The following is provided as an example of a CE course proposal. The exact information entered during the proposal submission process may vary slightly from the sample proposal outlined below.

**Course Title:** Risk Assessment, DART, and Endocrine Disruption: A World View

**Primary Endorser:** Reproductive and Developmental Toxicology Specialty Section

**Other Endorser(s): N/A**

**Course Chair:** First/Last Name, Corteva Agriscience.
Email: email@corteva.com
Member Status: Yes
Funding Needed: No SOT Funding Needed

**Course Co-Chair:** First/Last Name, Pfizer Inc. Groton, CT.
Email: email@pfizer.com
Member Status: Yes
Funding Needed: No SOT Funding Needed

**Course Description:** Protection of humans from excessive exposures to chemicals and pharmaceuticals associated with toxicity can be managed through risk assessment. Developmental and Reproductive Toxicity/Endocrine Disruption (DART/ED) hazard identification (ID) is a critical component of the risk assessment process. DART/ED hazard ID also is used independent of exposure assessment considerations to label compounds with DART or ED properties and, in some cases, limit or prevent sales in certain geographies. Although risk assessment or hazard ID applications can differ across sectors and geographies, scientists often collaborate on best practices for methods and interpreting endpoints within DART and endocrine-specific toxicity studies. This course will therefore provide a view of the regulatory landscape for DART/ED assessments, focusing on specific case studies as examples of applying DART/ED data to the end goal of protection of human health through risk assessment. The first talk will focus on the application of DART data for regulatory decision-making in the pharmaceutical sector. The second talk will then cover specific pharmaceutical case studies with DART data from nonclinical studies and the determination of human risk. The third talk will give an overview of endocrine disruption and how DART data apply to ED-specific requirements for chemicals across geographies, with examples of regulatory decisions based on existing datasets. The fourth talk will provide an overview of the US perspective on application of DART and ED data to the risk assessment process for chemicals, with a specific example focused on thyroid assessments. Finally, the fifth talk will introduce alternative approaches for DART/ED assessments and the vision for application of alternative approaches to regulatory decision-making. This will be a crash course on the current regulatory approach to use of DART/ED data, with a view to the future, considering alternatives to animal testing approaches.

As such, this course will offer broad appeal to audience members of different backgrounds and may be of interest to trainees interested in a career in regulatory toxicology.

**Presentation #1:** DART in Risk Assessment for Pharmaceuticals

**Presenter #1:** First/Last Name, US FDA/CDER, Washington, DC.
Email: email@fda.hhs.gov
Member Status: No
Funding Requested: Registration Waiver Only

**Presenter #1 Abstract:** The goals of reproductive and developmental toxicity safety testing are to identify and characterize the potential reproductive and developmental hazards of a drug using animal data and assess potential reproductive risk with clinical use of a drug. This presentation will discuss ICH regulatory guidance documents relevant to nonclinical reproductive and developmental toxicity studies needed for safety assessments of pharmaceuticals, including S9, S6(R1), S5(R3), and M3(R2). The differences between these guidance documents will be discussed, as well as how results from studies outlined in these guidance documents are used to communicate risk in the clinical setting throughout the drug development process, including labeling.

**Presentation #2:** Case Studies of Regulatory Decision-Making Based on DART Data for Pharmaceuticals

**Presenter #2:** First/Last Name, Pfizer Inc., Groton, CT.
Email: email@pfizer.com
Member Status: Yes
Funding Requested: No SOT Funding Needed

**Presenter #2 Abstract:** ICH Guidelines specific to developmental and reproductive toxicity (DART) testing provide a regulatory framework for devising reasonable safety assessment strategies with the main goal of generating useful data to communicate human risk of pharmaceuticals. In the determination of human risk from DART study data, there are several factors to consider: mechanism of action, species specificity, and maternal toxicity, among others. This presentation will discuss several pharmaceutical case studies that will highlight some of these complexities and factors that are associated with informing human risk. Case examples will include taking a look at how DART data are used on the label to inform human risk (including a look at the application of class labeling), how developmental toxicity in animals lead to contraception requirements in humans, monitoring human sperm (translation of animal data to humans), and other risk:benefit considerations, as is the case with non-oncology versus oncology drugs.

**Presentation #3:** Sufficiency of Pesticides DART Data Package for Endocrine Disruption Assessments: A Global Perspective on Regulatory Requirements for Human Health

**Presenter #3:** First/Last Name, Corteva Agriscience, Newark, DE.
Email: email@corteva.com
Member Status: Yes
Funding Requested: No SOT Funding Needed

**Presenter #3 Abstract:** This presentation will describe the global requirements for DART testing for crop protection chemical registration. The talk will further introduce the topic of endocrine disruption and describe the application of endocrine-relevant endpoints evaluated across DART test guideline studies to regulatory decision-making for pesticides in various geographical regions. The talk will provide an overview of how "ED" is viewed in risk-based versus hazard-based regulatory environments and review specific ED testing paradigms and assessments used for pesticides, including case examples.

**Presentation #4:** Thyroid Hormone Assessment: Implications for Developmental and Reproductive Toxicology

**Presenter #4:** First/Last Name, US EPA/OPP, Washington, DC.
Email: email@epa.gov
Member Status: Yes
Funding Requested: No SOT Funding Needed

**Presenter #4 Abstract:** Thyroid hormones regulate a wide array of bodily functions in mammals (e.g., metabolism, thermoregulation, body weight, neurodevelopment). Therefore, it is important to consider the impact of thyroid function perturbations in the context of developmental and reproductive toxicity. There is uncertainty as to whether adult animals would be more or less sensitive to thyroid disruption than pregnant females, the fetus, and newborns. In the US, the US Environmental Protection Agency Office of Pesticide Programs (OPP) regulates pesticide registration—a scientific and legal process governed mainly by three statutes: Federal Food, Drug, and Cosmetic Act (FFDCA); Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA); and Food Quality Protection Act (FQPA). Although toxicity data requirements for pesticides are comprehensive, including studies of different durations across several species and routes of exposure, thyroid assessments are typically limited to thyroid weights and histopathology in adults. Recognizing the need for information on possible differences in thyroid function across life stages and potential impact on risk assessment, the OPP—in collaboration with the Agency's Office of Research and Development (ORD)—developed a study design to generate thyroid data for pregnant females, the fetus, and newborns to establish protective points of departure for human health risk assessment. The comparative thyroid assay (CTA) measures thyroid weights, histopathology, and hormone levels across multiple life stages. OPP uses a risk-based decision framework that considers both hazard and exposure data while considering on a case-by-case basis if the CTA will be required. This presentation will discuss the CTA study design, how it is used in pesticide human health risk assessments, and the decision framework that OPP uses to determine when the study will be required.

**Presentation #5:** Application of Alternative Approaches for DART/ED to Regulatory Decisions

**Presenter #5:** First/Last Name, Proctor & Gamble, Mason, OH.
Email: email@pg.com
Member Status: Yes
Funding Requested: No SOT Funding Needed

**Presenter #5 Abstract:** Alternative approaches for DART are simpler systems that cover only a part of the reproductive cycle and/or developmental program. They work best when used in a hypothesis-driven way (i.e., by selecting test systems that respond to the modes of action that are relevant for the agents being tested). Endocrine disruption is an endpoint that is particularly well-suited for an alternative approach because it is a collection of modes of action. Models have been developed that cover receptor-ligand interactions and inhibition of enzymes that are relevant in androgen, estrogen, and thyroid hormone signaling. Research shows that *in vitro* assays are highly concordant with *in vivo* screening methods and can fully replace those methods for regulatory decisions regarding potential endocrine activity. Similar approaches can be taken for other DART modes of action, but it is important to select models that are appropriate for the question being asked. Certain stem cell assays have shown promise in identifying agents that affect embryonic development and are probably adequate to detect most teratogens. Other parts of the reproductive cycle and outcomes besides structural malformation will depend on a thorough understanding of underlying modes of action. Work is well underway to develop an ontology of DART modes of action, which will facilitate alternative model development and selection. In the meantime, approaches that cover a broad range of modes of action, like global gene expression analysis, will be useful for screening as well as mode-of-action identification.