

Written Comments of the Teratology Society and the Organization of Teratology Information Specialists to the PRGLAC.

Bolded are the presented statements. Full comments to also be submitted to the public docket.

August 22, 2019

To the members of the PRGLAC Task Force:

My name is Janet Hardy. I am a perinatal pharmacoepidemiologist and I am here on behalf of The Teratology Society and the Organization of Teratology Information Specialists, OTIS. Both are professional societies comprised of interdisciplinary scientists and health care providers dedicated to healthy pregnancy outcomes through research, education, and communication. We thank you for the opportunity to contribute to your efforts to drive a cultural change that no longer protects women *from* research, but protects women and their children *through* research.

We would like to outline several points pertinent to the PRGLAC mandate. They are organized according to the four Working Groups. A more detailed rationale for our suggestions are described in the accompanying written document, submitted earlier to PRGLAC Task Force Members and to the public.

Work Group 1: Research and Training Recommendations

- **Increase the training in obstetrics and pediatrics to include evidence-based training in therapeutics during pregnancy and lactation; and leverage the expertise of members in the Teratology Society and OTIS to develop training and research programs.**
 - Existing medical programs in obstetrics and pediatrics may not emphasize reliable research on the effects of pharmaceutical products on pregnancy and lactation, and consequently defer to a “no treatment” approach despite the potential benefits of treatment for mother and offspring. **Broadly available evidence-based training, as found in subspecialty programs such as maternal-fetal medicine, would improve the understanding of the health professionals that provide care to the majority of pregnant and lactating women.**
 - **Partner with the Teratology Society and OTIS, through our existing education efforts, to jumpstart the educational mission of the PRGLAC effort.** Meetings of organizations such as the American College of Obstetricians and Gynecologists (ACOG), the American College of Nurse Midwives (ACNM), the Association of Women’s Health, Obstetric and Neonatal Nurses (AWHONN), the American Academy of Pediatrics (AAP), the Society of Maternal-Fetal Medicine (SMFM), the American Academy of Physician Assistants, the American Academy of Family Physicians, and the American Association of Nurse Practitioners could include educational sessions organized and taught by members of the Teratology Society and OTIS. As examples: an annual course, the Human Teratogens course, was founded by Lew Holmes of the Massachusetts General Hospital. This renowned course has been conducted for decades, providing clinicians with cutting edge teratogen updates while providing continuing medical education credits. This course is now held at the University of South Florida with the support of the Teratology Society and the Organization of Teratology Information Specialists, OTIS. Additionally, OTIS and Teratology

Society recently joined with The National Society of Genetic Counselors and the Society for Maternal-Fetal Medicine for a national webinar on the opioid epidemic and its impact on pregnant and breastfeeding women. Collaboration and support for these programs could result in the expansion of educational opportunities for clinicians to include additional continuing education resources.

- **Incentivize training and research through fellowships and funding for early-career faculty and clinicians, as well as NIH-funded research programs in pregnancy and lactation therapeutics.**
 - **Motivation to pursue research that increases our understanding of risk-benefit tradeoffs for treatment during pregnancy and breastfeeding can only occur if funding for this research exists.** Support through training grants, FDA-funded research programs in pregnancy and lactation therapeutics, and incentives such as debt or loan forgiveness for clinicians pursuing these fields would provide motivation to increase the number of experts in this field.
 - **Increased long-term funding sources** for training, original research, and data banks for biological specimens such as breast milk **will reduce existing knowledge data gaps that currently hinder health decision making.**

Work Group 2: Regulatory Recommendations

- **The Teratology Society and OTIS expertise can be utilized to inform and guide Task Force approaches to address regulatory considerations of the PRGLAC recommendations in order to achieve change in the clinical research agenda.**
- **Remove regulatory barriers to research in pregnant women through mandates and incentives for drug manufacturers to include pregnant women in clinical trials.**
 - **Incentives and mandates could be modeled on the FDA approach used for pediatric testing of drugs.**
 - **Prioritize efforts towards therapeutics used to treat diseases that may be of life-long prevalence in women, such as diabetes or Crohn's disease, conditions specific to pregnancy, such as hyperemesis or preeclampsia, or diseases for which there are additional safety concerns and/or unmet medical needs in pregnancy, including diseases resulting from infections such as Zika virus or malaria.**
 - **Reduce liability to facilitate evidence-based decision making for new therapeutic products that may be used by women of reproductive age or are pregnant or lactating.**
 - **Training programs** to improve the general understanding of our obstetric care providers, as recommended in our comments for WG 1, **will begin to address the current limitations to understanding risk-benefit information.** Physicians may have concerns about enrolling or treating pregnant patients because they are unable to interpret the data from animal studies. Additionally, there may be no clear understanding of how to balance risk vs. benefit, i.e., the decision of whether to treat a pregnant woman should involve both an evaluation of the risk of the drug as well as the benefit of the treatment (i.e., risk of not treating). Unfamiliarity with animal studies may also hinder decisions of what information should be communicated in the drug label information.
 - **Continue efforts to more clearly communicate risks and benefits in the Pregnancy and Lactation sections of product labeling**

Work Group 3: Communication Recommendations

- **Jump start successful creation of a public awareness campaign, and develop evidence-based communication strategies with health care providers, through partnership with professional organizations that have active outreach communication strategies to health care providers and the public.**
 - **Communication needs identified in the PRGLAC Task Force recommendations are currently addressed in ongoing activities by the Teratology Society and OTIS. These sister societies have addressed these issues for over fifty years. Their missions include promoting multi-disciplinary research, communicating information effectively to health professionals and the public, and providing education and training.** Members of these societies are experts in researching reproductive hazards and assessing and evaluating medication risks as they relate to optimal pregnancy and breastfeeding outcome.
 - **Model such partnerships upon examples such as the collaboration with CDC to coordinate information on the dangers of Zika virus exposure** during pregnancy, and assist with recruiting women who had Zika-exposed pregnancies for outcome research.
 - **Align with and support communication tools such as the OTIS/MotherToBaby fact sheets available to healthcare providers and the public:** <https://mothertobaby.org/pregnancy-studies/>
 - Utilize the infrastructure of OTIS to help develop effective patient messaging about each topic
 - Through collaboration with our societies, leverage our experience to develop a communication strategy that utilizes multiple platforms such as social media, professional networks, educational formats, and professional journal approaches for the broadest stroke of impact.
- **FDA can accomplish the PRGLAC communication recommendations by leveraging efforts through established communication activities by organizations such as Teratology and OTIS with recognized expertise in public outreach and successful communication strategies.** Specifically, PRGLAC participation in collaborative communication forums such as webinars and workshops at professional meetings would:
 - Communicate FDA PRGLAC priorities as they develop through the Task Force
 - Connect scientists with existing research resources such as databanks for cord and maternal blood, breast milk
 - Obtain input to guide development of registries for treatments of reproductive conditions such as hyperemesis
 - Utilize the infrastructure of OTIS to help develop effective patient messaging about each topic
 - The value of participation in research to the health of future infants and mothers
 - Risk-benefit balances for treatment during pregnancy for informed patient decisions
- **Optimize registries for pregnancy and lactation by consistently requiring post-approval pregnancy studies of all eligible products and enforcing FDA recommendations.**
 - **The FDA's current authority** – to require or recommend post-approval pregnancy studies when the product is likely to be used by women of reproductive age and to collect additional information based on potential safety concerns that were seen in other drugs in the same pharmacologic class, in animal studies, in pre-approval clinical trial studies, or case reports - **is through Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 61 355(o)(3)), added by section 901 of the Food and Drug**

Administration Amendments Act of 2007 authorizes FDA to require certain postmarketing studies or clinical trials for prescription drugs approved under section 505(b) of the FD&C Act and biological products approved under section 351 of the Public Health Service Act (42 U.S.C. 262).

- Manufacturers of a generic form of a product that has an ongoing required post-approval pregnancy study(s) are currently not required to participate in those studies. Multi-drug or disease-based post-approval pregnancy studies may provide a larger sample size and consistency of methodology; may provide an internal comparison group; and may be more time and resource efficient relative to individual drug/individual manufacturer-based studies. For studies originated in academic or non-profit organizations, there is precedent for such multi-manufacturer participation. However, the above cited Act does not permit the FDA to require manufacturers to originate and participate in multi-drug and/or disease-based multi-manufacturer post-approval pregnancy studies.
- **The FDA should consistently require that manufacturers include lactation investigations within post-approval studies.**
- **We urge that:**
 - **The FDA allocate adequate resources to fulfill their existing mandate to consistently require and enforce post-approval pregnancy and lactation studies for all eligible products.**
 - **The existing Act, cited above, be amended permitting the FDA, as they see appropriate, to require manufacturers of generic products, upon approval, to actively contribute to post-approval pregnancy and lactation studies** for associated brand products through resources, awareness and recruitment efforts, and other relevant study activities.
 - **That manufacturers be required to initiate and/or participate in multi-drug or disease-based post-approval pregnancy and lactation studies.**

Work Group 4: Drive drug discovery and a foundation of evidence-based research

- **Prioritize PRGLAC efforts to drive drug discoveries towards health conditions that lack sufficient information.**
 - For example, OTIS has published a list that was developed through questions from concerned women and their health providers, representing real-world public health concerns.
 - **An oversight committee could be developed to gather the lists, determine priorities, and utilize existing or develop new grant-funding processes to encourage further research.**
- **Develop risk-benefit guidance communication tools through the use of existing paradigms both clinical and nonclinical and alternative models to predict risks** for the use of therapeutic products in women. Both OTIS and the Teratology Society have members with expertise to support such efforts.
- **Develop more robust nonclinical testing paradigms for improved human predictions for adverse effects to improve the translatability of nonclinical data to humans.**
 - Continue to utilize the well-established non-clinical testing paradigm in animals for DART hazard assessment, while incorporating additional methods/models to understand

mechanism of action (e.g., stem cells, zebrafish) and computer learning (e.g., adverse outcome pathways, PBPK modeling) for greater prediction and translatability.

- **Develop data linkages** leveraged through organizations with networks of scientists and research programs with existing data, data linkage projects, or potential to develop data linkages.
 - **Create an oversight committee to gather data needs, determine priorities, and utilize existing or develop new grant-funding processes to encourage further data collection and research.** Existing projects and grants could be further expanded, by expanding to other states or expanding staff within projects, such as the National Birth Defects Prevention Study (NBDPS), Biomedical Advanced Research and Development Authority (BARDA), National Institute of Allergy and Infectious Diseases vaccines project, Department of Defense Birth and Infant Health Registry project, Vaccines and Medications in Pregnancy Surveillance System (VAMPSS), condition and product pregnancy registries, etc.
 - Existing data sources are usually not linked and organizations with those data sources have difficulty collaborating due to institutional regulations, security issues, and non-standard data sets.
 - **Creation of a centralized, national, government data system may be necessary to link certain health information when private organizations are unable or unwilling to share and link data would be a long-term solution.** A centralized data source would provide economy of scale, set standards for data elements, and be able to access resources to address security and programming issues. A suggested test in developing a centralized data system could be to link Medicaid, CHIP, TRICARE, the Military Health System Data Repository, and the Defense Manpower Data Center since Medicaid provides supplemental insurance for 1 in 9 military children with special health care needs and common clients/records would likely be found across those data systems.
- **Establish long-term resources for PRGLAC activities through funding from government, industry, and private sources.**
 - Government grants and projects exist with responsibilities and oversight for research, communication, and other PRGLAC activities including the National Birth Defects Prevention Study (NBDPS), the Maternal and Child Environmental Health Network (MCEHN), National Center for Toxicological Research (NCTR), and other funded projects.
 - **For example, as the U.S. healthcare system is built around health insurance, a per-person, per-year fee could be obtained from government (Medicaid, CHIP, Medicare, TRICARE, Federal Employees Health Benefits, etc.) and private health insurance plans to add to the funding for PRGLAC activities.** Every person is born and is at risk for birth defects including structural malformations and developmental delays. Nearly all pregnancies and breastfed infants are exposed to therapeutic products if only for the recommended vaccines and vitamins. Including funding for research and communication regarding therapies for pregnant and breastfeeding women ensures that all individuals benefit from that research and communication. For a U.S. population of 329,000,000 individuals, a \$0.20 fee from health insurance would generate approximately \$65,000,000 for PRGLAC activities. The oversight committee could determine a funding formula for PRGLAC activities, for example, 50% for research, workforce development, and discover activities; 25% for data activities; 20% for communications activities; and 5% for regulatory and administrative activities.

- The European ConcePTION initiative, which also addresses gaps in research regarding medications in pregnancy and lactation, uses a formula of 53% government funding and 47% industry funding to build 32,000,000 Pounds for its collaborative activities.

In conclusion, we applaud the PRGLAC Task Force for addressing a vital topic. Medical education, regulations, registries and future research need to be expanded, sufficiently funded, and encouraged through oversight and government actions, or implementation of the Task Force recommendations will founder. OTIS and the Teratology Society are already focused on these topics, have the expertise to help make the recommendations happen, and should be utilized by the Task Force to achieve successful changes to the culture surrounding research needs for pregnant and lactating women.

We thank the PRGLAC Task Force for including our comments in today's meeting and we look forward to advancing the PRGLAC recommendations.

Respectfully,

Teratology Society
11190 Sunrise Valley Drive
Suite 300
Reston, VA 20191
703.438.3104
www.teratology.org

Organization of Teratology Information Specialists
5034A Thoroughbred Lane
Brentwood, Tennessee 37027
615.649.3082
www.mothersbaby.org