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May 18, 2016

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
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Re: Docket No. FDA-2016-D-0785: Draft Guidance for Industry – *General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products*

On behalf of Acura Pharmaceuticals, Inc. ("Acura"), we respectfully submit these comments in response to FDA's recently-published Draft Guidance, *General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products.* (the "Generic ADO Draft Guidance").

I. INTRODUCTION AND BACKGROUND

Acura is a publicly-traded specialty pharmaceutical company whose mission is to develop and commercialize innovative formulations of commonly-abused drug products to address the problem of medication abuse and misuse. For more than a decade, Acura has been on the forefront of developing solutions to combat the national epidemic of prescription and over-the-counter drug abuse, with products utilizing the Company's proprietary abuse deterrent technologies, AVERSION®, IMPEDE®, and LIMITX™. Acura's AVERSION Technology is incorporated in the FDA-approved product OXAYDO® (oxycodone HCl) immediate release tablets, which is designed to address both intravenous and nasal snorting routes of abuse. The LIMITX Technology is intended to address abuse by excess oral consumption of multiple tablets and provide a margin of safety during accidental over-ingestion of tablets. In development pursuant to a grant from the National Institute On Drug Abuse ("NIDA") of the National Institutes of Health, the LIMITX Technology has demonstrated the ability to limit the release of the active opioid ingredient from tablets when multiple tablets are ingested and reduce the peak systemic absorption of that active ingredient. Acura's IMPEDE Technology platform is an advanced polymer matrix that is used in the OTC drug products NEXAFED® (pseudoephedrine HCl) tablets and NEXAFED® Sinus Pressure + Pain (Pseudoephedrine HCl/acetaminophen) tablets. The use of the IMPEDE technology limits and disrupts the ability to extract pseudoephedrine from the tablets for conversion into the illicit drug methamphetamine.

In 2011, after eight (8) years of intense effort and investment in research and development, Acura received FDA approval of OXAYDO, the first FDA-approved immediate-release opioid product with abuse-deterrent properties described in its labeling.[1] OXAYDO was developed and approved several years before FDA's first published guidance for developing abuse deterrent opioids,[2] and in fact, many of the elements of FDA's abuse-deterrent opioid guidance, like the use of nasopharyngeal effect scales in snorting studies, and the bi-polar drug like/dislike scale, were pioneered by Acura as far back as 2008.

[1] OXAYDO was originally approved under the trade name OXECTA and briefly marketed under that name by Pfizer pursuant to a joint venture with Acura. When the Acura-Pfizer joint venture was terminated, Acura re-branded the product as OXAYDO and the product is now marketed by Eagalet Pharmaceuticals under license from Acura.

[2] *See* FDA, Guidance for Industry, *Abuse-Deterrent Opioids — Evaluation and Labeling* (April 2015), available at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm334743.pdf.

The OXAYDO formulation utilizes Acura's AVERSION Technology which contains specific types of inactive ingredients to impart physical/chemical barriers to abuse as well as the use of aversive ingredients. OXAYDO's "abuse-deterrent properties [are] described in its labeling" under section 9.2 ("DRUG ABUSE AND DEPENDENCE; Abuse")[3] which discusses the results of a double-blind active comparator crossover clinical study in non-dependent opioid abusers. FDA has previously recognized the abuse deterrent benefits of OXAYDO when it contrasted OXAYDO with another immediate release oxycodone product, Roxicodone, by noting that unlike OXAYDO, "Roxicodone does not claim reduced drug liking or abuse deterrence potential."[4] Moreover, FDA officially received for review several Abbreviated New Drug Applications ("ANDAs") that specifically referenced OXAYDO as the Reference Listed Drug ("RLD") sought to be copied, owing to OXAYDO's status as a unique and distinct abuse-deterrent product, as compared to previously-available immediate-release oxycodone tablets.

FDA has recognized that one modality of abuse-deterrence is to formulate products with "an excipient that functions as an aversive agent."[5] As outlined above, Acura is a leader in the development of abuse-deterrent opioid products that incorporate functional inactive ingredients for aversive purposes, and has developed particular expertise and interest in formulation and testing requirements for this class of abuse-deterrent technology. Acura can thus offer unique and important insights and recommendations on the scientific and regulatory policies and standards that should apply for abuse deterrent products. These comments, accordingly, are primarily directed to those aspects of the Generic ADO Draft Guidance that address testing and approval requirements for purported generic products that seek to copy the aversive functionality and performance of an innovative product referenced by the ANDA applicant.

II. ACURA'S COMMENTS AND RECOMMENDATIONS ON THE DRAFT GUIDANCE

A. In the Interest of the Public Health, FDA Must Assure, Beyond Any Reasonable Doubt, That Generic ADO Versions Are in Fact Equivalent

Acura acknowledges the public health crisis related to the abuse and misuse of opioid analgesics and commends the FDA's efforts to encourage the development and use of abuse-deterrent opioids (ADO's) as part of a comprehensive solution to that crisis. The Generic ADO Draft Guidance appropriately reflects that "FDA considers development of these [innovative abuse-deterrent opioid] products a high public health priority."

The FDA has also long held that the availability of generic products is in the public health interest as offering cost-effective alternatives to innovator products. To facilitate the development of generic drugs under the abbreviated approval process of the Hatch-Waxman Amendments[6], the FDA has typically, as with the Generic ADO Draft Guidance, proposed scientific testing methods and standards less rigorous than required of innovator products, to facilitate their rapid and cost effective entry to the market.

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[3] *See* Generic ADO Draft Guidance at 3.

[4] FDA Decision Letter in Docket No. FDA-2012-P-1009 (Feb. 15, 2013) at p. 3, n. 4, available at http://www.regulations.gov/contentStreamer?objectId=09000064811fb0f9&disposition=attachment&contentType=pdf.

[5] Generic ADO Draft Guidance at 8.

[6] The Abbreviated New Drug Application ("ANDA") process for generic drugs was established by the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. 98-417, and are codified in major part at 21 U.S.C. § 355(j).

However, the FDA recognizes the public health risks that may arise due to the abbreviated requirements for generic drug products, including specific public health risks that are inherent to short-cut testing of purported generic versions of abuse deterrent opioid products:

> it is also important that the availability of such [ADO] generics does not exacerbate the public health problems associated with prescription opioid abuse. Where abuse-deterrent properties are described in the labeling of an RLD, marketing a generic version of the RLD that is less abuse-deterrent could lead opioid abusers to preferentially seek out and abuse such easier-to-abuse generics.[7]

Thus, the FDA acknowledges that the surrogate testing proposed for Generic ADOs must, beyond any reasonable doubt, assure comparable, if not superior abuse-deterrent performance compared to the innovator drug for a Generic ADO to be approvable. Acura respectfully submits that the Generic ADO Draft Guidance fails to adequately address the complexities involved in formulating and testing generic abuse-deterrent products that rely on the use of aversive functional excipients to help achieve their abuse deterrent effect.

B. The Draft Guidance Proposes Inappropriate Testing and Approval Standards for Generic Products That Use Aversive Ingredients

The general principle of the Generic ADO Draft Guidance is that if a generic product's labeling is to describe the same abuse-deterrent properties and performance as an abuse-deterrent RLD (which it must, pursuant to the ANDA "same labeling" requirement under Hatch-Waxman[8]), approval of the proposed generic version will require "comparative evaluation of the abuse deterrence" of the two products, according to one or more sets of principles set forth in the Guidance. The types of testing recommended vary according to the specific type of abuse-deterrent technology(ies) incorporated into the product, and the route(s) of abuse addressed by the product and its technology.

With respect to aversive technology, the only route of abuse identified as relevant by the Guidance is "insufflation (nasal route or snorting)."[9,10] For abuse deterrent technologies other than aversive approaches, the Draft Guidance states that comparative *in vitro* studies, and in some cases pharmacokinetic (PK) studies, will, if successful, generally be all that is required for the approval of a generic product.[11] For aversive technologies designed to deter abuse by nasal insufflation, however, the Guidance recognizes that pharmacodynamic studies with "drug liking" endpoints may be necessary,

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[7] Generic ADO Draft Guidance at 2.

[8] *See* 21 U.S.C. § 355(j)(2)(A)(v) and 21 C.F.R. § 314.94(a)(8).

[9] Generic ADO Draft Guidance at 5, and Appendix 4.

[10] We note that aversive technology has been and is being researched to address other routes of abuse, including the oral route of abuse. When such a product is approved by FDA, the Guidance will likely require revision to address the unique properties and physiological effects of such products.

[11] Generic ADO Draft Guidance at 8 ("Generally, comparative in vitro and PK studies provide sufficient evidence to demonstrate that T product is no less abuse-deterrent than R product.").

especially if the proposed generic product differs from the reference drug with respect to the specific aversive excipient used, and the amount of such excipient that is used, in the generic product.[12]

The Generic ADO Draft Guidance describes the Agency's recommendations on testing requirements for proposed generic versions of opioid products that contain an aversive agent designed to reduce likability by the "addition of excipients that produce an unpleasant effect (e.g., nasal mucosal irritation) if the dosage form is milled and insufflated."[13] According to the Draft Guidance, "if the amount and concentration of [an] aversive agent" in the generic product is greater than or equal to the amount and concentration in the reference product (and is the same aversive ingredient), then the generic product "is considered to have similar abuse deterrence and no additional testing is needed."[14] Conversely, "If the amount or concentration of aversive agent" in the generic product is lower than in the reference product, the generic "product is considered to be less abuse-deterrent than [the reference] product."[15] There are several deficiencies in this part of the Guidance, as discussed below.

1. The Draft Guidance Incorrectly Presumes That Abuse-Deterrent Products Contain at Most A Single Aversive Ingredient and That Such Ingredient Can Readily be Identified.

First, the Guidance seems to presume that an aversive abuse-deterrent product will have only a single aversive ingredient such that a simple chemical/quantity comparison will be sufficient. This presumption is unwarranted, both in theory and in current practice, because an abuse-deterrent product may in fact, like OXAYDO, have multiple ingredients that are known to cause aversive effects but the relative contribution to the aversive effect may not have been fully characterized or quantified for each ingredient. For example, 30% of subjects snorting OXAYDO indicated they would be unwilling to snort the drug again, compared to just 5% for a traditional formulation. But, this clinical endpoint is a composite result of all of the effects generated by OXAYDO's multi-ingredient abuse-deterrent formulation.

As one of FDA's own review staff noted in analyzing the data in the OXAYDO NDA, "it is difficult to assess if the potential abuse deterrent properties of the formulation are related to the specific product composition, or if they are related to the number and amount of excipients in the formulation."[16] The Guidance presumes that the FDA can discern which ingredients are in fact the known aversive agents when, in fact, FDA's own reviewers cannot discern the contribution of any of the ingredients in a formulation to the overall composite abuse-deterrent effect demonstrated in the clinical studies of an abuse deterrent innovator drug. Also, *in vitro* testing of certain abuse-deterrent effects, for example a gelling phenomenon, may not be readily adaptable to the effects of the same ingredients in the human nasal cavity.

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[12] *See* Generic ADO Draft Guidance at 8.

[13] *Id.* at 29.

[14] *Id.* (emphasis added).

[15] *Id.*

[16] *See* NDA No. 20-2080, FDA Review Memorandum by Silvia N. Calderon, Ph.D., Team Leader, FDA Controlled Substance Staff (CSS), regarding Labeling Recommendations for Oxecta [OXAYDO] (June 17, 2011) at p. 2 (available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/202080Orig1s000OtherR.pdf) (the "Calderon Review Memo").

Thus, a proposed generic product must be required to contain all of the same known and potential aversive ingredients in the same amounts as the RLD in order to assure comparable performance. Otherwise, a clinical study is the only means to assure the sameness of aversive effect that FDA recognizes as a requisite approval criteria for a generic ADO product.

2. Generic Products With a Greater Amount of an Aversive Ingredient Cannot be Presumed to Have Equivalent or Greater Aversive Effect.

Even if one or more specific aversive ingredients could be conclusively identified, it would be inappropriate to presume that having the same or greater amount of an aversive ingredient will lead to equivalent abuse deterrence. For example, an aversive ingredient may only produce aversive effects up to a certain amount or concentration in a finished dosage form, but show reduced aversive effect at higher amounts or concentrations. FDA and the International Conference on Harmonization (ICH) have recognized this phenomenon as a reason to require sponsors to conduct parallel dose response studies in the drug development process. As noted in the ICH Guideline for Industry, *Dose-Response Information to Support Drug Registration* (ICH-E4, Nov. 1994),[17] "[t]he parallel dose-response study also offers protection against missing an effective dose because of an inverted 'U-shaped' (umbrella or bell-shaped) dose-response curve, where higher doses are less effective than lower doses, a response that can occur, for example, with mixed agonist-antagonists." (emphasis added). Indeed, "there are well over 1000 citations to molecules with this behavior in the literature."[18] It is entirely possible that one or more particular aversive ingredients would exhibit this so-called "hormetic dose-response," or "hormesis," and be less aversive if contained in a higher amount or concentration in a generic product than in the relevant reference product. FDA cannot and should not assume that possibility out of existence with respect to aversive ingredients simply for the sake of expediency.

Moreover, the Draft Guidance is self-contradictory in proposing to exempt from clinical studies generic products that have a greater "amount and concentration" of a presumed aversive ingredient. This is because for multiple-aversive-ingredient products where one such ingredient is used in a higher amount (and thus higher concentration) than in the RLD, other aversive ingredient(s) used in the same amount as in the RLD would as a matter of math, occur at a lower concentration relative to the overall finished product than in the reference product, and thereby not be exempt from clinical testing.

For these reasons as well, a proposed generic product must be required to contain all of the same known and potential aversive ingredients in the same amounts as the RLD in order to assure comparable performance. Otherwise, a clinical study is the only means to assure the sameness of aversive effect that FDA recognizes as a requisite approval criteria for a generic ADO product.

3. Multiple Aversive Ingredients May Have Additive or Synergistic Effects.

The mechanism or mechanisms of action of an aversive-ingredient product may not be known to FDA or even to the sponsor of the reference product. This is especially true for a product with a combination of

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[17] Available at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073115.pdf.

[18] *See* Owen, S., et al, *Colloidal Drug Formulations Can Explain "Bell-Shaped" Concentration–Response Curves*, ACS Chem. Biol. 2014 Mar 21; 9(3): 777–784, available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3985758/.

ingredients, which may produce an overall aversive effect by either additive or synergistic means, or by both.

For example, the labeling for OXAYDO highlights the gelling properties of the formulation in the DOSAGE AND ADMINISTRATION section. These same gelling ingredients may have contributed to the aversive effects observed in the OXAYDO clinical snorting study, described in section 9.2 of the labeling, in which subjects indicated an unpleasant increase in nasal congestion. Moreover, Acura is aware that the *in vitro* gelling properties of OXAYDO are enhanced by the addition of selected other ingredients in the formulation. The potential effects of these other ingredients when the tablets are crushed and snorted by humans have not, however, been differentially demonstrated beyond the composite pharmacodynamic effects observed in the OXAYDO clinical study. Thus, FDA has no basis to ascertain the specific contribution of these effects to the labeled clinical results, such as a reduction in liking or a preference not to take the drug again.

Thus, if a generic sponsor and/or the FDA inaccurately identifies the aversive ingredient(s) from among all of the ingredients in the formulation based on *in vitro* tests that may not correlate to human conditions, then FDA risks putting potentially inferior generic ADO products on the market.

4. All Ingredients in the Generic Products Must Also Be Identical Because They May Also Impact the Overall Aversive Effect.

Even where a proposed generic ADO product has the same amounts of all of the same ingredients that FDA and/or the generic sponsor deems to be "aversive" under the agency's proposed definition of that term, a presumption of equivalent abuse deterrent effect would be flawed if the generic product has different types or amounts of other inactive ingredients, because those ingredients may also contribute to the clinical effect. This is because the Guidance defines aversive effect and "likability" too narrowly.

Specifically, this section of the Guidance defines aversion as "Reduced likability [which] may be accomplished by addition of excipients that produce an unpleasant effect (e.g., nasal mucosal irritation) if the dosage form is milled and insufflated."[19] However, in the real world, "aversion" and "likeability" are not solely functions of whether the product produces an "unpleasant effect."

A lower likability score under many of these assessment instruments may be due not only, or not at all, to an "unpleasant effect" produced by the excipient(s), but may simply reflect a reduced (or delayed) drug effect (euphoria) which can be caused by the increased volume of milled test product resulting in a slower absorption of the opioid, or the inability to even insufflate the full amount of the product. Thus, for example, a low "drug liking" score, or a low score on the "take drug again" question (used in standard abuse aversion studies[20]), may reflect that the subject did not experience a significant euphoric effect even in the absence of experiencing any "unpleasant effect." And, because these tests use experienced drug abusers, a low liking score may also simply reflect that the user experienced a lower euphoric effect than he or she is used to with a non-abuse-deterrent product (again even in the absence of an unpleasant effect). For example, Section 9.2 of the label for OXAYDO summarizes a clinical study in which subjects had "a decreased ability to completely insufflate two crushed tablets within a fixed time period (21 of 40 subjects)".

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[19] Generic ADO Draft Guidance at 29 (emphasis added).

[20] *See* Abuse Deterrent Opioid Guidance, *supra* note 2, at 13.

The same study indicated an increase in nasopharyngeal effects for subjects taking OXAYDO including nasal burning and nasal congestion. FDA's review of the OXAYDO NDA also noted that the study "does not provide data to rule out the deterrent effects that might be associated with the weight and mass of the tablets."[21] In other words, any and all the excipients in the formulation may be implicated in the subjects' inability to completely insufflate the tablets. The observed deterrent effect, therefore, may be attributable to the weight/mass, the irritation, the congestion, or a combination of any and all of these effects – including some effects that were not measured or considered.

Moreover, the agency has historically, and in the Generic ADO Draft Guidance, recognized the potential importance of the total volume of crushed product in achieving an aversive or abuse-deterrent effect. For example, early in Acura's development of OXAYDO, FDA required that the test and control formulations used in the clinical aversion studies needed to be equivalent not only on the dose of oxycodone but also in terms of the total amount of crushed material in the dosage form to be snorted. And, in Appendix 4 of the Generic ADO Draft Guidance, FDA reiterates that

> Reduction in opioid availability may be accomplished by inclusion of excipients that impart hardness to the formulation and make it difficult to mill, retard the rate of release of the opioid from the milled product, and/or increase the size of the drug product, thereby increasing the amount of milled powder and proportionally decreasing the amount of opioid to be insufflated.[22]

In contrast to this FDA recognition of the importance of equivalent product volume for aversive deterrence products, the Generic ADO Draft Guidance proposes a clinical study exemption for generic products that would not necessarily contain the same product volume, i.e., generic products that contain a greater "amount or concentration" of the same known aversive ingredients.[23] The Guidance suggests that *in vitro* testing of individual excipients can somehow determine the exact contribution to clinical outcomes of a combination of multiple ingredients. In fact, the clinical outcomes in a drug liking study are based on all the ingredients, in quality and quantity, and are the result of known, suspected, and in some cases unknown, aversive effects of each ingredients and the interaction of those ingredients. To suggest otherwise would reduce any reasonable assurance that the Generic ADO will have comparable abuse-deterrent performance.

For a clinical exemption, Generic ADO's must therefore have all of the same ingredients in the same amounts as the RLD. Otherwise, a clinical study should be required as the only means to assure the sameness of aversive effect that FDA recognizes as a requisite approval criteria for a generic ADO product.

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[21] Calderon Review Memo, supra, note 16, at p. 3.

[22] Generic ADO Draft Guidance at 26.

[23] *But see* sections II.B.1 and II.B.3, *supra*, concerning the inability to presume to conclusively know the identity and contributions of aversive ingredients.

III. CONCLUSION

Acura applauds the FDA's attention to the need for a robust armamentarium of innovative abuse-deterrent opioid products, and its responsiveness to Congressional calls to facilitate more rapid development of such products. Generic versions of such products will also play an important public health role in the fight against opioid abuse and addiction, but for them to do so, FDA must adopt standards to ensure that generic versions of abuse-deterrent opioid products are only approved based on sound scientific principles. The Generic ADO Draft Guidance is an important first step toward that goal, but as set forth hereinabove, the Guidance has several shortcomings with respect to ADO products that rely upon aversive functional inactive ingredients. FDA should therefore amend the Draft Guidance to require that proposed generic products utilize all of the same ingredients and all in the same amount and concentration, as the relevant reference drug, in order to qualify for an exemption from clinical testing.

Respectfully submitted,

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