Environmental Assessment: Questions and Answers Regarding Drugs With Estrogenic, Androgenic, or Thyroid Activity Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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TABLE OF CONTENTS

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I. INTRODUCTION

This guidance is intended to supplement FDA's guidance for industry on *Environmental Assessment of Human Drug and Biologics Applications*, issued July 1998 (the EA Guidance),[2] by addressing specific considerations for drugs that have potential estrogenic, androgenic, or thyroid hormone pathway activity (E, A, or T activity) in environmental organisms. It is intended to help sponsors of such drugs determine whether they should submit environmental assessments (EAs) for new drug applications (NDAs) and certain NDA supplements, and to clarify what information such sponsors should include if they submit a claim of categorical exclusion instead of an EA.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

The National Environmental Policy Act of 1969 (NEPA)[3] requires all Federal agencies to assess the environmental impact of their actions and to ensure that the interested and affected public is informed of the environmental analyses. To comply with NEPA, the Food and Drug Administration (FDA) considers the environmental impacts of its actions as an integral part of its regulatory process. FDA regulations at 21 CFR part 25 specify that EAs must be submitted as part of certain NDAs, abbreviated new drug applications (ANDAs), biologic license applications

[1] This guidance has been prepared by the Office of Pharmaceutical Quality in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[3] See http://www.nepa.gov.

(BLAs), supplements to such applications, and investigational new drug applications (INDs), as well as for various other actions, unless the action qualifies for a categorical exclusion. Failure to submit either an EA or a claim of categorical exclusion is sufficient grounds for FDA to refuse to file or approve an application (21 CFR 25.15(a), 314.101(d)(4), and 601.2(a) and (c)).

Categorical exclusions for actions related to human drugs and biologics are listed at 21 CFR 25.31. This guidance focuses on the categorical exclusion for actions on NDAs and NDA supplements that would increase the use of an active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment would be below 1 part per billion (1 ppb) (21 CFR 25.31(b)). Although an action that qualifies for this exclusion ordinarily does not require an EA, FDA will require "at least an EA" if "extraordinary circumstances" indicate that the specific proposed action (e.g., the approval of the NDA) may significantly affect the quality of the human environment (21 CFR 25.21).[4] One example of extraordinary circumstances provided in FDA's regulations is an action for which available data establish that, at the expected level of exposure, there is the potential for serious harm to the environment (21 CFR 25.21(a)).

Consistent with these regulations, when the sponsor of an NDA or NDA supplement[5] submits a claim of categorical exclusion under 21 CFR 25.31(b), FDA considers whether extraordinary circumstances exist under 21 CFR 25.21. If extraordinary circumstances exist, FDA will require the sponsor to submit an EA. If FDA needs more information to determine whether extraordinary circumstances exist, FDA may ask the sponsor to submit additional information concerning the potential environmental effects of approval of the sponsor's application or supplement. In light of research indicating that drugs with endocrine-related activity and, more specifically, drugs with E, A, or T activity, have the potential to cause developmental or reproductive effects in the aquatic environment at concentrations below 1 ppb,[6] FDA has, on a case-by-case basis, requested additional information from sponsors to help it determine whether extraordinary circumstances exist. However, late cycle requests for additional environmental information have the potential to delay approval of applications. Accordingly, this guidance is intended to clarify that sponsors of drugs with potential E, A, or T activity should consult with the Agency early in product development concerning the information FDA may need to determine whether an EA will be required or whether a claim of categorical exclusion will be acceptable, and what information should be included in the EA or claim of categorical exclusion.

[4] FDA evaluates the information in a sponsor's EA, along with relevant, additional information, in making the determination whether to prepare an environmental impact statement (21 CFR 25.22(b)).

[5] Unless extraordinary circumstances exist, INDs are categorically excluded from the requirement to submit an EA (21 CFR 25.31(e)).

[6] For example, see Section II.C (pp. 7-13) of USFDA, 2013, "Response to Citizen Petition to the FDA Commissioner under the National Environmental Policy Act and Administrative Procedure Act Requesting an Amendment to an FDA Rule Regarding Human Drugs and Biologics," Docket No. FDA-2010-P-0377; U.S. Environmental Protection Agency (USEPA), Endocrine Disruptor Screening Program (EDSP), last accessed February 17, 2015 at http://www.epa.gov/endo; and Organisation for Economic Co-operation and Development (OECD), OECD Work Related to Endocrine Disrupters, last accessed February 17, 2015 at http://www.oecd.org/env/ehs/testing/oecdworkrelatedtoendocrinedisrupters.htm.

III. QUESTIONS AND ANSWERS

Q1. What is a categorical exclusion?

A. Certain classes of Agency actions are subject to "categorical exclusion" and, therefore, ordinarily do not require the preparation of an EA because, as a class, these actions, individually or cumulatively, do not significantly affect the quality of the human environment (21 CFR 25.15(c), 40 CFR 1508.4). The categorical exclusions for CDER regulated products are listed at 21 CFR 25.31. To claim a categorical exclusion the applicant must provide: (1) a statement that the action requested qualifies for a specific categorical exclusion, citing the particular categorical exclusion that is claimed; and (2) a statement that, to the applicant's knowledge, no extraordinary circumstances exist (21 CFR 25.15(d)).

Q2. What are extraordinary circumstances?

A. Extraordinary circumstances are conditions under which a specific proposed action may significantly affect the quality of the human environment, including actions that ordinarily would fall under a categorical exclusion. If such extraordinary circumstances exist, FDA will require at least an EA (21 CFR 25.21). Several examples of extraordinary circumstances for FDA actions are listed at 21 CFR 25.21 and in Section III.C of the EA guidance. The Agency can also determine on a case-by-case basis whether extraordinary circumstances exist for a specific action, such that the submission of additional environmental information may be necessary.

Q3. What drugs are addressed by this guidance?

A. This guidance addresses drugs that are estrogenic, androgenic, or thyroid hormones, drugs that are based on these hormones (e.g., estrogen derivatives), and drugs that are not based on these hormones but that have the potential to interact with E, A, or T hormone pathways (e.g., aromatase inhibitors, which block a key enzyme from converting androgens into estrogens).

Q4. Which categorical exclusions are addressed by this guidance?

A. This guidance focuses on the categorical exclusion for actions on NDAs and NDA supplements if approval of the application would increase the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 ppb (21 CFR 25.31(b)).[7]

[7] See 21 CFR 25.5(b)(4) for the definition of "increased use" and Attachment B of the EA Guidance for examples of "increased use" applications. In general, abbreviated applications (ANDAs) are *not* considered to result in increased use of an active moiety if approved by the Agency (EA Guidance, Attachment A).

Q5. What extraordinary circumstances does this guidance address?

A. One example of extraordinary circumstances provided in the regulations is an action for which available data establish that, at the expected level of exposure, there is the potential for serious harm to the environment (21 CFR 25.21(a)). Accordingly, in determining whether extraordinary circumstances exist for an Agency action on an NDA or NDA supplement for a drug with E, A, or T activity that falls within the categorical exclusion under 21 CFR 25.31(b), FDA intends to consider available scientific research concerning the potential for such drugs to produce developmental or reproductive effects in the aquatic environment at expected levels of exposure below 1 ppb. FDA also intends to consider any information provided by the sponsor in support of the sponsor's statement that no extraordinary circumstances exist.

Q6. How can the sponsor determine whether the drug has E, A, or T activity?

A. The sponsor can evaluate existing information such as nonclinical studies (e.g., receptor-binding and enzyme assays, pharmacology studies, repeat-dose toxicity studies, developmental and reproductive toxicity studies, carcinogenicity studies), ecological toxicity studies (fish and invertebrate short-term and life cycle studies), Endocrine Disruptor Screening Program (EDSP) studies,[8] existing literature on the same or related compounds, modeling (including computational toxicology assessments reviewed with the use of expert knowledge), structural elements, or other scientific data. Based on a thorough evaluation of the totality of these data, the sponsor should assess whether the data are adequate for a determination of E, A, or T activity or whether additional studies should be conducted to further characterize the drug's potential E, A, or T activity.[9]

Q7. If the drug has or may have E, A, or T activity, and the proposed Agency action would fall within the categorical exclusion under 21 CFR 25.31(b), what should the sponsor submit with the application?

A. The sponsor should submit either an EA or a claim of categorical exclusion that is accompanied by information supporting the sponsor's statement that no extraordinary circumstances exist under 21 CFR 25.21. Such information should support the conclusion that approval of the application would not, at the expected level of exposure, significantly affect the quality of the human environment despite the drug's E, A, or T activity. For example, the sponsor could provide information demonstrating negligible introductions of the active moiety or its metabolic products into the environment, or information demonstrating that the active moiety would not be expected to produce developmental or reproductive toxicity in the aquatic environment at expected levels of exposure. In either case, the sponsor should consult with the Agency as needed prior to the submission of the NDA as described below.

[8] USEPA op. cit.

[9] A similar approach is described in greater detail in *Guidance for Industry, Endocrine Disruption Potential of Drugs: Nonclinical Evaluation* (USFDA, September 2013, Draft).

Q8. When and how should the sponsor consult with the Agency?

A. If the sponsor knows or suspects that the drug has E, A, or T activity, the sponsor should consult with the Agency early in product development and preferably before initiation of clinical trials. The sponsor can submit a Type C meeting request and include the relevant E, A, or T information in the pre-meeting package. By consulting early with the Agency, the sponsor may learn whether specific studies are needed and whether to submit a claim of categorical exclusion or an EA with the NDA. Such knowledge can help the sponsor avoid late cycle information requests that could delay approval of the application and is especially important in the context of expedited drug development.

Q9. How does the tiered approach to ecotoxicity testing recommended in the EA guidance apply to drugs with E, A, or T activity?

A. Tier 1 and Tier 2 studies described in Section IV.B.1 of the EA Guidance are used both to assess a drug's acute toxicity and to determine whether Tier 3 chronic and life-cycle studies (e.g., fish reproduction assays) should be conducted. For drugs with E, A, or T activity, however, sponsors generally should conduct Tier 3 studies, regardless of the outcome of Tier 1 and Tier 2 studies. The sponsor of a drug with E, A, or T activity should consult with the Agency as needed during drug development for guidance on study recommendations.

Q10. How will the Agency determine when extraordinary circumstances exist with respect to actions involving other types of drugs?

A. FDA intends to continue monitoring new research and data with respect to other types of drugs and to continue exercising its authority to determine on a case-by-case basis whether extraordinary circumstances exist and an EA will be required for an Agency action that falls within a categorical exclusion under Part 25. If FDA concludes that it needs more information to determine whether extraordinary circumstances exist for a proposed action involving another type of drug (e.g., approval of an application), FDA may ask the sponsor to submit additional information concerning the potential environmental effects of the action. FDA also may issue additional guidance on EA considerations for other types of drugs.