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June 16, 2026

Re: Docket No. FDA-2018-P-4088

Dear Dr. Healy,

This letter responds to your citizen petition, which was received on October 29, 2018 (Petition). In the Petition, you request that the Food and Drug Administration (FDA, Agency, or we) (Petition at 1):

> Require the immediate revision of all isotretinoin product labels (including branded and generic formulations) to warn of serious risks, as follows:
>
> 1. Add warnings, precautions, and highlights of prescribing information to inform that the use of and withdrawal from isotretinoin can result in erectile dysfunction, decreased libido, decreased vaginal lubrication, genital anesthesia, decreased orgasmic sensation, and anorgasmia.
>
> 2. Add warnings, precautions, highlights of prescribing information and a boxed warning to inform that sexual side effects can sometimes persist indefinitely after discontinuation of the drug, can emerge on treatment and remain afterwards, or emerge or worsen when the drug is stopped.

We have carefully considered your Petition, comments submitted to the docket, and other relevant information available to the Agency. Based on our review of these materials, and for the reasons stated below, your Petition is granted in part and denied in part.

I. BACKGROUND

A. Prescription Drug Product Labeling

1. Overview of Relevant Regulatory Requirements

FDA-approved drug product labeling summarizes the essential scientific information needed for the safe and effective use of the drug and reflects FDA's finding on the safety and effectiveness of the drug under the labeled conditions of use.[1] The primary purpose of FDA-approved labeling

[1] See section 505(d) of the Federal Food, Drug, and Cosmetic Act (FD&C Act); 21 CFR 201.56(a).

for prescription drug products is to provide health care practitioners with the essential scientific information needed to facilitate prescribing decisions, thereby supporting the safe and effective use of prescription drug products and reducing the likelihood of medication errors. Prescription drug product labeling includes the *Prescribing Information*,[2] which is directed to health care practitioners, and may also include additional FDA-approved labeling directed at the patient or caregiver (commonly referred to as *patient labeling*).

2. Certain Labeling Content Requirements and Related Agency Guidances

FDA regulations govern the content and format of prescription drug product labeling.[3] The regulations are intended to organize labeling information to effectively communicate to health care practitioners the "information necessary for the safe and effective use of prescription drugs."[4]

Labeling regulations are further discussed in FDA guidances about specific topics related to the content and format of prescription drug product labeling. When final, guidances describe the Agency's current thinking on the topics addressed.[5] Currently available labeling-related guidances may address a single section of labeling, multiple sections, or a discrete topic related to prescription drug product labeling.

The statutory and regulatory requirements for the three sections of labeling for which revisions are requested in the Petition are discussed briefly below.

a. WARNINGS AND PRECAUTIONS section of labeling

The WARNINGS AND PRECAUTIONS section[6] of prescription drug product labeling must describe "clinically significant adverse reactions," other potential safety hazards, limitations in use imposed by them, and steps that should be taken if these situations occur when "reasonable

[2] For ease of reading, when the term *labeling* is used in this Petition response, it is referring to the Prescribing Information.

[3] See, for example, 21 CFR 201.56 and 201.57; see also 21 CFR 201.100(c).

[4] See preamble of final rule "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products" (Physician Labeling Rule Preamble) published Jan 24, 2006 (71 FR 3922 at 3928). For the content and format requirements for the labeling of older prescription drug products that are not subject to the labeling requirements in 21 CFR 201.56(d) and 201.57, see 21 CFR 201.56(e) and 201.80. The specific labeling requirements for older drug products differ in certain respects and generally are not referenced in this Petition response.

[5] Labeling guidances are available on the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[6] For the purposes of this Petition response, we are interpreting your request that FDA require the addition of *warnings* and *precautions* to be a request for revisions to the WARNINGS AND PRECAUTIONS section of labeling in the Full Prescribing Information as described in 21 CFR 201.57(c)(6).

evidence of a causal association" between the drug and such hazards exists.[7] FDA regulations require that the labeling "be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established."[8] FDA adopted that standard in part to "prevent overwarning" of potential risks, which, if included in the WARNINGS AND PRECAUTIONS section, could dilute other "more important warnings" or "deter appropriate use" of the drug.[9]

The FDA guidance for industry *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products—Content and Format* (Warnings Guidance)[10] explains that the WARNINGS AND PRECAUTIONS section of labeling is intended to identify and describe a discrete set of adverse reactions[11] and other potential safety hazards that are serious or are otherwise clinically significant because they have implications for prescribing decisions or for patient management. The Warnings Guidance also identifies some factors to consider in assessing whether there is reasonable evidence of a causal association, including:

> (1) the frequency of reporting; (2) whether the adverse event rate in the drug treatment group exceeds the rate in the placebo and active-control group in controlled trials; (3) evidence of a dose-response relationship; (4) the extent to which the adverse event is consistent with the pharmacology of the drug; (5) the temporal association between drug administration and the event; (6) existence of dechallenge and rechallenge experience; and (7) whether the adverse event is known to be caused by related drugs.[12]

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[7] See 21 CFR 201.57(c)(6)(i).

[8] Id.

[9] See preamble of final rule "Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices" published Aug 22, 2008 (73 FR 49603 at 49605–49606).

[10] See guidance for industry *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products—Content and Format* (October 2011) at 3, available at https://www.fda.gov/media/71866/download (Warnings Guidance). We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[11] *Adverse reactions* are a subset of all *adverse events*. FDA's regulation at 21 CFR 201.57(c)(7) defines "adverse reaction" as follows: "an *adverse reaction* is an undesirable effect, reasonably associated with the use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events observed during use of a drug, only those for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event." See also Warnings Guidance at 17. The Warnings Guidance states that "[f]or the purposes of this guidance, an *adverse event* refers to any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related." Id.

[12] See Warnings Guidance at 3.

b. BOXED WARNING section of labeling

A boxed warning may be required in labeling for certain contraindications or serious warnings, particularly those that may lead to death or serious injury;[13] this information is especially important for a health care practitioner to consider in assessing the risks and benefits of a drug for an individual patient. The BOXED WARNING section must briefly explain the risk and then refer to the CONTRAINDICATIONS or WARNINGS AND PRECAUTIONS section of labeling, where the risk is explained in more detail.[14]

As stated in the Warnings Guidance,[15] a boxed warning is ordinarily used when:

- There is an adverse reaction so serious in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using the drug

  OR

- There is a serious adverse reaction[16] that can be prevented or reduced in frequency or severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patients in a specific manner, avoiding use in a specific clinical situation)

  OR

- FDA approved the drug with restrictions to ensure safe use because FDA concluded that the drug can be safely used only if distribution or use is restricted.[17]

[13] See 21 CFR 201.57(c)(1).

[14] Id.

[15] See Warnings Guidance at 11.

[16] FDA's regulation at 21 CFR 314.80(a) defines *serious adverse drug experience* as "[a]ny adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse." The Warnings Guidance includes a similar definition of the term *serious adverse reaction* for purposes of that guidance. See Warnings Guidance at 13.

[17] For example, under 21 CFR 314.520 and 601.42, or under section 505-1(f)(3) of the FD&C Act (21 U.S.C. 355-1(f)(3)).

c. Highlights of Prescribing Information

FDA regulations require that the labeling of most prescription drug products include, at the beginning, Highlights of Prescribing Information (Highlights),[18] which are intended to summarize for prescribers the information that is most important for safe and effective use of the product and to facilitate access to the more detailed information within drug product labeling.[19]

As stated in FDA guidance:[20]

> The purpose of Highlights is to provide immediate access to the information to which practitioners most commonly refer and regard as most important. Highlights also helps guide the practitioner to the section in the [Full Prescribing Information] where details can be obtained about a specific topic.

Highlights includes, among other information from the Full Prescribing Information, concise, informative summaries of select information from the WARNINGS AND PRECAUTIONS section[21] and, when there is one, the BOXED WARNING section.[22] From the ADVERSE REACTIONS section of the Full Prescribing Information, Highlights are required to include only the most frequently occurring adverse reactions, along with the criteria used to determine inclusion (e.g., incidence rate).[23,24]

3. FDA Authorities to Require Certain Labeling Changes

a. Safety labeling changes

Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)[25] authorizes FDA to require certain holders of approved applications for prescription drug products to make safety labeling changes if the Agency becomes aware of *new safety information* that FDA believes should be included in the drug's labeling. New safety information is information or other scientific data deemed appropriate by the Agency:

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[18] See 21 CFR 201.56(d)(1) and 201.57(a).

[19] See Physician Labeling Rule Preamble at 3931.

[20] See guidance for industry *Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements* (February 2013) at 6, available at https://www.fda.gov/files/drugs/published/Labeling-for-Human-Prescription-Drug-and-Biological-Products---Implementing-the-PLR-Content-and-Format-Requirements.pdf (Implementation Guidance).

[21] See 21 CFR 201.57(a)(10).

[22] See 21 CFR 201.57(a)(4).

[23] See 21 CFR 201.57(a)(11).

[24] See Implementation Guidance at 13.

[25] 21 U.S.C. 355(o)(4).

> about a serious risk or an unexpected serious risk associated with use of the drug that the [Agency] has become aware of (that may be based on a new analysis of existing information) since the drug was approved, since [a] risk evaluation and mitigation strategy (REMS) [for the drug] was required, or since the last assessment of the approved REMS for the drug[.][26]

Application holders have an opportunity to object to such labeling and may enter into discussions with the Agency to reach agreement on whether the labeling for the drug should be modified to reflect the new safety information.[27] FDA has the authority to issue an order requiring that the safety labeling changes be made.[28]

b. MODERN Labeling Act

Section 503D of the FD&C Act was added by section 324 of the Consolidated Appropriations Act, 2021 (Public Law 116-260), "Modernizing the Labeling of Certain Generic Drugs" (commonly known as the MODERN Labeling Act or MODERN).[29] Under MODERN, FDA may require labeling for certain ANDAs associated with a reference listed drug that was withdrawn for reasons other than safety or effectiveness to be updated when doing so would benefit the public health and when (1) there is new scientific evidence available pertaining to new or existing conditions of use that is not reflected in the approved labeling, (2) the approved labeling does not reflect current legal and regulatory requirements for content or format, or (3) there is a relevant accepted use in clinical practice that is not reflected in the approved labeling.[30]

Under MODERN, if an ANDA holder informs FDA that it does not agree to the labeling changes and provides a statement detailing the reasons, the Agency shall provide an opportunity for discussion to reach agreement. Upon conclusion of such discussions, FDA may issue an order requiring that the ANDA holder make the labeling changes FDA determines are appropriate.

B. FDA-Approved Isotretinoin Product Labeling

Isotretinoin is a synthetic derivative of vitamin A and belongs to the class of drugs known as retinoids. Isotretinoin capsules are approved in the United States for the treatment of severe recalcitrant nodular acne in nonpregnant patients with multiple inflammatory nodules with a

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[26] See section 505-1(b)(3) of the FD&C Act (21 U.S.C. 355-1(b)(3)).

[27] See section 505(o)(4) of the FD&C Act (21 U.S.C. 355(o)(4)).

[28] Id.

[29] 21 U.S.C. 353d.

[30] For such ANDAs, designated as *covered drugs* under MODERN, the reference listed drug must have been approved under section 505(c) of the FD&C Act; have no unexpired patents included in the list under section 505(j)(7) of the FD&C Act and no unexpired period of exclusivity; and have had approval of its application withdrawn for reasons other than safety or effectiveness. See section 503D(a)(1) of the FD&C Act (21 U.S.C. 353d(a)(1)).

diameter of 5 millimeters or greater.[31] The labeling further explains that isotretinoin should be reserved for use in patients with severe nodular acne who are unresponsive to conventional therapy, including systemic antibiotics, because of the risk of significant adverse reactions.

The first isotretinoin product, Accutane (isotretinoin capsules), was approved in 1982 under new drug application (NDA) 018662. The product approved under this NDA is no longer marketed, and approval of the NDA has been withdrawn.[32] Multiple abbreviated new drug applications (ANDAs or generic versions) for isotretinoin, relying on Accutane as the reference listed drug,[33] are approved and marketed.

In addition, isotretinoin is approved under NDA 021951 with the proprietary name Absorica and under NDA 211913 as Absorica LD,[34] approved in 2012 and 2019, respectively.[35] FDA has also approved multiple ANDAs relying on Absorica as the reference listed drug.[36]

When FDA approved Absorica LD, a combined labeling document was created for both Absorica and Absorica LD. The combined labeling currently states, in the ADVERSE REACTIONS section under the heading "Reproductive System":[37]

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[31] Labeling for newer isotretinoin capsule products additionally clarifies that they are indicated "[in patients] 12 years of age and older." See currently approved combined labeling for Absorica and Absorica LD, available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/021951s024,211913s011lbl.pdf (Absorica/Absorica LD Labeling).
We note that FDA's 2018 draft guidance on the INDICATIONS AND USAGE section of labeling recommends the inclusion of age groups in indications. See draft guidance for industry *Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (July 2018) at 4–5, available at https://www.fda.gov/media/114443/download.

[32] See 75 FR 39024, Jul 7, 2010, in which FDA announced its determination that Accutane was not withdrawn from sale for reasons of safety or effectiveness; see also 75 FR 71135, Nov 22, 2010, in which FDA announced the withdrawal of approval of the NDA for Accutane pursuant to 21 CFR 314.150(c) in response to a request from the application holder.

[33] A *reference listed drug* "is the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA" (21 CFR 314.3(b)).

[34] Absorica LD has a different bioavailability from that of Absorica due to its modified formulation, which allows for the use of a lower dose of administered isotretinoin than is used for the original Absorica product.

[35] Absorica and Absorica LD were approved under the section 505(b)(2) pathway of the FD&C Act, under which at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use (21 U.S.C. 355(b)(2)). The approved drug upon which both of these applications relied was Accutane.

[36] Absorica products (i.e., Absorica, Absorica LD, and Absorica-based ANDAs) and Accutane-based ANDA products are not therapeutically equivalent to each other and, thus, are not considered substitutable or interchangeable at the pharmacy level. Likewise, Absorica and Absorica-based ANDAs are not substitutable or interchangeable with Absorica LD because of differences in bioavailability and recommended dosages.

[37] See Absorica/Absorica LD Labeling.

> Abnormal menses and **sexual dysfunction, including erectile dysfunction, decreased libido, decreased vaginal lubrication, and vaginal dryness** [38] [emphasis added]

Three of the four sexual dysfunction adverse events that are currently included in the combined labeling for Absorica and Absorica LD — erectile dysfunction, decreased libido, and decreased vaginal lubrication — are among the six adverse events that you requested be added to the WARNINGS AND PRECAUTIONS section and Highlights in the labeling for all isotretinoin products (Petition at 1).

At present (and when the Petition was received), the approved labeling for isotretinoin generic drug products relying on Accutane does not include any information on sexual dysfunction.[39]

II. DISCUSSION

In the Petition, you request that FDA require certain revisions to the WARNINGS AND PRECAUTIONS and BOXED WARNING sections and to the Highlights of labeling for isotretinoin products (Petition at 1). These three requests are discussed separately below.

A. Request for Additions to the WARNINGS AND PRECAUTIONS Section

1. Information Reviewed by FDA

In support of the requests in the Petition, you presented summaries of (1) case reports from the FDA Adverse Event Reporting System (FAERS)[40] (Petition at 1–3), (2) published case reports and case series from the medical literature (Petition at 1), (3) your own published observational studies (Petition at 3–4), and (4) postmarketing adverse event information from regulatory agencies outside of the United States (Petition at 3–4). To respond to the Petition, FDA performed its own comprehensive review of FAERS and the medical literature, and we reviewed the information submitted in the Petition and comments submitted to the public docket.

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[38] *Vaginal dryness* refers to vaginal mucosa and vulva that have become dry, thin, and inflamed and most frequently occurs due to reduced levels of estrogen. *Decreased vaginal lubrication* refers to less wetness during sex.

[39] Although the labeling for a drug product approved under the section 505(b)(2) pathway of the FD&C Act generally follows that of the relied-upon drug, there is no *same labeling* requirement as exists for ANDAs, which are required to have the same labeling as the reference listed drug (except for changes required because of differences approved under a suitability petition (see section 505(j)(2)(C) of the FD&C Act and 21 CFR 314.93) or because the generic drug and the reference listed drug are "produced or distributed by different manufacturers") (see section 505(j)(2)(A)(v) and (j)(4)(G) of the FD&C Act, and 21 CFR 314.94(a)(8)(iv) and 21 CFR 314.127(a)(7)). Labeling for Accutane was last revised on February 1, 2010, while subsequent approvals for Absorica and Absorica LD updated and modernized the labeling in certain respects, as is permitted for drug products approved under the section 505(b)(2) pathway of the FD&C Act.

[40] At the time the Petition was submitted and FDA performed its review, the FAERS database was used to collect information on adverse event and medication error reports submitted to FDA to support the Agency's postmarketing safety surveillance program for drug and therapeutic biological products. On March 11, 2026, FDA announced the launch of the FDA Adverse Event Monitoring System, which replaced platforms previously used to collect postmarketing safety reports for FDA-regulated products, including FAERS.

2. FDA Assessments on Sexual Dysfunction Adverse Events During Treatment With Isotretinoin

As noted above, the standard for adding an adverse event to the WARNINGS AND PRECAUTIONS section is that "there is reasonable evidence of a causal association with a drug," but that "a causal relationship need not have been definitively established."[41] From our review of the materials identified above, including those submitted with your Petition, we have not identified reasonable evidence of a causal association between isotretinoin and the sexual dysfunction adverse events identified in the Petition during isotretinoin use; thus, inclusion of such information in the WARNINGS AND PRECAUTIONS section of labeling of isotretinoin products is not warranted. As discussed earlier in this Petition response, the Warnings Guidance recommends consideration of several factors to assist in assessing whether there is reasonable evidence of a causal association. These include:

> (1) the frequency of reporting; (2) whether the adverse event rate in the drug treatment group exceeds the rate in the placebo and active-control group in controlled trials; (3) evidence of a dose-response relationship; (4) the extent to which the adverse event is consistent with the pharmacology of the drug; (5) the temporal association between drug administration and the event; (6) existence of dechallenge and rechallenge experience; and (7) whether the adverse event is known to be caused by related drugs.[42]

Below, we address in more detail the basis for our conclusion that the materials reviewed in connection with this Petition do not provide reasonable evidence of a causal association between isotretinoin and the sexual dysfunction adverse events described in your Petition.

First, the articles from the medical literature cited in the Petition, as well as those identified by FDA, consist primarily of individual case reports, case series, and observational studies, all with limitations that preclude a determination on causality. For example, the case report of a single patient[43] and case series of six patients[44] describing reported sexual dysfunction adverse effects were small sample sizes, and neither provided information from which conclusions could be drawn about whether the sexual dysfunction reported by the patients was attributable to isotretinoin and not another factor (or factors). Of the observational studies identified by FDA, one study summarized anecdotal information from YouTube interviews,[45] and a second

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[41] See 21 CFR 201.57(c)(6); see also Warnings Guidance at 3.

[42] See Warnings Guidance at 3.

[43] Coleman R, MacDonald D, 1994, Effects of Isotretinoin on Male Reproductive System, Lancet, 344(8916):198, doi: 10.1016/s0140-6736(94)92803-7.

[44] Tirado Sánchez A, León Dorantes G, 2005, Disfunción Eréctil Durante el Tratamiento con Isotretinoína [Erectile Dysfunction During Isotretinoin Therapy], Actas Urol Esp, 29(10):974–-976, doi: 10.1016/s0210-4806(05)73379-9.

[45] Ghadimi TR, Martinez MJ, Rieder EA, 2023, Self-Reported Long-Term Side Effects of Isotretinoin: A Case Series, J Drugs Dermatol, 22(4):423–424, doi: 10.36849/JDD.2303.

uncontrolled study described sexual dysfunction from isotretinoin as an uncommon occurrence.[46] FDA identified one controlled study; however, because of its limited sample size, the study estimated isotretinoin-associated risks imprecisely (i.e., the confidence intervals were unacceptably wide) to provide evidence bearing on causality.[47] Furthermore, the authors acknowledged that the small sample size, along with other limitations of their study, namely the potential for residual confounding and ascertainment bias (as not all patients will seek care for sexual dysfunction), could contribute to imprecision in the results.

Second, among the literature reviewed were two publications on which you are a co-author that you cited in the Petition as evidence of a causal association between sexual dysfunction and isotretinoin use.[48,49] Because of serious limitations in the methodology of these studies as described below, they did not provide interpretable data from which any causal relationships between the sexual dysfunction adverse events reported and isotretinoin use could be identified. Specifically, these two studies were not adequately designed to provide interpretable data on the relationship between isotretinoin and any of the sexual dysfunction adverse events evaluated. They were uncontrolled, retrospective, observational studies relying on patients' online self-reports of sexual dysfunction submitted through a web portal entitled "RxISK."[50] The studies' authors collected data online, without examining or treating the patients who responded to queries on the web portal. Given the limitations of the assessment methods, the investigators could not adequately assess for the presence of other potentially confounding risk factors for sexual dysfunction (e.g., depression, anxiety, refractory acne or other medical conditions, psychosocial stressors, relationship factors). Furthermore, the studies did not use validated assessments of sexual function, and investigators conducted directed queries using specific adverse event terms, which can stimulate, influence, and bias adverse event reporting and data collection. The studies' authors stated that they performed causality analyses of these reports based on patient responses to structured questions, but did not provide more detailed information about any of the specific structured questions or directed queries. In addition, as noted by the authors in one of the studies, the RxISK website includes numerous articles describing "enduring sexual dysfunction" attributed to the use of a variety of drugs, including isotretinoin, which could introduce bias by potentially stimulating the reporting of sexual dysfunction adverse events.[51]

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[46] Chung JG, Turner M, Merika EE, 2024, Self-Reported Male Genital Side-Effects in a UK Cohort Taking Isotretinoin, Clin Exp Dermatol, 49(10):1245–1246. doi: 10.1093/ced/llae134.

[47] Thang CJ, Garate D, Golovko G, Barbieri JS, 2024, Isotretinoin Exposure Does Not Appear To Be Associated With Risk of Adverse Male Sexual Health Outcomes in Acne Patients, Int J Dermatol, 63(2):e54–e57, doi: 10.1111/ijd.16865.

[48] Hogan C, Le Noury J, Healy D, Mangin D, 2014, One Hundred and Twenty Cases of Enduring Sexual Dysfunction Following Treatment, Int J Risk Saf Med, 26(2):109–116. doi: 10.3233/JRS-140617.

[49] Healy D, Le Noury J, Mangin D, 2018, Enduring Sexual Dysfunction After Treatment With Antidepressants, 5α-Reductase Inhibitors and Isotretinoin: 300 Cases, Int J Risk Saf Med, 29(3–4):125–134. doi: 10.3233/JRS-180744 (Healy et al.).

[50] Available at https://rxisk.org, accessed Dec 5, 2024.

[51] See Healy et al. at 126.

For these reasons, these studies were not designed to provide interpretable data bearing on any causal association between the reported adverse events and the use of isotretinoin.

Third, the Petition cited summary analyses of postmarketing reports performed by regulatory agencies outside the United States. These were summary analyses of limited numbers of postmarketing reports from the Netherlands, Canada, and the United Kingdom, with case-level details available for some cases, but not for all. From our review, we determined that these data do not provide evidence bearing on a causal association between use of isotretinoin and sexual dysfunction adverse events.

Fourth, we evaluated FAERS reports cited by the Petition and FAERS reports from our own review. It is important to note that FAERS data have limitations. FDA does not require that a causal relationship between a product and an event be proven for submission of an adverse event report to FAERS, and reports do not always contain enough detail to properly evaluate an event. There are also many factors that can influence whether an adverse event will be reported, such as the length of time a drug product has been marketed and publicity about a specific adverse event, and FDA does not receive reports for every adverse event that occurs with a drug product. Lastly, FAERS data cannot be used to calculate the incidence of an adverse event in the U.S. population.

FAERS data are particularly useful for identifying unexpected (unlabeled), rare, serious adverse events that are temporally associated with use of a drug product and for which the background rate of events is low. Sexual dysfunction is highly prevalent in the U.S. general population and worldwide, as shown in an epidemiological study of a highly representative sample of U.S. women and men ages 18 to 59 years indicating that 43 percent of women and 31 percent of men report problems with sexual functioning.[52] As discussed in further detail below, particularly given the relatively few reports submitted to FAERS and the high background rates of sexual dysfunction in the general population, it is difficult to interpret whether there may be a causal relationship between isotretinoin and sexual dysfunction from FAERS data. Assessing any causal association between sexual dysfunction and treatment with isotretinoin, from FAERS data or other sources, is further complicated by the fact that patients with serious dermatologic conditions like severe acne have an increased risk of sexual dysfunction, as well as increased

[52] Laumann EO, Paik A, Rosen RC, 1999. Sexual Dysfunction in the United States: Prevalence and Predictors, JAMA, 281:537–544, doi: 10.1007/BF01541933.

risks of depression, anxiety, and other psychiatric conditions that themselves increase the risk of sexual dysfunction.[53,54,55,56]

For each of the FAERS reports reviewed, we assessed factors such as the quality and completeness of the report, the time to onset of the adverse event in relation to the initiation (or discontinuation) of isotretinoin, and the presence or absence of other potential causes of sexual dysfunction or risk factors contributing to sexual dysfunction (e.g., underlying severe dermatologic disease, comorbid depression or anxiety, other medical disorders that can cause sexual dysfunction, concurrent medications, relationship status, psychosocial stressors).

For most of the relevant FAERS reports regarding three of the adverse events from the Petition — erectile dysfunction, decreased libido, and decreased vaginal lubrication — as well as a fourth adverse event already included in the labeling for Absorica and Absorica LD — vaginal dryness — the reports featured young, overall healthy men and women without specifically stated additional risk factors for sexual dysfunction (i.e., who did not report concurrent medical problems or use of concomitant drugs thought to be associated with sexual dysfunction). Among the cases that reported a time to onset, we found suggestions of temporal relationships between isotretinoin use and some of the reports of these four sexual dysfunction adverse events, as well as some positive dechallenge and rechallenge experiences (where the adverse event abated when the drug was discontinued and, in cases when the drug was restarted, the adverse event reemerged). Furthermore, decreased vaginal lubrication and vaginal dryness are consistent with the known pharmacology of isotretinoin, i.e., that the drug inhibits secretions and induces atrophy of sebaceous glands. However, the number of sexual dysfunction adverse event reports is relatively low given the many decades of usage of isotretinoin, and we have not identified any adequately designed placebo-controlled studies or other adequate evidence to inform a causal association between isotretinoin and the sexual dysfunction adverse events identified. In addition, assessment of a causal association based on FAERS data is complicated by factors such as inherent limitations in a voluntary reporting system, high background rates of sexual dysfunction in the general population, and potential alternative explanations for sexual dysfunction adverse events in this population. Because of these noted limitations of FAERS data, the information on possible temporal relationships, dechallenge/rechallenge experiences, and isotretinoin pharmacology does not represent reasonable evidence of a causal association that would warrant placement of information in the WARNINGS AND PRECAUTIONS section of labeling.

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[53] Kurek A, Peters EM, et al., 2012, Profound Disturbances of Sexual Health in Patients With Acne Inversa, J Am Acad Dermatol, 67(3):422–428, 428-e1, doi: 10.1016/j.jaad.2011.10.024.

[54] Misery L, Taïeb C, et al., 2020, Psychological Consequences of the Most Common Dermatoses: Data From the Objectifs Peau Study, Acta Derm Venereol, 100(13):adv00175, doi:10.2340/00015555-3531.

[55] Ladizinski B, Federman DG, 2013, Approaching Erectile Dysfunction in Dermatology Patients, JAMA Dermatology, 149(7):783–784, doi: 10.1001/jamadermatol.2013.289.

[56] Gupta MA, Gupta AK, 2014, Current Concepts in Psychodermatology, Curr Psychiatry Rep, 449–457, doi: 10.1007/s11920-014-0449-9.

We note, however, that the threshold for including information in the ADVERSE REACTIONS section of labeling is lower than that for the WARNINGS AND PRECAUTIONS section. The ADVERSE REACTIONS section of prescription drug product labeling describes "the overall adverse reaction profile of the drug."[57] FDA's regulations define an adverse reaction, for purposes of prescription drug product labeling, as "an undesirable effect, reasonably associated with use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence."[58] FDA has explained in guidance that when adverse events identified from spontaneous reports in the postmarketing setting are considered for inclusion in the ADVERSE REACTIONS section of labeling, the basis for inclusion is "typically based on one or more of the following factors: (1) seriousness of the event, (2) number of reports, or (3) strength of causal relationship to the drug."[59] The FDA guidance further recommends that listings of adverse reactions in labeling be preceded by a statement that because these adverse events "are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure" (italics removed).[60]

With respect to the adverse events already included in the labeling for Absorica and Absorica LD — erectile dysfunction, decreased libido, decreased vaginal lubrication, and vaginal dryness — none of the data and information submitted with your Petition, or that FDA otherwise reviewed in the course of responding to this Petition, suggest that these four adverse events are no longer appropriate for the Absorica and Absorica LD labeling.[61] Moreover, the information reviewed provides no basis to conclude that there are differences between Absorica and Absorica LD and the other approved isotretinoin products such that labeling including these four adverse events would be appropriate for the former, but not the latter.

For the remaining three sexual dysfunction adverse events for which you requested that FDA require inclusion in the labeling for isotretinoin products — decreased orgasmic sensation, anorgasmia, and genital anesthesia — there were very few reports identified in FAERS or the medical literature. The limited information available is inadequate to provide a basis for inclusion in labeling, either in the ADVERSE REACTIONS section or, as requested in the Petition, in the WARNINGS AND PRECAUTIONS section.

For the reasons outlined above, your request that FDA require the addition of information on the risk of sexual dysfunction adverse events to the WARNINGS AND PRECAUTIONS section of labeling is denied. However, although we did not find reasonable evidence of a causal association to justify the inclusion of information in the WARNINGS AND PRECAUTIONS section of labeling, we have determined that the following sexual dysfunction adverse events

[57] See 21 CFR 201.57(c)(7).

[58] Id.

[59] See Adverse Reactions Guidance at 8.

[60] Id. at 7–8.

[61] See Absorica/Absorica LD Labeling.

reported in the postmarketing setting warrant inclusion in the ADVERSE REACTIONS section of labeling for isotretinoin products: erectile dysfunction, decreased libido, decreased vaginal lubrication, and vaginal dryness.

3. FDA Assessments on Sexual Dysfunction Adverse Events After Discontinuation of Isotretinoin

As part of our review of the Petition requests, we also evaluated the potential for the sexual dysfunction adverse events identified in the Petition or during our review to persist, worsen, or emerge after discontinuation of isotretinoin. Materials reviewed included those previously described (see section II.A.1.).

For the same reasons cited above for denying the Petition request to require that the labeling for isotretinoin include information in the WARNINGS AND PRECAUTIONS section about sexual dysfunction that may occur during treatment, the materials reviewed, including medical literature (submitted in the Petition or identified by FDA), summary analyses of postmarketing reports performed by regulatory agencies outside the United States, and FAERS reports did not provide reasonable evidence of a causal association with isotretinoin use and sexual dysfunction adverse events that persist, worsen, or emerge after discontinuation of the drug. The case reports and other literature (including the information from regulatory agencies outside the U.S.) reviewed described small numbers of reported cases with little detail, and the observational studies suffered from the methodological concerns previously raised. Likewise, the FAERS reports had the previously described limitations, including that the reported adverse events could have been related to another factor (or factors). Accordingly, your request that FDA require information be added to the WARNINGS AND PRECAUTIONS section of labeling on sexual dysfunction that persists, worsens, or emerges after discontinuation of isotretinoin is denied.

We have concluded, however, that the evidence of risk of erectile dysfunction, decreased libido, vaginal dryness, and decreased vaginal lubrication that may continue after discontinuation of the drug warrants inclusion in isotretinoin product labeling in the ADVERSE REACTIONS section.

As discussed above, FDA has determined that these four adverse events should be included in the ADVERSE REACTIONS section of labeling for isotretinoin products. We have now additionally determined that information on the possible continuation of the four previously identified sexual dysfunction adverse events after isotretinoin is stopped is appropriate for inclusion in the ADVERSE REACTIONS section. Although the underlying causes of these adverse events remain unknown, and other endogenous and exogenous factors may play a role, the continuation of these adverse events is reported to have had notable impacts on patients, especially given the young patient population for whom isotretinoin is most frequently prescribed. The median age of the patients who reported sexual dysfunction adverse events that continued after discontinuation of isotretinoin in cases we evaluated was 21, and some patients required treatment with sildenafil or vaginal lubricants as well as referrals to specialists (e.g., urologists), often with little to no improvement reported in sexual dysfunction. Taken collectively, the available information supports the inclusion of information in the ADVERSE REACTIONS section of labeling on these specific sexual dysfunction adverse events that may continue after isotretinoin is stopped.

Although we concluded that the risk for certain sexual dysfunction adverse events to continue after isotretinoin is stopped should be included in the ADVERSE REACTIONS section of labeling as described above, the available evidence does not support including in labeling that any sexual dysfunction adverse event may worsen or first emerge after discontinuation of the drug. We have previously described the limitations of the publication cited in the Petition[62] describing worsening or emerging sexual dysfunction adverse events, and we found no FAERS reports of sexual dysfunction that worsened or first emerged after isotretinoin discontinuation. As such, you have not provided, and FDA has not otherwise identified, any basis to require the addition of information in isotretinoin drug product labeling on sexual dysfunction adverse events that worsen or first emerge after drug discontinuation.

4. Overview of FDA Findings and Next Steps Regarding Petition Requests for Additions to the WARNINGS AND PRECAUTIONS Section of Labeling

a. Overview of FDA determinations

FDA has reviewed the Petition and its accompanying references, as well as other information available to the Agency, and we have determined that there is inadequate support for adding information on sexual dysfunction adverse events to the WARNINGS AND PRECAUTIONS section of labeling for isotretinoin products. The information cited in the Petition or otherwise identified by FDA does not provide reasonable evidence of a causal association between isotretinoin and the sexual dysfunction adverse events identified in the Petition that occurred during treatment with isotretinoin. The data included spontaneous postmarketing reports submitted to regulatory agencies or published in the medical literature, as well as a small number of limited observational studies and one controlled study that had considerable problems with design and methodology. In some cases, the information was significantly problematic because it was derived from solicited reporting and methods using directed querying, which can stimulate and bias the reporting and collection of adverse events.

Although FDA has determined that there is not reasonable evidence of a causal association for sexual dysfunction adverse events during treatment with isotretinoin use to warrant their inclusion in the WARNINGS AND PRECAUTIONS section of labeling, we have determined that, for three of these adverse events identified in the Petition — erectile dysfunction, decreased libido, and decreased vaginal lubrication — their occurrence, as reported in the postmarketing setting during isotretinoin use, warrants inclusion in labeling in the ADVERSE REACTIONS section. FDA has reached the same determination for a fourth adverse event — vaginal dryness — that was not listed in the Petition. As noted above, these four adverse events are currently included in the ADVERSE REACTIONS section of approved labeling for Absorica and Absorica LD.

Moreover, FDA has determined that there is not reasonable evidence of a causal association between isotretinoin use and sexual dysfunction adverse events that persist, worsen, or emerge after discontinuation of the drug to warrant inclusion of information in the WARNINGS AND PRECAUTIONS section. However, we have determined that the potential for the four

[62] See Healy et al.

aforementioned sexual dysfunction adverse events to continue after discontinuation of isotretinoin warrants inclusion in the ADVERSE REACTIONS section of labeling.

b. Today's FDA actions

FDA is today notifying application holders for all isotretinoin products that the Agency has determined that their product labeling should be revised to include specific information on sexual dysfunction adverse events. These labeling revisions will be undertaken in accordance with section 505(o)(4) of the FD&C Act and MODERN authorities, as outlined below.

Today's notifications require the submission of applications to revise isotretinoin product labeling to include the following information that FDA believes should be in the ADVERSE REACTIONS section of labeling:

> Reproductive System
> Abnormal menses, sexual dysfunction that may continue after discontinuation of treatment (including erectile dysfunction, decreased libido, decreased vaginal lubrication, and vaginal dryness)

i. Revisions to the labeling of isotretinoin NDAs

In accordance with section 505(o)(4) of the FD&C Act, FDA is today notifying the NDA holder for Absorica and Absorica LD that they are required to submit an application proposing to revise the labeling to include the information (outlined immediately above) that FDA has determined should be included in the ADVERSE REACTIONS section of labeling.[63]

For the combined labeling for Absorica and Absorica LD, these revisions will provide for the addition of the information that the four sexual dysfunction adverse events already included in the combined labeling may continue after discontinuation of treatment with isotretinoin.[64]

ii. Revisions to the labeling of Accutane-based ANDAs

In accordance with 503D of the FD&C Act, FDA is today notifying application holders of isotretinoin ANDAs relying on Accutane as the reference listed drug that their labeling has been

[63] The NDA holder has also been notified that, alternatively, as outlined above (see section I.A.3.a.), they can notify the Agency that they do not think the changes are warranted and include a statement detailing why. If the NDA holder does not submit the required changes or the Agency disagrees with alternative language proposed by the NDA holder, the FD&C Act provides timelines for discussions between FDA and application holders. At the conclusion of those discussions, FDA may issue an order directing the NDA holder to make the changes as appropriate.

[64] Once the revised labeling for Absorica is approved, application holders for ANDAs referencing Absorica are expected to update their labeling accordingly. FDA recommends that ANDA holders submit their revised ANDA labeling at the earliest time possible because the labeling of a generic drug generally must be the same as that of the corresponding reference listed drug (with certain permissible differences, described at 21 CFR 314.94(a)(8)(iv)). See guidance for industry *Revising ANDA Labeling Following Revision of the RLD Labeling* (January 2024) at 3, available at https://www.fda.gov/media/175654/download.

selected for revisions under MODERN.[65] FDA identified Accutane as a covered drug because we determined that: the approved labeling for Accutane does not reflect current legal and regulatory requirements for content and format; there is new scientific evidence available pertaining to new or the existing conditions of use that is not reflected in the approved labeling; and that updating the approved labeling would benefit the public health.[66] Along with the revisions being proposed for isotretinoin ANDA labeling under MODERN (which are unrelated to sexual dysfunction), changes also include the addition of the language on sexual dysfunction that FDA believes should be included in the labeling.[67] Specifically, the proposed revisions to the ADVERSE REACTIONS section of labeling include the full text above, notably (1) the four sexual dysfunction adverse events and (2) that these adverse events may continue after discontinuation of isotretinoin.

c. Summary of FDA responses to Petition requests for revisions to the WARNINGS AND PRECAUTIONS section of isotretinoin product labeling

In sum, today's notifications to isotretinoin application holders are informing them of information that FDA has determined should be included in the labeling for isotretinoin products regarding certain sexual dysfunction adverse events reported in the postmarketing period, specifically to include (1) four adverse events — three of the six adverse events you requested be required in labeling (erectile dysfunction, decreased libido, decreased vaginal lubrication) plus vaginal dryness, and (2) information that these adverse events may continue after isotretinoin has been discontinued. To the extent that you are requesting that FDA require addition of information to the WARNINGS AND PRECAUTIONS section of labeling on the risks of sexual dysfunction, including that sexual dysfunction may persist, worsen, or emerge after isotretinoin is discontinued, those requests are denied. To the extent that you are requesting that FDA require specific sexual dysfunction adverse events appear in labeling, including that those adverse events "can sometimes persist indefinitely," we are granting that request in part with today's notifications to isotretinoin product application holders that FDA has determined that their labeling should include specific sexual dysfunction adverse events reported in the postmarketing setting, as presented above, in the ADVERSE REACTIONS section of labeling.

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[65] ANDA holders have also been notified that, alternatively, as outlined above (see section I.A.3.b.), if an ANDA holder informs FDA that it does not agree to the labeling changes and provides a statement detailing the reasons, the Agency shall provide an opportunity for discussions to reach agreement. Upon conclusion of such discussions, FDA may order ANDA holders to make the labeling changes FDA determines are appropriate.

[66] MODERN states that FDA may not identify or select a drug for updating under the MODERN provisions "solely based on the availability of new safety information" (see section 503D(h)(3) of the FD&C Act (21 U.S.C. 353d(h)(3))). As noted here, FDA did not identify or select isotretinoin products referencing Accutane for revisions under MODERN based solely on the availability of new safety information.

[67] We note that FDA has authority under both MODERN (section 503D of the FD&C Act) and safety labeling changes (section 505(o)(4) of the FD&C Act) provisions to require certain changes to the labeling for isotretinoin products referencing Accutane, a drug for which approval of the NDA has been withdrawn. In the interest of efficiency for both the application holders and FDA, the labeling changes being proposed today for the isotretinoin products referencing Accutane, including those related to sexual dysfunction, are being made under the Agency's processes for MODERN.

B. Request for Addition to the BOXED WARNING Section

Your Petition requests that FDA require the addition of a new BOXED WARNING to the labeling of isotretinoin products "to inform that sexual side effects can sometimes persist indefinitely after discontinuation of the drug" and that "they can emerge on treatment and remain afterwards, or emerge or worsen when the drug is stopped" (Petition at 1).

As outlined earlier, a boxed warning may be required in labeling for certain contraindications or serious warnings, particularly those that may lead to death or serious injury;[68] this information is crucial for a health care practitioner to consider in assessing the risks and benefits of a drug for an individual patient. The BOXED WARNING section must briefly explain the risk and refer the reader to the CONTRAINDICATIONS or WARNINGS AND PRECAUTIONS section of labeling, where the risk is explained in more detail.[69]

In this Petition response, FDA has explained that the currently available information does not support the addition of information about the risk of the sexual dysfunction adverse events identified in your Petition (or any others identified by the Agency) that may persist, worsen, or emerge after discontinuation of the drug to the WARNINGS AND PRECAUTIONS section of labeling. Given our determination that such information does not warrant inclusion in the WARNINGS AND PRECAUTIONS section, there is no underlying basis for inclusion of a BOXED WARNING. Accordingly, we deny your request that FDA require the addition of a BOXED WARNING on the risk of sexual dysfunction adverse events that persist, worsen, or emerge after discontinuation of the drug to the labeling for isotretinoin products.

C. Request for Additions to Highlights

In the Petition, you request that FDA require that the Highlights for isotretinoin product labeling be revised to include information under the Warnings and Precautions heading to inform that the use of and withdrawal from isotretinoin can result in erectile dysfunction, decreased libido, decreased vaginal lubrication, genital anesthesia, decreased orgasmic sensation, and anorgasmia. You also request that FDA require that Highlights include information in a boxed warning and under the Warnings and Precautions heading to inform that sexual side effects can sometimes persist indefinitely after discontinuation of the drug, can emerge on treatment and remain afterward, or emerge or worsen when the drug is stopped (Petition at 1).

As explained earlier, FDA regulations require[70] that the labeling of most prescription drug products include Highlights, which are intended to summarize for prescribers the information that is most important for safe and effective use of the product and to facilitate access to the more detailed information within the drug product labeling. Highlights contains selected information

[68] See 21 CFR 201.57(c)(1).

[69] Id.

[70] See 21 CFR 201.56(d)(1) and 201.57(a).

from the Full Prescribing Information that health care practitioners most commonly reference and consider most important, including summaries of information from the WARNINGS AND PRECAUTIONS section and, if there is one, the BOXED WARNING section. Highlights must also include, among other information, "[a] list of the most frequently occurring adverse reactions, as described in [the Full Prescribing Information, ADVERSE REACTIONS], along with the criteria used to determine inclusion (e.g., incidence rate)" under the Adverse Reactions heading.[71]

In this Petition response, FDA has explained that the available information does not support requiring the addition of information on sexual dysfunction to either the WARNINGS AND PRECAUTIONS section or the BOXED WARNING section in the Full Prescribing Information for isotretinoin products. Because Highlights is derived from the Full Prescribing Information, you have not provided a basis for addition of information on sexual dysfunction under either of these headings in Highlights. Lastly, although we have determined that certain sexual dysfunction adverse events should be included in the ADVERSE REACTIONS section of the Full Prescribing Information, the labeling regulations require inclusion of only the most frequently occurring adverse reactions in Highlights.[72] Because the sexual dysfunction adverse events identified for inclusion in the ADVERSE REACTIONS section of labeling for isotretinoin products are not among those shown to be most frequently occurring, inclusion in Highlights is not warranted.

For these reasons, we deny your request to require the addition of information on sexual dysfunction to Highlights.

D. Summary of FDA Decisions on the Petition Requests

In summary, we have determined that the following adverse events listed in the Petition warrant inclusion in the ADVERSE REACTIONS section of isotretinoin product labeling: erectile dysfunction, decreased libido, and decreased vaginal lubrication. To the extent that you are requesting that FDA require that application holders of isotretinoin products include these three adverse events in the WARNINGS AND PRECAUTIONS section of labeling, that request is denied because you have not provided, and we have not otherwise identified, reasonable evidence of a causal association. To the extent that you are requesting that FDA require inclusion of these three adverse events in labeling for isotretinoin products, that request is granted with today's notifications to isotretinoin product application holders, pursuant to sections 505(o)(4) and 503D of the FD&C Act, that those sexual dysfunction adverse events be included in the products' labeling. FDA has also determined that a fourth sexual dysfunction adverse event, vaginal dryness, which was not included in the Petition requests, should be included in all isotretinoin product labeling. Because the adverse events that FDA has determined should be included in the ADVERSE REACTIONS section of the Full Prescribing Information have not been shown to be among those most frequently occurring, your request that FDA require that

[71] See 21 CFR 201.57(a)(11).

[72] Id.

they be included in Highlights is denied. We again note that these four adverse events are already included in the ADVERSE REACTIONS section of labeling for Absorica and Absorica LD.

Furthermore, we have also determined that the labeling should state in the ADVERSE REACTIONS section that certain sexual dysfunction adverse events listed in the Petition — erectile dysfunction, decreased libido, and decreased vaginal lubrication — may continue after isotretinoin is stopped. To the extent that you are requesting that FDA require inclusion of information in the WARNINGS AND PRECAUTIONS and BOXED WARNING sections of labeling that these adverse events may persist, worsen, or emerge after drug discontinuation, those requests are denied because, among other things, we have determined that there is not reasonable evidence of a causal association. To the extent that you are requesting that FDA require that application holders include in labeling that certain sexual dysfunction adverse events may continue after the drug is stopped, that request is granted with today's notifications to application holders for isotretinoin products that erectile dysfunction, decreased libido, and decreased vaginal lubrication that may continue after the drug is stopped should be included in the ADVERSE REACTIONS section of labeling. Although we have determined that the ADVERSE REACTIONS section of the Full Prescribing Information should state that these three adverse events may continue after isotretinoin is stopped, your request that FDA require their inclusion in Highlights is denied; these adverse events have not been shown to be among those most frequently occurring. We note that FDA has also determined that the ADVERSE REACTIONS section of labeling should include that vaginal dryness, which was not among the adverse events listed in the Petition, may continue after isotretinoin is stopped.

Lastly, you have not provided, and FDA has not otherwise identified, reasonable evidence of a causal association between isotretinoin and the three remaining adverse events listed in the Petition — genital anesthesia, anorgasmia, or decreased orgasmic sensation. Thus, your request that FDA require the addition of these three adverse events to the WARNINGS AND PRECAUTIONS section of labeling is denied. Your request that FDA require additions to the WARNINGS AND PRECAUTIONS section that these adverse events may persist, worsen, or emerge after drug discontinuation is similarly denied. For the reasons explained above, we also deny your request that FDA require the addition of information about persistence, worsening, and emergence of these three adverse events after drug discontinuation to the BOXED WARNING section. In sum, we have determined that, at this time, the available information does not support FDA action to communicate to application holders regarding inclusion of these three adverse events in any section of labeling.

III. CONCLUSION

Based on our review, and for the reasons set forth above, your Petition is granted in part and denied in part. As is done for all FDA-approved drug products, we will continue to monitor and review available safety information related to isotretinoin products throughout the product life cycles and will take further action if we determine it is appropriate to do so.

Sincerely,

MICHAEL C. DAVIS -S
Digitally signed by MICHAEL C. DAVIS -S
Date: 2026.06.16 20:48:09 -04'00'

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