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Federal Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC)

HESI DART written statement for August 21-22, 2017 Meeting

The ILSI Health and Environmental Sciences Institute (HESI) Technical Committee for Development and Reproductive Toxicology (DART) respectfully submits the following comments on how nonclinical research can improve the clinical development of safe and effective therapies for pregnant and lactating women.

HESI DART is a tripartite organization comprising scientists from academia, government and industry. Our core mission centers around building consensus on optimal nonclinical testing strategies and how to translate developmental and reproductive hazards identified in nonclinical studies into meaningful human risk assessments.

The thalidomide tragedy of the early 1960s magnified the importance of identifying potential risks to the developing fetus and newborn infant during the drug development process. There have been considerable advances in our scientific understanding of the biology of pregnancy and lactation, especially around the transport mechanisms responsible for enabling drug exposure to the developing conceptus and breastfed infant. This increased knowledge has informed the design of comprehensive nonclinical testing strategies aimed at identifying developmental hazards. Implementation of these testing paradigms coupled to clinical trial exclusion criteria and/or stringent contraception requirements have helped mitigate a possible repeat of the thalidomide tragedy. But significant gaps remain. The most fundamental one is that the above diligence means that the very population we are trying to protect (pregnant women) are largely excluded from clinical trials. It has been estimated by the CDC, that <10% of drugs that come to market have sufficient information to inform the human risk for birth defects. In addition to the challenges this presents to healthcare professionals trying to treat certain conditions during pregnancy, tragically, the unknown level of risk can also lead to the termination of wanted pregnancies through fear. And for women who wish to breastfeed but need medications, the lack of adequate risk information is even more acute, leading to the painful choice to discontinue nursing their child.

So what can we do about this? Prior to marketing approval, the main avenue that enables hazard identification during pregnancy and lactation is via nonclinical testing, using animals as well as an extensive array of *in vitro* and other alternative systems. Our continued reliance on these systems underscores the importance of being able to translate what these nonclinical data mean for humans. The work of HESI DART and other organizations such as the Teratology Society, have contributed significant progress against this goal.

While the core framework of nonclinical testing has remained largely unchanged for over 50 years, there have been significant modifications to meet the needs of the ever-changing drug development landscape. So while the overarching paradigm remains focused on identifying hazards to the three fundamental components of the reproductive cycle; fertility, embryo-fetal development and postnatal development, testing protocols have evolved to accommodate the introduction of new drug modalities, such as biopharmaceuticals. For these molecules, secretion into breast milk and the ability to cross the placental barrier are generally much more limited than

for traditional small molecule drugs. In addition, due to their more targeted nature, many biopharmaceuticals only cross react with nonhuman primates (and not rat and rabbit, the more traditional species for these studies) which creates some advantages in terms of informing human risk, such as species similarities in the placental transfer of Fc-containing biotherapeutics. Integrating these advantages with our continued drive to reduce use of nonhuman primates however, is not without challenge. For example, to ensure the unnecessary use of nonhuman primates, dosing of drug candidates to assess effects on embryo-fetal development does not begin until pregnancy has been confirmed, which means that the earliest stages of pregnancy, such as implantation, are not fully assessed. And based on lower group sizes together with substantially longer gestation and maturation periods, mating studies become quite impractical.

As well as evolving testing strategies to cater for changes in drug modalities, significant advances have been made in our scientific understanding of normal vs abnormal development e.g. through identification of adverse outcome pathways. These achievements have been complemented by the development of a wide array of alternative models aimed at enhancing our ability to interrogate mechanisms of abnormal development (and their relevance to humans) and improving the efficiency of drug development. For example, models such as embryonic stem cells and Zebrafish have enabled us to identify developmental hazards sooner and further refine the chemistry of new drug candidates before they are tested in humans.

In summary, nonclinical testing will continue to remain the bastion for identifying developmental hazards. And while significant progress has been made to help inform the human risk of developmental hazards identified in nonclinical systems, continued nonclinical research is needed. This is especially true for effects on lactation (which is often only indirectly assessed via pup survival) and for effects in early pregnancy. This latter point is perhaps of greatest clinical relevance given that often, women taking medications may not realize they are pregnant until organogenesis is well underway.

We thank the Task Force for the opportunity to highlight the importance of nonclinical research for the development of safe and effective therapies for pregnant women and lactating women and encourage you to include these considerations in your final report.

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