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Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

CITIZEN PETITION

Allergan Holdings Unlimited Company ("Allergan") respectfully submits this Citizen Petition under 21 U.S.C. § 355 and 21 C.F.R. Part 10 to request that the Commissioner of Food and Drugs ("FDA" or "the Agency") take the actions described below.

ACTIONS REQUESTED

Allergan requests that FDA:

1. Publish an updated and revised draft guidance document, consistent with recent and current guidances for other locally acting drugs, and solicit comments, to provide recommendations with respect to analyses for the approval of a generic version of VIBERZI® (eluxadoline) tablets ("VIBERZI") that requires clinical endpoint testing of this locally-acting, poorly permeable drug product;
2. Refuse to receive, and refuse to approve, any abbreviated new drug application ("ANDA") that refers to VIBERZI and that does not include comparative clinical endpoint data to demonstrate that the ANDA product is bioequivalent to VIBERZI (a locally-acting drug product, with low bioavailability, and highly variable pharmacokinetics);
3. Refuse to receive, and refuse to approve, any ANDA that refers to VIBERZI and that does not include scientific and clinical data that demonstrate either (1) that the active ingredient is the same polymorphic form (Form Alpha) as the active ingredient in

VIBERZI, or (2) that the active ingredient is a different polymorphic form and the formulated product does not have greater abuse potential than VIBERZI;

4. Publish and receive public comment concerning the criteria and scientific rationale that FDA applies when considering whether a generic oral drug may raise abuse or scheduling issues (whether or not the product has chemistry extraction study information in the label) and therefore warrants review by the FDA Controlled Substances Staff (“CSS”), including issues relating to “sameness” criteria with respect to abuse potential, and abuse potential testing requirements for innovator and generic drugs.

DISCUSSION

Allergan respectfully requests that FDA refuse to approve any ANDA submitted pursuant to 21 U.S.C. § 355(j) seeking approval to market a generic version of VIBERZI unless and until the generic drug applicant has: (1) demonstrated bioequivalence to VIBERZI through scientifically appropriate methods, including in vivo comparative clinical endpoint studies; and (2) demonstrated that the proposed product contains the same polymorphic form (Form Alpha) of eluxadoline or that the product will not be more susceptible to misuse or abuse as a controlled substance compared to the reference listed drug (“RLD”). The following issues must be addressed before the Agency can make an evidence-based determination to approve any ANDA that may be filed:¹

1. VIBERZI is a locally acting gastrointestinal (“GI”) drug that has very low permeability and a high degree of in vivo pharmacokinetic variability.² These combined factors preclude the use of traditional, comparative pharmacokinetic measures (C_{max} and AUC) to determine whether a proposed generic drug product is bioequivalent to the RLD. No in vitro assessment has been validated as a surrogate to establish that the in vivo rate and extent of absorption of a proposed generic product is equivalent to the RLD. Consequently, it is necessary that any contemplated ANDA sponsor

¹ Currently, no ANDA may be received or reviewed by FDA because of the new chemical entity exclusivity period that governs VIBERZI through May 27, 2020. Allergan requests that FDA consider all relevant factors as it initiates review activity.

² See VIBERZI Prescribing Information, Section 12.3.

perform a bioequivalence study that relies on comparative clinical endpoints to demonstrate bioequivalence to VIBERZI.

2. The active ingredient eluxadoline in VIBERZI is a novel crystalline form (Form Alpha) of 5-({[2-amino-3-(4-carbamoyl-2,6-dimethyl-phenyl)-propionyl]-[1-(4-phenyl-1h-imidazol-2-yl)-ethyl]-amino}-methyl)-2-methoxy-benzoic acid. Allergan selected and developed this novel crystalline form due to, *inter alia*, its utility in the treatment of irritable bowel syndrome, its anhydrous nature, the high level of purity achievable, improved stability, and handling. Other crystalline or amorphous forms of eluxadoline exist, and, in a general context, FDA has acknowledged that the “polymorphic form [of a drug substance] may affect intrinsic dissolution rate and solubility,”³ both of which are directly relevant to drug performance. An ANDA applicant thus must be required to incorporate Form Alpha of eluxadoline into a proposed generic equivalent of VIBERZI. Alternatively, if some other form (whether crystalline or amorphous) is considered, the sponsor must define the scope of variances and submit data to demonstrate that the generic form will exhibit the same physicochemical properties as the Form Alpha reference listed drug.
3. Furthermore, only VIBERZI formulated with its Form Alpha active ingredient and specific blend of excipients, was tested and evaluated with respect to abuse potential and controlled substance scheduling. If a proposed generic drug differs with respect to its active ingredient (e.g., a form of active ingredient more susceptible to manipulation, such as having increased solubility in abusable media) and/or differs with respect to excipients (individual ingredients or quantity), it may present different or enhanced drug exposure and potential abuse risks. If the active ingredient form differs from VIBERZI, an ANDA sponsor must perform a product-specific evaluation with respect to abuse potential and demonstrate that the product does not have greater abuse-liability risk than VIBERZI.

³ FDA Response to Rifaximin-related Citizen Petitions in Dockets FDA-2016-P-3418 and FDA-2008-P-0300 (March 16, 2017) (“Rifaximin CP Response”) at 17. See also n. 37, *infra*.

FDA Must Ensure Generic Versions of VIBERZI Provide Equivalent Therapy To Patients

VIBERZI is indicated in adults for the treatment of irritable bowel syndrome with diarrhea (“IBS-D”),⁴ a condition defined by recurrent abdominal pain or discomfort at least three days per month over the last three months, and associated with two or more of the following symptoms: improvement of pain with defecation, onset of pain associated with a change in frequency of stool, or onset associated with a changed stool form (consistency/diarrhea).⁵ Diarrhea predominant IBS accounts for approximately one-third of all cases of IBS, and is defined as IBS with loose or watery stools with ≥25% of bowel movements.⁶ The pathophysiology of IBS is complex, and remains uncertain. The symptoms of IBS are believed to relate to a number of physiological factors including colonic dysmotility, enhanced visceral hypersensitivity, altered mucosal immune and inflammatory function (including changes in bacterial flora), and dysregulation of intestinal motor sensory and CNS function (brain-gut dysfunction). Psychosocial factors, including daily stress, also may impact the manifestation of IBS related symptoms.⁷ IBS prevalence (all types) is estimated at 10% to 20% of the U.S. population, and at any time up to 2% of the population experiences active symptoms. Women are up to 3 times more likely to develop IBS than men in the United States, and those with the condition are at increased risk of ectopic pregnancy and miscarriage.⁸

FDA has acknowledged that IBS’ chronic, relapsing nature has a significant impact on patient quality of life and day-to-day functioning:

IBS has been shown to impact not only an individual’s physical symptoms, but emotional and social functions as well. IBS is associated with significant direct and indirect medical expenses, as well as increased indirect costs to patients and the community through work absenteeism.⁹

⁴ VIBERZI Prescribing Information (PI), Section 1 (Indications and Usage).

⁵ NDA 206940, Division Director Summary Review at 3.

⁶ NDA 206940, Cross Discipline Team Leader Review at 2.

⁷ Id.

⁸ “Irritable Bowel Syndrome: Newer Drugs Provide Relief,” Pharmacy Times (July 16, 2018), available at <https://www.pharmacytimes.com/publications/issue/2018/july2018/irritable-bowel-syndrome-newer-drugs-provide-relief>.

⁹ Id.

When FDA approved VIBERZI in May 2015, the Agency noted that the current treatment options for IBS-D are limited.¹⁰ Thus -- while it is always essential for FDA to ensure that ANDA-approved drug products will deliver equivalent safety and effectiveness when substituted for an innovator -- it is particularly important to ensure that patients with limited options can receive the intended therapeutic benefits of products (innovator or generic) available to them.

The Local Site of Action, Low Permeability, and High Pharmacokinetic Variability of VIBERZI Require A Bioequivalence Determination Using Clinical Endpoints

VIBERZI is a locally-acting drug,¹¹ with low permeability, and a high degree of pharmacokinetic variability.¹² These factors (individually and collectively) necessitate an ANDA sponsor's use of comparative clinical endpoint studies in order to evaluate and demonstrate bioequivalence to the RLD. FDA recently acknowledged:

If a drug is intended to act locally rather than systemically, traditional PK studies that measure systemic concentrations of a drug over time may be inadequate to demonstrate bioequivalence. Some locally acting products may not produce measurable concentrations of drug in an accessible biologic fluid. For those that do, there may be a lack of evidence of a correlation between the systemic

¹⁰ The Cross-Disciplinary Review at 2 states: "The current treatment options for IBS-D are limited. There are currently no unrestricted prescription products on the market for the treatment of IBS-D. Alosetron, a selective serotonin 5-HT3 receptor antagonist, is the only product approved for use in IBS-[D] in the US; however, it is approved only for women and under restricted distribution due to safety concerns related to severe constipation and ischemic colitis. Loperamide ... is a frequently used antidiarrheal, but it has not been shown to have significant effectiveness in managing the abdominal pain associated with IBS-D, and it is associated with treatment related constipation. Bile acid binders including cholestyramine and colestevam may provide some relief of diarrhea symptoms when associated with bile acid malabsorption, and antidepressants are frequently employed, not only for treatment of associated depression, but for their neuromodulatory and analgesic properties as well. There is a need for additional treatment options in IBS-d that improve both diarrhea and abdominal pain and discomfort, without significant adverse effects." Rifaximin was approved in May 2015 for the treatment of IBS-D in adults.

¹¹ The site of action of VIBERZI is locally in the gut, and not systemic. Eluxadoline is a mu-opioid receptor agonist, as well as a delta opioid receptor and a kappa opioid receptor agonist. The binding affinities of eluxadoline for the human mu and delta opioid receptors are 1.8 nM and 430 nM, respectively. The binding affinity of eluxadoline for the human kappa opioid receptor has not been determined; however, the binding affinity for guinea pig cerebellus kappa opioid receptor is 55 nM. In animals, eluxadoline interacts with opioid receptors in the gut. See PI Section 12.1.

¹² PI, Section 12.3 (Pharmacokinetics).

concentrations and concentrations at the site of drug action for the drug or metabolite.¹³

Both of these limitations support the need for clinical endpoint studies in this instance. There has been no correlation of plasma concentrations of eluxadoline from VIBERZI with concentrations at the site of action for the product. Further, the pharmacokinetic values that were measured for VIBERZI following oral administration show highly variable PK values (ranging from 51% to 98%).¹⁴ Unlike the scenario with respect to the locally-acting, low-solubility drug product rifaximin, for example, in the case of VIBERZI there is no currently available or credible basis to rely on PK studies to judge bioequivalence.¹⁵ A showing of “equivalence” using PK data in this scenario could result simply from the play of chance.

If a form of eluxadoline other than Form Alpha were used, there may be even more doubt about comparisons that do not include clinical endpoint analyses. As FDA has acknowledged, polymorphic forms of a drug can differ with respect to solubility and bioavailability.¹⁶ This introduces a new variable into an already-unreliable PK comparison. Instead, the only credible means to determine whether the alternative forms are providing bioequivalent activity would be to compare data for the clinical safety and effectiveness of Form Alpha with similar evidence of safety and effectiveness of the alternative form.

Should FDA believe that a PK comparison could establish bioequivalence of a proposed generic version of VIBERZI, the Agency must update its historical draft guidance with respect to eluxadoline, which recommends only one fasting and one fed *in vivo* study in healthy

¹³ FDA’s Response to Linzess CP, Docket No. FDA-2016-P-1962 (Dec. 28, 2018) (“Linzess CP Response”) at 3. FDA agreed that PK studies currently are not appropriate to determine bioequivalence of linaclotide capsules. “Because linaclotide is a locally acting drug that is administered in small doses and not systemically absorbed, the drug is not expected to be detectable in blood or urine when administered orally.” Id. at 2.

¹⁴ PI, Section 12.3 (Pharmacokinetics).

¹⁵ FDA found that “[r]ifaximin, like linaclotide and sucralfate, is a locally acting gastrointestinal drug. And like sucralfate, rifaximin is poorly soluble in water, which makes for an inappropriate comparison to linaclotide. [However], in higher doses, rifaximin is detectable in plasma, which makes it possible to conduct PK-based bioequivalence studies.” Linzess CP Response at 7.

¹⁶ Indeed, a different polymeric form, having different particle sizes, for example, may make a modestly dissolvable compound more rapidly dissolve, and could affect pharmacokinetic profile of the drug product and/or its abuse potential.

volunteers, to include measuring clinical endpoints.¹⁷ After FDA published the VIBERZI draft guidance, the Agency addressed the locally-acting, low-solubility product rifaximin (although, as noted, rifaximin is different to the extent it may be feasible to reliably compare certain plasma measurements). Significantly, with respect to rifaximin, FDA advised:¹⁸

- In addition to in vivo PK data, the sponsor of a proposed rifaximin ANDA must perform in vitro dissolution testing of the proposed generic compared to the RLD under multiple, physiologically-relevant pH conditions and surfactant levels.
- The in vitro tests must be designed to demonstrate bioequivalence, not primarily address product quality.
- Dissolution under sink conditions is not a suitable predictor of in vivo drug release of locally-acting GI rifaximin for the purpose of establishing bioequivalence. FDA stated: Non-sink conditions provide a more accurate picture of in vivo release because they allow the concentration of the drug in the dissolution medium to build up such that the solution becomes supersaturated. This is what commonly occurs under finite conditions in the GI tract. In addition, rifaximin does not dissolve under sink conditions with the addition of a large quantity of surfactant to the dissolution media. Such a large quantity of surfactant does not reflect in vivo conditions and would mask differences in intrinsic solubility of various rifaximin forms.
- Comparative dissolution studies should be conducted under multiple non-sink conditions, at multiple pH levels, to reflect the range of pH levels found along the GI tract,¹⁹ and at multiple surfactant levels, to reflect the varying levels of surfactants (e.g., bile) found there.

¹⁷ Draft Guidance on Eluxadoline Oral Tablets (April 2016), available at https://www.accessdata.fda.gov/drugsatfda_docs/psg/Eluxadoline_oral%20tab_RLD%20206940_RC04-16.pdf.

¹⁸ Rifaximin CP Response at 22-23.

¹⁹ VIBERZI dissolution is affected by pH differences. E.g., Memorandum from Controlled Substances Staff to Director, Division of Gastroenterology and Inborn Errors Products (April 21, 2015) at 11 ("The extraction of eluxadoline was highly efficient in acidic and basic solutions (0.1 M HCl, pH 2 and 10 buffers)]. For water saline, ethanol, pH 4 and pH 7 buffers and isopropanol were relative effective, hexane and acetone were not good solvents for extraction.").

The foregoing recommendations have only been applied if a drug product has the same formulation (Q1/Q2) as the RLD. FDA has consistently advised that, if the formulation is not Q1/Q2, then clinical endpoint bioequivalence studies would be required.²⁰ At a minimum then, FDA should require clinical endpoint studies for all non-Q1/Q2 generic formulations of eluxadoline.

Importantly, however, unlike rifaximin, eluxadoline does *not* have a validated pharmacokinetic correlation. Given this important difference, Allergan respectfully submits that FDA require clinical endpoint studies for all generic formulations of eluxadoline.

ANDAs Must Include The Form A Polymorph That Was Tested For Abuse Potential Or, If Approval Of A Different Polymorph Is Desired, The Sponsor And FDA Must Perform New Abuse Potential Analyses

Eluxadoline is a Schedule IV controlled substance. This petition is submitted at a time when there is unprecedented awareness and concern surrounding both (i) patient and (ii) broader societal risks associated with drug products that are, or contain, controlled substances.²¹ At the same time, FDA is taking unprecedented steps to increase the distribution of generic drug products pursuant to ANDAs²² – including (but not limited to) products that are, or contain, controlled substances. FDA and sponsors must address these efforts in careful tandem. If not thoughtfully approached and scientifically/clinically vetted, FDA's current

²⁰ Rifaximin BE Guidance; Rifaximin CP Response at 22.

²¹ According to the Centers for Disease Control and Prevention, more than 130 Americans die every day from overdoses involving opioids. FDA News Release, "FDA approves first generic naloxone nasal spray to treat opioid overdose" (April 19, 2019), available at <https://www.fda.gov/news-events/press-announcements/fda-approves-first-generic-naloxone-nasal-spray-treat-opioid-overdose>. In October 2017, the Department of Health and Human Services declared a nationwide public health emergency regarding the opioid crisis, describing current circumstances as "the most daunting and complex public health challenge of our time." <https://www.hhs.gov/about/news/2019/04/24/hhs-fact-sheet-combating-the-opioid-crisis.html>. FDA has acknowledged the need to employ risk mitigation and evaluation strategies, prescriber education, and more novel tools (e.g., packaging limitations) to attempt to allow access to critical medications, while also taking steps to control drug misuse or abuse. See Timeline of Selected FDA Activities and Significant Events Addressing Opioid Misuse and Abuse, available at <https://www.fda.gov/drugs/information-drug-class/timeline-selected-fda-activities-and-significant-events-addressing-opioid-misuse-and-abuse>.

²² See, e.g., FDA's Drug Competition Action Plan, creating programs to speed up and increase the number of generic drugs being developed and approved in the U.S. See, e.g., 2018 Office of Generic Drugs Annual Report, available at <https://www.fda.gov/drugs/2018-office-generic-drugs-annual-report#Fortifying>.

activities carry the potential to increase or introduce new risks related to diversion, misuse, and abuse of insufficiently vetted drugs.

Allergan strongly aligns with FDA that: “[I]t is important that the availability of [less costly generic versions of approved controlled drugs] do not exacerbate the public health problems associated with … abuse.”²³ That said, however, FDA has published extremely limited guidance related to the assessment of abuse potential from generic drugs or how the industry and Agency may determine that adequate controls will be applied.

For example, the Center for Drug Evaluation and Research’s (“CDER”) Manual of Policies and Procedures states that

All CDER Offices and Divisions are required to consult CSS to evaluate drugs from an abuse perspective during the review of investigational new drug application (INDs), new drug applications (NDAs), biological licensing agreements (BLAs), and abbreviated new drug applications (ANDAs). CDER Offices and Divisions are also required to consult CSS to participate on a multidisciplinary team to evaluate new abuse and dependence-related information.²⁴

However, we have found no elaboration whether or how examination of ANDA product-specific abuse potential occurs in routine practice.

We request that FDA require ANDA sponsors to proactively and robustly compare potential risks associated with their proposed versions of innovator products that are controlled substances. Specific to this VIBERZI petition, for example, and consistent with our bioequivalence concerns raised above, we ask FDA to (1) require a new abuse potential assessment if and when an ANDA sponsor proposes a different polymorphic form active ingredient compared to the clinically and abuse-potential tested RLD product, and (2) clarify what types of abuse potential data must and may appropriately be submitted and reviewed pursuant to an ANDA. FDA has acknowledged that, “[u]nder some rare circumstances, the

²³ FDA, “Guidance for Industry – General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products” (Nov. 2017) (“General Principles Guidance”).

²⁴ Manual of Policies and Procedures (“MAPP”) 4200.3, Rev. 1 (March 6, 2017), available at <https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm073580.pdf>. The only other guidance we have identified concerns abuse-deterrence claims and how an ANDA applicant should evaluate abuse-deterrent properties of solid oral dosage form products. See General Principles Guidance.

Office of Generic Drugs (OGD) should consult CSS, such as when an ANDA involves a drug product for which a new Eight-Factor Analysis and scheduling recommendation is necessary.”²⁵ We urge FDA to require, with respect to a controlled scheduled product, an ANDA sponsor to routinely submit an Eight-Factor analysis whenever a drug substance is not identical to the polymorphic form in the RLD and there is credible evidence – such as here -- that the difference in form may be relevant to abuse potential.

Allergan’s sponsor predecessor-in-interest was required to, and did, test VIBERZI (containing polymorphic Form Alpha²⁶) before the product could be approved and marketed in the United States. Through its review of VIBERZI, for example, FDA concluded that eluxadoline has abuse potential because it may be psychoactive following oral, intranasal, and intravenous routes of administration in animals and/or humans.²⁷ Eluxadoline also demonstrates analgesic activity after subcutaneous and intravenous administration.²⁸ Although oral administration did not have antinociceptive effect, supratherapeutic oral doses (300 mg and 1000 mg) produced small increases compared to placebo in subjective responses such as Drug Liking and Take Drug Again.²⁹ Intranasal administration had small increases compared to placebo in subjective responses such as Drug Liking, Subjective Drug Value, Good Effects, High and Euphoria.³⁰

The company accordingly evaluated potential physical manipulations, pretreatment, solubility/extractability, syringibility, simulated smoking, and other pathways to assess drug liking and abusability. Based on the data, the Eight-Factor Analysis considering the VIBERZI data determined that, although the product has some properties warranting control under applicable law, the degree of potential risk was limited by its inherent chemistry. For example, animal and human data showed that eluxadoline is psychoactive following oral, intranasal and intravenous routes of administration in animals and/or humans.³¹ However, intranasal

²⁵ MAPP at 3.

²⁶ The commercial drug substance eluxadoline is described in, inter alia, U.S. Pat. Nos. 7,741,356, 8,609,709 and 8,69,1860, which are listed in the Orange Book as applicable drug substance patents.

²⁷ FDA CSS Report, page 2.

²⁸ Id. at 3.

²⁹ Id.

³⁰ Id.

³¹ CSS Report at 2.

insufflation is unlikely due to difficulty extracting drug substance from the drug product³²; the large size of commercial tablets relative to small active drug load (only 12% of total tablet weight is drug substance); and significant disliking of intranasal insufflated crushed eluxadoline tablets.³³ The occurrence of thermal decomposition of the drug substance eliminated smoking as an alternate route. Importantly, the modest solubility at neutral pH of eluxadoline (Form Alpha) in VIBERZI theoretically eliminate buccal/sublingual/transmucosal abuse.³⁴ Evaluators reported:

- Difficulty in solubilizing free base crystalline drug substance in small volumes of aqueous solvents
- Difficulty in purifying drug substance from the commercial drug product, with low yield.

³² CSS Report at 40-41 (only 14 of 32 (44%) of subjects in study were able to insufflate greater than 70% of the presented 200 mg intranasal dose; of the remaining 18 subjects, 14 of 32 (44% were not able to insufflate greater than 25% of the presented dose; and 4 of 32 (12%) were able to insufflate 26-69% of the presented eluxadoline dose). In addition, the reported adverse events showed that 50% of subjects who received the 200 mg dose of eluxadoline had nasal congestion. In contrast, 90-96% of subjects presented with intranasal oxycodone doses was able to be insufflated by subjects (with 25-28% nasal congestion). Id at 40.

³³ CSS Report at 37-46. Extraction of drug product presented some level of difficulty. Recovery of eluxadoline was variable under the conditions studied. The Department of Health and Human Services (HHS) assessed, for example, that "once tablets were cracked, they could easily be crushed using a tablet crusher or a mortar and pestle. However, when attempting extraction of eluxadoline, recovery of eluxadoline was variable under most of the conditions tested. The extraction studies showed that the unique physicochemical properties of eluxadoline may present a challenge in attempts to isolate eluxadoline for purposes of abuse, as the predictive value of in vitro manipulation data is limited to experimental conditions which were tested." HHS, Basis for the Recommendation to Place Eluxadoline and its Salts into Schedule IV of the Controlled Substances Act (May 5, 2015) ("HHS Recommendation") at 16-17, available at <https://regulations.gov/document?D=DEA-2015-0014-0005>; see also CSS Report At 13. CSS Report At 13. An ANDA applicant with a different form of drug substance should conduct similar studies to determine the manipulability and abuse potential of the proposed generic product, where, as the FDA has recognized, "[p]olymorphic forms of a drug substance can have different chemical and physical properties, including melting point, chemical reactivity, apparent solubility, dissolution rate, optical and mechanical properties, vapor pressure and density." FDA Guidance for Industry -- ANDAs: Pharmaceutical Solid Polymorphism Chemistry, Manufacturing, and Controls Information (Polymorph Guidance), at 2, available at <https://www.fda.gov/downloads/Drugs/Guidances/UCM072866.pdf> ("FDA Polymorphism Guidance").

³⁴ E.g., HHS Recommendation at 6 (acknowledging free base form of the commercial formulation (Form Alpha) to be unsuitable for injection purposes).

Intravenous abuse studies likewise were not required to be conducted because the preparation of a solution for intravenous use is difficult.³⁵ Buccal, sublingual, and transmucosal absorptions were not studied because the pharmacokinetic data would be limited by the modest solubility at neutral pH of this particular form of eluxadoline.³⁶

Systemic concentrations of eluxadoline (Form Alpha) needed to generate reinforcement would require much larger amounts of drug substance to be in solution than are currently achievable with the commercialized free base substance. If, however, a different polymorph form (e.g., a polymorph with higher solubility³⁷) were used as the active ingredient, it is entirely possible that FDA would find different results. At least, the Eight Factor Analysis prepared by Allergan and CSS Report conducted by FDA is directed at the current commercial drug product, and is silent with respect to an ANDA applicant seeking approval for a different form of eluxadoline. Polymorphic forms of the drug substance can affect the performance characteristics of the drug product and an ANDA applicant is required to demonstrate that, among other things, the ANDA drug product is bioequivalent to the RLD.³⁸

Allergan is not aware of any reported incidents of abuse of VIBERZI since the product launched. However, differences in the drug substance have the possibility to change the abuse potential (e.g., make intranasal abuse easier or more attractive) and associated controls, especially for a product approved for ongoing use with a chronic disease. Accordingly, if a proposed ANDA product has a different form of drug substance from that of VIBERZI, possible differences in physicochemical properties must be thoroughly considered (e.g., do they ease purification and/or increase yield?). ANDA applicants should be required to submit their own data and Eight-Factor Analysis if they are deviating from known products and data.

³⁵ Id. at 46. IV preclinical studies had to be done with a particular salt form to address (the lack of) solubility.

³⁶ Id. at 47.

³⁷ For example, the approved crystalline form of eluxadoline is expected to have lower solubility than amorphous forms. Scientific literature consistently indicates that amorphous forms of a drug substance may have orders of magnitude higher solubility compared to crystalline forms. Hancock and Parks, "What is the True Solubility Advantage for Amorphous Pharmaceuticals?" Pharm. Res (2000) 17:397-405 (10 to 1600-fold); Murdande et al., "Solubility Advantage of Amorphous Pharmaceuticals: II. Application of Quantitative Thermodynamic Relationships for Prediction of Solubility Enhancement in Structurally Diverse Insoluble Pharmaceuticals," Pharm. Res (2010) 27:2704-2714 (1.4x to over 22x increase in experimentally determined solubility from crystalline to amorphous forms) (copies attached).

³⁸ FDA Polymorphism Guidance at 6.

FDA has acknowledged that there are circumstances when OGD should consult CSS and require a new Eight-Factor Analysis and scheduling recommendation for an ANDA.³⁹ The agency has not provided further guidance; however, we submit that proposed generic versions of VIBERZI that are not identical to the innovator fall within this category. This is augmented by the fact that FDA found at the time of approval that “[e]luxadoline is not chemically similar to any opioid agonist that is currently scheduled under the Controlled Substances Act.”⁴⁰ In other words, FDA does not have extensive experience from which to extrapolate about this product.

In addition to specifically addressing the standards for ANDAs that refer to VIBERZI, Allergan requests that FDA generally elucidate the general approach it will apply to identify and control risks that may accompany expanded efforts for generic drug approvals.⁴¹ Allergan continues to support the review and approval of generic drugs when standards are evidence-driven, transparent, consistent, and in accordance with applicable law.⁴² It is not evident, however, that the current ANDA review process yields consistent, evidence-based assessments of ANDA products including controlled substances. Before simply augmenting the volume of products in the pipeline, FDA should provide considered guidance how safety-related distinctions can be reconciled. The public may also have useful comment, so a transparent process should be developed.

ENVIRONMENTAL IMPACT

The actions requested in this Citizen Petition are subject to the categorical exclusion under 21 C.F.R. § 25.31.

ECONOMIC IMPACT

Allergan will provide information on the economic impact of this petition at the request of the Commissioner of Food and Drugs.

³⁹ Note 24, supra.

⁴⁰ CSS Report at 2.

⁴¹ For example, it is unlikely that suitability petitions for a change in dosage form would be approvable, as there have been multiple instances where such a change has led to increased product access and abuse. 67 Fed. Reg. 62354 (Oct. 7, 2002) (oral formulation more likely available for abuse than injectable formulation).

⁴² E.g., Citizen Petition from Allergan in Docket 2017-P-4745 (Aug. 5, 2017) and related documents (generic standards for cyclosporine ophthalmic emulsion).

CERTIFICATION

Allergan submits the following certification in accordance with 21 C.F.R. § 10.31 and FDA's statement in the associated final rule preamble that the Agency is broadly "making § 10.31 apply to all petitions that request an action that could delay the approval of an ANDA, a 505(b)(2) application, or a 351(k) application, regardless of whether an application subject to the petition's requested action is pending at the time the petition is submitted."⁴³ However, to the extent FDA is not in receipt of any ANDAs at the time of this submission, this petition should not be considered subject to the provisions of 21 U.S.C. § 355(q).⁴⁴

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: on or about December 28, 2018. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: my employer, Allergan. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Sincerely,



Thomas F. Poché, Ph.D.

Attachments

⁴³ FDA, "Amendments to Regulations on Citizen Petitions, Petitions for Stay of Action, and Submissions of Documents to Dockets," 81 Fed. Reg. 78500, 78503 (Nov. 8, 2016).

⁴⁴ Id. ("If there is no related ANDA, 505(b)(2) application, or 351(k) application pending at the time the petition is submitted, then the requirements of § 10.31 will apply to the petition, but we will not consider the provisions of section 505(q) of the FD&C Act to apply to the petition.").