FDA Issues Draft Guidance for Environmental Assessment of Drugs with Estrogenic, Androgenic, or Thyroid Activity

FDA’s Center for Drug Evaluation and Research (CDER) announced on April 29, 2015 the release of draft guidance for industry entitled, "Environmental Assessment: Questions and Answers Regarding Drugs with Estrogenic, Androgenic, or Thyroid Activity," to supplement FDA’s guidance for industry on, “Environmental Assessment of Human Drugs and Biologics Applications,” issued July 1998 (the EA Guidance). This supplemental draft guidance (available online) considers human drugs with potential endocrine-related (e.g., estrogenic, androgenic, or thyroid activity [E, A, or T activity]) in non-target organisms (e.g., aquatic life and terrestrial species). The public comment period for this draft guidance closed on June 29, 2015. This guidance may be altered substantially in its final form based on comments received from the public.

Background

FDA must comply with the National Environmental Policy Act of 1969 (NEPA) and consider all environmental impacts of its actions, which may include conducting environmental assessments (EAs) for certain new drug applications (NDAs), abbreviated NDAs, biologics license applications, and supplements to such applications, and investigational new drug applications. The EA Guidance provides direction on when an EA for drug applications should be submitted and recommendations on how to prepare EAs for submission to CDER, unless the action qualifies for a categorical exclusion.

Drugs with E, A, or T Activity May Require Additional Information

The EA Guidance allows categorical exclusions for actions related to NDAs and NDA supplements that would increase the use of the human drug, but which still results in estimated concentrations of the active moiety at the point of entry into the aquatic environment below 1 part per billion (ppb) (21 CFR 25.31(b)). The EA Guidance states that FDA will require at least an EA if “extraordinary circumstances” indicate the proposed action (e.g., approval of a NDA) may significantly affect the quality of the human environment.
Because environmental research has shown that drugs with endocrine-related activity have the potential to cause development or reproductive effects in aquatic life at concentrations less than 1 ppb, under the draft supplemental guidance, FDA may request additional information from the sponsor of a drug with E, A, or T activity to determine if an EA is required or if a categorical exclusion is acceptable. FDA recommends that sponsors consult with FDA prior to submission of the NDA, and preferably during product development, since additional ecotoxicity testing may be needed for the submission.

**Drugs Addressed by this Draft Supplemental Guidance**

Sponsors must submit information to FDA on whether a drug has E, A or T activity or potential activity. FDA may accept existing information collected by the sponsor to make this determination. Such information may include nonclinical studies, ecotoxicity studies, EPA Endocrine Disruptor Screening Program (EDSP) studies, modeling data, or information available from the scientific literature. In some cases, additional studies may be warranted to determine if a drug has E, A, or T activity.

**Determining What to Include in the Application Submission**

Either an EA or a claim of categorical exclusion with information to support that no “extraordinary circumstances” exists should be submitted in the NDA and NDA supplements. The sponsor should provide information that supports the conclusion that the expected level of exposure of the drug with E, A, or T activity would not significantly affect the quality of the human environment. Environmental concentrations of the drug, incorporating fate and transport information, may be taken into account when assessing the potential for effects on aquatic life.

**Tiered Ecotoxicity Testing Approach for a Drug with E, A, or T Activity**

The EA Guidance also recommends a 3-tiered approach to testing of a new drug so that the appropriate data are available to assess the potential environmental impact of the new drug while minimizing the costs to industry of collecting such data. Under the draft supplemental guidance, Tier 3 studies should be conducted on a drug with E, A, or T activity regardless of the results of the Tier 1 and Tier 2 ecotoxicity tests.

**How Can Exponent Help?**

Exponent has expertise in all aspects of conducting EAs for pharmaceuticals, including those with endocrine activity. We have evaluated fate and transport properties, developed exposure scenarios, assessed ecological effects on non-target organisms, and calculated risk for all potentially affected environmental compartments. In addition, Exponent scientists are recognized leaders in endocrine disruption and policy, with experience conducting and evaluating significant studies in the area of endocrine activity and in the identification of potential hormonal signals from standard nonclinical studies. Our consultants have provided valuable support and assistance to clients at every step, from initial strategy development through placement and monitoring of studies, preparation of the environmental assessment, and regulatory negotiations.
References


For More Information, Please Contact:

Jane Staveley, M.S.P.H.
Senior Managing Scientist, Ecological & Biological Sciences
jstaveley@exponent.com
(919) 228-6480

Margaret E. McArdle, M.S.
Managing Scientist, Ecological & Biological Sciences
mcardle@exponent.com
(978) 461-4611
Exponent’s Nonclinical Services

Exponent’s Center for Toxicology and Mechanistic Biology provides the highest quality technical, regulatory, and safety assessment services to assist our clients with issues related to pharmaceutical and biotechnology products, with a particular focus on nonclinical development and regulatory support.

We have several in-house staff with direct pharmaceutical experience, coming to Exponent from both large and small pharmaceutical and biotechnology companies. Our unique range of skills and experience in drug development helps our clients maximize the value of their research and development efforts in bringing medications to the market.

Aspects of the nonclinical developmental process for which Exponent is posed to assist include:

- Development of customized nonclinical testing strategies to reduce costs and maximize the likelihood of moving your candidate into the clinic and beyond
- Identification of appropriate animal models for nonclinical safety assessment
- Expertise in small and large molecules, and other novel therapeutics
- CRO selection, study design and management, including toxicity, safety pharmacology, and toxicokinetic evaluations
- Appropriate dose selection for nonclinical safety testing (including carcinogenicity testing) and first-in-human studies
- Nonclinical issues research and resolution
- Particular expertise in developmental / reproductive toxicology, juvenile, and genetic toxicology
- Data analysis and regulatory document preparation
- Preparation of pregnancy and lactation labeling content
- Regulatory support in preparation of Investigational New Drug (IND) applications and New Drug Applications (NDAs)
- Knowledge of global regulatory requirements, and responses to regulatory questions
- Representation during meetings with the FDA and other regulatory bodies
- Environmental impact assessments for US and EU regulatory authorities.

Beyond Nonclinical

Exponent is positioned to provide guidance across the entire product lifecycle for clients. Examples of areas beyond nonclinical in which Exponent can assist include the selection and prioritization of therapeutic indications and the development of target product profiles; defining the commercial strategy or competitive landscape; streamlining the regulatory approval process through the incorporation of biomarkers and tools for managing patients; the design of post-marketing surveillance strategies; and economic modeling to prioritize pipeline assets and provide predictions regarding success. We also have expertise in development of devices and device-drug combination products. We provide these services by leveraging the knowledge and experience of more than 90 technical disciplines across our firm.
Our Nonclinical Support Staff

**John DeSesso, Ph.D., DABFM, DABFE, FACFEI, FABCHS, Fellow ATS**
*(571) 227-7261 • jdesesso@exponent.com*

Dr. DeSesso has over 35 years of experience in the areas of developmental and reproductive toxicology, general toxicology, risk assessment, and human health effects and has published widely in these areas. He has assisted companies with assessment of data needs; design and interpretation of studies to meet regulatory requirements; preparation of INDs and NDAs for pharmaceutical substances; and preparation for and attendance at various FDA and Advisory Panel meetings. He is an adjunct professor of Biochemistry and Molecular Biology at Georgetown University School of Medicine, where he has been a faculty member for more than 30 years.

**Bhaskar Gollapudi, Ph.D.**
*(989) 486-8782 • bgollapudi@exponent.com*

Dr. Gollapudi specializes in genetic and molecular toxicology/chemical carcinogenesis. He has over 30 years of research and issue management experience at a major multinational industry addressing the safety of a diverse portfolio of substances. He is widely published in the area of genotoxicity and risk assessment, is an adjunct Associate Professor at the University of Michigan School of Public Health, and serves on a number of scientific committees, including the OECD Expert Committee on Genetic Toxicology Guidelines and the Committee on Toxicology of the U.S. National Research Council. Dr. Gollapudi is a recent recipient of the 2014 Arnold J. Lehman Award from the Society of Toxicology in recognition of his contributions to the field of risk assessment and chemical regulation.

**Karyn Hentz, MSPH, RAC, DABT**
*(571) 227-7208 • khentz@exponent.com*

Ms. Hentz is Regulatory Affairs Certified (RAC) in U.S. FDA regulations and provides regulatory support for a range of healthcare products. She assists companies with the identification of data gaps in their regulatory submissions, and collaboration in the conduct of studies or development of a rationale for waiving specific requirements. When studies have been needed, she has performed study monitoring on behalf of her clients, to ensure compliance and timely preparation of reports to meet regulatory deadlines. She has provided regulatory support for proprietary drug substances, generics, and excipients, leading to the submission of INDs, ANDAs, and NDAs.

**Jane Staveley, MSPH**
*(919) 228-6480 • jstaveley@exponent.com*

Ms. Staveley has over 35 years of experience in environmental toxicology, ecological risk assessment, and product stewardship. She has conducted environmental assessments of pharmaceuticals, both for human and animal use, for submission to the U.S. FDA and European regulatory authorities. This work has involved the placement, monitoring, and interpretation of ecotoxicity and environmental fate studies, as well as the development of novel exposure assessment approaches, including a watershed-level assessment. Ms. Staveley served as the moderator of a U.S. Congressional Briefing in 2010 on the topic of “Pharmaceuticals in Our Water: Concerns and Responses.” She also served on the steering committee of a 2011 workshop sponsored by SETAC and Health Canada on “The Top Research Questions on Pharmaceuticals and Personal Care Products in the Environment.”
Dr. White has over 16 years of experience in pharmaceutical drug development of small and large molecules, with emphasis on developmental and reproductive toxicology (DART), and juvenile and general toxicology. She advises pharmaceutical and biotech companies on nonclinical safety assessment strategies throughout the entire drug development process, including planning customized nonclinical strategies, placing and monitoring studies, developing human risk assessments for toxicity issues, addressing regulatory questions, and contributing to regulatory documents (IBs, INDs, Briefing Books, PIPs/PSPs, NDAs). Within the pharmaceutical industry, she has had extensive experience as a Study Director, safety assessment project team representative, and lead investigator on developmental toxicity mode-of-action studies for a diverse range of pharmaceutical products. She is currently Vice President of the Teratology Society.

Dr. Williams is a board-certified toxicologist with more than 20 years of experience in the evaluation of pharmaceuticals, as well as chemical and physical agents, for potential adverse effects on human health. She specializes in general toxicology, developmental and reproductive toxicology, and endocrine disruption. Dr. Williams has assisted companies in the design, monitoring, and interpretation of preclinical safety studies, in the evaluation of excipients, and in the preparation of NDAs for regulatory submission. Dr. Williams also has significant experience communicating health risks to the public.

**Recent Publications**


About Exponent

Exponent is a leading engineering and scientific consulting firm. Our team of scientists, physicians, engineers, and regulatory consultants performs investigations in more than 90 technical disciplines. We analyze failures and accidents to determine their causes and we evaluate complex human health and environmental issues to find cost-effective solutions.

www.exponent.com