, can take decades to reach an adequate sample size

Quality of the data

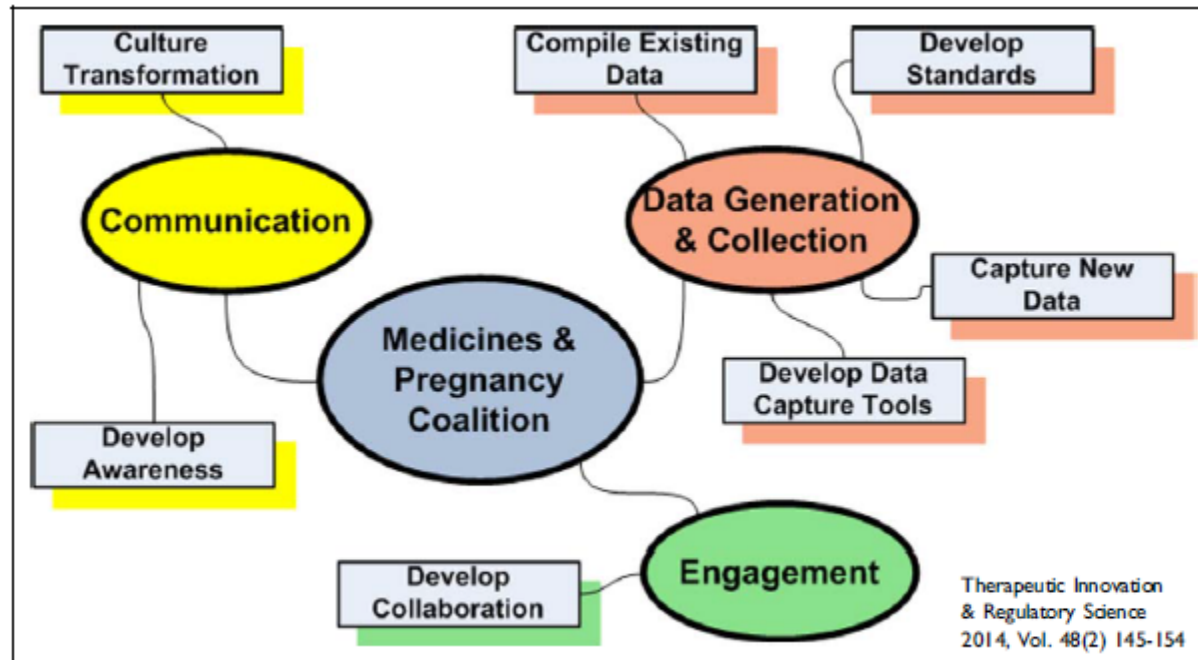


- ◆ Timing of breast milk sample in relation to dose intake varied and is often lacking
- ◆ Selection bias due to retrospective nature
- ◆ Infant dose is not known exactly
- ◆ Lack of control group for lactation study to evaluate drug effect on milk production and composition
- ◆ Confounding data – breastfeeding experience vs breast milk, epigenetics

Removing roadblocks



What can we learn from our experience in studying medications during pregnancy?



Might a similar approach guide us to remove roadblocks to clinically relevant data?

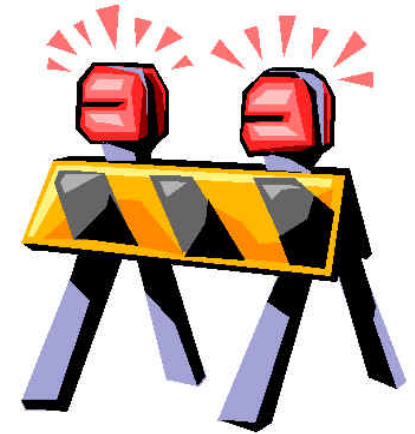
Remove roadblocks to obtaining clinically relevant information?

◆ Guidance:

- ◆ Lactation data most relevant to patient care
- ◆ Consideration of stepwise approach for conduct of lactation studies
- ◆ Address ethical considerations

◆ Collaboration

- ◆ Communication
- ◆ Engagement
- ◆ Data Generation



Agenda

- ◆ What are roadblocks to obtaining clinically relevant information related to lactation?
- ◆ **What are the roadblocks (?) or HURDLES to incorporating lactation information that is already known into labeling?**

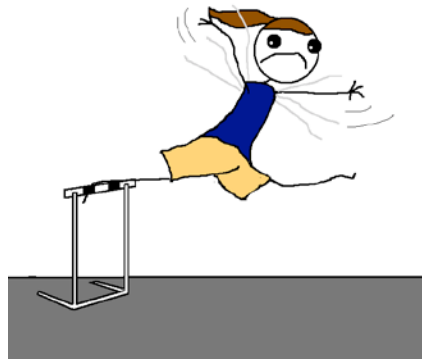
Sponsor responsibility: Characterize benefit /risk profile of the product for the indicated population to inform the provider and patient

What are the hurdles to incorporating information that is already known into labeling?



- ◆ Level of evidence
 - Substantial evidence
 - Case report
 - Database mining, pharmacoepidemiologic studies
 - Observational studies
 - Animal data
- ◆ Post marketing surveillance
- ◆ Litigation concerns

Requirement for substantial evidence



- Section 505(d) of the Federal FD&C Act describes substantial evidence as evidence consisting of **adequate and well-controlled investigations**, including clinical investigations...on the basis of which it could be concluded that the drug will have the effect it is represented to have under the conditions of use proposed in labeling

What is substantial evidence?



- Food And Drug Administration Modernization Act Sec. 115
 - “Data from **one** adequate and well-controlled clinical investigation **and** confirmatory evidence” may constitute substantial evidence if FDA determines that such data and evidence are sufficient to establish effectiveness

Relevance of animal data



- ◆ Animal data are more available than human data
- ◆ Limited ability in predicting:
 - the amount of drug in breast milk
 - infant exposures to drug in breast milk
- ◆ Difficult to assess the levels of risk based entirely on animal studies.
- ◆ Without an animal toxicology background the information can be confusing or misleading
- ◆ May be predictive of certain situations that require more or less evaluation and inform study designs

Post marketing surveillance



- ◆ Provides the basis for the evolving safety of the profile and supports all the components of risk management
- ◆ Conducted in marketed products regardless of indication or population.
- ◆ Signals may come from many sources
- ◆ Review and interpret all relevant data in integrated fashion (within the context of biological plausibility)
- ◆ Determine if risk impacts the benefit risk balance of the product or has implication for public health

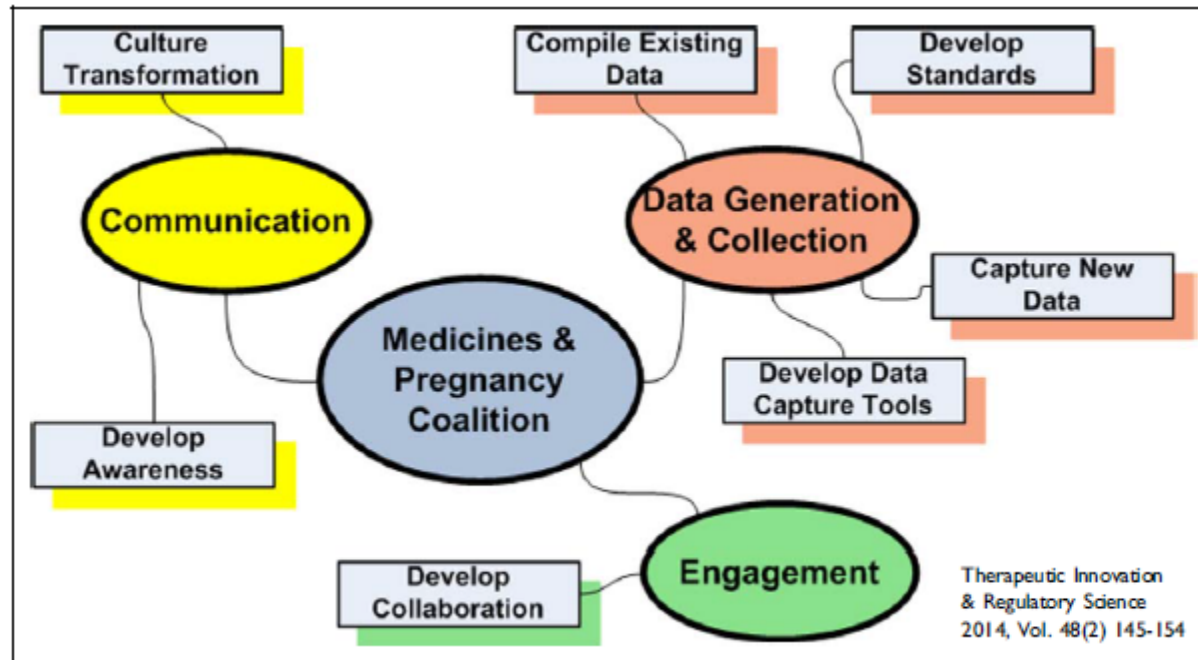
If signals are confirmed to be identified or potential risks, they are included in the labels.

Litigation risk



Litigation risk does not drive decision making

Removing roadblocks and clearing hurdles



Thanks to the FDA for the public workshop to foster the collaborative effort needed to remove roadblocks and hurdles to clinically relevant information.