Evaluation of the Safety of Drugs and Biological Products Used During Lactation: Workshop Summary

J Wang[1], T Johnson[2], L Sahin[2], MS Tassinari[2], PO Anderson[3], TE Baker[4], C Bucci-Rechtweg[5], GJ Burckart[6], CD Chambers[7], TW Hale[4], D Johnson-Lyles[2], RM Nelson[8], C Nguyen[9], D Pica-Branco[2], Z Ren[10], H Sachs[2], J Sauberan[11], A Zajicek[10], S Ito[12] and LP Yao[2]

This report serves as a summary of a 2-day public workshop sponsored by the US Food and Drug Administration (FDA) to discuss the safety of drugs and biological products used during lactation. The aim of the workshop was to provide a forum to discuss the collection of data to inform the potential risks to breastfed infants with maternal use of medications during lactation. Discussions included the review of current approaches to collect data on medications used during lactation, and the considerations for future approaches to design and guide clinical lactation studies. This workshop is part of continuing efforts to raise the awareness of the public for women who choose to breastfeed their infants.

Public health initiatives, including the Health Resources and Services Administration Women's Preventive Services Guidelines, have brought renewed focus on the health benefits of breastfeeding and the need for comprehensive efforts to increase the rate of breastfeeding in the US.[1] In the US, ~10% of reproductive-age women become pregnant each year, leading to more than 6 million pregnancies and more than 4 million deliveries annually.[2,3] Women take an average of three medications during their entire pregnancy, and four medications during lactation.[3] When a lactating woman takes a drug and the drug is present in her milk, the infant is exposed to both the benefits afforded by milk as well as the potential risks from a drug that is not intended to treat a condition in the infant.

Despite significant efforts to improve drug labeling for medication use during lactation, there remains a paucity of human data in these understudied populations.[4] Lactating women and their healthcare providers often make decisions about drug treatment and about continuation of breastfeeding during therapy in the absence of quality human data in product labeling. In order for that decision to be evidence-based, needed information would include at a minimum the amount of drug in human milk, the effect of the drug on milk production, and an understanding of the risks of the drug on the breastfed infant based on expected levels of exposure.

The US Food and Drug Administration (FDA) has recognized that data from clinical lactation studies, along with all other available data (e.g., drug physicochemical characteristics, mechanisms of medication entry into breast milk, and important infant factors) could be leveraged to inform the safety of a drug when used during lactation.[5,6] Thus, in November 2007, the Pediatric Advisory Committee (PAC) meeting discussed issues related to the 2005 US FDA draft *Guidance for Industry: Clinical Lactation Study – Study Design, Data Analysis, and Recommendations for Labeling*. The PAC members agreed that information from clinical lactation studies would be useful to practitioners and breastfeeding women when making risk/benefit decisions regarding

[1]Office of Drug Evaluation IV, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland, USA; [2]Division of Pediatric and Maternal Health, Office of Drug Evaluation IV, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland, USA; [3]Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California San Diego, La Jolla, California, USA; [4]Infantrisk Center, Texas Tech University Health Sciences Center Amarillo, Amarillo, Texas, USA; [5]Novartis Pharmaceuticals Corporation, One Health Plaza, East Hanover, New Jersey, USA; [6]Office of Clinical Pharmacology, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland, USA; [7]School of Medicine, University of California San Diego, La Jolla, California, USA; [8]Office of Pediatric Therapeutics, U.S. Food and Drug Administration, Silver Spring, Maryland, USA; [9]Division of Bone, Reproductive, and Urologic Products, Office of Drug Evaluation III, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland, USA; [10]Obstetric and Pediatric Pharmacology and Therapeutics Branch, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institute of Health, Bethesda, Maryland, USA; [11]Neonatal Research Institute, Sharp Mary Birch Hospital for Women and Newborns, San Diego, California, USA; [12]Division of Clinical Pharmacology & Toxicology, Department of Pediatrics, Hospital For Sick Children, Toronto, Ontario, Canada. Correspondence: LP Yao (Lynne.Yao@fda.hhs.gov)

medication use during breastfeeding. The Committee also discussed 1) different types of study designs to collect specific lactation data and drug characteristics that might fit with each type of study; 2) the challenging issues of when and how to conduct clinical lactation studies; and 3) how to assess the influence of drugs and therapeutic biological products on lactation.

In this report, we provide a summary of the workshop entitled "*Evaluation of the Safety of Drugs and Biological Products Used During Lactation*" held on April 27–28, 2016, in Silver Spring, MD. The workshop was sponsored by the Division of Pediatric and Maternal Health, Office of Drug Evaluation IV at the FDA.

WORKSHOP OVERVIEW AND THEMES
The purpose of this FDA public workshop was to facilitate dialog among stakeholders on safety evaluation of drugs and biological products used during lactation. Four major objectives of the workshop were:

1. to review current approaches to the collection of data when drugs are used or expected to be used during lactation;
2. to discuss and consider novel approaches to improve the quality and quantity of data available to assess the safety of medications used during lactation, and to inform the public of the potential risks of medication use during lactation;
3. to review and discuss strategies to communicate safety information related to maternal use of medications during lactation; and
4. to raise awareness and engage stakeholders regarding safety information related to maternal use of medications during lactation.

Distinguished speakers in the field from academia, industry, the National Institutes of Health (NIH) and the FDA presented scientific talks and engaged in the panel discussion. Each workshop session identified the major points that emerged during the sessions along with issues that warrant more focused attention.

The following sections of this report describe the essence of the presentations, discussions, and recommendations from each session. This review, presented as key take-away points from the workshop, highlight and elaborate on the next steps necessary for advancing the safety evaluation of drug and biological product use during lactation.

BREASTFEEDING: BENEFITS AND BARRIERS
Benefits of breastfeeding
Breastfeeding carries many benefits for child health and also for maternal health.[7] The workshop discussed the benefits of breastfeeding to both mother and infant, along with review of relevant literature data.

Human milk reduces the risk of morbidity and mortality in infants by boosting the immune system and improving developmental outcomes.[8] In addition to its well-known psychological and nutritional advantages, breastfeeding also provides protection from various infectious diseases and allergies.[8–10] For example, exclusive breastfeeding during the first 6 months of life is associated with a 43% reduction in the incidence of acute otitis media by 2 years of age.[11] Breastfeeding for 6 months or more may also help lower childhood leukemia incidence.[9] Furthermore, analyses indicated that breastfeeding is associated with increased cognitive development of the infant, and reduction in subsequent development of obesity and diabetes in the breastfed child.[10,12,13] The gut microbiota in breastfed infants contain a lower prevalence of pathogenic bacteria compared to that of formula-fed infants, although the long-term clinical significance is unclear.[14,15] Breastfeeding may also have lifelong implications for the infant based on recent findings of stem cells in human milk.[16] Similarly, mothers who breastfeed may also sustain health benefits, including reduced risk of long-term comorbidities such as cancer, obesity, and diabetes, postmenopausal osteoporosis, and rheumatoid arthritis, as well as psychological benefits.[10] Currently, professional organizations including the American Academy of Pediatrics recommend exclusive breastfeeding at least for the first 6 months of life.[17]

Barriers to breastfeeding
Despite the accumulating evidence of its advantages, several factors may interfere with establishing and maintaining effective breastfeeding. Factors such as infant refusal, multiple births, returning to work, and concern about medication use may interfere with establishment of effective breastfeeding.[18]

Healthcare providers may face barriers in identifying adequate information on lactation. For example, healthcare providers may not be aware of what drug information resources to refer to, and what the best recommendations are for their breastfeeding patients. Additionally, attitudes and behaviors about breastfeeding can be negatively affected in women who must take medications.[19] Finally, healthcare providers may not be aware of strategies to minimize infant exposure when a breastfeeding mother must take a medication. Such strategies include optimal drug product selection, dosage timing, temporarily pumping and discarding milk, and observing the infant for potential signs or symptoms of exposure.

The lack of data to adequately inform the benefit/risk of medications used while breastfeeding may lead to inaccurate lactation advice.[2,5] Often, providers may advise mothers to stop breastfeeding while taking medications based on incomplete or outdated breastfeeding safety information. Or, providers may use the risk information for pregnancy to make decisions for breastfeeding, leading to fear in mothers that medications harmful during pregnancy can harm their infants during breastfeeding, which is not usually the case.

SAFETY INFORMATION ON MEDICINE USE DURING LACTATION
Paucity of data
Many drugs are used by women during pregnancy and lactation. The proportions of pregnant women reporting use of four or more medications during the first trimester has almost tripled (from 9.9% to 27.6%) from 1976 to 2008.[3] Between 2003 and 2012, however, 92.9% of pregnancy data in the label of approved medications were based on animal studies, and only 5.2% of data were based on human pregnancy data.[4] The data on use of medications during lactation is similarly scarce. During the same

2003–2012 timeframe, 47.9% of drugs had no data on breast-feeding, 42.7% had some animal data, and only 4.7% had human data.[4] Thus, use of most medications during lactation represents an unknown risk to breastfed infants, and raises difficulties in making evidence-based recommendations on medication use during lactation.

The safety information to evaluate the compatibility of medications and breastfeeding has strengths and weakness due to their data quality and study approaches. Based on their data acquisition approaches, these safety data may be arbitrarily categorized as follows: 1) predictive models of drug excretion into milk based on physiochemical characteristics of the drug; 2) animal experiments; and 3) clinical safety data.

Predictive models

There are predictive models of a milk-to-plasma concentration ratio based on physiochemical characteristics of the drug (e.g., ionization property, molecular weight, protein binding affinity, and lipophilicity), which explain diffusion components of drug transfer into human milk. However, they are not considered sufficient to predict drug concentration profiles in human milk, particularly because transporter-mediated secretion is difficult to account for.[2,20] These predictive models may become useful if they incorporate factors such as transporter specificity and maternal pharmacokinetic/pharmacogenetic variations. Underlying maternal pharmaco-genotype can alter metabolic or elimination pathways and lead to increased drug exposure in their breastfed infant. For example, a high degree of variability exists for CYP2D6-mediated conversion of codeine to morphine because of underlying genetic differences in CYP2D6 activity. Patients with certain CYP2D6 genotypes (i.e., ultrarapid metabolizers) may convert codeine to morphine more extensively. There is a published report of a fatality in a nursing neonate who was exposed to high levels of morphine in breastmilk because his mother was a CYP2D6 ultrarapid metabolizer.[21] More important, such predictive models will eventually need to include factors that affect infant responses, such as the age of the infant, underlying comorbidities, and ontogeny of drug elimination pathways. For instance, certain medications can cause adverse events in younger infants due to higher exposures because of immaturity of organ function and/or metabolic pathways.

Animal study

Animal data are generally not useful in predicting drug concentrations in human milk. Although similar hormonal control of milk production across species has been reported, there is a lack of quality data characterizing species differences.[22] Major interspecies differences lie within mammary gland anatomy, storage and release of milk into ducts, and protein and lipid composition of milk. In addition, variability in drug transport processes across the mammary epithelium may yield discordant milk-to-plasma (M/P) drug concentration ratios in humans compared to mice.[23] In addition, it is unclear which drug transporters are relevant in animals compared to humans. For example, in one study, M/P values were more than 3-fold higher in mouse relative to human for diltiazem (3.3-fold), metformin (7.7-fold), praziquantel (5.9-

fold), propylthiouracil (45.6-fold), quetiapine (3.1-fold), and terbutaline (8.7-fold).[23] Therefore, although animal data may provide information on the simple presence or absence of a drug in human milk, animal data alone are insufficient to predict the drug concentration profiles in human milk. The FDA's Pregnancy and Lactation Labeling Rule (PLLR) recommends that "Animal data not be included if human data exists" and "Animal data, when included, should only state presence or absence of drug in milk."[24]

In general, animal reproductive toxicity testing follows guidelines established internationally.[25] These studies include pre-/postnatal development studies in the presence of maternal drug exposure, and juvenile toxicity studies. Prenatal and postnatal development studies are designed to collect information on *in utero* exposure of a drug in animals, as well as collection of information on exposure via milk. These studies collect information in nursing pups, including evaluations of survival, growth, behavior (e.g., motor activity, learning and memory, reflex development) effect on reproduction, and measurement of systemic exposure to the drug (via breastmilk). However, important lactation information is not required and, therefore, often not collected. For example, the amount of drug transferred from the mother to the breastmilk is not typically measured. Therefore, the amount of drug ingested by the pup cannot be calculated, even though systemic levels of the drug in the pup may be known. Moreover, even when systemic exposure in nursing pups is measured, the interpretation of the data is often confounded because the pups have prenatal exposures as well. It is difficult to use the data from pre-/postnatal studies to inform the exposure of drugs in nursing pups because the studies were not designed specifically to provide sufficient quality or quantity of information to evaluate in a given species or across species.

Juvenile toxicity studies in animals are generally conducted to support clinical studies in pediatric patients. However, juvenile animal studies are not intended to assess the exposure to a drug in juvenile animals through breastmilk because the dams are not dosed. Consequently, there is no information collected on the levels of drug in animal milk. Information that is often collected in juvenile toxicity studies includes effects of the exposure to the drug on survival, growth, behavior (e.g., motor activity, learning and memory, reflex development), and reproduction. Information obtained from juvenile animal studies is not confounded by *in utero* exposure, which is the case in prenatal and postnatal animal studies. However, the acquired data may not always be applicable because the age of the animal may not correspond to a breastfed infant.

Because of the reasons described above, it is potentially misleading to simply add quantitative animal data to the FDA labeling without providing sufficient clinical context. However, animal data could provide valuable information in certain cases. For such cases, PLLR should better clarify the expectations for generating and using animal data.

Clinical study

In the field of drugs in breast milk, the human clinical data available in the literature and in drug labeling are mainly derived

Table 1 Challenges in conducting clinical lactation studies

Operational	○ Sponsors have limited experience in conducting lactation studies ○ Concern over liability and limited market value of studies are disincentives ○ Resources to accommodate mother/infant availability during study, and in follow-up
Enrollment	○ Difficult to enroll lactating patients on a particular drug because drug is generally already approved ○ Study interference with establishment or maintenance of lactation ○ No clear benefit to participation
Study design	○ Adequacy of type of milk (colostrum vs. foremilk vs. hindmilk) and timing of milk collection relative to dosing of drug ○ Validation of drug assays in milk ○ Development of assessment strategies (e.g., modeling and simulation strategies)

from case studies and case series. Although these data are informative and may draw attention to a potential safety concerns, they are not considered sufficient to establish a risk or an absence of risk, because lack of standardization makes interpretation difficult. Clinical pharmacology and pharmacokinetic profiles of drug, including its concentrations in human milk and infant serum, are considered necessary to fully assess its potential to clinically affect the breastfeeding infant. However, lactation studies in human subjects often face several challenging issues (**Table 1**).

Information currently collected on lactation in a postmarketing setting is scarce. As of April 2016, there were nine products with ongoing or completed postmarketing lactation studies, compared to about 60 products with ongoing or completed postmarketing studies for pregnancy-related safety concerns. In general, most lactation postmarketing requirement (PMR) studies are for drugs that have the potential to be absorbed by a nursing infant, have a potential safety risk, and are anticipated to be used in women of reproductive age.

CHALLENGES

Given the tangible advantages of breastfeeding over infant formula, the risk–benefit assessment for lactating women on medications requires balanced evaluation of both toxicity risks due to drugs in milk and infant unfavorable outcomes due to loss of breastmilk-associated benefits. However, as described so far, tremendous knowledge gaps remain before informed risk–benefit assessment becomes possible for many drugs. Although animal studies and predictive models based on drug characteristics circumvent challenges of clinical lactation study conduct such as enrollment difficulties, validity of animal studies is limited, and predictive model approaches require further development. There is also limited availability of high-quality clinical data (e.g., data from clinical lactation studies) to inform about the risks and benefits of most drugs used during lactation. Moreover, there is wide variability in design and conduct of clinical lactation studies (e.g., variations in sampling time and collection methodology) that limits the interpretability of data across clinical lactation studies. Lack of validated assays for measurement of drug concentrations in breast milk poses another challenge. In addition to these difficulties, FDA labeling does not always consistently present available lactation information, further complicating this already confusing field.

PATH FORWARD
Prioritization of drugs for lactation studies
Given the number of drugs and biological products likely to be used by lactating women, prioritizing products for clinical studies is essential. Products that are commonly used by women of reproductive age (e.g., antimicrobials; antiinflammatory drugs, immunotherapies; cardiovascular drugs, hormonal therapies, and drugs to treat neurological and psychiatric disorders) should be prioritized. For example, despite multiple publications on antimicrobials, there are few data available for the quinolones that are used as treatment for acute pneumonia, urinary tract infections, and sexually transmitted infections, which can occur in breastfeeding mothers. Other considerations regarding antibiotic use include the effect of antibiotic therapy on intestinal flora diversity in the infant's microbiota, regardless of absorption by the infant. Biologics constitute a unique group of drugs for their diverse therapeutic targets and indications common in women of childbearing age, calling for lactation studies. If used in pre- and postpartum periods, these monoclonal antibodies show complex pharmacology in the mother, fetus, and the infant, and their pharmacokinetics in human milk may deviate from a prediction based on their molecular size, as demonstrated in a lactating patient receiving natalizumab.[26]

In addition, drugs that pose a potential health risk for an exposed infant or drugs that have no available data in the literature should also be prioritized. Drugs for which validated or commercially available assays have been developed should also be leveraged to increase the information available through lactation studies.

In the 2016 FDA public workshop, an approach to prioritization of drugs for lactation studies was discussed. The panel generally agreed that if a drug is considered safe for treatment of neonates, lactation studies would have low priority. In addition, if the physicochemical properties of a drug suggest that transfer into breast milk would be unlikely (e.g., drug that is not systemically absorbed), then lactation studies would also have low priority. However, the panel also agreed that drugs used commonly in women with no available lactation data and with presumed low risk to the nursing infant based on nonclinical data should be made a research priority. A consistent approach to presentation of information in the lactation section of labeling would also improve the utility to patients and prescribers.

Conducting lactation studies
Ethical considerations. There are three populations of lactating women who could potentially participate in a clinical lactation

study in which milk, infant serum, and clinical outcomes are analyzed:

1. women who are prescribed the drug in a clinical setting;
2. women who are prescribed the drug to treat their medical condition in a research setting;
3. women who are healthy volunteers and are prescribed the drug in a research setting.

When evaluating the research risks of a clinical lactation study, only those risks and benefits to the lactating woman and her breastfeeding infant that may result from research participation should be considered. In the clinical setting, the woman's decision to use a medically necessary drug must be clearly separate from the decision to enroll in a clinical lactation study. Therefore, the drug exposure to the infant would be considered a clinical risk, rather than a research risk. In this context, given the known benefits, a woman may decide to continue breastfeeding in spite of the potential risks to an infant from drug exposure through human milk. In a research setting, a lactating woman may want to start an investigational drug for an existing or new disorder or condition. In this setting, the potential drug exposure of a breastfeeding infant must be considered a research risk (and offers no clinical benefit to the infant). In this situation, breastfeeding must be discontinued, absent a narrow exception where infant feeding with alternative formula carries greater risk and less benefit than continued breastfeeding during maternal exposure to the investigational drug. In a research setting with healthy lactating women who volunteer for a clinical lactation study, breastfeeding must be discontinued for the duration of the study so that an infant is not exposed to the investigational drug through breastfeeding.

In considering the situations in which lactating women and their nursing infants can participate in a clinical lactation study, the panel of the workshop noted that there should be efforts to separate the maternal decision to use a medically necessary drug from the decision to participate in a clinical lactation study. The panel also noted that informed consent from the lactating woman and parental permission for the infant to participate in a lactation study must be obtained.

Patient enrollment. One of the difficulties in conducting drug studies in lactating women is recruitment of study subjects. An industry perspective on conducting a lactation study was presented at the workshop with a case example of certolizumab pegol (Cimzia) in inflammatory diseases,[27,28] where an open enrollment model provided access to a patient population that may not otherwise be willing or able to participate. Also, in this case, home healthcare nursing visits were particularly essential to successful recruitment and study conduct, which is relevant to other lactation studies of medications with longer half-lives, when there are many visits over a period of several weeks. Finally, the success of the lactation study is attributed to a dedicated multidisciplinary team (clinical, bioanalytics, medical, epidemiology, regulatory, legal, and compliance) and external expert advisors (pediatrician, obstetrician, lactation specialist).

Pregnancy exposure registries (PER) can be used to recruit and enroll breastfeeding women in lactation studies. PERs are studies that collect health information on exposure to medical products such as drugs and vaccines during pregnancy and report on birth outcomes. Women enrolled in a PER are already taking a drug during pregnancy, and because they will likely continue treatment after delivery, these women are an ideal population in which to study milk levels. However, the postnatal infant's environment, growth, and development are not routinely reported in PERs. In order to maximize its capability of signal detection in infant outcomes, optimization of data collection is essential. In addition, neonatal ICU and special care nursery patients may be an optimal population to study, as the mother is on documented medication, the family of a sick baby is motivated, and the environment is standardized. Research milk banks may be utilized more fully for data collection because extensive maternal information is recorded before donation.

Overall, clinical lactation studies can be successfully conducted. However, in order to maximize the successful and efficient completion of lactation studies, collaboration with multidisciplinary expertise is essential.

Study design considerations. Clinical lactation studies vary in their study designs, which include the choice between colostrum vs. mature milk, mother–infant pair vs. mother only, exclusive breastfeeding vs. supplemental feeding, and administering the drug of interest to women enrolled in a lactation study vs. enrolling patients already on treatment (**Table 2**).

Modeling and simulation

Physiologically based pharmacokinetic (PBPK) modeling (of the mother and/or the infant), and population pharmacokinetic modeling of drug concentration profiles in milk have been reported in the literature to predict drug exposure of infants.[29–31] Such an approach can project results to large populations to assess the range of possible exposures, for either therapeutic or toxicological assessment. Although the approach is attractive, the utility of PBPK models, combined with milk concentration profile predictions, to inform clinical practice is still limited, as there are challenging issues on model validation.[20]

Sophisticated computerized quantitative structure–activity relationship (QSAR) methods are promising methods for predicting the M/P ratio.[20] QSAR prediction of the M/P ratio followed by population pharmacokinetic (e.g., nonlinear mixed-effects modeling) or PBPK modeling may be able to simulate breastmilk exposure to drugs, decreasing the requirement for more stringent sampling schedules. However, the QSAR methods need to be compared head-to-head using a common set of M/P ratios derived from studies that have been validated.

In all cases of model-based simulation, the results should be validated with at least breastmilk drug concentration measurements. If the model is extended to predict infant plasma concentrations, measured infant concentrations would be beneficial for model validation. In constructing an adequate infant drug concentration model, the following should be considered: 1) preterm vs. term infant; 2) total drug excretion in breast milk; 3) oral

Table 2 Considerations on clinical lactation studies

Topic	Major comments
Type of milk collected	The difference in composition of foremilk vs. hindmilk needs to be accounted for with some drugs. Sampling should ideally take place after the lactogenesis II stage (approx. > 3 days postpartum), as opposed to colostrum collection which may falsely elevate the milk concentration due to a more porous mammary epithelium. Additionally, for all samples the specific timing of the milk sample must be collected.[22]
Mother-infant pair vs. lactating mother only	Lactating mother only study can provide information regarding: (1) timing of maternal dose relative to breastfeeding, (2) duration recommended to discard milk, (3) when to resume breastfeeding relative to dose or exposure, and (4) can help validate proposed pharmacokinetic models. If the concentration of drug in breastmilk is exceedingly low, this could preclude the need for further studies. Mother-infant pair studies can provide further information on infant drug disposition and safety.
Exclusive breastfeeding vs. supplemental feeding	Although including only women who are exclusively breastfeeding is preferred, including mothers who are supplementing provides "real life" data, and may allow for easy collection of pumped milk that would otherwise be discarded. However, studies should report the extent of breastfeeding.
Milk volume	While a 150 mL/kg/day feeding volume is a reasonable assumption, greater volumes do occur in early infancy, and often correlate to the time of most reported infant adverse drug reactions (ADRs). Consideration should be given to estimates infant risk based on a 200 mL/kg/day milk consumption. If infant outcomes are being assessed, direct measurement of participant milk volumes, or weighing infants before and after feeding, are methods that provide milk volume data for use in calculating infant exposure.
Milk sampling method	Collect the entire milk volume from both breasts at each collection over 24 hours, save the necessary aliquot for assay, and refeed the remainder to the infant preferably using techniques that are less likely to cause nipple confusion. The amount taken for assay should not deprive the infant of their nutritionally required volume. As a more practical alternative, samples of equal volume can be collected pre-and post-feed at several points over a dose interval. Use of an electric pump over hand expression is preferred. "Hospital grade" pumps are not necessary; modern personal electric pumps utilize the same technology and are less costly.
Milk sampling period	Sampling should occur when at steady-state; samples should be collected every 2-4 hours during a dosing interval.
Milk concentration reporting	Average concentration should be based on AUC derived from collections at multiple time points, not just a single point in time. Maximum concentration and time of maximum concentration should be reported.
Milk/plasma (M/P) ratios	Should be based on AUC and on multiple time points, not just a single point in time.
Sample size	The sample size for any lactation study will vary and input from experts should be obtained to ensure adequate sample size.
Balance between burden of data collection on mother vs. the need for enough information for data evaluation	The study should support continued breastmilk feeding and avoid disruption of breastfeeding routine.

bioavailability; 4) infant renal function; and 5) metabolizing enzyme ontogeny. Infant age is an important factor contributing to the ontogeny of the metabolizing enzymes and renal functions, which are involved in drug metabolism and elimination.

These modeling approaches could be used as a screening and supporting tool to identify drugs of concern (M/P prediction followed by infant PBPK), but should not entirely replace human lactation studies. Rather, knowledge obtained through modeling and simulation should be used to inform clinical lactation studies in prioritizing drugs for study and optimizing study designs.

Although the modeling and simulation approach remains to be further developed and refined for prediction of milk levels and infant exposures, the methodology is important because the results will enrich our knowledge before actual exposures of breastfeeding mother–infant pairs. We may be on the verge of a great improvement in our ability to predict before marketing which drugs urgently need to be studied *in vivo* and to identify which are likely to be relatively safe during breastfeeding.

Mechanisms and incentives to promote lactation studies
As there is a critical need for information to make appropriate risk/benefit decisions for medication use while breastfeeding, stable and long-term funding is essential for future lactation studies. Potential funding sources identified by the workshop panel included:

- Incentives for companies (e.g., Written Request from the FDA)
- Public–private partnership (e.g., International Neonatal Consortium)
- National Institutes for Health-Best Pharmaceuticals for Children Act Program
- National Academy of Medicine.

Lactation labeling

Effective June 30, 2015, the FDA released a new Pregnancy and Lactation Labeling Rule (PLLR).[32] The new rule removes the old pregnancy letter categories, combines the "Labor and Delivery" subsection with the "Pregnancy" subsection, renames the "Nursing Mothers" subsection "Lactation," and adds a new subsection on "Females and Males of Reproductive Potential."

The "Lactation" subsection provides information about medication use during lactation, and this information should be updated when new data are published. The section includes a risk summary, clinical considerations, and data sections. The risk summary outlines information on drug absorption, concentration in milk, actual or estimated infant daily dosage, effect of drugs on infant or milk production, and a risk/benefit statement. The clinical considerations section describes recommendations on how to minimize drug exposure and how to monitor for adverse reactions. The data section includes any clinical or nonclinical studies available that support the risk summary. When human data are available, animal data must not be included unless the animal model is specifically known to be predictive for humans.

A consistent approach to labeling content and format will improve usability by all stakeholders. However, what level of evidence (e.g., substantial evidence, case reports, database mining, observational data, computational models, animal data) should be included in the labeling warrants further discussions.

The workshop panel considered the utility of including a standard measure of drug excretion in labeling, such as the relative infant dose (RID), which is the percent of the weight-adjusted maternal dose consumed in breastmilk over 24 h. A 10% RID has been a generally accepted value by the breastfeeding medicine community as a reference point representing unlikely risk, although no consensus has been reached. However, in certain situations, there may be a concern for infant toxicity at exposures less than 10% RID. For example, many antineoplastic drugs may cause toxicity in an infant even in low doses. Nevertheless, if RID were included in the labeling, a description of the variability (i.e., confidence intervals) would also need to be included. Finally, the panel discussed the level of evidence that would be necessary to support labeling statements about the absence of risk, and the difficulty in establishing the absence of any risk. Although there was no clear consensus, the panel suggested considering whether a comparison of data obtained in developmental toxicity studies with data from lactation studies could provide sufficient information to establish the absence of risk.

COMMUNICATION AND OUTREACH
Knowledge translation

Health professionals should be supported by trusted, accurate, comprehensive, and consistent information about maternal medication and breastfeeding management to inform decision-making.[33] The following knowledge translation strategies were highlighted at the workshop.

The National Library of Medicine (NLM) described the free online resource database, LactMed,[34] which provides information on drugs used during lactation based on the available scientific literature. It is part of NLM's TOXNET system, a web-based collection of resources covering toxicology, chemical safety, and environmental health (http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm). In order to advance TOXNET and LactMed outreach, the NLM has developed programs, such as presenting at professional and consumer conferences, providing informative handouts, publishing in professional journals, communicating via social media, and training healthcare professionals through in-person or online courses.

The Academy of Breastfeeding Medicine (ABM) described its efforts to advocate for breastfeeding mothers' well-being by advancing physician education, expanding knowledge about breastfeeding science, and encouraging collaboration to exchange information. As an organization of physicians, the ABM develops and provides several literature-based guidelines on medications used during breastfeeding. As an example, the choice of breastfeeding by a postpartum woman with a history of past or current illegal/illicit drug abuse or legal substance use is challenging for many reasons.[35] The ABM has published a literature-based guideline for the evaluation and management of the woman with substance use or a substance use disorder who is considering breastfeeding. Of note, these protocols serve only as guidelines for the care of breastfeeding mothers and infants and do not delineate an exclusive course of treatment or serve as standards of medical care.

The MotherToBaby organization's services for counseling on medication exposures while breastfeeding were also presented (https://mothertobaby.org/). This is a service of the nonprofit Organization of Teratology Information Specialists, dedicated to providing evidence-based information to mothers, healthcare professionals, and the general public about medications and other exposures during pregnancy and breastfeeding. The services are funded by state, regional, and federal sources to respond to the need for educating women about drug exposures that are anticipated or have occurred. The experts behind MotherToBaby have created easily accessible fact sheets that answer frequently asked questions about exposures during pregnancy and breastfeeding. In addition, mothers and healthcare providers can call for information through toll-free numbers. The organization also conducts observational studies in pregnant women. Over 3,900 women have volunteered and 2,900 healthcare providers have referred their patients to participate in their pregnancy studies. MotherToBaby represents an important two-way communication channel and provides valuable feedback from mothers, which, in turn, facilitates identification of priority areas for future research.

In addition to the above-described communication and outreach program, other available resources for information on

medication and breastfeeding management include "Medications and Mothers Milk" by Hale,[36] "Drugs in Pregnancy and Lactation" by Briggs and Freeman,[37] and the Infant Risk Center website, www.infantrisk.com. These are all reliable evidence based resources used by mothers and healthcare providers.[5,38]

However, these resources are often not where women considering breastfeeding will look for information. Many times, these women search the internet for sites, blogs, forums, social media, or advertisements that are not necessarily peer-reviewed for the information they provide. This is a significant public health issue, as this information can be misleading or wrong. There is a need to develop a contemporary common resource where women can receive appropriate information that is also easily accessed by, or integrated into, internet and social media networks. However, social media can assist clinical lactation researchers to identify potential study participants.

Research data must have relevance for the intended knowledge users. One of the key knowledge users in this field is a lactation consultant interacting with breastfeeding women. At the workshop, major challenges in their practice were outlined, which included: drug interactions with other medications or dietary supplements taken by the mother; healthcare provider recommendations to wean or pump and discard when not necessary; lack of breastfeeding management related to times when medication concentration in breastmilk is low; healthcare provider use of outdated references; and lack of adequate lactation safety information on newly marketed drugs. Potential solutions may be hospital/prenatal packages and communication tools (e.g., Text4Baby app) for effective knowledge dissemination, in addition to a consistent research effort to delineate the effects of multiple drugs, the effects on milk production and milk components, the effects on preterm infants and long-term child development, dosing optimization, and better physician education.

Better communication strategies
There is a need to reinvigorate efforts to better communicate the clear benefits of breastfeeding, as well as the safety information related to maternal use of medications during lactation:

- The aim is not just to improve communication with obstetricians and pediatricians, but also pharmacists and all other healthcare providers in practice.
- Promote education of healthcare providers in training.[39]
- There is a need to develop "trusted sources" of information on the safety of drugs when used while breastfeeding (see above).
- There is a need to use electronic medical record (EMR) platforms to disseminate the best available information at the point of drug treatment decision making for lactating mothers.

SUMMARY
The benefits of breastfeeding to both mother and infant are evident. Although a drug taken by the mother may be excreted into breast milk, it does not necessarily mean that it should be contraindicated during breastfeeding. Any decision to limit a woman's ability to breastfeed must be justified by the fact that the risk to her infant clearly outweighs the health benefits conferred by breastfeeding.

For many drugs, there is a lack of high-quality clinical data in the literature and in drug labeling about the use in lactating women and their infants. The available toxicity information is mainly from case reports, which are informative, drawing attention to a potential safety concern, but are not considered sufficient to establish a firm risk–benefit balance or to confirm safety. Similarly, a drug's physiochemical properties are useful, but are not sufficient alone to predict drug concentrations in human milk. Prospective studies measuring drug concentrations in human milk are necessary to allow an accurate benefit/risk assessment, which is further enhanced by measuring infant serum concentrations and infant clinical outcomes. Novel techniques, such as PBPK and population PK modeling have been used for a few drugs and are promising future approaches to predict milk drug concentrations.

The efforts of all stakeholders should be leveraged to communicate the benefits of breastfeeding, as well as the safety information related to the maternal use of medications during lactation. There is a need to establish a "trusted" source of information on the safety of drugs when used during lactation, as many currently available and easily accessed information sources for the public are considered incorrect, incomplete, or outdated. Outreach strategies including education and online communication channels are critical for effective knowledge translation. Furthermore, further collaborations among academia, industry, and regulatory agencies are necessary to facilitate lactation studies for the safe use of drugs and biological products during lactation.

DISCLAIMER
This workshop was organized by an independent planning committee whose role was limited to the identification of topics and speakers. This workshop summary was prepared as a factual summary of the presentations and discussions that took place at the workshop. Statements, recommendations, and opinions expressed are those of individual presenters and participants, are not necessarily endorsed or verified by the US Food and Drug Administration.

CONFLICT OF INTEREST
The authors have no conflicts of interest relevant to this article to disclose.

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